BRAIN AND COGNITION FOR ADDICTION MEDICINE: FROM PREVENTION TO RECOVERY

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BRAIN AND COGNITION FOR ADDICTION MEDICINE: FROM PREVENTION TO RECOVERY

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Editorial: Brain and Cognition for Addiction Medicine: From Prevention to Recovery

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Editorial on the Research Topic

Brain and Cognition for Addiction Medicine: From Prevention to Recovery

In 2018, 269 million people around the world had used drugs, and over 35 million were suffering from substance use disorders (SUDs) (1). However, there is a serious limitation in the available treatments for SUDs that are effective in the long term (2–4). A question frequently raised by addiction medicine practitioners around the world is how recent advancements in different fields of brain and cognition studies—from molecular to cognitive neuroscience—can help them improve their daily practice for prevention, treatment, and rehabilitation of SUDs.

There is a growing body of evidence on neurocognitive alterations that contribute to developing a SUD and to hampering recovery, alongside a plethora of social and environmental factors (5, 6). However, there is a lack of neurocognitive markers and related outcome measures that are sufficiently sensitive and specific to addiction mechanisms, engaged by interventions, repeatable, and indicative of disorder progression and recovery. There is preliminary, but promising evidence for different neural and cognitive markers measured with brain mapping and cognitive assessments that (1) engage key mechanisms of addiction (incentive salience, negative emotionality, and cognitive control), (2) predict reduction of drug use (the gold standard for treatment outcomes), and (3) detect acute and chronic responses to interventions with therapeutic potential (7). However, none of these neurocognitive markers have yet approached formal qualification paths [e.g., Biomarker Qualification Program (BQP) of the FDA] or are being widely used in daily clinical practice. Some of the reasons that none of these markers are playing a formal role as a qualified biomarker in addiction prevention or treatment is because they lack methodological harmony, publicly available tools and normative databases, and strong replication and reliability/validity data.

Indeed, although there is a significant body of evidence from brain and cognition studies about SUDs, the impact of this evidence in the daily practice of addiction medicine is minimal and yet to be established. As part of our leadership roles in the *Neuroscience Interest Group* of the *International Society for Addiction Medicine* (ISAM-NIG), we believe that we need an orchestrated international effort to bring pieces of basic and clinical evidence together to develop a roadmap from bench to bedside and policy. We also need consensus and guidelines on how to translate currently available evidence to different dimensions of clinical practice, ranging from prevention to recovery.

In this cross-listed Research Topic in *Frontiers in Psychiatry* and *Frontiers in Human Neuroscience*, our overall goal was to invite researchers to provide evidence that can help bridge the gap between the neuroscientific knowledge of SUDs and its pragmatic use in routine clinical practice. In this successful Research Topic, we published 30 articles (17 original research articles,

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nine reviews, one systematic review, two mini-reviews, and one brief research report), from 146 authors from 13 countries that overall elicited 86,787 views at the time of submission of this editorial. Contributors to our Research Topic mainly sought to provide evidence on susceptibility/risk, diagnostic, predictive, and treatment monitoring evidence for different neural and cognitive markers. We also received articles providing evidence for different mechanistic-informed interventions (two cognitive/behavioral, one pharmacologic, and two brain stimulation interventions) that effectively engaged these markers. These markers spanned across molecular and biological assessments, genetics, different imaging techniques, cognitive assessments etc.

In this e-book, we (Verdejo-Garcia et al.) wrote a consensus paper with a group of ISAM-NIG members about strategies and suggestions to apply the neuroscientific knowledge of addiction medicine into daily practice which has shaped the scope of this Research Topic. In the following sections, we present select highlights of the contributions which we hope will convey a sense of how neuroscience can help increase the understanding of underlying mechanisms of SUDs and how it can inform the development of more impactful interventions.

EVIDENCE FOR SUSCEPTIBILITY/RISK MARKERS

A susceptibility/risk marker in addiction medicine can estimate how likely it is for someone to develop SUDs in the future. Burns et al. in their review discuss how molecular imaging shows that genetics can increase proneness to opioid use disorder and how these inter-individual differences in opioid and dopamine systems underlie the person's reward, cognition, and stress pathways leading to heightened risk of being an opioid user in the future. Among other contributions to this Research Topic, Abram et al. investigated undergraduate university students with a foraging task to assess their ability to associate reward pursuit and reward valuation. They found that in people with more externalizing traits, which confer risk for SUDs, pursuit and valuation were less related. Rose et al. propose distinctive pathways that may increase liability for developing SUDs. The authors discuss how addressing neural mechanisms that differentially characterize these pathways can inform preventive strategies, treatment development, and long-term outcomes. Thus, this e-book brings together promising results on how genetics can predict the level of cognitive functioning and how deficits or delays in specific cognitive dimensions might predict risk to developing SUDs. However, there remain several outstanding questions on the percent variance in this susceptibility/risk for developing a SUD that can be explained by cognitive and neural markers. Supporting evidence with validated cognitive and neuroimaging assessments will be needed on how these susceptibility/risk markers can be used in real world contexts to strengthen neural substrates and circuits of cognitive functioning in individuals at high risk of using preventive strategies/interventions to decrease the incidence of new cases with SUDs.

EVIDENCE FOR DIAGNOSTIC/SEVERITY MARKERS

A diagnostic marker is used to identify subjects with SUDs. In the current Research Topic, researchers aimed to investigate how cognitive functions and imaging results differ between people with and without SUDs, and they report these differences among people with SUDs to illustrate how they are associated with other markers. Noorbakhsh et al. in a cohort study of 3,826 students from grades seven to eleven, found that among female students, working memory functioning, assessed by a neuropsychological test battery, was more negatively affected by the amount of cannabis use. The cause/risk/effect nature of these cognitive markers in relationship to SUD has yet to be explored. Tolomeo et al. showed that people with an opioid use disorder who received either methadone or buprenorphine treatment, have impaired visuospatial memory but those who are abstinent for a period of time do not. The authors also report that the impairment in visuospatial memory is correlated with higher mood and anxiety symptom severity scores. In a study conducted by Deldar et al. it was shown that abstinent methamphetamine users, in comparison with a control group, had lower reaction time in the Sternberg task when viewing drug-related stimuli. Schroder et al., in an ERP working memory task, found that hazardous alcohol drinkers have larger amplitude than light drinkers, mainly around P300 and P600 EEG components, which might be considered a diagnostic factor for risk of developing an alcohol use disorder. Sharman et al. found that two different subtypes of gamblers have different neuropsychosocial problems assessed by decision-making tasks and mental health indices; the authors suggest that treatment providers take these differences into consideration. Albein-Urios et al. evaluated psychological and cognitive problems in cocaine users and found that dysfunctional personality beliefs are correlated with poorer emotion recognition. Roberts et al., using a sample of daily smokers performing a Go/No-Go task after usual smoking and after a period of abstinence, found that during abstinence, smokers have faster information accumulation (accretion) with a lower threshold for prior information before execution (caution). Chen et al. showed that during an Implicit Association Test, people with an internet addiction, compared to controls, show increased activation in the occipital lobe measured by EEG. Jansen et al. (a) reported an fMRI study during an emotion regulation task and found that, although people with alcohol use disorder show no deficiencies in emotion processing compared to healthy people, they have reduced activation in the posterior insula, precuneus, operculum, and superior temporal gyrus when watching positive/negative cues. They also found that higher craving at baseline is associated with less reduced activation when viewing alcohol cues. Smallwood et al., in an fMRI study using structural equation modeling found that chronic pain and opioid use disorder have overlapping neural pathways. Common neural mechanisms and shared markers between chronic pain and opioid use disorder could inform future assessment and intervention studies. Coppens et al. in their review, summarize the role of inflammatory markers in cognition among people

with alcohol use disorder; they detail how inflammation affects cognitive function and in turn how alcohol use impacts the inflammation. In conclusion, they suggest that inflammation may be a target in the treatment of alcohol use disorder.

Diagnosis of SUD is currently based on self-reports of use disorder signs and symptoms during structured clinical interviews; toxicology measures for presence of the drug or its metabolites in the human body are often used to corroborate use. The neurocognitive diagnostic/severity markers that are investigated in this Research Topic, along with thousands more annual publications in the field of addiction neuroscience, attempt to uncover sensitive, valid, and objective measures of mechanistic pathways specific to SUD to accurately assess SUD and its severity, ultimately leading to therapeutic intervention. Given the heterogeneity of deficits among people with SUDs, these diagnostic/severity markers might also be helpful to inform therapeutic interventions optimized for different subgroups within people with SUD. There is still a long road ahead to achieve this ambitious but vital goal.

EVIDENCE FOR PREDICTIVE/PROGNOSTIC MARKERS

Predictive markers estimate how likely it is that an individual with SUD would benefit from a certain treatment. Prognostic markers evaluate overall likelihood of recovery in the long term. Kearny-Ramos et al., in a single-blinded active sham-controlled crossover study, to evaluate the effect of medial prefrontal cortex (mPFC) using repetitive transcranial magnetic stimulation (rTMS) on drug cue-reactivity, found that lower striatal network activation at baseline predicts a higher change in this network in the participants after the act compared to sham. Destoop et al. conducted a systematic review and concluded that anhedonia associated with SUDs negatively affects the success of treatment in long-term.

As reported in this Research Topic, there are hopes that different neural and cognitive markers can help determine the likelihood of the person responding to a specific treatment or recovery/abstinence in general. Ultimately, these markers should inform clinical decision making to optimize the preventive/therapeutic intervention at the individual level.

EVIDENCE FOR MONITORING MARKERS

Monitoring markers are used with the goal of evaluating the effectiveness of a treatment by assessing whether that treatment can change a mechanistic impairment in a person with SUDs. Stewart et al. reviewed opioid use disorder in a three-stage brain model with negative reinforcement processes, binge/intoxication processes, and preoccupation/anticipation processes. They continue by evaluating neuroimaging studies on opioid use disorder monitoring the effects of different interventions in both cross-sectional and longitudinal settings and discussing their limitations and strengths. They conclude with recommendations for future neuroimaging research of opioid use disorder. Vonmoos et al., in a cohort study on chronic cocaine users, assessed socio-cognitive deficits and cluster B personality disorder symptoms, and showed that they are negatively correlated with the change in the amount of substance use following 1 year after baseline assessments. There is still no FDA approval for any neural or cognitive marker to be used as a proxy measure for substance use recovery in clinical trials. However, studies in this area may open doors for novel monitoring markers which serve as key dependent variables in intervention development for addiction medicine.

EVIDENCE FOR MECHANISM-INFORMED INTERVENTIONS

The ultimate goal of all types of markers introduced above is to first target and accurately measure a mechanistic deficit in people susceptible to or who suffer from SUDs, which then informs therapeutic interventions to modulate the deficit. The feedback loop between the mechanistic markers and interventions should pragmatically lead to new and better tailored interventions (8). In this Research Topic, we published different sample interventional studies trying to contribute to this marker/intervention feedback loop. These mechanism-informed interventions could be categorized into cognitive/behavioral, pharmacologic, and brain stimulation interventions.

Cognitive/Behavioral Interventions

Halcomb et al. review methods to measure negative urgency in cross-species translational studies, how negative urgency can inform treatment development, and provide some suggestions for the future direction of the field. Contributing to this Research Topic, Grodin et al., in an fMRI study of heavy alcohol users, assessed the motivation to change after one session of brief drinking intervention. They found that the individuals who received real intervention compared to a sham intervention, had higher scores in the importance to change, and this was associated with higher activation in the precuneus, posterior cingulate, and insula during fMRI alcohol cue-reactivity task. Costa et al. reviewed the role of physical exercise as an adjuvant to routine substance use treatment. The beneficial effect of exercise may be attributable to improving executive function. Kouimtsidis et al. discuss how pre-rehabilitation plays a significant role in successful alcohol detoxification. In a clinical trial with neurocardiac modulation, Bates et al. showed that cardiac resonance paced breathing can alter alcohol cue reactivity in persons with an alcohol use disorder. The active intervention group compared to the sham group showed lower activation to alcohol cues in visual areas, and increased activation in self-control, directed cognition, and brain-body integration areas. Behavioral manipulation of the baroreflex mechanism extends neuroscience-informed addiction intervention approaches to include modulation of bi-directional signaling between the brain and the cardiovascular system.

Pharmacological Interventions

Joseph et al. reported the results of a trial using a graph-theory functional connectivity analysis and machine learning as a monitoring marker among people with cocaine use disorders

to assess the effect of oxytocin on resting-state fMRI. The authors found that oxytocin compared to a placebo increases the connectivity between salience nodes and default mode network nodes differently among women and men, and that childhood trauma and years of cocaine use modulated the effect. Chye et al. first discuss the role of the endocannabinoid system in SUDs and then review the role of cannabidiol on SUDs treatment. This evidence leads to a discussion on potential pharmacological interventions targeting the endocannabinoid system in people with SUD. Butler and Le Foll in their review cover various pharmacotherapies used to treat SUD and to determine how they affect the executive functions of the participants, why there are mixed results, and how to move forward with using both pharmacological and non-pharmacological therapies to enhance cognitive functioning.

Brain Stimulation Interventions

Jansen et al. (b) assessed the effect of right dlPFC-rTMS on emotional processing, reappraisal and craving, and their neural correlates by fMRI during an emotion reappraisal task among people with alcohol use disorder. They found that rTMS compared to a sham reduces dlPFC activation and also modulates self-reported experienced emotions. However, they were unable to find any change in the craving levels, or on reappraisal related brain function.

Altogether, the articles included in this Research Topic on mechanism-informed interventions, along with trials using monitoring markers, illustrate the breadth and depth of international efforts to enhance the feedback loop between markers and interventions in addiction medicine. We endeavor to coordinate and harmonize these efforts as a necessary next step to consolidate research advances and to foster pragmatic clinical translation.

We request funding agencies around the world to support studies that aim to generate datasets that enable researchers to rigorously examine the reliability and validity of neural and cognitive markers, with a goal to establish performance of these markers sufficient to meet formal biomarker qualification standards, similar to that offered by the FDA (9). Our shared long-term goal within the community of addiction neuroscientists is to establish publicly available neural and cognitive markers and their tools, which can be used broadly by multiple investigators (10, 11). This approach will accelerate intervention development and provide outcome measures in RCTs in research settings that can ultimately be used to predict treatment response, inform personalized treatment selection, and monitor treatment efficacy in daily clinical practice.

To reach this goal, we propose the following as initial steps. (1) We need to determine the relationship between true and observed effect sizes with proposed neural and cognitive markers using test-retest reliability measures like intraclass correlation coefficient (ICC). This is a critical need that has not yet received enough attention. (2) We need to determine the validity (risk/susceptibility, diagnostic, predictive, and treatment monitoring) of proposed neural and cognitive markers as biomarkers. (3) We need to repeat Steps 1 and 2, searching for the best set of derived multivariate measures and their pre-registered analysis pipelines in different subjective, physiological, immunological, neural, cognitive, and behavioral markers. Using machine learning methods with proper linear and non-linear models and cross-validation will increase confidence for reasonable replicability (12). (4) Then ultimately, we need to compile, collect, and aggregate the best measures with optimum reliability and multi-dimensional validity based on the standards for biomarkers to inform future mechanism-based intervention development. These resources of tasks/tests of known reliability/validity should be publicly available in repositories like Github or open science framework (OSF) platforms (13).

We further assert that there is a need for methodological checklists to harmonize the parameter space in the field and to promote transparency. As an example, we are working on a new methodological checklist we have recently put forward within the ENIGMA addiction cue reactivity initiative (ACRI) to promote harmonization and open sourcing within the community of labs using fMRI drug cue reactivity as a potential biomarker (14). We encourage addiction neuroscientists to work on similar checklists for other core phenotypes. The successful completion of the proposed pathway in this editorial has the potential to yield a set of brain-based biomarkers for SUDs that can be used in research and practice in addiction medicine.

AUTHOR CONTRIBUTIONS

HE and MZ-B have prepared the initial draft of the editorial. All authors have contributed to make the final draft of the editorial. All authors have agreed on the final draft of the editorial.

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The Neural Correlates of Implicit Cognitive Bias Toward Internet-Related Cues in Internet Addiction: An ERP Study

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Internet addiction is a sort of non-psychoactive substance dependence. The Implicit Association Test (IAT) is used to measure implicit cognition. Event-related potential (ERP) is one of the most widely used methods in cognitive neuroscience research to investigate the physiological correlates of cognitive activity associated with processing information. Further investigating the ERP characteristics of implicit cognitive bias in Internet addiction would be helpful in understanding the nature of Internet addiction. This study investigated the ERP characteristics of implicit cognitive bias in Internet addiction. The participants included 60 Internet-addicted individuals (IAG) and 60 normal controls (NCG). All participants were measured with ERPs using the IAT. The results showed that there was a significant difference in the Internet-related IAT effect for reaction times between IAG and NCG, and there were stronger positive implicit associations toward Internet related cues in IAG than NCG. Using P1, N2, P3, and N4 as dependent variables, a mixed repeated-measures analysis of variance (ANOVA) on the mean latencies and mean amplitudes revealed a significant interaction between the groups (IAG vs. NCG) and stimulus condition (compatible trials vs. incompatible trials) for the N2 and P3 amplitudes; the simple effects analysis showed that the N2 and P3 amplitudes were larger under the IAG-compatible trial conditions than under the IAG-incompatible trial conditions. In the IAG group, the positive implicit associations with Internet-related cues elicited larger N2 and P3 amplitudes at the occipital lobe sites. These results indicated that Internet addictive individuals show stronger positive implicit associations toward Internet-related cues, and the positive implicit associations toward Internet-related cues elicited ERP changes at occipital lobe sites.

Keywords: internet addiction, implicit cognition, the implicit association test, event-related potentials, internet-related cues

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INTRODUCTION

Internet addiction refers to excessive Internet use that has a highly adverse effect on individuals' daily lives. Based on previous studies using neuropsychological and neuroimaging methods, Internet addiction is a sort of non-psychoactive substance dependence (i.e., a type of behavioral addiction) (1–4). To date, there has been an agreement that Internet addiction include four

subtypes: Internet gaming, online social networking, Internet pornography, and Internet shopping (5, 6); however, the psychopathological or aetiological mechanism of Internet addiction has been unclear. Using neuropsychological measurements and neuroimaging methods might clarify the nature of Internet addiction.

Implicit cognition is a key term in cognitive psychology; it primarily refers to the perceptual, comprehension, memory, understanding, reasoning, and performance processes that occur through unconscious awareness (7). Previous studies have indicated that some behavior-related associations might be appraised with authenticated associative memory evaluations that get close to and activate pre-existing associations in memory system (8, 9). The Implicit Association Test (IAT) is used to measure implicit cognition. IAT refers to a reaction time-based categorization task that examines the differential associative strength between bipolar targets and appraising attribute concepts as an approach to indexing implicit biases (10). IAT is a commonly used indirect test of association in memory (11, 12). Many studies have reported that implicit cognition is a predictor for some mental disorders, such as alcohol dependence and tobacco dependence (13, 14). For example, previous studies, which have used the IAT to evaluate implicit associations in tobacco, alcohol, marijuana, and cocaine use, have demonstrated that the IAT effectively differentiated substance users from non-users (15–18).

Because of the potential role for psychopathology or etiology, research of implicit cognition has increased, particularly within many mental disorders. A recent study reported that negative associations between Internet addiction and implicit learning abilities (19). To identify the potential mechanisms of dyscontrolled Internet use in individuals with Internet gaming addiction, a study investigated the positive motivational implicit response to Internet gaming cues and concluded that individuals with Internet gaming addiction had a positive motivational implicit response to screenshots of online games; implicit cognition might also be associated with dyscontrolled online gaming (20).

In the past decades, the mechanisms of implicit cognition basis in substance addiction has been evaluated with neuroimaging methods, such as functional magnetic resonance imaging (fMRI) and event-related potentials (ERPs). For example, a previous study assessed activation in the neural substrates involved in implicit associative processes through fMRI of an alcohol-IAT focused on positive outcomes of alcohol use, and the results showed that the striatum is responsible for the mediation of implicit associations underlying habit, and the prefrontal cortex is responsible for the mediation of the controlled behaviors (9). Another study used ERPs to investigate the responses of binge drinkers to alcohol-related pictures and showed that the P100 amplitudes elicited by the alcohol-related pictures were significantly larger than those elicited by the non-alcohol pictures (21).

ERP is one of the most widely used methods in cognitive neuroscience research to investigate the physiological correlates of cognitive activity associated with processing information. In particular, ERP is suited to study item on the speed of neural activity. Further investigating the ERP characteristic of implicit cognitive bias in Internet addiction would be helpful in understanding the nature of Internet addiction. To date, there have been no reported studies examining the ERP characteristics of implicit cognitive bias in Internet addiction. In this study, the participants included an Internet addiction individual group (IAG) and a normal control group (NCG). All participants were measured with ERPs using an Internet information-related IAT. The study investigated the ERP characteristics of implicit cognitive bias in Internet addiction.

METHODS

Time and Setting

This study was conducted at Wuxi Mental Health Center, Jiangsu Province, China, from January 2015 to February 2018.

Characteristics of the Samples

Internet Addiction Group

The diagnostic criteria used for Internet addiction consist of the following five items: (I) individuals with Internet addiction should meet the criteria of the modified Diagnostic Questionnaire for Internet Addiction (22); (II) 18 years of age or older; (III) did not meet the criteria of any of the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) axis I disorders or personality disorders; (IV) not diagnosed with tobacco or alcohol dependence; and (V) not diagnosed with some central nervous systemic diseases. Clinical assessments of all subjects were conducted by two psychiatric residents to collect patient medication and sociodemographic data and to confirm or exclude a DSM-5 diagnostic criterion for any mental illness and a diagnostic criterion for Internet addiction; the duration of each individual's Internet addiction was determined through a retrospective diagnosis. Researchers required the Internet addictive individuals to recall their lifestyles. IAG participants were recruited from the Wuxi Mental Health Center, China. A total of 60 Internet addictive individuals were recruited into the IAG group, including 51 outpatients and 9 inpatients. The reliability of these self-reports from the individuals with Internet addiction was determined by visiting their roommates and intimate friends. Individuals with Internet addiction spent 11.48 h/day (standard deviation = 2.07) on online activities. The duration of being online each week was 6.29 days (standard deviation = 0.57).

Normal Control Group

Normal controls were selected from the local community through local advertisements. All normal controls underwent clinical assessments by two psychiatric residents to collect patient medication and sociodemographic data and to confirm or exclude a DSM-5 diagnostic criterion for any mental illness. Normal controls were tested with the modified Diagnostic Questionnaire for Internet Addiction to exclude a diagnosis of Internet Addiction. Normal controls were excluded from the research if they were substance dependants or were diagnosed with some central nervous systemic diseases. Sixty individuals were matched by sex and age with IAG participants and served as

the NCG. Referring to the previous Internet addiction study (3), only normal controls who spent less than 2 h/day on the Internet were placed in the NCG.

Prior to the experiment, a psychiatric associate chief physician re-checked the participants' profiles. All participants' emotional states were tested with the Hamilton Depression Scale (HAMD, 17-item version) and Hamilton Anxiety Scale (HAMA). The Annett handedness scale (3) was used to evaluate all participants' handedness.

The subjects and normal controls received written informed consent forms and provided their own written informed consent to participate in this research. All participants were paid $48.39 plus travel costs. The Ethics Committee of Wuxi Mental Health Center, China, approved the protocol for the research project.

NEUROPSYCHOLOGICAL TEST

Internet-Related Implicit Association Test

The subjects and normal controls performed an Internet-related IAT. The Internet-related IAT was referred from an alcohol-IAT that was employed in a previous study by Ames et al. (9). Neither the subjects nor the normal controls received any instructions during the experiment. All participants were asked to go as fast as they could (correctly). The stimuli to be categorized were randomly presented target categories (Internet-related pictures vs. mammal pictures) and attribute categories (positive words vs. neutral words). The target categories (prime stimuli) were six Internet-related pictures and six mammal pictures, and the attribute categories were six positive and six neutral word (two Chinese character words) categories, which were identified through open-ended questionnaires from 180 undergraduate students (40 senior high school students, 101 undergraduate students, and 39 graduate students). Six Internet-related pictures, six mammal pictures, six positive, and six neutral word categories were selected, according to their frequency. Thirty students used a 7-point Likert response format to rate the six Internet-related pictures on their perceived relevance to Internet, and the average score was 6.09 (standard deviation = 0.51). The Internet-related pictures included the WeChat icon, King of Glory (online-game) icon, Taobao icon, Google Chrome icon, Internet explorer icon, and Tencent QQ icon; the mammal pictures included a Dog, Monkey, Horse, Pig, Sheep, and Dolphin. Positive words included Happy, Attractive, Relaxed, Excited, Friendly and Sociable, and neutral words included Common, Calmness, Impartial, Brown, Stationary, and Objective. Thirty students used a 7-point scale ranging from 1 (very approved) to 7 (very disapproved) to rate the affective intensity of six positive and six neutral words; the average score of the Positive words was 6.33 (standard deviation = 0.71), the average score of Neutral words was 3.55 (standard deviation = 0.30).

Combinations of Internet-related picture + positive word vs. mammal + neutral word were compatible trials, while combinations of mammal picture + positive word vs. Internet-related picture + neutral word were incompatible trials.

The target categories (prime stimuli) and the attribute categories were presented on a 17-inch computer monitor using E-Prime 2.0 software. The attribute words (Size 40) and the red "+" (1.0 × 1.0 cm) were presented centrally on the screen.

In this IAT, there were 80 exposures in compatible blocks and 80 in incompatible blocks. Blocks of compatible trials and incompatible trials were counterbalanced, and trials within the blocks were randomly ordered. Fixation point trials were baseline. A red "+" was used in the presentation of the fixation with onset timing ranging from 1.0 to 4.5 s, followed by stimuli presentation. Maximum exposure of test stimuli was for 2 s. There was an intertribal interval (2 s) after a participant pressed a response key, and then the trial was over and followed by the next trial.

Referred from Ames et al. (9), the Internet-related IAT consisted of the following blocks: (I) a target category practice (20 trials), during the experiment, all participants were requested to press the A key for the Internet-related picture and press the L key for the mammal picture; (II) an attribute category practice (20 trials), during the experiment, all participants were requested to press the A key for the positive word and press the L key for the neutral word; (III) a compatible block with both target and attribute category practice (20 trials), during the experiment, all participants were requested to press the A key for combinations of the Internet-related picture + the positive word and press the L key for the mammal + neutral word; (IV) a compatible block with both target and attribute category tests (60 trials), during the experiment, all participants were requested to press the A key for combinations of the Internet-related picture + the positive word and press the L key for the mammal + neutral word; (V) a target category only used in the reversed positions practice (20 trials); (VI) an incompatible block with both a reversed target category and the attribute category practice (20 trials); and (VII) an incompatible block with both the reversed target category and the attribute category test (60 trials) (**Figure 1**). Only the data from block IV and block VII were used for the analysis. According to the previous algorithm used for D-600 measurements (23), the IAG and NCG response latencies were calculated separately.

Event-Related Potential Measurements

Referencing the international 10/20 system, electroencephalograms were recorded with the Stellate Harmonie Electroencephalogram device (Physiotec Electronics Ltd., Canada) using Electro-Cap Electrode System (ECITM Electro-Caps, Electro-cap International, INL, USA). Combined ear electrodes served as a reference, and the ground electrode was attached to the forehead. Vertical and horizontal electrooculograms were recorded from above and below the right eye and at the right and left outer canthi. The inter-electrode impedance was below 5 kΩ. The band-pass filter was 0.05–100 Hertz (Hz), and the sample rate was 250 Hz. Electroencephalogram and electrooculogram waveforms were filtered with bandpass filter 0.01–40 Hz, 24 dB/oct. The stimulus conditions of the ERPs included following two trials: compatible trials (combinations of the Internet-related picture + positive word vs. mammal + neutral word) and incompatible trials (combinations of the mammal picture + positive word vs. Internet-related picture + Neutral word). The trials in blocks 3, 4,

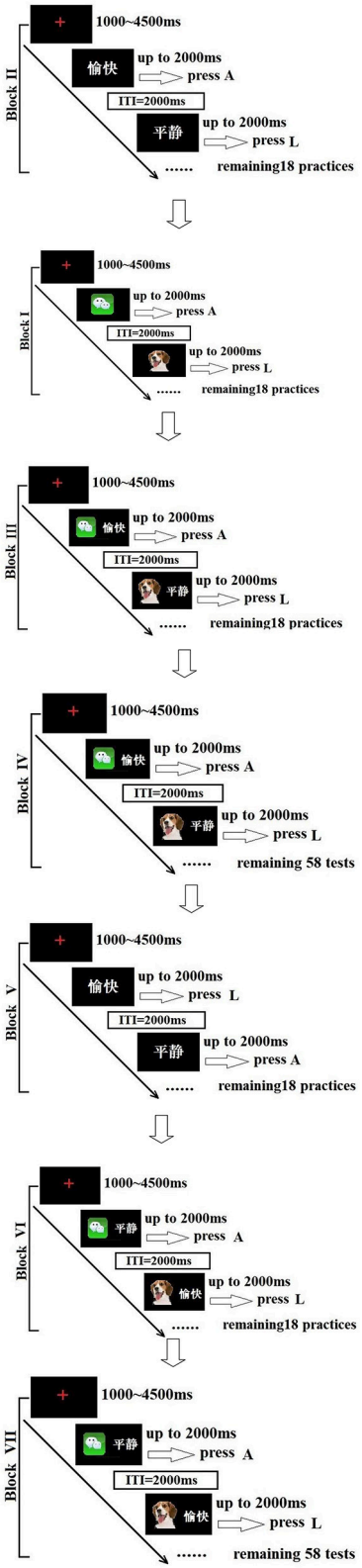

FIGURE 1 | A cartoon illustrating the Internet-related IAT. 愉快, happy; 平静, calmness. ITI, intertribal interval; ms, millisecond.

6, and 7 for Internet-related IAT were used for ERP analysis. The confirmation of ERP components depended on the latency after the stimulus onset, and the ERP components included the peak amplitudes of P1, N2, P3, and N4. ERP data from the following six scalp regions, 14 electrode sites altogether, were analyzed: frontal lobe sites (F3, Fz, and F4); parietal lobe sites (P3, Pz, and P4); central lobe sites (C3, Cz, and C4); left temporal lobe sites (T3) and right temporal lobe sites (T4); and occipital lobe sites (O1, Oz, and O2). The ERP epoch in each stimulus condition was 1000 milliseconds (ms) (including 200 ms before the stimulus onset and 800 ms after the stimulus onset). ERP component P1 was defined as the peak negativity within a 0–150 ms latency window, N2 was defined as the peak negativity within a 150–250 ms latency window, P3 was defined as the peak positivity within a 250–350 ms latency window, and N4 was defined as the peak negativity within a 350–450 ms latency window.

Statistical Analysis

All data were analyzed with Statistical Product and Service Solution 18.0 statistical software (SPSS 18.0, WIN version, Inc., Chicago, IL, USA). Comparisons of the demographic and clinical characteristics (education years, HAMA scores and HAMD scores) between IAG and NCG were performed using independent-sample *t*-tests. Comparisons of handedness between IAG and NCG were performed using chi-squared tests. Comparisons of ERP data between IAG and NCG were performed using mixed repeated measures analysis of variance (ANOVA). The degrees of freedom of the F ratio were corrected, according to the Greenhouse–Geisser method. Least square difference tests were performed as *post-hoc* analyses, if indicated.

RESULTS

The Demographic and Clinical Characteristics of the Samples

The demographic characteristics of all samples are described in **Table 1**. There were no significant differences in the sex ratio, mean age, age range, mean education years, and handedness between the two groups. Although the mean scores of HAMA

TABLE 1 | Demographic and clinical characteristics of the samples.

	IAG	NCG	Test statistic
Sex ratio (M/F)	60 (32/28)	60 (32/28)	–
Mean age (SD)	23 (5)	23 (5)	–
Handedness (R/M/L)	23/15/22	22/17/21	x^2 =3.60, $p = 0.18$, NS
Age range	18–28	18–28	–
Education years (SD)	10.3 (2.2)	10.1 (2.2)	$t = 0.585$, $p = 0.560$, NS
Dependence duration (month, SD)	35.1 (11.0)	–	–
HAMA (SD)	9.4 (3.2)	8.4 (2.8)	$t = 1.762$, $p = 0.081$, NS
HAMD (SD)	15.2 (4.8)	13.5 (5.1)	$t = 1.928$, $p = 0.056$, NS

IAG, Internet addition group; NCG, Normal control group; M, male; F, female; SD, standard deviation; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; NS, not significant.

and HAMD of IAG were higher than those of NCG, no significant differences were observed between the two groups.

Internet-Related IAT Effect

The mean D-600 measure for IAG was 0.3152 (standard deviation = 0.3440), and the mean D-600 measure for NCG was 0.0625 (standard deviation = 0.2063). Accord to an independent sample *t*-test, there was a significant difference in the Internet-related IAT effect for the reaction times between IAG and NCG, and it showed stronger positive implicit associations toward Internet-related cues in IAG than in NCG ($t = 6.901$, $p = 0.001$).

The error rate for IAG was 0.0251 (standard deviation = 0.0187), and the error rates for NCG was 0.0260 (standard deviation = 0.0191). According to an independent sample *t*-test, no significant differences in the error rates for the Internet-related IAT were observed between IAG and NCG ($t = -0.356$, $p = 0.672$).

Analysis of Event-Related Potential Data

The mean latencies and mean amplitudes of ERP component (P1, N2, P3, and N4) of all participants are shown in **Tables 2**–**5** and **Figures 2**–**5**. The sketch map of grand average waveforms elicited by IAG-compatible trial stimuli, IAG-incompatible trial

TABLE 2 | All participants' ERP P1 mean latencies [mean (SD), ms] and mean amplitudes [mean (SD), μV] *.

Scalp regions	IAG				NCG			
	Compatible trials		Incompatible trials		Compatible trials		Incompatible trials	
	Latencies	Amplitudes	Latencies	Amplitudes	Latencies	Amplitudes	Latencies	Amplitudes
Frontal lobe	136 (10)	3.5 (0.4)	133 (10)	3.4 (0.4)	135 (10)	3.3 (0.4)	139 (12)	3.5 (0.3)
Parietal lobe	130 (15)	3.5 (0.5)	134 (9)	3.5 (0.6)	138 (11)	3.5 (0.5)	136 (11)	3.7 (0.6)
Central lobe	137 (12)	3.6 (0.5)	136 (16)	3.3 (0.6)	141 (12)	3.6 (0.4)	133 (11)	3.6 (0.6)
Temporal lobe (T3)	130 (15)	3.4 (0.5)	140 (13)	3.5 (0.5)	134 (12)	3.4 (0.5)	136 (10)	3.3 (0.8)
Temporal lobe (T4)	135 (10)	3.5 (0.4)	135 (10)	3.6 (0.5)	133 (13)	3.5 (0.6)	135 (11)	3.7 (0.6)
Occipital lobe	134 (11)	3.6 (0.7)	132 (11)	3.5 (0.6)	138 (10)	3.3 (0.5)	132 (12)	3.6 (0.6)

**The sum of all corresponding scalp region latencies and amplitudes divided by the number of electrode sites are the mean latencies and mean amplitudes, respectively.*

TABLE 3 | All participants' ERP N2 mean latencies [mean (SD), ms] and mean amplitudes [mean (SD), μV] *.

Scalp regions	IAG				NCG			
	Compatible trials		Incompatible trials		Compatible trials		Incompatible trials	
	Latencies	Amplitudes	Latencies	Amplitudes	Latencies	Amplitudes	Latencies	Amplitudes
Parietal lobe	196 (14)	−3.6 (0.7)	200 (12)	−3.7 (0.6)	201 (8)	−3.6 (0.7)	195 (13)	−4.2 (0.6)
Central lobe	203 (16)	−3.5 (0.9)	199 (10)	−4.0 (0.8)	197 (11)	−3.7 (0.5)	197 (13)	−3.7 (0.8)
Temporal lobe (T3)	195 (11)	−3.8 (0.5)	198 (10)	−3.9 (0.9)	199 (16)	−3.8 (0.7)	202 (8)	−3.9 (0.9)
Temporal lobe (T4)	194 (15)	−4.0 (0.8)	195 (16)	−3.8 (0.6)	201 (12)	−4.0 (0.4)	198 (14)	−4.0 (0.8)
Occipital lobe	197 (13)	−6.2 (0.9)	196 (15)	−4.1 (0.5)	197 (10)	−3.6 (0.6)	194 (16)	−4.2 (0.8)

**The sum of all corresponding scalp region latencies and amplitudes divided by the number of electrode sites are the mean latencies and mean amplitudes, respectively.*

TABLE 4 | All participants' ERP P3 mean latencies [mean (SD), ms] and mean amplitudes [mean (SD), μV] *.

Scalp regions	IAG				NCG			
	Compatible trials		Incompatible trials		Compatible trials		Incompatible trials	
	Latencies	Amplitudes	Latencies	Amplitudes	Latencies	Amplitudes	Latencies	Amplitudes
Frontal lobe	297 (18)	4.5 (0.6)	296 (15)	4.4 (0.7)	296 (18)	4.5 (0.8)	300 (9)	4.8 (1.0)
Parietal lobe	296 (19)	4.6 (0.8)	302 (12)	4.7 (0.9)	301 (11)	4.6 (0.7)	305 (17)	4.9 (0.6)
Central lobe	301 (16)	4.5 (0.9)	299 (17)	4.7 (0.8)	297 (15)	4.7 (0.6)	297 (13)	4.7 (0.7)
Temporal lobe (T3)	295 (14)	4.8 (0.7)	298 (13)	4.9 (0.9)	304 (16)	4.8 (0.7)	302 (18)	4.9 (0.9)
Temporal lobe (T4)	294 (17)	4.5 (1.0)	303 (16)	4.8 (0.6)	301 (12)	5.0 (0.6)	298 (16)	5.0 (0.6)
Occipital lobe	299 (16)	6.8 (0.9)	302 (17)	4.8 (0.8)	297 (18)	4.6 (0.9)	306 (16)	4.8 (0.8)

**The sum of all corresponding scalp region latencies and amplitudes divided by numbers of electrode sites are the mean latencies and mean amplitudes, respectively.*

TABLE 5 | All participants' ERP N4 mean latencies [mean (SD), ms] and mean amplitudes [mean (SD), μV] *.

Scalp regions	IAG				NCG			
	Compatible trials		Incompatible trials		Compatible trials		Incompatible trials	
	Latencies	Amplitudes	Latencies	Amplitudes	Latencies	Amplitudes	Latencies	Amplitudes
Frontal lobe	405 (14)	−4.0 (0.6)	403 (15)	−3.9 (0.7)	403 (15)	−4.1 (0.8)	400 (19)	−4.3 (1.0)
Parietal lobe	400 (19)	−4.1 (0.8)	402 (19)	−4.2 (0.9)	401 (11)	−4.1 (0.7)	405 (17)	−4.5 (0.8)
Central lobe	401 (17)	−4.0 (0.5)	402 (17)	−4.2 (0.6)	400 (19)	−4.3 (0.6)	406 (14)	−4.6 (0.7)
Temporal lobe (T3)	406 (15)	−4.3 (0.6)	401 (13)	−4.1 (0.5)	404 (16)	−4.2 (0.8)	402 (18)	−4.1 (0.9)
Temporal lobe (T4)	399 (17)	−4.1 (1.0)	407 (18)	−4.2 (0.5)	401 (17)	−4.0 (0.6)	400 (16)	−4.0 (0.6)
Occipital lobe	402 (18)	−4.3 (0.8)	402 (17)	−4.0 (0.6)	405 (18)	−4.1 (0.8)	406 (16)	−4.2 (0.6)

*The sum of all corresponding scalp region latencies and amplitudes divided by the number of electrode sites are the mean latencies and mean amplitudes, respectively.

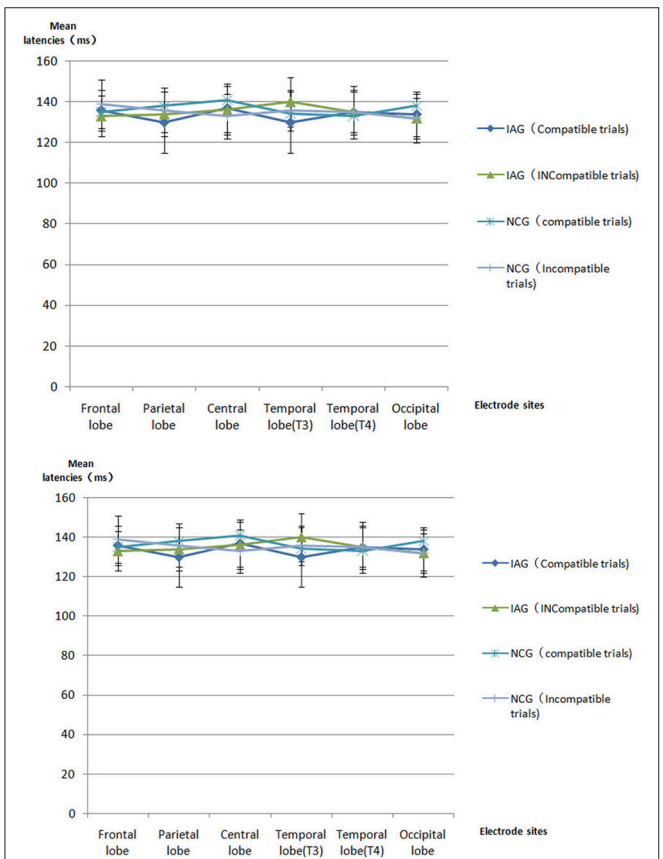

FIGURE 2 | ERP P1 component the latencies and amplitudes.

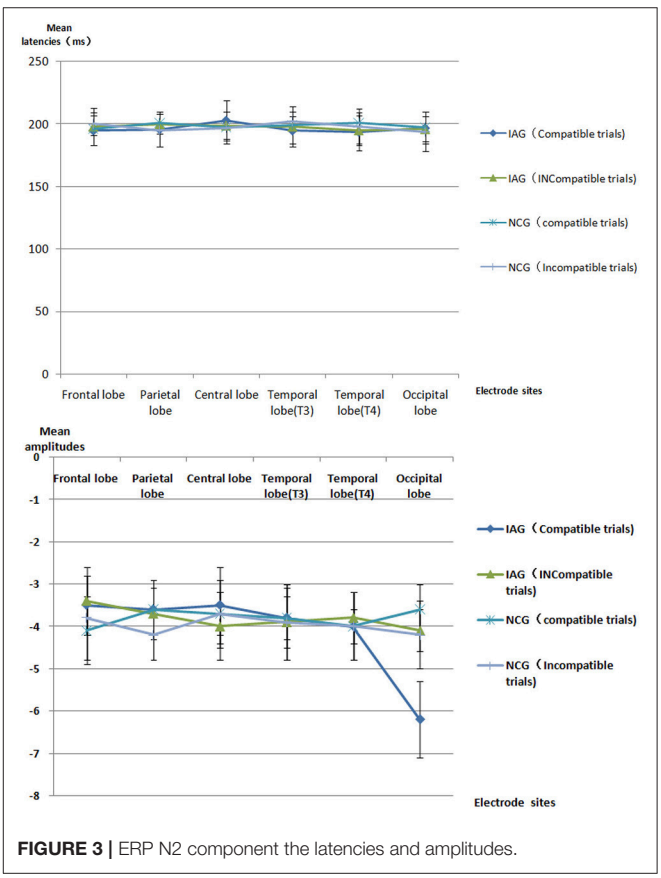

FIGURE 3 | ERP N2 component the latencies and amplitudes.

stimuli, NCG-compatible trial stimuli, and NCG-incompatible trial stimuli at Fz, Cz, Pz, T3, T4, Oz, O1, and O2 is shown as **Figure 6**.

Using P1, N2, P3, and N4 as dependent variables, a 2 × 2 × 6 mixed repeated measures ANOVA on the mean latencies and mean amplitudes, with group (IAG vs. NCG) as a between-subject factor and stimulus condition (compatible trials vs. incompatible trials) and scalp regions (frontal lobe, parietal lobe, central lobe, temporal lobe (T3), temporal lobe (T4), and occipital lobe) as within-subjects factors, was performed.

P1 Component

There were no significant effects for P1 latency and amplitude.

N2 Component

There were no significant effects for N2 latency. The results revealed a significant interaction between group (IAG vs. NCG) and stimulus condition (compatible trials vs. incompatible trials) [$F_{(1, 119)} = 32.76$, $p = 0.000$]. The simple effects analysis

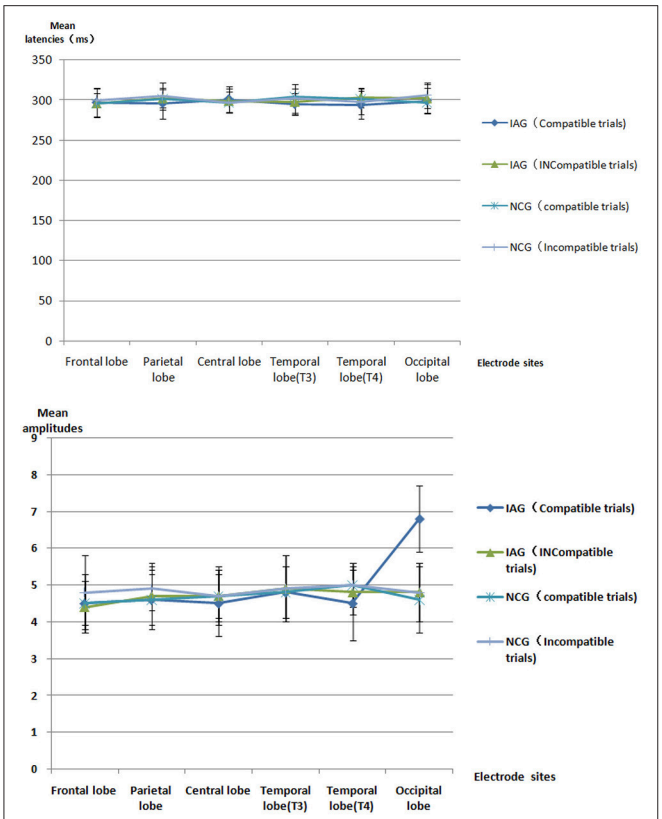

FIGURE 4 | ERP P3 component the latencies and amplitudes.

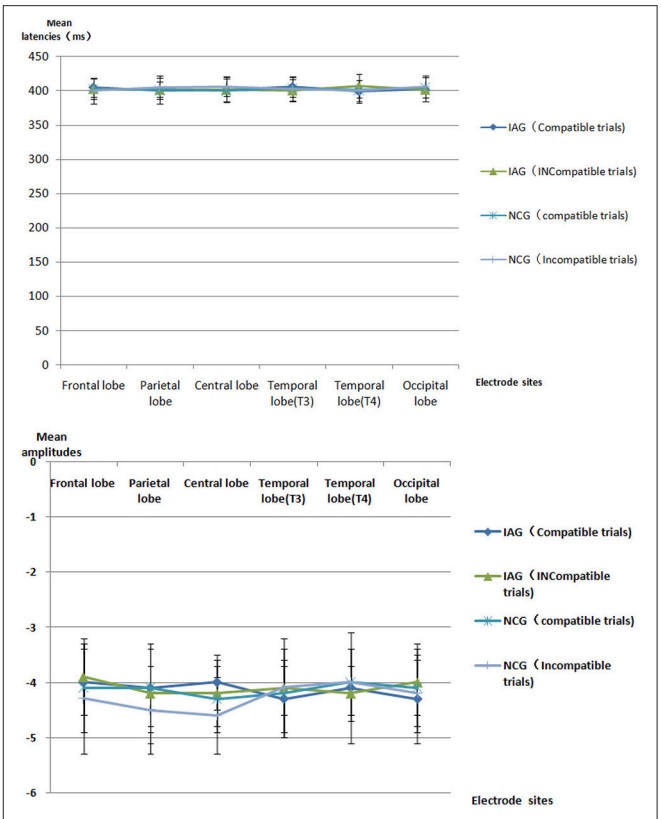

FIGURE 5 | ERP N4 component the latencies and amplitudes.

showed that N2 amplitudes were larger under the IAG-compatible trial conditions than under the IAG-incompatible trial conditions [$F_{(1, 119)} = 5.10$, $p = 0.018$]. In IAG, the positive implicit associations toward Internet related cues elicited larger N2 amplitudes. There was a significant three-way interaction between group (IAG vs. NCG), stimulus condition (compatible trials vs. incompatible trials) and scalp regions (frontal lobe, parietal lobe, central lobe, temporal lobe (T3), temporal lobe (T4), and occipital lobe) [$F_{(4, 236)} = 9.35$, $p = 0.000$]. The simple effects analysis showed a significant interaction between group (IAG vs. NCG) and stimulus condition (compatible trials vs. incompatible trials) on the occipital lobe sites [$F_{(1, 119)} = 29.78$, $p = 0.000$]. At the occipital lobe sites, IAG-compatible trials evoked larger N2 amplitudes than IAG-incompatible trials. There were no significant effects in the frontal lobe, parietal lobe, central lobe, temporal lobe (T3), and temporal lobe (T4) sites.

P3 Component

There were no significant effects for P3 latency. The results revealed a significant interaction between group (IAG vs. NCG) and stimulus condition (compatible trials vs. incompatible trials) [$F_{(1, 119)} = 35.86$, $p = 0.000$]. The simple effects analysis showed that the P3 amplitudes were larger under the IAG-compatible trial conditions than under the IAG-incompatible trial conditions [$F_{(1, 119)} = 6.47$, $p = 0.025$]. In IAG, the positive implicit associations with Internet-related cues elicited larger P3 amplitudes. There was a significant three-way interaction between group (IAG vs. NCG), stimulus condition (compatible trials vs. incompatible trials) and scalp regions (frontal lobe, parietal lobe, central lobe, temporal lobe (T3), temporal lobe (T4), and occipital lobe) [$F_{(4, 236)} = 8.65$, $p = 0.000$]. The simple effects analysis showed a significant interaction between group (IAG vs. NCG) and stimulus condition (compatible trials vs. incompatible trials) at the occipital lobe sites [$F_{(1, 119)} = 30.42$, $p = 0.000$]. At the Occipital lobe sites, IAG-compatible trials evoked larger p3 amplitudes than the IAG-incompatible trials. There were no significant effects in the frontal lobe, parietal lobe, central lobe, temporal lobe (T3), and temporal lobe (T4) sites.

N4 Component

There were no significant effects for N4 latency and amplitude.

DISCUSSION

This study is the first to use ERPs to investigate the neural correlates of implicit cognitive bias toward Internet-related cues in Internet addiction. Our study results showed stronger positive implicit associations toward Internet-related cues in IAG than in NCG, and in IAG, the positive implicit associations toward Internet-related

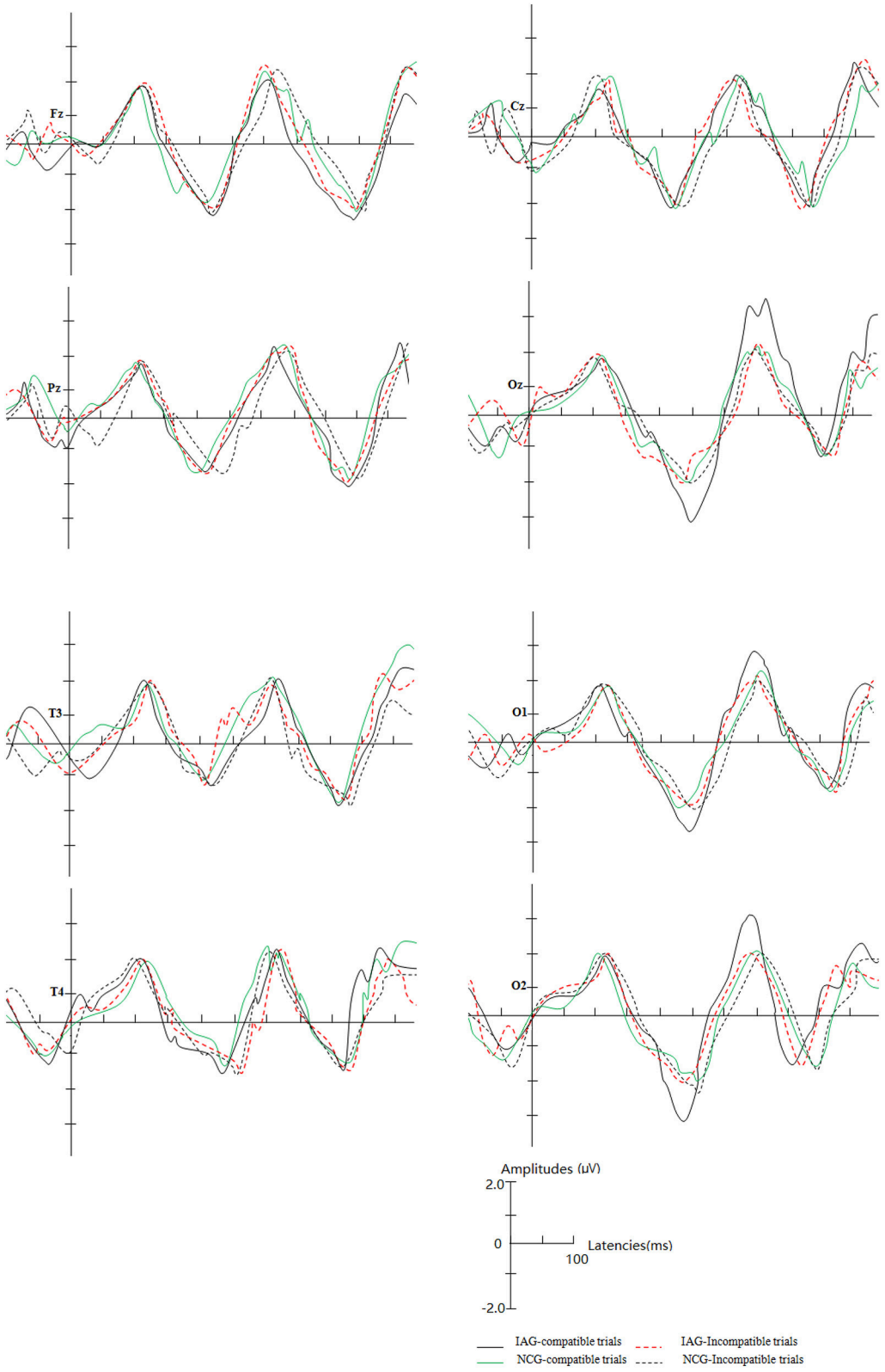

FIGURE 6 | The sketch map of grand average waveforms elicited by IAG-compatible trial stimuli, IAG-incompatible trial stimuli, NCG-compatible trial stimuli, and NCG-incompatible trial stimuli at Fz, Cz, Pz, T3, T4, Oz, O1, and O2. In IAG, at the Oz, O1, and O2 sites, the positive implicit associations with Internet-related cues elicited larger N2 and P3 amplitudes.

cues elicited larger N2 and P3 amplitudes at occipital lobe sites.

Previous studies have indicated that, as a sort of behavioral addiction, Internet addiction shares many psychopathological features with substance dependence (1, 24). Studies of substance dependence have demonstrated that key processes related to reinforcement and cognition in the development and maintenance of substance dependence, particularly the cognition process, represent viable treatment targets for psychosocial and pharmacological interventions (25).

Many scholars have suggested that implicit associations play a crucial role in substance and behavioral addiction (26). In the past decades, many studies, using IAT, have verified whether substance or behavioral addiction present implicit cognition bias. For example, a study used the IAT-Recoding Free (IAT-RF) to measure the predictive validity of recoding-free implicit alcohol associations with positive arousal (27); another previous study, which used IAT modified with pornographic pictures, investigated whether heterosexual male participants have tendencies toward cybersex addiction (26). The above two studies have demonstrated that implicit associations with positive arousal may play a key role in substance and behavioral addiction.

Consistent with a previous study, our results indicated that Internet addictive individuals have tendencies toward Internet related cues.

Event-related potential is a sort of high temporal resolution measures of human brain processing. Because ERPs present the rapid fluctuations associated with the key neurocognitive processes, it is suited to expand our understanding of the underlying neural mechanisms of change during the onset of substance and behavioral addiction (25).

Many studies have investigated the ERP characters when subjects were engaged in an IAT task. In a previous study, two positively valenced stimuli and two negatively valenced stimuli were used as category labels. The results displayed shorter response latencies for compatible trials compared to incompatible trials, and compatible trials tended to generate more positive waveforms in the central and parietal areas compared to incompatible trials (28). A study showed that when the participants performed an IAT task, the recorded ERPs presented an N2 that was larger in the incompatible stimuli, and they deduced that the ERP N2 amplitude reflected greater response monitoring (29). Another study displayed that many brain regions, including medial frontal, cingulate, insular, left-temporal, and parietal cortex, were responsible for ERP N2- and P3-related activity during performed IAT (10).

In this study, under the stimulus conditions of compatible trials, the positive implicit associations toward Internet-related cues elicited larger N2 and P3 amplitudes at occipital lobe sites in Internet addictive individuals. Although the ERP is poor in spatial resolution, it may provide evidence that some cerebral cortices (such as the posterior cingulate cortex) at occipital lobe sites are responsible for the implicit bias toward Internet-related cues in Internet addictive individuals.

Summary, individuals with Internet addiction present stronger positive implicit associations toward Internet-related cues, and the positive implicit associations toward Internet-related cues elicited changes in ERPs (i.e., larger N2 and P3 amplitudes at occipital lobe sites).

Determining the ERP characteristics of implicit cognitive bias in Internet addiction would be helpful in understanding the nature of Internet addiction; furthermore, the results can provide a theoretical basis for the development of possible prevention and treatment strategies for Internet addiction.

This study has some limitations. On the one hand, using the modified Diagnostic Questionnaire for Internet Addiction as a diagnostic tool for Internet addiction is not accurate because its validity as a diagnostic instrument has been not confirmed. On the other hand, to determine the neurotic mechanism of implicit cognitive bias toward Internet-related cues in Internet addiction depends on the integration between temporal resolution and spatial resolution in neuroimaging; however, ERP only provides an excellent temporal resolution. Future studies should use the reliable diagnostic instrument for Internet addiction and fMRI to measure the neurotic mechanism of implicit cognitive bias in Internet addiction.

AUTHOR CONTRIBUTIONS

ZZ and HZhou designed the study. LC, HZhou, YG, SW, JW, LT, HZhu, and ZZ performed the experiment. LC, HZhou, YG, SW, JW, LT, HZhu, and ZZ analyzed the data and wrote the manuscript. All authors approved the final version of the manuscript for publication.

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The Endocannabinoid System and Cannabidiol's Promise for the Treatment of Substance Use Disorder

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Substance use disorder is characterized by repeated use of a substance, leading to clinically significant distress, making it a serious public health concern. The endocannabinoid system plays an important role in common neurobiological processes underlying substance use disorder, in particular by mediating the rewarding and motivational effects of substances and substance-related cues. In turn, a number of cannabinoid drugs (e.g., rimonabant, nabiximols) have been suggested for potential pharmacological treatment for substance dependence. Recently, cannabidiol (CBD), a non-psychoactive phytocannabinoid found in the cannabis plant, has also been proposed as a potentially effective treatment for the management of substance use disorder. Animal and human studies suggest that these cannabinoids have the potential to reduce craving and relapse in abstinent substance users, by impairing reconsolidation of drug-reward memory, salience of drug cues, and inhibiting the reward-facilitating effect of drugs. Such functions likely arise through the targeting of the endocannabinoid and serotonergic systems, although the exact mechanism is yet to be elucidated. This article seeks to review the role of the endocannabinoid system in substance use disorder and the proposed pharmacological action supporting cannabinoid drugs' therapeutic potential in addictions, with a focus on CBD. Subsequently, this article will evaluate the underlying evidence for CBD as a potential treatment for substance use disorder, across a range of substances including nicotine, alcohol, psychostimulants, opioids, and cannabis. While early research supports CBD's promise, further investigation and validation of CBD's efficacy, across preclinical and clinical trials will be necessary.

Keywords: endocannabinoid system, ECS, substance use disorder, treatment efficacy, cannabidiol, CBD, addiction

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INTRODUCTION

Substance use disorder (SUD) is a global problem, with over 30 million individuals estimated to have an SUD (1). Within the United States alone, SUD-related expenditure (e.g., treatment and productivity cost) exceeded 23 billion USD per year (2), presenting a worrisome issue. Treatment to date has had minimal success, with a high likelihood of relapse (3). There is also no reliably established pharmacotherapy for SUDs, such as cannabis, and stimulant use disorder; and current pharmacotherapies (e.g., opiate substitution with methadone; naltrexone for alcohol use disorder;

nicotine replacement) have limited efficacy in relapse prevention (4, 5). SUD has been conceptualized as a maladaptive and relapsing cycle of intoxication, binging, withdrawal and craving that results in excessive substance use despite adverse consequences (6). Recent models implicate major brain circuits involved in reward saliency, motivation, and memory/learned associations in maintaining addiction (7). Critically, these circuits may largely be modulated by the endocannabinoid system (ECS), presenting a promising pharmaceutical avenue for treating SUDs.

THE ENDOCANNABINOID SYSTEM

The ECS consists of cannabinoid receptors (e.g., CB1R, CB2R), the endogenous ligands that bind to these cannabinoid receptors [e.g., anandamide and 2-arachidonoylglycerol (2-AG)], and enzymes for their biosynthesis and degradation [e.g., fatty acid amide hydrolase (FAAH) and monoacylglyrecol lipase (MAGL)] (8). Over the past decade, primary interest has focused on CB1Rs, for their purported role across a range of physiological functions, including directing the psychoactive effect of delta9-tetrahydrocannabinol (THC), a phytocannabinoid present in cannabis (8, 9). CB1Rs are one of the most common G-protein-coupled receptors in the central nervous system, preferentially residing on presynaptic neurons across diverse regions including the neocortex, striatum, and hippocampus (10, 11). Their widespread distribution allows them to guide a host of functions ranging from cognition, memory, mood, appetite, and sensory responses (8). Endocannabinoids themselves function as neuromodulators that are released by post-synaptic neurons, and bind to the presynaptic CB1Rs to moderate the release of neurotransmitters, such as gamma-aminobutyric-acid (GABA), glutamate, and dopamine (DA) (10, 12, 13). While the specific CB1R function depends on the cell population and region in which they reside, their role in retrograde signaling permits them to regulate signaling activity across cognitive, emotive, and sensory functions, lending therapeutic capacity (14).

ECS ROLE IN REWARD SIGNALING

Of the functions that the ECS is involved in, of critical interest, is its influence on the brain reward circuitry, particularly in response to substances of abuse. The rewarding effect of substances of abuse is thought to be primarily mediated by the mesolimbic DA pathway, originating from dopaminergic cell bodies in ventral midbrain [ventral tegmental area (VTA)], carrying reward-related information to the ventral striatum [nucleus accumbens (NAc)] (15). The acute reinforcing effect of addictive substances is thought to be due to their direct or indirect activation of DA neurons along this pathway (16). The VTA-NAc pathway as such plays a key function in reward assessment, anticipation, and valuation, making it a critical component underlying substance use and addiction (17).

DA activity is intrinsically tied to cannabinoid activity. CB1Rs are particularly densely located across the striatal regions that mediate reward function (i.e., NAc and VTA) (18), and their regulatory role on the VTA-NAc pathway may be crucial in modulating overall reward tone (19, 20). Rodent studies have demonstrated that THC increases neuronal firing rates in the VTA (21), likely through local disinhibition of DA-ergic neurons, by binding to CB1Rs present on glutamatergic and/or GABAergic neurons (although it is prudent to note that THC's capacity to potentiate DAergic release differs between rodents and humans) (15, 20, 22, 23). Similarly, other substances of abuse (e.g., opioids, cocaine) have also been demonstrated to potentiate dopaminergic activity via the ECS (24, 25). For example, alcohol is found to have a downstream potentiation effect on the ECS in rats (26), such as an increase in endogenous cannabinoid (anandamide and 2-AG) levels (27, 28) and downregulation of CB1R expression (29). Alcohol-induced DAergic release is furthermore dependent on the presence of CB1Rs (30). Nicotine activates DA neurons in the VTA either directly through stimulation of nicotinic cholinergic receptors or indirectly through glutaminergic nerve terminals that are modulated by the ECS (31). Meanwhile opioid receptors are often co-located with CB1Rs in the striatum (32), and may be modulated by and interact with CB1R activity reciprocally (33, 34). Only psychostimulants are suggested to act directly on DAergic axon terminals in the NAc, potentially avoiding upstream endocannabinoid involvement in the VTA (35).

CB1R's role in the motivational and reinforcing effects of rewards has been demonstrated in animal models with CB1R agonists. For example, acute exposure to CB1R agonists (e.g., THC; CP 55,940; WIN 55,212-2; HU 210) augments NAc DA transmission (36), lowers the brain-reward threshold (17), induces conditioned place preference (CPP) (37), and establishes persistent self-administration of substances of abuse, including cannabis and alcohol (17, 38). Meanwhile, CB1R antagonists (e.g., rimonabant) have been shown to attenuate reinforcing effects of these substances, blocking the increase of DA release in the NAc (37, 39). While substances of abuse, such as alcohol, stimulants, nicotine and opioids have differing upstream mechanisms of action (14, 40), the evidence suggest the downstream involvement of the ECS in their reward mechanism.

In summary, the ECS, by direct CB1R activity, modulates and is modulated by mesolimbic DA activity (41). While the action of individual substances may differ, they share a common effect of precipitating DAergic activity from the VTA neurons (42), with this DA-ergic activity mediated by the ECS (14). It is thus thought that the disruption of endocannabinoid signaling may prove effective in treating SUDs (41). Nevertheless, it is necessary to note that this is a simplistic understanding, given the potential involvement of non-DA-ergic neurons in the VTA, and additional neuronal circuits including those involving glutamatergic and opioids, that are yet to be fully elucidated (39, 43).

ECS ROLE IN SUBSTANCE USE DISORDER (SUD)

Besides the ECS role in reward, it is necessary to acknowledge that substance reward and reinforcement are different from substance dependence. Where the former explain initial substance use, and

are suggested to be related to increased DA in striatal and limbic (NAc and amygdala) regions (44, 45); the latter reflects further compulsive substance intake, loss of control, and persistent intake despite the substance's adverse effects and tolerance to its pleasurable responses (44, 46, 47).

Several lines of thought suggest SUD to be a learned habit (48, 49) mediated by persistent changes in striatal function (e.g., synaptic plasticity occurring during learning) (50). Substances of abuse are thought to influence long-lasting plastic changes across corticostriatal circuits, through repeated perturbation of DA activity, thus making it difficult for addicts to cease their substance use, and enhancing risk of relapse (48, 50–52). In this role, CB1Rs present across the corticostriatal circuits, such as the PFC and striatum, mediate synaptic transmission, in their capacity as neuromodulators (35, 53). Evidence demonstrates the necessity of cannabinoid signaling on CB1Rs to induce long-lasting synaptic plasticity, such as long-term depression (LTD) of glutamatergic release across the dorsal and ventral striatum (19, 54). Such functional changes, particularly across the striatal structures responsible for the rewarding and motivational effects of substances of abuse, are not only necessary in providing reward salience, but also in establishing compulsive substance use habit (39, 55). The ECS thus represents a necessary contributor toward cellular adaptations in the transition from recreational substance use to a use disorder (50, 56).

A further function of ECS-mediated synaptic plasticity may be to facilitate emotional learning and memory processes, which promote increased emotional response to substance-related cues (57). The limbic system, in particular the amygdala and hippocampus, by supporting the formation of associative memory, promotes positive and negative reinforcement of rewards including those of substances of abuse (58). Indeed, animal models demonstrate memory performance to not only be dependent on emotional processes, but may be modulated by augmentation of ECS signaling (59–62). Phytocannabinoids, such as THC and CBD for example have been found to modulate brain activity level across limbic regions during emotional processing tasks (63, 64). Endocannabinoids may further induce long-term changes in synaptic strength across the hippocampus, mediating associative memory formation (65–67). Literature investigating cannabinoid agonists and antagonists on SUD solidifies the role of the ECS in emotional learning and memory processes. CB1R agonists and antagonists have respectively been demonstrated to facilitate and attenuate memory extinction in various fear and reward conditioning paradigms in animal models [see (57) for review]. Within the context of SUD, cannabinoid modulation of emotional memory may have implications for extinction, consolidation, and reinstatement of substance-related memory (68). These processes are primarily assessed through place conditioning paradigms, such as CPP. CB1R antagonism by rimonabant for example, has been demonstrated to disrupt the reconsolidation and facilitate the extinction of CPP to substances of abuse, such as methamphetamine and cocaine, potentially via disrupting reward-associated memory (69, 70). Nevertheless, evidence on SUD behavior is mixed and potentially dependent on type and dose of cannabinoids (70, 71).

The ECS's role in reward signaling and learning may as such shape addictive behavior in SUD. The following section details evidence of CB1R's involvement in SUD as demonstrated by cannabinoid agonism and antagonism in animal models.

Agonism of CB1R

CB1R agonism (either studied with the synthetic cannabinoid agonist WIN 55-212,2 or contrasted against CB1R knockout mice) has been shown to facilitate alcohol self-administration, CPP, and binge-like behavior in animals (38, 72–74). WIN 55,212-2 has also been found to increase motivation to self-administer nicotine, and facilitate cue-induced reinstatement in rats (75). Similar results are found in the heroin literature, with THC-induced CB1R agonism increasing substance self-administration in rats (76, 77).

Agonist substitution with CB1R agonists may have potential for treatment of cannabis use disorder by reducing withdrawal symptoms and the reinforcing effect of cannabis (78). Dronabinol—a stereoisomer of THC, and Nabilone—a synthetic analog of THC, originally intended for nausea and weight loss (55), have both been shown to have efficacy for cannabis withdrawal (79, 80). However, Dronabinol and Nabilone may not prevent cannabis use or relapse (78). It is likely that while these substances are efficacious in attenuating withdrawal symptoms by acting as a "proxy-substances," they do not directly normalize substance use-related circuits and behavior.

Antagonism of CB1R

CB1R antagonism has originally been assumed to be a promising target for SUD treatment. SR141716, known as rimonabant, an inverse agonist of CB1R, has been extensively investigated in SUD for its antagonist effect on drug seeking and relapse behavior in both animal and human models.

Animal studies have shown rimonabant as effective in reducing self-administration of alcohol (81, 82), nicotine (83, 84), and heroin (85). Antagonism of CB1R by rimonabant, reduces alcohol-induced sensitization and reinstatement of nicotine-seeking in rats (83, 84, 86). When investigating the efficacy of CB1R antagonists on stimulant use however, the literature is mixed. While rimonabant's CB1R antagonism has been shown to block CPP and attenuate cue- and substance-induced relapse to psychostimulants, such as cocaine and methamphetamines (87–89), evidence pertaining to self-administration is inconsistent (90–92).

Human studies have also been conducted investigating the efficacy of rimonabant in cannabis, nicotine, and alcohol use. Cannabis and nicotine use have both shown sensitivity to rimonabant antagonism. Rimonabant attenuated the acute physiological effects of cannabis including subjective level of intoxication (93, 94), and clinical trials demonstrate rimonabant to be effective in increasing smoking cessation (95). However, the efficacy of rimonabant for alcohol cessation has been less promising. In a 12-weeks clinical trial of relapse rate in recently detoxified alcohol-dependant patients, rimonabant only had a modest effect (that did not reach significance) compared to placebo (96). Rimonabant also had no effect on

alcohol consumption for non-treatment seeking heavy alcohol drinkers (97).

Despite promising findings of rimonabant against substance use and relapse, it has been found to produce significant negative psychiatric effects including depression, anxiety, and an elevated suicide rate, preventing it from being a viable treatment option (98). Nevertheless, the evidence indicates CB1R antagonism to have robust effects on some SUDs, highlighting a potential target for SUD treatment. One such candidate drug that antagonizes CB1R, and is increasingly being investigated as a therapeutic option for SUD, is cannabidiol (CBD).

CANNABIDIOL (CBD)

CBD is a phytocannabinoid found in cannabis that has recently emerged as a promising treatment for SUDs (99, 100). CBD is non-rewarding, and acts on a number of receptor systems including the opioid (101), serotonergic (102, 103), and cannabinoid (22) systems. Within the cannabinoid system, it is a non-competitive antagonist of CB1R with a low affinity for CB1Rs' primary ligand site (104, 105), instead acting through negative allosteric modulation (105, 106). CBD is found to inhibit endocannabinoid signaling in a dose-dependent manner, likely by binding to CB1Rs' allosteric site and altering the potency of other primary ligands (e.g., endocannabinoids, THC) (106, 107). Its ability to modulate overall ECS tone despite lacking intrinsic efficacy (105) meant that it may decrease CB1R activity without CB1 inverse agonist-related side effects, such as those produced by rimonabant (108, 109). Indeed, CBD has a good safety profile, with generally mild side effects in animal preclinical studies or human studies (110, 111). This, coupled by the limited abuse liability of CBD (112, 113), makes it a good therapeutic candidate. Systemically administered CBD has also been demonstrated to regulate mesolimbic DA activity (114), and potentially attenuate substance-induced dysregulation of the mesolimbic circuitry (115, 116), suggesting its utility against SUDs. Though its efficacy may be dependent on a range of factors including the sequence of administration (i.e., whether CBD is administered in conjunction with, prior to, or post substance-use), and dose ratio (117). A number of papers are urging for the investigation of CBD as a therapeutic option for SUD of multiple substances including stimulants (118), opioids (119, 120), and nicotine use disorder (31). The following section details evidence of CBD treatments for cannabis, alcohol, nicotine, opioid, and stimulants. **Table 1** further lists this evidence by SUD constructs.

Cannabis

Pharmacological approaches to treating cannabis dependence via agonist replacement (i.e., Dronabinol and Nabilone) have limited efficacy (141). CBD itself has been trialed in rats, and found to be effective in ameliorating conditioned place aversion (CPA) produced by THC injection, but did not alter CPP (142). In human case studies, CBD has also been found to reduce self-reported cannabis use to non-use in a dependent male (128), and to reduced cannabis withdrawal in another (135), although the latter case study did find the subject to have relapsed after a 6-months follow up (135). CBD may have potential in reducing euphoria associated with cannabis use, despite not directly reducing cannabis use (124). However, investigative efforts with pure CBD have been limited. Instead most studies have focused on nabiximols—an oromucosal spray containing 2.7 mg of THC and 2.5 mg of CBD—for cannabis dependence (143).

A number of human case studies suggest nabiximols to be efficacious, in combination with behavioral therapy, in reducing cannabis use and withdrawal symptoms (129). However, case study evidence should be taken cautiously. Further case-control studies indicate nabiximols to be effective in reducing withdrawal, but not cannabis use (123, 130, 144). Nor did it improve abstinence rate (123). It was noted that while therapeutics may assist in short-term withdrawal, it is unlikely that ongoing abstinence can be achieved without psychosocial or clinical support (145). Additionally, the THC component of nabiximols causes the drug to have abuse potential and should not be used lightly (146).

Alcohol

In animal studies, CBD was effective in reducing ethanol self-administration, and at high enough concentration (120 mg/kg but not 60 mg/kg) attenuated ethanol relapse (131). Further animal studies show CBD (at 15 mg/kg) to effectively reduce cue and stress induced reinstatement of ethanol administration, up to 138 days post-CBD treatment (140). However, one study found CBD alone to be ineffective in attenuating ethanol sensitization, which is suggested to be the first step in drug-associated plasticity (121). Comparatively, pure THC and a 1:1 ratio of THC:CBD was found to be more efficacious in reducing ethanol sensitization. In a human trial of 10-weeks of daily CBD administration in cannabis users, no changes in alcohol or tobacco use was observed either, although the study sample was not dependent on alcohol (124).

Tobacco

In a placebo controlled study of 24 smokers, those who received a CBD inhaler significantly reduced the number of smoked cigarettes relative to the placebo group, despite no reported difference in craving between groups (125). In another study, oral CBD reduced the salience of cigarette cues, after overnight abstinence in smokers, relative to placebo, but did not reduce craving or withdrawal (126).

Opioids

Initial studies on the efficacy of cannabinoids in alleviating morphine withdrawal and abstinence symptoms occurred 40 years ago, with rodent models suggesting that CBD alone has low efficacy in alleviating signs of abstinence in rats, but CBD in combination with THC (5:1 ratio) did so significantly (136). THC itself was demonstrated to be more effective than CBD in inhibiting morphine abstinence syndrome in mice (137, 138). Nevertheless, more recent studies demonstrate that treatment with CBD blocked the reward-facilitating effect of morphine (132), reduced morphine CPP and CPA, and prevented drug and stress-induced reinstatement of CPP (71, 127). CBD was also found to have some efficacy in heroin studies in rats. While it did not specifically alter maintenance of self-administration, nor did it aid extinction of self-administration, it did attenuate cue-induced (but not drug-primed) self-administration following

TABLE 1 | CBD's efficacy for the treatment of substance use disorders.

Study	Sample	Substance	Treatment*	Outcome*	Effect
SENSITIZATION					
Filev et al. (121)	Mice	Ethanol	CBD (2.5 mg/kg)	Locomotor activity	–
			THC:CBD (2.5:2.5 mg/kg)	Locomotor activity	↓
Gerdeman et al. (54)	Rats	Heroin	THC:CBD (10:10 mg/kg)	Locomotor activity	–
Luján et al. (122)	Mice	Cocaine	CBD (20 mg/kg)	Locomotor activity	–
REWARD FACILITATION					
Trigo et al. (123)	Humans	Cannabis	THC:CBD (27:25 mg/ml) as needed + MET and CBT	Craving—MCQ	–
Solowij et al. (124)	Humans	Cannabis	Daily oral CBD (200 mg)	CEQ euphoria	↓
Morgan et al. (125)	Humans	Nicotine	CBD as needed	Craving—TCQ	–
Hindocha et al. (126)	Humans	Nicotine	CBD (800 mg)	Craving—QSU-B	–
			CBD (800 mg)	Attentional bias—visual probe task	↓
			CBD (800 mg)	Pleasantness rating	↓
Markos et al. (127)	Mice	Morphine	CBD (2.5 mg/kg)	CPP	–
			CBD (5 mg/kg)	CPP	–
			CBD (10 mg/kg)	CPP	↓
			CBD (20 mg/kg)	CPP	–
Luján et al. (122)	Mice	Cocaine	CBD (5 mg/kg)	CPP	–
			CBD (10 mg/kg)	CPP	↓
			CBD (20 mg/kg)	CPP	↓
			CBD (30 mg/kg)	CPP	–
Parker et al. (113)	Rats	Amphetamine	CBD (5 mg/kg)	CPP	–
SELF-ADMINISTRATION					
Shannon et al. (128)	Human: case study	Cannabis	CBD (24-18 mg)	Abstinence	↓
Trigo et al. (129)	Humans: case series	Cannabis	THC:CBD (27:25 mg/ml) as needed + MET and CBT	Self-reported use	↓
Trigo et al. (123)	Humans	Cannabis	THC:CBD (27:25 mg/ml) as needed + MET and CBT	Abstinence	–
Allsop et al. (130)	Humans	Cannabis	THC:CBD (27:25 mg/ml) + psychosocial intervention	Abstinence	–
Solowij et al. (124)	Humans	Cannabis	Daily oral CBD (200 mg)	Self-reported use	–
Viudez-Martínez et al. (131)	Rats	Ethanol	CBD (30 mg/kg)	Self-administration	↓
Morgan et al. (125)	Humans	Nicotine	CBD as needed	Self-reported use	↓
Ren et al. (115)	Rats	Heroin	CBD (5 mg/kg)	Self-administration	–
			CBD (20 mg/kg)	Self-administration	–
Katsidoni et al. (132)	Rats	Morphine	CBD (5 mg/kg)	ICSS threshold	–
		Cocaine	CBD (5 mg/kg)	ICSS threshold	↓
Luján et al. (122)	Mice	Cocaine	CBD (20 mg/kg)	Self-administration	↓
Mahmud et al. (133)	Rats	Cocaine	CBD (5 mg/kg)	Self-administration	–
			CBD (10 mg/kg)	Self-administration	–
Hay et al. (134)	Rats	Methamphetamine	CBD (20 mg/kg)	Self-administration	–
			CBD (40 mg/kg)	Self-administration	–
			CBD (80 mg/kg)	Self-administration	↓
EXTINCTION					
Parker et al. (113)	Rats	Cocaine	CBD (5 mg/kg)	CPP	↓
		Amphetamine	CBD (5 mg/kg)	CPP	↓
WITHDRAWAL					
Crippa et al. (135)	Human: case study	Cannabis	CBD (600 mg)	MWC	↓
Allsop et al. (130)	Humans	Cannabis	THC:CBD (27:25 mg/ml) + psychosocial intervention	CWS	↓
Trigo et al. (123)	Human	Cannabis	THC:CBD (27:25 mg/ml) as needed + MET and CBT	MWC	–

(Continued)

TABLE 1 | Continued

Study	Sample	Substance	Treatment	Outcome	Effect
Hindocha et al. (126)	Humans	Nicotine	CBD (800 mg)	MPSS	–
de Carvalho and Takahashi (71)	Rats	Morphine	CBD (10 mg/kg)	CPP following naltrexone-precipitated withdrawal	↓
Hine et al. (136)	Rats	Morphine	CBD (10 mg/kg)	Abstinence symptoms	–
			THC:CBD (2:10 mg/kg)	Abstinence symptoms	↓
Bhargava (137)	Mice	Morphine	CBD (5 mg/kg)	Naloxone-precipitated withdrawal	↓
			CBD (10 mg/kg)	Naloxone-precipitated withdrawal	↓
			CBD (20 mg/kg)	Naloxone-precipitated withdrawal	↓
Chesher and Jackson (138)	Rats	Morphine	CBD (5 mg/kg)	Naloxone-precipitated withdrawal	–
			CBD (20 mg/kg)	Naloxone-precipitated withdrawal	–
			CBD (80 mg/kg)	Naloxone-precipitated withdrawal	–
REINSTATEMENT					
Drug-primed					
Ren et al. (115)	Rats	Heroin	CBD (5–20 mg/kg)	Self-administration	–
de Carvalho and Takahashi (71)	Rats	Morphine	CBD (10 mg/kg)	CPP	↓
Luján et al. (122)	Mice	Cocaine	CBD (20 mg/kg)	Self-administration	–
Karimi-Haghighi and Haghparast (139)	Rats	Methamphetamine	CBD (10 μg/5 μl)	CPP	↓
Hay et al. (134)	Rats	Methamphetamine	CBD (20 mg/kg)	Self-administration	–
			CBD (40 mg/kg)	Self-administration	–
			CBD (80 mg/kg)	Self-administration	↓
Context-induced					
Viudez-Martínez et al. (131)	Rats	Ethanol	CBD (60 mg/kg)	Self-administration	–
			CBD (120 mg/kg)	Self-administration	↓
Gonzalez-Cuevas et al. (140)	Rats	Alcohol	CBD (15 mg/kg)	Self-administration	↓
		Cocaine	CBD (15 mg/kg)	Self-administration	↓
		Cocaine	CBD (10 mg/kg)	CPP	↓
de Carvalho and Takahashi (71)	Rats	Morphine	CBD (5 mg/kg)	CPP	–
			CBD (10 mg/kg)	CPP	↓
Cue-induced					
Ren et al. (115)	Rats	Heroin	CBD (5–20 mg/kg)	Self-administration	↓
Mahmud et al. (133)	Rats	Cocaine	CBD (5 mg/kg)	Self-administration	–
			CBD (10 mg/kg)	Self-administration	–
Stress-induced					
Gonzalez-Cuevas et al. (140)	Rats	Alcohol	CBD (15 mg/kg)	Self-administration	↓
		Cocaine	CBD (15 mg/kg)	Self-administration	↓

**CBD, cannabidiol; THC, delta-9-tetrahydrocannabinol; MET, motivational enhancement therapy; CBT, cognitive behavioral therapy; MCQ, marijuana craving questionnaire; CEQ, Cannabis Experiences Questionnaire; TCQ, tiffany craving scale; QSU-B, questionnaire of smoking urges–brief; CPP, conditioned place preference; ICSS, intercranial self-stimulation; MWC, marijuana withdrawal checklist; CWS, cannabis withdrawal scale; MPSS, mood and physical symptoms scale craving.*

14 days of abstinence, with CBD's effect lasting up to 2 weeks post-administration (115).

Stimulants

Evidence of CBD efficacy for stimulant use is mixed. Neither CBD, nor a 1:1 ratio of THC:CBD reversed the cocaine sensitization effect (although rimonabant did) (54, 122). Some studies suggest that acute CBD administration does not block the reward-facilitating effect of cocaine (132), reduce cocaine self-administration, or attenuate cue-induced cocaine seeking in rats (133). However, others did find CBD to disrupt acquisition of cocaine self-administration and CPP (122), and

impair drug-primed reinstatement of CPP for methamphetamine (139). Further studies on relapse are similarly mixed with one demonstrating CBD's ability to attenuate reconsolidation of CPP (1 week post-CPP acquisition) for cocaine in mice (71), and effectively reduce cue and stress-induced reinstatement of cocaine seeking up to 48 days post-CBD treatment (140), whilst another suggested no effect of CBD on drug-primed reinstatement post-extinction (122). Dose dependency may explain contradictory findings, as Hay et al. (134) demonstrated that 80 mg/kg (and not less) of CBD was needed to significantly reduce motivation to self-administer methamphetamine and reinstatement post-extinction. While evidence for CBD use for stimulant addiction in animals is weak, a longitudinal observational study of 122 participants did find cocaine users who self-report using cannabis to control their cocaine use, to have reduced their cocaine use over a 3 years period (147). Nevertheless, street cannabis generally has low amounts of CBD (148) and findings cannot be extrapolated to CBD's therapeutic efficacy.

The relatively weaker evidence of CBD in disrupting the reward-facilitating effect and self-administration of substances of abuse, despite its comparative efficacy in CPP reinstatement paradigms, may reflect its role in attenuating reward-related memory, without altering the rewarding properties of substances *per se*. Evidence of CBD's role in regulating emotional memory is supported by studies of other conditions, such as anxiety and PTSD-related fear memory [see (47) and (141) for a more extensive review of cannabinoid's role in emotional memory processing across other paradigms]. However, evidence of CBD's role in the consolidation and extinction of substance-related memory in humans is yet limited.

SUMMARY AND FUTURE DIRECTIONS

CBD shows some promise in alleviating negative withdrawal effects and reducing motivation to self-administer or reinstatement of drug use in animals. However, evidence on its efficacy is limited and mixed. CBD alone may not be sufficiently effective in maintaining long-term abstinence without ongoing support and behavioral therapy, as evidenced by its lack of efficacy over treatments, such as cognitive behavioral therapy and motivational enhancement therapy (123, 129). A combination of pharmacotherapy and behavioral therapy may increase treatment potency and adherence (149), and CBD may be better suited as an adjunct treatment to primary behavioral or psychosocial therapy (124).

There is also much that is unknown about how CBD may be targeting and alleviating SUD-related effects. Recent evidence suggests that within the mesolimbic system, CBD also influences the serotonergic system, as an agonist of the serotonin 1A (5-HT_{1A}) receptor (102, 103), which in addition to contributing to reduction in stress and anxiety (150), may be responsible for (i) blunting the reward-facilitating effect of substances of abuse (e.g., morphine in rats) (132); and (ii) modulating the formation of associative emotional memory related to substances of abuse (151). A number of studies have suggested the potential of selective serotonin reuptake inhibitors and other antidepressants in reducing substance (e.g., alcohol and nicotine) use via alleviating mood symptoms (152). CBD's capacity to alleviate stress, anxiety, and depressive symptoms may be mediating its treatment effect on SUDs (124, 153, 154). Indeed, CBD has been found to have therapeutic potential in alleviating affective and cognitive processing disturbances that may be induced by chronic substance (e.g., cannabis) use (63, 64, 155), proving potential utility in moderating the deleterious course of impairment, particularly in adolescent initiates of substance use (156). Additionally, other receptor and enzyme functions targeted by CBD, such as cannabinoid CB2Rs, non-cannabinoid transient receptor potential vanilloid type-1 (TRPV1) and type-2 (TRPV2) receptors, and ECS' catabolic enzymes FAAH and MAGL, should also be investigated for their role in the ECS and SUD (157–161).

In sum, some early research supports CBD's promise as pharmacotherapy against SUD. However, further investigation into CBD's mechanism of action, and validation of its efficacy, across preclinical and clinical trials will be necessary.

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YC wrote the core sections of the manuscript with the assistance of EC. NS and MY provided intellectual input and edits.

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REVIEW
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Impact of Substance Use Disorder Pharmacotherapy on Executive Function: A Narrative Review

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Substance use disorders are chronic, relapsing, and harmful conditions characterized by executive dysfunction. While there are currently no approved pharmacotherapy options for stimulant and cannabis use disorders, there are several evidence-based options available to help reduce symptoms during detoxification and aid long-term cessation for those with tobacco, alcohol and opioid use disorders. While these medication options have shown clinical efficacy, less is known regarding their potential to enhance executive function. This narrative review aims to provide a brief overview of research that has investigated whether commonly used pharmacotherapies for these substance use disorders (nicotine, bupropion, varenicline, disulfiram, acamprosate, nalmefene, naltrexone, methadone, buprenorphine, and lofexidine) effect three core executive function components (working memory, inhibitory control and cognitive flexibility). While pharmacotherapy-induced enhancement of executive function may improve cessation outcomes in dependent populations, there are limited and inconsistent findings regarding the effects of these medications on executive function. We discuss possible reasons for the mixed findings and suggest some future avenues of work that may enhance the understanding of addiction pharmacotherapy and cognitive training interventions and lead to improved patient outcomes.

Keywords: addiction, cognitive enhancement, cognitive flexibility, executive function, inhibitory control, pharmacotherapy, substance use disorder, working memory

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INTRODUCTION

Substance use disorders are chronic, relapsing conditions (1) with huge costs to the individual and to society. For example, using data from 2015, Peacock et al. (2) estimate global prevalence of past 30 day heavy alcohol use, daily smoking and past year opioid use at 18.4, 15.2, and 0.37%, respectively and they estimate disease burden with the number of disability-adjusted life years (the number of years lost due to ill-health, disability, or early death) as 170.9 million, 85.0 million and 27.8 million for tobacco smoking, alcohol, and illicit drug use, respectively. Indeed, alcohol, heroin, and tobacco have previously been rated amongst the most harmful misused drugs when considering harms to both the individual and to others (3).

There are several psychological/behavioral treatments available for substance use disorders [for a brief overview see McGovern and carroll (4)]. While there are no approved pharmacotherapies for stimulant and cannabis use disorders, evidence-based pharmacological agents are available for tobacco, alcohol and opioid use disorders (TUD, AUD, and OUD, respectively). Medications currently approved for these disorders include nicotine replacement therapy, bupropion, varenicline (for TUD), disulfiram, acamprosate, naltrexone, nalmefene (for AUD), methadone, buprenorphine, naltrexone, and lofexidine (for OUD). While previous research has found these drugs to be efficacious, relapse in drug dependence is 40–60% (5) suggesting efficacy is limited and that there is room for improvement in the management of addictions.

Cognitive processes may be important targets for the treatment of substance use disorders (6, 7). In particular, executive dysfunction is considered a hallmark of addiction (8, 9) and may represent a good transdiagnostic target across addictive disorders. Impairments in executive function may contribute to the initiation and maintenance of problematic drug use. For instance, executive function at an early age predicts subsequent substance use (10) and performance comparisons across drug users, non-addicted family members and healthy controls suggest that deficits in executive function may be a cognitive endophenotype associated with drug dependence vulnerability (11, 12). Executive function deficits are also related to relapse, worse clinical outcomes and poor treatment adherence (13–19) with exacerbation of executive function impairments observed during early abstinence which may contribute to relapse (20–22).

While the clinical efficacy of approved pharmacotherapy for TUD, AUD, and OUD is recognized, there has been far less research conducted on the cognitive effects of these medications (23) despite potential cognitive enhancement effects contributing to clinical efficacy. Therefore, the goal of this review is to provide a brief and selective, narrative summary of the evidence examining the impact of nicotine, bupropion, varenicline, disulfiram, acamprosate, nalmefene, naltrexone, methadone, buprenorphine, and lofexidine on executive function. We do not include medications used off-label to treat substance use disorders due to the wide-range of off-label prescribing practices, limited, or inconsistent evidence for clinical efficacy and because we cannot be certain which of these medications will continue to look effective as the evidence base for them increases. This review complements the recent systematic review that investigated general cognitive effects of pharmacotherapy for substance use disorders (23). While this earlier review provides a good overview of the cognitive impact of substance use disorder medication, its discussion of the impact on executive function could be considered limited by the general approach to cognition that has been taken. The current review fractionates executive function and focuses on working memory, inhibitory control, and cognitive flexibility as there is general agreement that these are the three core executive function components and that other higher-order executive functions such as decision-making, planning, problem-solving, and reasoning may require these basic components (24, 25). Additionally, the current review also takes a translational approach by including relevant findings from research with non-human animals where human research is scarce or it adds to an understanding of drug effects.

PHARMACOTHERAPIES FOR TOBACCO USE DISORDER

Nicotine

The nicotinic acetylcholine receptor agonist nicotine is used in those with TUD as a replacement therapy where it can be delivered in many forms including chewing gum and adhesive skin patches. When used as an aid to quit smoking or chewing tobacco, nicotine replacement therapy helps to manage withdrawal symptoms associated with cessation and can increase the rate of quitting by up to 50–70% (26). Both $\alpha_4\beta_2$ and α_7 nicotinic receptor subtypes have been implicated in cognitive enhancement (27). Indeed, a considerable amount of evidence exists regarding the cognitive enhancing effects of nicotine. For instance, nicotine can improve some abstinence associated cognitive impairments (28). Additionally, a 2010 meta-analysis suggests that fine motor, alerting attention-accuracy and response time, orienting attention reaction time, short-term episodic memory accuracy, and working memory reaction time are particularly sensitive to enhancement following administration of nicotine (29). Furthermore, because the studies included in this meta-analysis used non-smokers or non-/minimally deprived smokers the cognitive enhancement is unlikely to be driven by relief from withdrawal but, instead, represents true cognitive enhancement.

However, reported effects of nicotine on working memory are far from consistent. Animal work suggests that working memory (radial-arm maze) performance is improved by nicotine administration (30) and that methamphetamine or ketamine-induced impairments in working memory (radial-arm maze, odor span task) can be improved by nicotine (31, 32). On the other hand, no effect on working memory (digit recall, serial addition/subtraction, n-back task, digit span, spatial span, letter-number sequencing, odor span task) has been seen in human studies that have administered 2 and 4 mg nicotine gum relative to placebo in healthy non-smoking participants (33–35). Another study found that 15 mg nicotine patches improved working memory (n-back task reaction time) in deprived smokers relative to placebo while they had no benefit in healthy non-smokers but instead impaired performance with significantly fewer hits, more misses and false alarms and a trend toward longer reaction times (36). Taken together this suggests that nicotine may improve working memory when there is impaired baseline performance present but has no effect or impairs performance when baseline performance is higher (37).

Nicotine administration has also been found to improve inhibitory control (antisaccade task, errors of commission on a continuous performance task) deficits that are induced by overnight smoking abstinence (38). However, 7 mg nicotine patches do not improve inhibitory control (stop-signal task, go/nogo task, antisaccade task) in healthy non-smokers (39, 40). In contrast to the findings of these studies, several nicotine

administration studies in animals have shown that nicotine can induce disinhibition with increased impulsive responding evident across a range of behavioral tasks (41–47). Similarly, acute cigarette smoking may bias responding to more impulsive action and impulsive choices (48, 49). As with the effect of nicotine on working memory, the mixed findings with nicotine apparently able to improve, impair or have no effect on inhibitory control may be due to baseline differences in performance and several previous studies support this idea. For example, nicotine enhances inhibitory control (fewer errors of commission on a continuous performance task) in non-smokers that have low levels of attention but not in those with high levels of attention (50) while in another study, nicotine enhanced inhibitory control (fewer errors of commission on a continuous performance task) in those with a diagnosis of schizophrenia but not in healthy controls (51). Finally, the effect of chronic nicotine exposure on impulsivity in rats may be influenced by baseline levels of impulsivity with nicotine inducing greater impulsive choice in those with lower trait impulsivity (52, 53).

Few studies have examined the effects of nicotine on cognitive flexibility and those which have reveal mixed findings, much as studies assessing working memory and inhibitory control have. Acute cigarette smoking has been shown to impair cognitive flexibility (more intra-dimensional set-shifting errors on an intra-extra dimensional set-shifting task) in high but not low dependent smokers (54) and (greater difficulty integrating reinforcement history on a reversal learning task) relative to never and former smokers (55). Cognitive flexibility has also been shown to be impaired (poorer learning of strategies to complete the task in the Wisconsin Card Sorting test) by 7 mg nicotine patch administration relative to placebo in non-smokers with high but not low levels of attention (50). Nicotine administration at high (18 mg/Kg/day × 4 weeks) but not low dose (6.3 mg/Kg/day × 4 weeks) also impaired cognitive flexibility (increased perseverative responding to previously non-reinforced stimuli in a reversal learning task) in mice (56). Conversely, improvements in cognitive flexibility (attentional set-shifting task) and reversal of nicotine withdrawal-induced impairment in cognitive flexibility (reversal learning task) have both been reported in rats (57, 58). While in another human study, cognitive flexibility (attentional switching on the flexibility of attention test) was not changed by nicotine (59). As with working memory and inhibitory control, mixed findings like these suggest that baseline performance levels may be influential in determining cognitive effects of nicotine. As nicotine can induce dopamine release (60), as smoking does in humans (61), a more biological explanation for the mixed findings reported throughout this section might be that performance and dopamine levels are related such that at optimal dopamine levels executive function performance is at its peak i.e., the inverted "U" curve theory (62, 63). Release of dopamine by nicotine could therefore improve or impair performance depending on initial dopamine levels.

Bupropion

Used clinically for depression as well as a smoking cessation aid, bupropion is a norepinephrine-dopamine reuptake inhibitor and a nicotinic acetylcholine receptor antagonist. Bupropion reduces the severity of nicotine craving and withdrawal symptoms, its clinical effectiveness as a smoking cessation aid is comparable to nicotine replacement therapy and is independent of its antidepressant effect (64, 65). Symptoms that improve in depressed patients that respond to bupropion include those reflecting cognitive disturbance (66). Indeed, one study in patients with major depressive disorder has shown that while serotonin selective reuptake inhibitor-treated patients show cognitive impairments including worse cognitive flexibility relative to matched healthy controls, bupropion-treated patients had normalized cognitive performance with better cognitive flexibility but with no significant mean difference compared to controls (67). Further, another study in those with major depressive disorder found that 8 weeks of bupropion treatment lead to improvements on tasks requiring cognitive flexibility (Trail Making B), working memory and reasoning [A not B Task; (68)].

Few studies have investigated the effects of bupropion on executive function in smokers and the findings of existing studies have been equivocal. One study in 24 smokers with high interest in quitting reported that working memory (correct response times on an N-Back task) was improved by bupropion compared to placebo on the first day of a quit attempt (69). In contrast, another study in 58 smokers (36 male, 22 female) found that bupropion enhanced working memory (Digit Span task) in females but not males whereas it enhanced inhibitory control (inhibiting choice of immediate rewards over a larger, delayed reward) in males but not females during early abstinence (70). A final study in smokers investigated effects of both abstinence and bupropion on cognitive function in adults with schizophrenia. However, in this study 1 week of abstinence was not associated with deficits in working memory (Digit Span task) and controlling for abstinence status, bupropion wasn't associated with better working memory performance (71). Similar null findings have been observed in healthy participants where working memory (Digit Span task) was not improved by either a single dose (150mg) or 2 weeks repeated administration (150 mg x 6days followed by 300 mg x 8days) of bupropion (72). However, in an animal study there were positive effects of bupropion on inhibitory control. In this study, rats were perinatally exposed to polychlorinated biphenyls thought to decrease medial prefrontal cortical dopamine levels and cause subsequent inhibitory control deficits assessed with a differential reinforcement of low rates of responding (DRL) task. This study showed that bupropion improved inhibitory control performance on the DRL task (73).

Varenicline

As a partial agonist at $\alpha_4\beta_2$ nicotinic acetylcholine receptors, varenicline has been found to reduce craving and the pleasurable effects of tobacco and is more effective for smoking cessation than both nicotine replacement therapy and bupropion (74). Varenicline can reverse withdrawal-associated working memory impairment (75). Patterson et al. (75) showed that in abstinent smokers varenicline, vs. placebo, improved reaction times on correct N-back trials with no significant effects on task

accuracy. Interestingly, slower correct responses on the N-Back task predict more rapid resumption of smoking during a short period of abstinence in smokers receiving placebo but not varenicline (76). Beyond simply improving withdrawal-associated impairment, varenicline (0.5 mg/day × 3days followed by 1 mg/day × 4days) administered to non-smokers has been shown to also improve working memory performance (77) with a significant positive association found between plasma varenicline levels and visual-spatial working memory in another non-smoker study (78). There are mixed findings regarding working memory performance in studies with other populations for instance varenicline (1 mg/day × 3 days) attenuated withdrawal-associated working memory impairments in smokers with schizophrenia (79) but did not improve working memory in smokers with schizophrenia who are not treatment-seeking and could continue to smoke (80, 81). Mixed working memory findings have also been found with varenicline in human studies with populations that have other substance abuse problems. For example, varenicline has been shown to improve working memory in heavy drinkers; with larger improvements predicting less alcohol-primed *ad libitum* drinking (82), but not in non-treatment seeking methamphetamine dependent participants (83). While an animal study found that varenicline improves working memory in cocaine-experienced monkeys (84). These mixed findings for other substances of abuse and across different species make it difficult to draw firm conclusions regarding varenicline's cognitive impact. However, as described above evidence suggests that there is some cognitive benefit for certain types of abstinent smoker (75).

Studies regarding varenicline effects on inhibitory control are also mixed. For instance, animal studies indicate that varenicline increases premature responding (failure to inhibit a response during a wait period) on a 5-Choice Serial Reaction Time task (85) however, using a similar 3-Choice task, Ohmura et al. (86) demonstrate that this pro-impulsive effect is evident for nicotine-naïve but not nicotine-exposed or nicotine-abstinent animals. In human studies there was no significant effect of varenicline, compared to placebo, on inhibitory control assessed with a stop-signal task in treatment-seeking smokers (87). In contrast, impulsive responding was increased on a stop-signal task by cigarette smoking and by varenicline [albeit to a smaller degree than smoking; (48)]. However, Austin et al. (48) also found that varenicline attenuated smoking-induced impulsive responding. Varenicline has also been found to reduce antisaccadic error rate (an oculomotor measure of disinhibition) in those with schizophrenia/schizoaffective disorder regardless of smoking status (80).

Fewer studies have reported effects of varenicline on cognitive flexibility. Animal studies have provided mixed findings with Gould et al. (84) finding no effect of varenicline on reversal learning (at doses that give maximum improvement in working memory) in rhesus monkeys. However, varenicline reduced ketamine-induced impairments in reversal learning (accuracy and perseverative responding) and improved working memory (accuracy at long delays on a delay match to sample task) in rhesus and pigtail monkeys (88). In studies related more specifically to smoking, varenicline reversed nicotine withdrawal-induced deficits in the number of reversals on a probabilistic reversal learning task administered to rats (58). While in a human study comparing 24 abstinent smokers with 20 non-smokers, impairments on a reversal learning task (increased response shifting with decisions less sensitive to available evidence) found in abstinent smokers were attenuated by varenicline. In addition, decreased mesocorticolimbic activity associated with shifting in abstinent smokers was increased to the level of non-smokers by varenicline (89). It should be noted that as with nicotine, varenicline produces elevation of dopamine (90).

PHARMACOTHERAPIES FOR ALCOHOL USE DISORDER

Disulfiram

By inhibiting the enzyme aldehyde dehydrogenase, disulfiram administration leads to acetaldehyde accumulation when alcohol is consumed. This results in an unpleasant reaction consisting of tachycardia, flushing, nausea, and vomiting. This aversion therapy creates the expectancy of negative consequences that are thought to deter alcohol use. Disulfiram is an efficacious treatment in supervised and high compliance open label studies but not blinded studies suggesting that expectancy may be a requirement of clinical effectiveness [for a review and meta-analysis of efficacy see Skinner et al. (91)]. There is evidence that anti-addictive effects may be mediated by an additional mechanism of action. For example, in rats disulfiram reduces drug-induced reinstatement of cocaine seeking via dopamine β-hydroxylase inhibition (92). Similarly reductions in chocolate self-administration and reinstatement of chocolate seeking have also been observed in rats treated with disulfiram (93) and there are reports that it may have potential for treatment of pathological gambling (94, 95) and cocaine dependence (96).

Few studies have investigated disulfiram's cognitive effects (see Pujol et al. (23) for an overview). In terms of executive function, there were no effects of disulfiram on working memory assessed with the Digit Span Test (97). Similarly, Gilman et al. (98) found no group differences on an extensive test battery, including tasks assessing executive function, when comparing 11 alcoholic patients receiving disulfiram and 37 alcoholic patients not receiving the drug. In contrast, disulfiram administration has been shown to improve inhibitory control (by inhibiting preference for immediate gain at the expense of reduced net gain) in rats that were making suboptimal choices but not those whose choices were already optimal (94).

Acamprosate

Although the precise mechanism of action is not fully understood, acamprosate is thought to correct imbalance in inhibitory and excitatory neurotransmission induced by chronic alcohol exposure (99). Acamprosate has been found to be a safe and efficacious anti-craving and anti-relapse agent (100). There have been limited studies examining acamprosate effects on executive function. The drugs proposed mechanism of action at NMDA receptors suggests acamprosate would have negative effects on learning and memory, indeed previous cognitive

work in healthy participants indicates an acamprosate-induced impairment in delayed free recall. However, working memory was unaffected by acamprosate in the same participants (101). Similarly, there was no significant effect of acamprosate on working memory performance of rats in a three-panel runway task. Although, performance (both errors and latency) was better in acamprosate and scopolamine-treated rats compared to when they were administered the muscarinic acetylcholine receptor antagonist alone (102). There have been mixed findings with studies investigating cognitive flexibility. While Ralevski et al. (103) found no significant effects of acamprosate in 23 alcohol-dependent schizophrenic patients on the Wisconsin Card Sorting Test, animal studies suggest that acamprosate reverses chronic alcohol-induced impairments in attentional set-shifting including reducing task perseveration (104). More recent evidence suggests that these cognitive effects may be related to acamprosate's calcium moiety as a sodium salt version of the drug failed to reverse chronic alcohol-induced deficits in cognition (105).

Nalmefene

Approved in Europe but not in America, nalmefene is an antagonist at μ-opioid and δ-opioid receptors as well as a partial agonist at κ-opioid receptors thus reducing the positive, rewarding effects of acute alcohol consumption. Nalmefene has greater affinity for κ-opioid receptors than naltrexone does (106). Nalmefene also differs from naltrexone in having a longer half-life, greater bioavailability and no observed dose-dependent liver toxicity [see review by Niciu and Arias (107)]. To the best of our knowledge, there has not been any published research investigating the effects of nalmefene on executive function. However, the κ-opioid receptor agonists nalfurafine and U50,488 produce deficits in inhibitory control (DRL, delay-discounting and stop-signal tasks) in mice and rats (108, 109). U50,488 also produces deficits in cognitive flexibility (modified water maze task) in mice that are reversed by the κ-opioid receptor antagonist nor-binaltorphimine (110). Another κ-opioid receptor agonist U69,593 enhances, while nor-binaltorphimine disrupts working memory (Y-maze) in mice (111). Future studies with nalmefene are warranted because these animal studies suggest that modulation of κ-opioid receptors effects executive function which may be beneficial in disorders characterized by executive dysfunction, such as addiction. Studies examining general cognitive effects of nalmefene are also scarce with one report suggesting increases in subjective alertness but no effect on a choice reaction time task (112).

PHARMACOTHERAPIES FOR ALCOHOL AND OPIOID USE DISORDERS

Naltrexone

Pharmacologically, naltrexone has greatest affinity for the μ-opioid receptor but is an antagonist at all opioid receptors and it reduces the rewarding effects as well as craving and desire for alcohol and opiates (113, 114). Indeed, mice lacking the μ-opioid receptor do not self-administer alcohol (115). There have been a small number of human and animal studies examining the effects of naltrexone on executive function. After 8 weeks of administration, Hatsukami et al. (116) found no significant differences in working memory (digit span backwards) in overweight men who were administered either naltrexone (300 mg/day) or placebo. In contrast, animal research suggests naltrexone in rats improves working memory performance (radial arm maze) compared to saline administration (117) and that naltrexone reverses deficits in working memory (radial arm maze) that have been induced by exposure to microwaves (118). However, one study did find the opposite with microwave exposure failing to induce deficits in radial arm maze performance and naltrexone treated rats taking longer to complete the task relative to saline treated animals (119).

In animal studies examining the effects of naltrexone on inhibitory control, naltrexone had no significant effect on delay discounting (inhibiting choice of immediate reward over a larger, delayed reward) when administered alone in rats and mice (120, 121). In contrast, naltrexone has been shown to improve inhibitory control in a rat gambling task (by inhibiting preference for immediate gain at the expense of reduced net gain) in animals that made more suboptimal choices at baseline (122). Additionally, naltrexone pre-treatment improved morphine-induced decrements in impulsive choice (120). Similarly, naloxone (a drug which is used clinically for acute opioid overdose and is a non-selective opioid antagonist which, like naltrexone, blocks μ-opioid receptors with greatest affinity) attenuates drug-induced inhibitory control deficits (five-choice serial reaction time task) in rats (123). In humans, the acute effect of naltrexone (50 mg) on inhibitory control (inhibiting choice of immediate reward over a larger, delayed reward) has been investigated in abstinent alcoholics and healthy controls. Naltrexone did not improve impulsive choice reliably across abstinent alcoholic participants, but performance was instead dependent on personality. Across both abstinent alcoholics and healthy controls, those with greater external locus of control made fewer impulsive choices on naltrexone and the opposite was true for individuals with greater internal locus of control (124). As perceptions of control may be influenced by tonic frontal dopamine (125) and frontal dopaminergic tone may account for individual differences in impulsive choice (126) it is interesting to note here that previous evidence suggests that the opioid system appears to have a role in modulating dopamine tone (127).

Research regarding the effect of naltrexone on cognitive flexibility has been mixed. A study in rats suggests that aged relative to young rats have impaired flexibility on an attentional set-shifting task (extradimensional shifting) and that this age-related impairment was reversed by naltrexone while there was no effect of naltrexone on the performance of younger rats (128). In humans, no significant difference in cognitive flexibility (Color Trails task) was found between abstinent heroin abusers receiving naltrexone therapy and healthy controls whereas buprenorphine-maintained patients showed impairments in cognitive flexibility (129) while, an earlier study in overweight men suggested there was no significant effect of receiving high dose naltrexone (300 mg/day) on cognitive flexibility (Trails B) after 8 weeks of treatment compared to placebo (116).

PHARMACOTHERAPIES FOR OPIOID USE DISORDER

Methadone

As a μ-opioid receptor agonist that also has antagonist properties at the glutamatergic NMDA receptor, methadone is used clinically as an analgesic and is used in OUD where it may be used in long-term maintenance therapy or to manage withdrawal during detoxification (130). Several studies have investigated executive function in patients receiving methadone maintenance therapy. Studies tend to differ in terms of the methadone dose and duration of treatment as well as by comparator i.e., healthy controls with no history of substance abuse, former opioid abusers not in methadone maintenance therapy, or within subject comparisons such as pre-/during therapy and peak/trough concentration following dosing (for studies comparing methadone maintenance therapy with buprenorphine see next section). These differences may account for some equivocal findings described below.

Studies have shown that methadone maintenance therapy is associated with poorer working memory. For instance, those who had been on short-term (at least 30 days) or long-term (at least 6 months) methadone maintenance scored in the lower portion of the normal range for working memory (letter-digit ordering) based on normative test data (131). Working memory (letter number sequencing) was also worse in those in methadone maintenance therapy (mean duration of treatment: 38.66 months; mean dose of methadone: 83.82 mg/day) compared to abstinent heroin abusers although this difference only approached significance (132). Methadone users (mean duration of treatment: 41.48 months) also had significantly worse working memory (2-back task) compared to healthy controls (133). While in another study using a within-subject design working memory (n-back task and modified Sternberg task) was assessed in methadone-maintained patients (mean duration of treatment: 48.9 months; mean dose of methadone: 97.5 mg/day) at approximately 120 min and 26 h after dosing (to coincide with peak and trough methadone concentrations). While there were no differences on the modified Sternberg task, *n*-back performance was slower when testing time coincided with peak methadone concentration. In addition, higher doses of methadone were associated with decreased n-back hit rate (134). However, some studies have found no significant differences in working memory when comparing methadone-maintained patients with healthy controls with no history of substance abuse (135) or with abstinent former opioid abusers (136). The average doses of methadone used in these two studies was 15.14 and 67.2 mg/day, respectively. Taken together it appears that methadone may impair working memory on certain tasks and when higher doses are taken. However, more studies are needed that take into account baseline cognitive performance levels.

Two studies (described above) assessed the effects of methadone maintenance therapy on inhibitory control (132, 133). These studies found that methadone maintenance was associated with poorer inhibitory control (five-digit test) compared to abstinent heroin abusers (132) and poorer inhibitory control (stop-signal task) when compared to healthy controls (133). In another study however, no correlations between dose or duration of methadone maintenance therapy were found in patients where the mean duration of treatment was 8.6 years and the mean dose was 124.2 mg/day (137). Perhaps the longer duration of treatment lead to tolerance of cognitive effects in some participants. Surprisingly, opposite findings have been observed with better inhibitory control (stop-signal task) found in methadone maintenance therapy compared to abstinent opiate dependent participants (138). In their study, Liao et al. (138) found that stop-signal reaction time was significantly shorter in methadone-maintained participants compared to abstinent participants and was no different when compared to healthy controls. Another study comparing methadone-maintained patients and healthy controls stratified patients by duration of treatment (short term: <12 months or long term: ≥12 months) and by dose (low dose: <80 mg/day or high dose: ≥80 mg/day). This study found that healthy participants made more inhibitory errors (errors of commission) on a continuous performance task compared to short term and low dose methadone-maintained patients (139). However, short term and low dose methadone-maintained patients also had the slowest reaction times on the task and the methadone group tended to have poorer sustained attention than healthy controls assessed on the same task. Therefore, the lower number of inhibitory errors found in short term and low dose methadone-treated patients could be due to general task disengagement in this group.

Most studies investigating the effects of methadone maintenance therapy on cognitive flexibility have demonstrated that treatment is associated with impaired flexibility. Those who had been on short-term (at least 30 days) or long-term (at least 6 months) methadone maintenance scored in the lower portion of the normal range for cognitive flexibility (trail making test) based on normative test data (131). In addition, worse cognitive flexibility assessed using a range of cognitive flexibility tasks (trail making test, oral trails, Wisconsin Card Sorting test, switching of attention task) has been reported in methadone-maintained patients compared to abstinent opioid abusers (132, 136) and healthy controls (135, 140, 141). One study found no improvement in cognitive flexibility (trail making test) when comparing opiate dependent participants at baseline and again following 2 months on methadone maintenance therapy (142) and surprisingly, in one study improved flexibility (trail making test) was found as methadone dose increased (134). A further study compared former opiate dependent participants that had been medication free for 10 years with those whom had been on methadone maintenance for the past 10 years (143). This study demonstrated that methadone maintenance was associated with a selective flexibility deficit. While both groups were able to acquire and reverse information about positive and negative outcomes under neutral conditions, Levy-Gigi et al. (143) found that the methadone-maintained group were impaired at reversing positive outcomes when these were presented in a drug-related context.

Buprenorphine

As a non-selective, mixed agonist-antagonist at opioid receptors (partial agonist at μ-opioid receptor, antagonist at κ- and δ-opioid receptors as well as weak partial agonist at nociception receptors) buprenorphine is used as an analgesic as well as to help manage withdrawal symptoms during opioid detoxification. During detoxification, buprenorphine may be used as short or long-term opioid replacement therapy (for longer-term use it is often combined with the pure opioid antagonist naloxone) and it appears to have similar clinical effectiveness to methadone at managing opioid withdrawal (144).

Few studies have investigated the effects of buprenorphine on executive function. One study investigating the impact of different doses on working memory administered buprenorphine/naloxone to opioid dependent patients at a starting dose of 8 mg/2 mg going up to 16 mg/4 mg and then 32 mg/8 mg with 7–10 days at each dose. This study found that there was no impairment in working memory (N-back task) as the dose increased four-fold (145). However, poorer working memory (Letter-Number Sequencing task, Paced Auditory Serial Addition task) has previously been found in opioid-dependent patients treated with buprenorphine/naloxone compared to healthy controls (146, 147). Rapeli et al. (147) also compare buprenorphine/naloxone treated patients with methadone-maintained patients at several time points (1. 2months, 2. 6–9months and 3. 12–17months after starting substitution therapy) and show that for one of the working memory tasks (Letter-Number Sequencing task) the buprenorphine/naloxone treated group improved between the second and third time points while the methadone treated groups performance remained stable across time. Working memory (digit span backwards) was however not found to be significantly different between patients on either buprenorphine (mean dose: 10.6 mg/day) or methadone (mean dose: 82.7 mg/day) maintenance therapy (mean duration of treatment 48 months across both maintenance therapies) or between these patients (combined in to one group) and healthy controls in a study from another group (148).

Very few studies have assessed the effect of buprenorphine on inhibitory control. One study already mentioned in this section above (148) found that opiate-dependent patients on either buprenorphine and methadone maintenance therapy didn't differ in inhibitory control (Haylings Sentence Completion test) but that when compared to healthy controls these patients (combined in to one group) performed significantly worse. However, another study comparing buprenorphine-maintained opioid dependent patients (mean duration of therapy: 5.4 years; mean dose: 9 mg/day) with both methadone-maintained patients (mean duration of therapy: 8.3 years; mean dose: 66 mg/day) and healthy non-opiate dependent controls found that the buprenorphine treated group performed better than the methadone treated group and no different from controls on the Iowa gambling task (149). The Iowa gambling task is traditionally considered a decision-making task but to perform well on the task it requires the ability to inhibit selection of decks that provide higher immediate gains but long-term losses (150). While, Haylings Sentence Completion test involves inhibition of sensible words that could be used to complete sentences (151). While inhibition is required by both tasks the Iowa gambling task is less semantic and the differing task demands and neural underpinnings may account for the differing findings from these studies.

Several studies have assessed the effect of buprenorphine on cognitive flexibility. Two studies already mentioned in this section above also included an assessment of cognitive flexibility (145, 149). One of these studies did not find impairments in cognitive flexibility (trail making task) with a four-fold increase in the dose of buprenorphine/naloxone given to opioid dependent patients (145). However, in the other study mentioned buprenorphine-maintained patients made fewer perseverative errors on the Wisconsin Card Sorting task compared to methadone-maintained patients with their performance falling somewhere between the group treated with methadone and healthy controls (149). In other studies, a within-subject design found that intravenous infusion of 0.6 mg of buprenorphine to healthy males over 150 min resulted in a significant deterioration in cognitive flexibility (trail making test) compared to a drug-free baseline assessment (152). Studies comparing opioid dependent patients on buprenorphine to healthy controls assessing cognitive flexibility (trail making test, color trails task) have tended to find that the treated patients perform less well than healthy control (129, 153). However, in tasks comparing the cognitive flexibility of buprenorphine and methadone-treated opioid dependent patients two studies failed to find a significant difference in cognitive flexibility in direct contrast to Pirastu et al. (149) (154, 155). While maintenance therapy doses and durations of treatment across these studies were similar, these two latter studies used the trail making test while the Wisconsin Card Sorting task was used by Pirastu et al. (149). The different cognitive demands of these tasks may help explain the differences seen across these studies. In the trail making test participants are required to shift backwards and forwards between numbers and letters in a predictable manner (156). While in contrast, in the Wisconsin Card Sorting task participants are unaware of what shifts will be required when task rules change and must work these out for themselves using feedback (157).

Lofexidine

Approved for the management of acute opioid detoxification in the United Kingdom in 1994 and more recently by the Food and Drug Administration in the United States in 2018, lofexidine is an α_{2A} adrenergic receptor agonist that has historically been used to reduce blood pressure and is now used to alleviate opioid withdrawal symptoms (158). To the best of our knowledge, there has not been any published research investigating lofexidine's effects on executive function. Studies examining general cognitive effects of lofexidine are also scarce. However, one report in 14 opioid dependent participants, suggests there may be a dose-related deterioration in simple reaction time, continuous performance, procedural memory, and mathematical processing when lofexidine is added to methadone maintenance therapy (159). Nevertheless,

other α_{2A} adrenergic receptor agonists have been shown to selectively improve prefrontal cortex mediated cognitive functions (160).

DISCUSSION

The aim of this review was to provide a brief narrative overview of the evidence for effects of some of the most commonly approved and prescribed pharmacotherapies for TUD, AUD, and OUD on the three core executive functions (working memory, inhibitory control and cognitive flexibility). Enhancement of executive function is likely to be an important target for the treatment of substance use disorders and may contribute to clinical efficacy of existing medications since executive dysfunction is thought to contribute to poor treatment adherence, worse clinical outcomes and relapse (13–19). However, for most of the approved pharmacotherapies reviewed it was difficult to draw firm conclusions regarding effects on executive function. This is due to a surprising lack of well-powered empirical research evaluating the effects of pharmacotherapy on executive function, and because of the extent of contradictory findings. A similar conclusion was made by a recent systematic review of the general cognitive effects of existing pharmacotherapy (23).

Both hypo- and hyperdopaminergic states have been postulated to account for various addiction phenomenon in the absence and presence of drug cues (161). Positron-emission tomography (PET) studies in substance abusing populations suggest that there are decreases in both dopamine release and dopamine D_2 receptors (162, 163). Indeed, the dopamine hypothesis of drug addiction (164) implicates a long-lasting hypodopaminergic state throughout the addiction cycle including persistence of this state in withdrawal. For example, PET imaging with a high affinity dopamine $D_{2/3}$ receptor radioligand has established that there is a smaller amphetamine-induced dopamine release in the cortex and midbrain of abstinent alcoholics than in healthy controls (165). Many of the pharmacotherapies reviewed here have direct or indirect effects on dopamine levels. In line with the inverted "U" shaped dose response curve for dopamine effects on executive function (62) drugs that enhance dopamine levels in individuals with a low baseline level of dopamine would be expected to enhance executive function while potentially impairing the performance of individuals with a higher dopaminergic starting point. Mixed findings in the current review may be attributable to differing dopaminergic baselines. In this regard, medicated substance dependent patients with lower baseline dopamine and greater cognitive impairments may receive greater cognitive benefit than less cognitively impaired patients with a higher dopaminergic baseline. While it may be more difficult to demonstrate cognitive improvements in healthy participants or there may be paradoxical impairment in performance.

Substance use disorder pharmacotherapies have been shown to be efficacious however they do not work for everyone. Identifying for whom they do, and do not, work is an important unmet clinical need. While it is evident that executive dysfunction is observed during early abstinence which may contribute to relapse (20–22) much more work is required in order to determine whether a drugs positive effects on executive function are predictive of positive cessation outcomes. Previous PET imaging studies with a high affinity dopamine $D_{2/3}$ receptor radioligand have suggested that the extent to which methylphenidate induces increases in dopamine are predictive of relapse and response to behavioral and psychological treatments in methamphetamine and cocaine abusers (166, 167). Future research should investigate whether clinical effectiveness of pharmacotherapy (i.e., sustained cessation) is related to individual differences in the ability of the drugs to improve cognitive function and whether this is associated with baseline differences or changes in dopamine levels.

Existing and novel cognitive enhancers may be beneficial for substance abuse disorders and studies investigating effects of cognitive enhancers are on-going (7). Whether it is existing pharmacotherapies being evaluated for their effects on cognition, or novel cognitive enhancers being evaluated for the potential to improve executive function and clinical outcomes in substance dependent populations, it is important to consider how cognition will be assessed. The current narrative review illustrates that even when the number of studies assessing different components of executive function are small, a wide variety of tasks and outcome measures are used which can make cross-study comparisons difficult. Future studies should carefully consider which tasks are best suited to assess relevant cognitive functions. Future work should also consider the potential cognitive enhancers mechanism of action and abuse potential. For example, modafinil is a promising cognitive enhancer but it's addictive potential has been illustrated in studies examining effects on behavioral sensitization and conditioned place preference (168).

An alternative approach to try and improve executive function in addiction has been with cognitive training most notably working memory training and inhibitory control training. Training of working memory has been found to improve working memory performance and reduce subsequent drug use in methadone-maintained patients and problem drinkers compared to control conditions (169, 170). Similarly, inhibitory control training using an alcohol-related Go/NoGo task has previously been found to reduce post-training alcohol consumption as effectively as a Brief Alcohol Intervention (171). Reduced drug use post-training suggests that interventions based on these types of training procedure may improve clinical outcomes and further supports the targeting of executive function in addiction. However, future studies should consider whether pharmacotherapy could compliment and even facilitate such training. Inhibitory control training, for example, may work via the devaluation of reward-related stimuli (172) and given that some of the drugs reviewed here e.g., varenicline, disulfiram, nalmefene, and naltrexone may devalue substances of abuse (either by reducing the positive rewarding effects of substances or by pairing them with an unpleasant reaction) it would be interesting to see whether these drugs are able to facilitate

inhibitory control training and improve dependent populations control over substance use in real-world settings.

In this review we have examined the evidence for executive function enhancement by commonly prescribed, labeled pharmacotherapy for TUD, AUD, and OUD as any such enhancement may contribute to clinical efficacy. However, it should be noted that the act of detoxification might itself be expected to improve executive function. Future studies should include appropriate controls or take this variable in to account when estimating the cognitive effects of medications used to assist detoxification maintenance. While a potential strength of this review is that it has evaluated the cognitive impact of only those medications with a high degree of evidence for efficacy in treating TUD, AUD, and OUD this does mean that we may have missed important trends in findings with those medications that are used off-label to treat these disorders (e.g., topiramate). In addition, this review excluded off-label pharmacotherapy for other substance use disorders such as the stimulants cocaine and methamphetamine. These disorders are persistent public health problems for which there are no approved pharmacotherapy options (173, 174). While the relative lack of evidence for consistent and positive pharmacotherapy effects, coupled with a wide-range of off-label prescribing practices lead us to exclude such research this too may have led to missing important trends in findings and consequently limited our discussion.

CONCLUSIONS

There are several efficacious pharmacotherapy options available for TUD, AUD, and OUD. Evidence is limited and conflicting regarding whether they can improve executive function in dependent populations. It should be noted that baseline differences in dopamine and performance may contribute to an explanation for why inconsistent findings exist. So far, strategies aimed at enhancing cognition to help with improving cessation rates in dependent populations have not been successfully implemented in the clinic. However, there has been limited research conducted in this area and cognitive enhancement remains a potential strategy that is worth exploring further. The issue of abuse liability of drugs that can be cognitive enhancers needs to be taken in to consideration when designing such studies. Moreover, studies should now move beyond simply assessing cognitive effects in order to establish whether an improved cognitive response is related to clinical efficacy and if this is also associated with baseline or changes in dopamine. This approach may assist future personalized medicine strategies.

AUTHOR CONTRIBUTIONS

All authors contributed to conception of this review, KB drafted the manuscript and all authors contributed to manuscript revision, read and approved the submitted version.

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frontiers in Psychiatry

REVIEW
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Forging Neuroimaging Targets for Recovery in Opioid Use Disorder

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The United States is in the midst of an opioid epidemic and lacks a range of successful interventions to reduce this public health burden. Many individuals with opioid use disorder (OUD) consume drugs to relieve physical and/or emotional pain, a pattern that may increasingly result in death. The field of addiction research lacks a comprehensive understanding of physiological and neural mechanisms instantiating this cycle of *Negative Reinforcement* in OUD, resulting in limited interventions that successfully promote abstinence and recovery. Given the urgency of the opioid crisis, the present review highlights faulty brain circuitry and processes associated with OUD within the context of the *Three-Stage Model of Addiction* (1). This model underscores *Negative Reinforcement* processes as crucial to the maintenance and exacerbation of chronic substance use together with *Binge/Intoxication* and *Preoccupation/Anticipation* processes. This review focuses on cross-sectional as well as longitudinal studies of relapse and treatment outcome that employ magnetic resonance imaging (MRI), functional near-infrared spectroscopy (fNIRs), brain stimulation methods, and/or electroencephalography (EEG) explored in frequency and time domains (the latter measured by event-related potentials, or ERPs). We discuss strengths and limitations of this neuroimaging work with respect to study design and individual differences that may influence interpretation of findings (e.g., opioid use chronicity/recency, comorbid symptoms, and biological sex). Lastly, we translate gaps in the OUD literature, particularly with respect to *Negative Reinforcement* processes, into future research directions involving operant and classical conditioning involving aversion/stress. Overall, opioid-related stimuli may lessen their hold on frontocingulate mechanisms implicated in *Preoccupation/Anticipation* as a function of prolonged abstinence and that degree of frontocingulate impairment may predict treatment outcome. In addition, longitudinal studies suggest that brain stimulation/drug treatments and prolonged abstinence can change brain responses during *Negative Reinforcement* and *Preoccupation/Anticipation* to reduce salience of drug cues, which may attenuate further craving and relapse. Incorporating this neuroscience-derived knowledge with the *Three-Stage Model of Addiction* may offer a useful plan for delineating specific neurobiological targets for OUD treatment.

Keywords: opioid use disorder, neuroimaging, magnetic resonance imaging, electroencephalography, event related potentials, recovery, abstinence

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THE DEVASTATION OF OPIOID USE DISORDER

Opioid use disorder (OUD) is a chronic, relapsing condition, associated with a staggering $75 billion public health burden and millions of years of premature mortality, attributable to a 350% increase in opioid-related deaths over the past two decades (2, 3). In 2016, more than 60 million patients had used and misused opioid-based anti-pain medication despite growing awareness of negative consequences and reduced effectiveness of long-term use (4). It is estimated that 20–30% of opioid-related overdoses are actually intentional suicide attempts, as opposed to accidents (5). It is not surprising that OUD-related suicide risk is over six times the national average, as individuals with OUD are struggling with disproportionate amounts of aversive mood states (anhedonia, dysphoria, suicidal ideation, irritability, anger, guilt, and shame) that are associated with heightened stress and drug craving (5–10). Moreover, the longer the temporary abstinence from drug use, the greater attention users devote to bodily sensations signaling a homeostatic imbalance. The process of attending to these sensations in an attempt to restore homeostasis, also known as allostasis (11), contributes to increased craving and withdrawal (9). Users actively attempt to avoid withdrawal comprised of agonizing physiological states (e.g., sweating, racing heartbeat, fever, nausea/vomiting, stomach cramps, diarrhea, generalized pain, depression, and anxiety) starting within hours of last use and lasting for days (12, 13). Opioid consumption relieves symptoms of negative affect as well as craving/urges in individuals with OUD (14), thereby increasing the likelihood of future drug use in the presence of negative affective and physical states, a process known as negative reinforcement. In short, individuals with OUD consume drugs to relieve emotional and/or physical pain. A *Three-Stage Model of Addiction* based on substantial animal and human studies highlights the importance of negative reinforcement, as well as binging and anticipation processes, to the exacerbation and maintenance of chronic substance use (1, 15). This model can be applied to various substance use disorders and further expanded to elucidate processes unfolding as a function of prolonged abstinence from use. At this point in time, however, we lack a comprehensive understanding of the underlying physiological and neural mechanisms involved in allostasis and negative reinforcement processes. As a result, we possess limited interventions to promote recovery and abstinence, and are left treating symptoms rather than underlying biological systems contributing to OUD.

Successful overdose-reversal and OUD treatment interventions are urgently needed to reduce mortality, increase quality of life, and lessen economic burden to society and healthcare systems. Modern neuroimaging technology advanced our ability to measure and quantify structural abnormalities and disrupted functionalities of brain circuitry. Neuroimaging research can be particularly beneficial for identifying brain circuitry and systems underlying allostasis and aversive states within OUD, thus leading to identification of targets for pharmacological and behavioral interventions to aid in addiction recovery. The goals of the present review are to: (1) highlight faulty brain circuitry and processes associated with OUD within the context of a *Three-Stage Model of Addiction* (1, 15); (2) discuss strengths and limitations of this imaging work with respect to study design and when available, individual differences such as opioid use chronicity/recency, comorbid symptoms, and biological sex that may influence interpretation of findings; and (3) translate gaps in the OUD literature into future research directions to lead toward a neuroscience-informed understanding of individual differences and potential points for intervention.

FRAMING OUD RESEARCH WITHIN THE NEUROCIRCUITRY OF ADDICTION

It is argued that three stages of motivational dysregulation instantiate and maintain the chronic cycle or stages of addiction: *Binge/Intoxication, Negative Reinforcement*, and *Preoccupation/Anticipation* (1, 15, 16). Within this model, these stages, which are likely not entirely separable from each other, are linked to aberrant patterns of activity within/between brain regions involved in reward processing [ventral striatum (VS)], cognitive control [frontocingulate regions including inferior frontal gyrus (IFG) and anterior cingulate cortex (ACC)], aversive emotional states [amygdala (AMG)], and a sense of the internal body state, known as interoception [insula (INS)]. **Figure 1** illustrates psychological and neurobiological processes associated with each stage.

Whereas the *Binge/Intoxication* stage lays the groundwork for initial transition to addiction, the latter two stages act to drive drug relapse. *Binge/Intoxication* reflects positive reinforcement processes that begin with recreational drug use, wherein rewarding consequences of drug use (e.g., euphoria, high), accompanied by increased VS (nucleus accumbens, globus pallidus) activity and dopamine release, increase the likelihood of future drug consumption. This cycle eventually leads to impulsive, intensified use that is difficult to control. Both animal and human research demonstrate that *Binge/Intoxication* initially weakens the brain's response to natural rewards while increasing drug tolerance by remapping striatal circuitry (consisting of decreased VS activity paired with increased dorsal striatum responses) to prioritize habitual drug rewards, a process termed incentive sensitization (17–20).

The *Negative Reinforcement* stage is thought to strengthen the likelihood of future drug use by reducing aversive mood, stress, and withdrawal states exacerbated by lack of recent drug administration. It is argued that a compulsive, habitual cycle persists: heightened anxiety and stress are briefly reduced as a result of drug use, but then build up over time, leading to obsessions about future drug-taking until the drug is used again (21). The extended AMG (comprised of AMG central nucleus, bed nucleus of the stria terminalis, and posterior nucleus accumbens shell) interacts with hypothalamic regions involved in neurochemical stress reactions and is also linked to aversive emotional reactions in humans (21). The stria terminalis, in particular, is implicated in norepinephrine hyperactivity associated with opioid withdrawal (22). Researchers theorize that

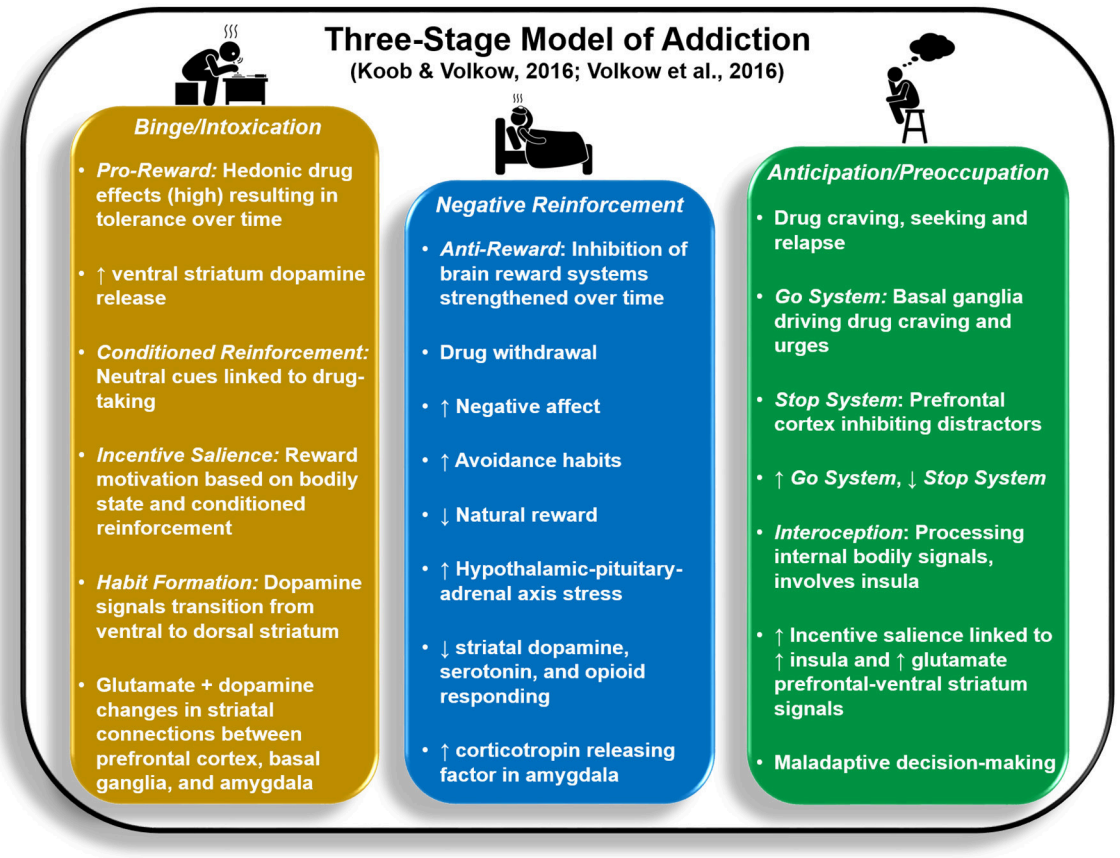

FIGURE 1 | Key psychological and neurobiological processes reflected in the *Three-Stage Model of Addiction* (1, 15).

stress-related brain systems/circuitry are activated first during the *Binge/Intoxication* stage to counteract excessive dopamine release; over time, neurochemical stress signals are thought to suppress dopaminergic responsivity to drug reward (23).

It is argued that the *Preoccupation/Anticipation* stage involves obsessive thoughts about future drug-taking that are prioritized over other goals, paired with weakened inhibitory control over drug craving/urges (1). Substantial evidence implicates INS in drug craving and aversive feeling states linked to withdrawal and short-term abstinence (24–26). In addition, heightened prefrontal cortex (PFC) and ACC activities evident within the context of drug cue-elicited craving theoretically drive increased preoccupation with and motivated actions toward drug-taking (25). While drug cues are often associated with exaggerated INS, ACC, and PFC responses (27), decision-making involving non-drug stimuli reflects attenuation in these regions as a function of addiction (28–30). With respect to recovery from drug addiction, however, it is still unclear how brain mechanisms implicated in *Preoccupation/Anticipation* and *Negative Reinforcement* stages change as a function of detoxification, early abstinence (e.g., 1–3 months sober), and prolonged abstinence (e.g., greater than 1 year sober), particularly within the same individuals over time, and whether brain changes parallel reductions in wanting to use drugs. As we review neuroimaging studies below, whenever possible we couch findings within the context of participant abstinence duration to develop predictions for what functions might improve with sobriety.

Taken together, neuroimaging studies provide compelling evidence that striatal, frontocingulate, AMG, and/or INS structure, function, and/or connections are disrupted in OUD. What do these disruptions mean with respect to specific impairments in OUD? Research findings indicate that the meaning of INS dysfunction depends on the particular location that is affected. Anterior INS, connected to IFG and dorsal striatum, is implicated in awareness of bodily feeling states as well as the learning and implementation of goal-directed actions that can be conceptually linked to cognitive control processes, whereas ventral INS is more strongly connected to AMG and VS and is thought to be involved in emotional salience and affective feeling states. In contrast, middle and posterior INS are connected with somatosensory regions (sensory and parietal cortices) associated with the processing of bodily feeling states, including pain signals (31, 32). Dorsolateral PFC is thought to work with ACC to regulate goal-directed behavior, wherein it is argued that dorsal ACC processes the value and difficulty of behavior change via its connections with dorsolateral

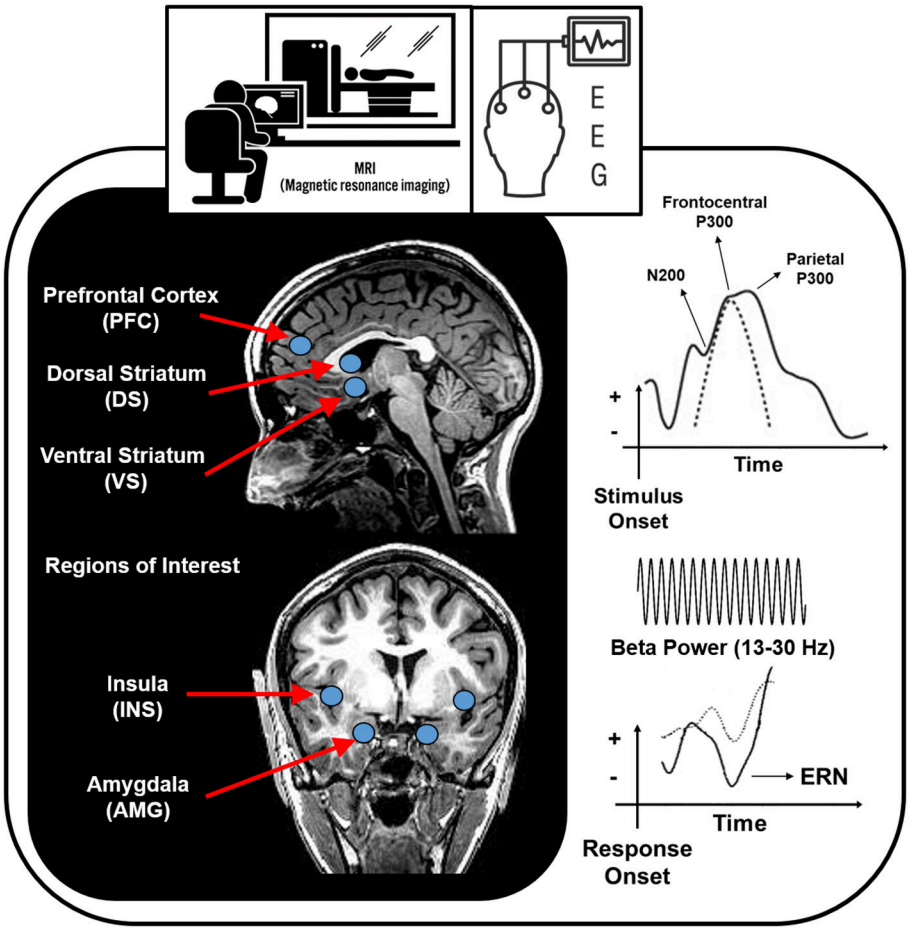

FIGURE 2 | Brain regions and processes that potentially map onto *Negative Reinforcement* and *Anticipation/Preoccupation* stages of the *Three-Stage Model of Addiction* (1, 15). EEG, electroencephalography; ERN, error related negativity.

PFC as well as AMG, dorsal striatum, and primary motor cortex (33). Within the context of stress, cognitive control functions in frontocingulate and anterior INS regions are argued to be hijacked by AMG connections. For example, although the dorsolateral PFC is thought to play an active role in pain suppression (34), within the context of aversive events, heightened AMG signals activate neurochemical stress reactions that serve to downregulate dorsolateral PFC in favor of salience-driven habitual, impulsive responses instantiated via dorsal striatum (35). Moreover, greater functional and structural links between basolateral AMG and anterior INS are associated with higher state and trait anxiety (36), instantiating aversive feeling states accompanying stress.

Deficits in the brain circuitry outlined above are present in conjunction with aberrant timing and allocation of neural resources to drug and non-drug related stimuli, consistent with the *Three-Stage Model of Addiction*. In the following sections, specific neuroimaging tools related to magnetic resonance imaging (MRI), functional near-infrared spectroscopy (fNIRs), electroencephalography (EEG), event related potentials (ERP), repetitive transcranial magnetic stimulation (rTMS) and deep brain stimulation (DBS) are briefly explained and cross-sectional and longitudinal OUD-relevant literature is summarized for each technique. **Figure 2** illustrates brain regions and processes of interest that are described in more detail below. Next, **Figures 3** and **4** summarize brain findings that appear to map onto *Negative Reinforcement* and *Anticipation/Preoccupation* stages. To compile research articles for this review, combinations of the following search terms were entered in Google Scholar: "opioid," "heroin," "MRI," "EEG," "rTMS," "fNIRs," "DBS," "ERP," "prescription opiate," "methadone," "naltrexone," "therapy," "abstinence," "relapse," "resting state fMRI," and "buprenorphine."

Structural MRI (sMRI)

With its high spatial resolution (typically in order of 1 mm^3), sMRI offers ways to differentiate different brain tissues, such as gray and white matter, and to quantify gray and white matter volume within various brain regions. Gray matter consists of cell bodies, dendrites, unmyelinated axons, and synapses that facilitate specialized information processing in cortical and subcortical regions, whereas white matter consists of myelinated axons that relay signals from one brain region to another. Studies employing sMRI demonstrate that OUD is characterized

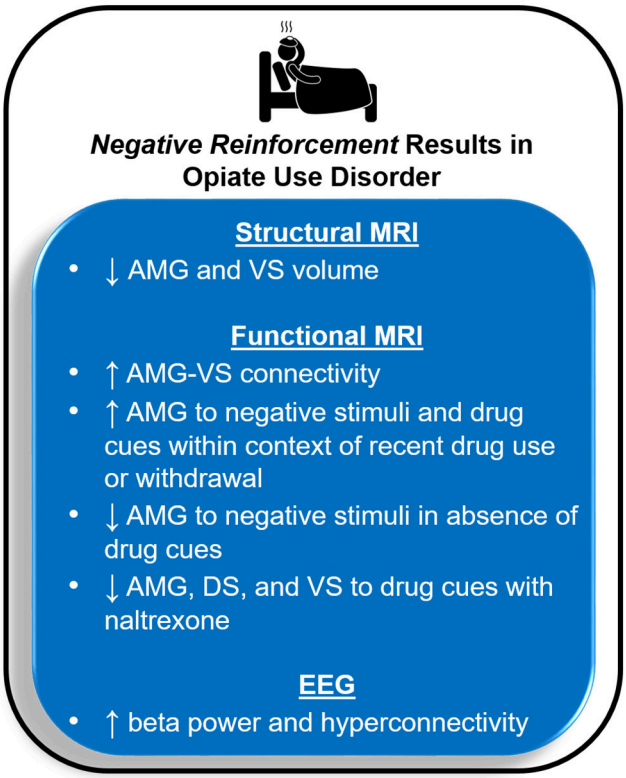

FIGURE 3 | Magnetic resonance imaging (MRI) and electroencephalography (EEG) results for opioid use disorder that may map onto the *Negative Reinforcement* stage of the *Three-Stage Model of Addiction* (1, 15). AMG, amygdala; VS, ventral striatum; DS, dorsal striatum.

by attenuated gray matter volume and white matter integrity in/surrounding striatum, frontocingulate regions (including IFG), AMG, and INS, with higher opioid use chronicity, use recency, and depression symptoms linked to greater reductions in specific regions (37–41). For instance, greater opioid use chronicity is associated with lower frontocingulate and/or INS cortical thickness in active as well as abstinent OUD users (37, 42, 43) in addition to decreased VS gray matter volume (44). Moreover, within individuals on opioid maintenance treatment for OUD, lower VS volume is associated with higher depression symptoms, whereas lower AMG volume is linked to greater daily opioid dose (40). Gray matter reductions within orbito-medial prefrontal cortex and bilateral globus pallidus are also associated with increased cognitive impulsivity among individuals on opioid maintenance treatment (45). With respect to abstinence, higher compulsive behavior reported by sober individuals with OUD is linked to lower white matter surrounding VS and rostral ACC when compared to that of active OUD users and healthy controls (44). In summary, brain regions implicated in *Binge/Intoxication* (VS), *Negative Reinforcement* (AMG), and *Preoccupation/Anticipation* stages (PFC, ACC, and INS) show structural attenuations, ostensibly contributing to various information processing impairments that may have a stronger impact when users are attempting to resist using opioids. For instance, VS attenuation may reflect the capacity for heightened drug tolerance and reduced euphoric effects of drug consumption. Additionally, PFC, ACC, and anterior INS volume reductions could manifest in impairments in adaptive goal-directed behavior, whereas diminished AMG structure might manifest in dysregulated stress and salience signaling in the presence/absence of drugs.

Functional MRI (fMRI)

fMRI offers good spatial resolution (typically in order of a few mm^3) to detect and measure temporal changes in blood flow, volume, and blood oxygenation (e.g., blood oxygenation level dependent, or BOLD contrast) while individuals are resting or performing various tasks. Active neurons in the brain require oxygenated blood to replenish energy; BOLD fMRI is affected by the differences in magnetic susceptibility between deoxygenated and oxygenated blood, and by local increases in blood flow and volume, signaling brain regions that are more active during one particular condition, stimulus, response, or timeframe vs. another. Researchers often quantify brain changes by computing the percent signal change between an active condition and a baseline condition. It is argued that the characterization of spontaneous (or intrinsic) brain signals during a resting state (e.g., without any particular task involved) are just as worthy of study as brain signals evoked by a particular stimulus and/or response because these spontaneous measurements reflect degree of energy consumption required to maintain default functioning in the absence of particular task demands (46, 47). Most fMRI research in OUD focuses on either drug-cue valuation processes compared to neutral cues and/or natural rewards (food, sex, social interactions, money), or decision-making in the absence of emotional, reward, or drug-related cues. Only a few studies have examined brain mechanisms involved in responses to negative stimuli, limiting interpretability.

Resting-State fMRI

Studies of spontaneous fMRI often focus on coherence (or connectivity) of signals across multiple spatially distinct cortical and subcortical brain regions. OUD is associated with weak frontocingulate functional connectivity with subcortical regions, but strong functional connectivity within subcortical regions such as striatum and AMG (48), findings consistent with a reward-control imbalance in OUD [stronger reward-stress connectivity paired with weaker cognitive control connectivity; (49)]. Multiple fMRI studies report weakened INS connectivity to IFG, striatum, and AMG, with those testing positive for opioids or reporting greater opioid use chronicity exhibiting the greatest dysfunction, findings in line with the *Preoccupation/Anticipation* stage (41, 49, 50). Finally, research indicates that individuals with OUD exhibit attenuated ACC activity and reduced connectivity with PFC and striatal regions; moreover, lower ACC signal within this context is linked to greater drug cue-induced craving (51, 52).

Task-Based fMRI: Cue Reactivity and Non-drug Rewards

OUD is marked by frontocingulate and striatal hyperactivation to drug cues, particularly within active users (up to a few hours sober), with degree of response decreasing as a function of longer

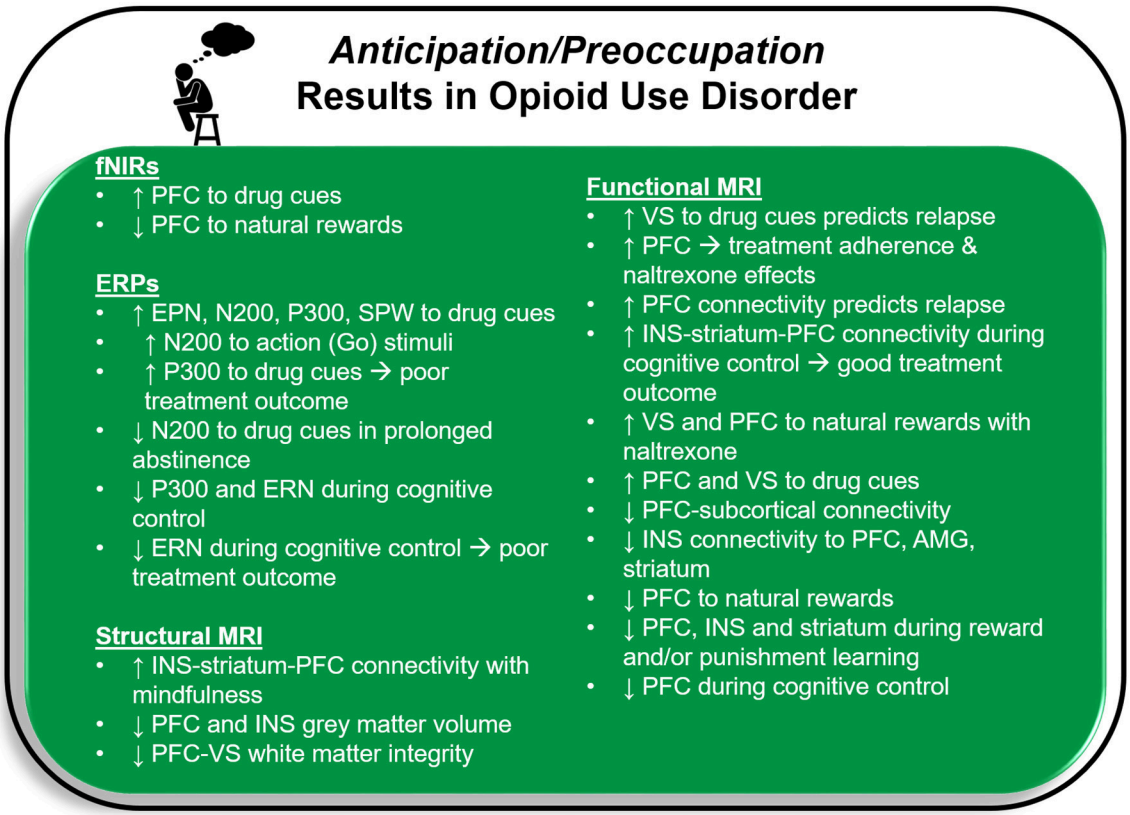

FIGURE 4 | Functional near-infrared spectroscopy (fNIRs), event related potential (ERP), and magnetic resonance imaging (MRI) results for opioid use disorder that may map onto the *Anticipation/Preoccupation* stage of the *Three-Stage Model of Addiction* (1, 15). PFC, prefrontal cortex, including anterior cingulate cortex; EPN, early positive negativity; SPW, slow positive wave; ERN, error related negativity; INS, insula; VS, ventral striatum; AMG, amygdala.

abstinence (i.e., 6–14 months as opposed to 1 month), findings consistent with the *Preoccupation/Anticipation* stage of addiction (53–62). Compared to non-substance using individuals, those with OUD show frontal attenuation to pleasant non-drug stimuli such as food, pornography, and interactive social situations (54, 63), although this pattern may dissipate as a function of abstinence [3 years; (54)]. With respect to reward sensitivity, users with OUD exhibit difficulty distinguishing between non-drug win and no-win outcomes in striatal brain regions (64); moreover, individuals with OUD show INS, ACC, and IFG attenuation during win/loss anticipation and feedback (65) in line with the *Preoccupation/Anticipation* stage of addiction.

Task-Based fMRI: Cognitive Control

OUD is associated with frontocingulate hypoactivation during tasks requiring sustained attention, working memory, and/or cognitive/behavioral inhibition compatible with the *Anticipation/Preoccupation* stage of addiction, with fMRI studies reporting this pattern regardless of abstinence duration or presence of opioid-replacement treatment (66–69). One study demonstrates no difference in ACC activation between users with OUD on opioid replacement therapy (buprenorphine or methadone) and non-users during behavioral control. However, users do not show a positive correlation between ACC activation and behavioral performance as seen in non-users, indicating a notable discrepancy between brain signaling and behavior (70); these findings suggest that even when recruited, these regions may not function as effectively for OUD. Some evidence suggests that cognitive control functions involving IFG and ACC may improve as a function of prolonged abstinence in OUD, given that former opioid users abstinent for at least 6 months perform similarly to healthy individuals and/or better than users on opioid replacement therapy during cognitive control tasks. However, the literature is far from conclusive and mixed results may be due, in part, to variability in opiate use chronicity and recency across studies (39).

Task-Based fMRI: Aversive Stimuli

On the whole, very limited research suggests that OUD is characterized by blunted brain responses to negatively valenced stimuli as well as punishing outcomes in the absence of drug cues. Two fMRI studies report hypoactive AMG responses to negative and positive as opposed to neutral stimuli in OUD individuals who are abstinent 2–5 months (71) as well as current users with OUD; it is important to note that these results are based on samples with comorbid borderline personality disorder who are also on opioid replacement therapy (72). Thus, findings may not easily generalize to other OUD samples. These reports of

blunted AMG signals are the opposite of what would be predicted by the *Negative Reinforcement* stage, which suggests that AMG responses should be intensified as a function of aversive cues. In contrast, two fMRI studies demonstrate that drug cues evoke AMG hyperactivation in individuals with OUD who are expecting to consume opioids or have recently withdrawn from opioids, potentially reflecting exaggerated salience associated with drug cues and/or bodily signals that in the past have signaled opioid withdrawal. More specifically, when active OUD users are administered saline as opposed to opioids, they display greater AMG activation than healthy individuals to fearful faces, a pattern that is linked to elevated state anxiety (73). Similarly, newly detoxified individuals with OUD exhibit hyperactive AMG responses to drug as opposed to neutral films, a pattern correlated with heightened craving (74). Furthermore, OUD patients on methadone replacement exhibit greater INS and AMG activation to opioid cues before as opposed to after ingestion of their daily methadone dose (75). Drug cues in abstinent individuals with OUD also appear to act as salient stimuli, linked to heightened anxiety, other negative emotions, and physiological blood pressure/heart rate increases (76). On the whole, these findings are accordant with the *Negative Reinforcement* stage.

Non-imaging data indicate that active OUD is associated with exaggerated self-reported arousal to negative non-drug images (77), suggesting that additional brain-behavior research is needed to determine whether patterns of AMG response to emotional stimuli change as a function of abstinence. Greater negative affect induced by film clips still increases drug craving in OUD users without the presence of drug cues, congruent with the *Negative Reinforcement* stage of addiction; furthermore, this relationship is stronger for users with high as opposed to low anxiety sensitivity (78). Moderation by anxiety sensitivity points to the importance of measuring individual differences in users' perceptions and awareness of bodily sensations, as these may intensify stress responses that hijack abstinence efforts.

Lastly, OUD is linked to difficulty differentiating punishing vs. non-punishing feedback within striatum (64). Behavioral studies indicate that individuals with active and/or former OUD show difficulties avoiding punishment (79–81) and demonstrate heightened risk-taking following punishment (82). This pattern of impaired decision-making in the face of punishment may be more relevant to the *Preoccupation/Anticipation* than the *Negative Reinforcement* stage, as a meta-analysis implicates INS in the implementation of punishment-related prediction errors and ACC and PFC regions in reinforcement-based decision making more generally (83).

Functional Near-Infrared Spectroscopy (fNIRs)

The fNIRs technology employs near-infrared light attenuation to quantify concentration of oxy- and deoxy-hemoglobin. fNIRs can differentiate skin, skull, and cortical surface tissue, and produce a BOLD contrast similar to fMRI, however without the ability to measure whole brain responses. Studies using this technology indicate that OUD patients recently detoxified from opioids show: (1) greater right dorsolateral PFC activation to opioid cues than individuals with OUD abstinent for at least 2 months (84); and (2) higher anhedonia symptoms paired with lower rostral and/or ventrolateral PFC to appetitive food and positive social interactions than healthy individuals (63). These results point to greater attentional resources being devoted to drug cues than other types of rewards, consistent with the *Preoccupation/Anticipation* stage of addiction.

Electroencephalography (EEG)

EEG Time and Frequency Domains

EEG, the continuous recording of ongoing brain electrical activity via scalp electrodes, possesses high temporal resolution (order of milliseconds) (85). Resting state EEG recordings measure the brain's pseudo-periodic oscillatory activity due to coherent activity from many neurons synchronized in time and space. For EEG signal frequency analyses, a Fast Fourier Transform (FFT) technique decomposes the EEG time series into a frequency spectrum by voltage (a measure of signal magnitude, or amplitude) matrix; this information can then be segmented as a function of specific frequency "bands" that are associated with various mental processes. Frequencies most studied in OUD samples include those segmented within theta, alpha, beta, and gamma bands. Theta band (4–7 Hz) activity is implicated in cognitive control processes including working memory and error monitoring (86–88). Decreases in alpha band (8–13 Hz) activity are associated with increases in active information processing involving attention (89), whereas beta band (13–30 Hz) decreases signal an impending voluntary motor action (90). Finally, gamma band (30–100 Hz) activity is theorized to reflect the comparison of a stimulus with information held in memory to determine a match or mismatch (91). EEG power (the square of the EEG magnitude of the signal amplitude within a particular band) is often calculated to compare between clinical groups or conditions. In addition, EEG coherence metrics are calculated to reflect how strongly oscillations between two or more measuring electrodes reflecting and mapping into synchronized brain regions activities within a particular frequency band.

Although EEG frequencies can be measured within the context of a particular task, resting-state EEG studies investigating frequency band differences as a function of OUD are the norm. On the whole, this literature indicates that EEG power and coherence are disrupted in chronic OUD users compared to healthy individuals, although findings are inconsistent as to directionality (which group is higher or lower) as well as which frequency band, hemisphere, or specific brain region is affected and whether these patterns normalize as a function of abstinence or methadone maintenance (92, 93). However, EEG frequency studies of OUD are atheoretical with respect to how findings map onto stages of addiction or cognitive/emotional functioning, and low spatial resolution of most EEG recording montages limit spatial (brain) localization of frequency signals within OUD samples.

The most consistent finding is that individuals with OUD (whether actively using, maintained on methadone for at least 6 months, or in the early stages of abstinence) exhibit greater beta power than healthy individuals [91–93). With respect to longer abstinence duration, one study reports no difference in

beta power between healthy controls and OUD users abstinent 1–6 months, whereas another study indicates that beta power decreases as a function of longer OUD abstinence (94). As beta power increases are thought to reflect decreased need for future motor actions, these results suggest that active opioid users can be characterized by reduced behavioral activation, at least during intrinsic processing. Additional research probing beta power changes during reward and stress states in opioid users may contribute to our understanding of *Binge/Intoxication*, *Negative Reinforcement*, and *Preoccupation/Anticipation* stages within the context of OUD. Perhaps beta power changes as a function of prolonged abstinence can track stages of recovery, although longitudinal studies are warranted to test this hypothesis.

In contrast to beta band results, findings for the alpha band are somewhat mixed, with: (1) active OUD users exhibiting either higher (93) or lower (95) power than healthy comparison subjects; (2) OUD users maintained on methadone for 6+ months displaying lower (96) or higher (93) power than non-users; and (3) abstinent OUD users showing similar levels of power as healthy individuals (97) or increasing alpha power as a function of sobriety duration (94). For theta band activity, active OUD users either exhibit lower (95) or higher (93) power than healthy individuals. However, OUD users abstinent 1–6 months display similar theta power as control subjects (97), findings suggestive of a state-like change in theta power as a function of current drug use. Time frequency analysis of short duration EEG frequency band distribution (as opposed to averaging frequency bands across the entire length of EEG recording) indicate that active OUD users exhibit higher occurrence of alpha and beta rhythms but lower occurrence of theta rhythms than comparison subjects; moreover, OUD users show greater occurrence of these rhythms in the right than the left hemisphere (98); these findings could be consistent with fMRI data suggesting weakened right frontal processing in OUD that could reflect inhibitory impairments associated with faulty IFG/ACC signaling, consistent with the *Preoccupation/Anticipation* stage of addiction.

With regard to EEG coherence within and across regions of the brain, active OUD exhibit local hyperconnectivity in alpha and beta frequency bands, a pattern that does not change as a function of early (2-week) abstinence. However, remote alpha and beta hypoconnectivity evident in active OUD users does appear to normalize during the early stages of sobriety (99, 100). Finally, gamma band findings indicate that active OUD as well as OUD on prolonged methadone treatment display greater gamma power than healthy individuals (50), and OUD abstinent at least 2 weeks exhibit greater fronto-occipital gamma band coherence within the left hemisphere than CTL, although the significance of this greater coherence is not well-understood (101).

EEG Event Related Potentials (ERPs)

ERPs are averaged periods of EEG recordings interpreted within the time domain that are elicited by a particular stimulus or a response. ERPs allow researchers to understand the onset and/or duration of perceptual, attentive, and other cognitive and emotional processes (85). Unlike fMRI studies suggesting that faulty cognitive control circuitry may normalize as a function of OUD abstinence, ERP studies provide mixed results, suggesting that this may not be the case (95, 102–110), although greater opioid use chronicity does appear to be associated with greater frontocingulate reductions (103). Temporal resolution differences between ERPs (milliseconds) and fMRI (seconds) suggest that aspects of early stimulus evaluation (measured by multiple ERP amplitude/latency components) are still disrupted in OUD at various stages of abstinence accordant with the Preoccupation/Anticipation stage of addiction.

ERP components

Details regarding timing and proposed function of various ERP components, including early posterior negativity (EPN), N200, P300, slow positive wave (SPW) and error related negativity (ERN), are provided below within the context of various paradigms, including cognitive control, cue reactivity, working memory, attention and emotion tasks.

EPN

The EPN is a positive ERP deflection occurring 200 ms post-stimulus, thought to reflect and associate with early perceptual processing in temporal/occipital brain regions (111). During an emotional Stroop task involving positive, negative, neutral, and opioid images, OUD users abstinent an average of 9 months show larger EPN amplitude to opioid images than healthy participants in the absence of behavioral differences between groups (109). These results indicate that even with prolonged sobriety, perception of drug cues is prioritized.

N200

N200 is a negative ERP deflection occurring 200–350 ms after a stimulus, thought to reflect and associate with conflict monitoring processes (112, 113). During a go/nogo task, individuals with OUD (abstinent for 4 months) show larger frontocentral N200 amplitudes to go (action) trials than healthy controls, but groups do not differ on N200 amplitudes to nogo (inhibition) trials (110); findings imply that neural resources are overly devoted to action tendencies, perhaps related to impulsivity. In contrast, however, former OUD and cocaine users display no N200 differences from non-users during response inhibition tasks involving neutral and emotional stimuli (114). OUD users abstinent at least 1 month show greater N200 amplitude to opioid images during a dot probe task than controls (115), in contrast, OUD users abstinent 8–24 months exhibit smaller N200 to opioid images than healthy subjects (108). These results suggest that addicted individuals experience inhibitory difficulties in the presence of drug cues as represented by the *Preoccupation/Anticipation* stage of addiction that may change as a function of prolonged recovery.

P300

P300 is a positive ERP deflection occurring 300–600 ms after a stimulus thought to reflect and associate with attention allocation, motivational salience, and/or updating of short-term memory, depending on the paradigm used (85). Among current OUD, findings point to exaggerated salience of opioid cues at the expense of other stimuli, accordant with the *Preoccupation/Anticipation* stage of addiction. Chronic users

with OUD display smaller P300 amplitude and longer P300 latency than healthy individuals during digit span and auditory oddball tasks, but larger P300 amplitude to opioid images during a cue reactivity task (95). P300 responsivity has also been examined among substance users with varying lengths of remission. For example, substance users in residential treatment with a history of addiction (cocaine use disorder with/without alcohol use disorder and OUD) exhibit lower P300 amplitude across the entire cortex than healthy individuals to targets during a visual continuous performance test; furthermore, across the three user groups, shorter abstinence is associated with smaller P300 amplitude (102). Similarly, individuals with OUD who are recently detoxified or on opioid replacement therapy exhibit greater P300 amplitude to opioid images than positive, negative, or neutral images, with larger opioid-related P300 amplitude linked to greater self-reported craving; however, OUD subjects do not differ in P300 amplitude from healthy individuals across conditions (116). Moreover, OUD users abstinent for at least 6 months show smaller P300 amplitudes during a working memory task than healthy individuals and current OUD users in frontal regions (105, 106). However, OUD users, their first-degree relatives, and healthy controls do not differ in P300 amplitude to auditory oddball targets (107). Overall, findings among recently abstinent and treatment-seeking individuals are inconsistent as to whether neural resources devoted to attention/salience of non-drug cues improve as a function of abstinence.

SPW

The SPW is a positive frontal ERP deflection that onsets at least 600 ms post-stimulus and lasts for several 100 ms, reflecting and associated with sensitivity to emotional valence as well as motivational salience (117, 118). OUD users abstinent for a minimum of 2 weeks show greater SPW amplitude to opioid than neutral images, whereas healthy individuals show no difference between opioid and neutral pictures; moreover, within users, greater central SPW amplitudes are associated with heightened arousal to opioid cues (101). These results are in line with SPN and P300 findings for opioid cues, indicating heightened resources devoted to drug cues in active or early-abstinent users with OUD.

ERN

The ERN is a negative ERP deflection occurring approximately 50 ms after an individual makes an error; the ERN is localized to anterior cingulate cortex and thought to reflect and associate with error monitoring processes (119). During an Eriksen flanker task, individuals with OUD exhibit faster reaction time to correct and incorrect trials than healthy controls, paired with smaller ERN amplitudes and faster latencies in frontocentral regions, suggestive of impairments related to impulsivity (103).

Repetitive Transcranial Magnetic Stimulation (rTMS)

rTMS utilizes a handheld coil placed against the scalp, transmitting transient electric current to produce a changing magnetic field. This magnetic field can painlessly penetrate the skull and deliver a magnetic pulse to stimulate nerve cells in the brain. The TMS coil can be positioned to selectively target a region of the brain and excite or inhibit cortical neurons. rTMS studies are more common among other substance use disorders including alcohol, nicotine, and stimulants. However, one study employed rTMS within a sample of 20 men with OUD. This randomized, sham-controlled crossover study demonstrated that active but not sham 10 Hz rTMS over left dorsolateral PFC reduced craving induced by viewing videos of opioid use. Continued rTMS treatment for an additional 4 days further reduced cue-induced craving (120). These results are consistent with the *Preoccupation/Anticipation* stage of addiction wherein overactivation of frontal regions in response to cue-elicited craving drives preoccupation with drug-taking, suggesting that targeted rTMS stimulation of frontal regions may be a potential avenue for recovery in OUD.

Deep Brain Stimulation (DBS)

In contrast to non-invasive rTMS, DBS is a invasive neuromodulation procedure administered via electrodes surgically implanted in subcortical brain areas. High frequency electrical stimulation is delivered to inhibit neural activity in targeted regions of the brain (121). DBS is used to treat movement disorders such as Parkinson's disease, and double-blind control trials show promise for its use in the treatment of refractory depression and obsessive compulsive disorder (122). Recently, DBS has been explored as an experimental treatment for patients with refractory substance use disorders, including OUD.

Among patients with OUD, DBS has been used to modulate activity in reward-network regions such as nucleus accumbens. Thus far, findings suggest that DBS is associated with partial to full remission and few side effects. For instance, within a small sample of chronic, treatment-resistant opioid users, DBS of the anterior limb of the internal capsule and nucleus accumbens resulted in prolonged sobriety greater than 2 years paired with reduced drug craving (123). Positron emission tomography scans also revealed increased glucose metabolism within bilateral IFG from pre- to post-DBS within these patients. Similarly, a case report demonstrated that an individual with a 5-year opioid use history underwent rapid detoxification and received DBS to bilateral nucleus accumbens for over 2 years. He subsequently maintained complete abstinence for the 6-year follow-up period after the electrode implantation surgery (121). Similarly, nucleus accumbens DBS in two chronic OUD patients resulted in decreased depression and anxiety paired with prolonged abstinence from opioids (124). However, an alternative case report of nucleus accumbens DBS stimulation in a man with 17 years of opioid use was unsuccessful in alleviating cravings 2 months post-DBS initiation. He relapsed eight times within the following 2 months and eventually overdosed within 5 months of DBS onset (122).

Abstinence following DBS treatment targeting reward-network regions is consistent with the *Binge/Intoxication* stage of addiction. DBS may reduce the reward response to drug use thereby interrupting the cycle that typically results in increased dopamine release and future drug use. While initial binge/intoxication may lead to incentive sensitization by

weakening the brain's response to natural rewards in favor of drug rewards, use of DBS may interrupt the reward response, thereby reversing this process and allowing the brain to return to its initial preference for natural rewards (123, 125).

Longitudinal Studies of Relapse and Treatment Outcome

Extant longitudinal neuroimaging studies of OUD combine imaging data with treatment to examine changes with treatment or baseline neural predictors of response. This research primarily concentrates on brain responses to drug cues, which within the context of abstinent individuals can be construed as appetitive and/or aversive. ERP results indicate that larger P300 amplitudes to opioid than pleasant images predicts greater opioid use frequency 6 months later (126), whereas lower frontal P300 amplitudes to non-drug distractors (127) and smaller ERN amplitudes during cognitive control (128) predict future treatment discontinuation. These findings point to executive function deficits within the *Preoccupation/Anticipation* stage that discount goals other than drug-seeking. Studies of fMRI prediction show that greater VS response (paired with higher self-reported craving) to opioid cues predicts relapse within 3 months (129), whereas higher medial PFC activation to opioid cues at baseline predicts more successful naloxone adherence (93) Additionally, functional connectivity fMRI studies demonstrate that although higher resting-state connectivity between ACC and medial PFC predicts relapse within 3 months (130), greater functional connectivity between INS, striatum, and ACC during a go/nogo task predicts successful 12-week substance use treatment (131). On the whole, these findings indicate that heightened salience of drug cues (particularly in striatal and frontal regions) forecasts difficulty maintaining sobriety, data congruent with the *Preoccupation/Anticipation* stage. Divergent task conditions across studies (cognitive control, resting-state, cue reactivity) may account for inconsistent findings; it would be helpful for future research to assess patterns of brain function across multiple paradigms to determine whether exaggerated or attenuated regions reflect global or context-dependent predictions.

Neuroimaging studies of OUD recorded at multiple timepoints demonstrate that naltrexone treatment: (1) decreases AMG and dorsal striatum signals while increasing medial PFC responses to opioid cues (132); (2) reduces VS and orbitofrontal responses to opioid cues as well as self- and clinician-reported withdrawal symptoms (133); and (3) increases VS activation to natural rewards (pictures of cute infants) (134). In contrast, a recent study shows that methadone maintenance treatment (>3 months) does not change frontocingulate mechanisms implicated in cognitive control during go/nogo task performance (135). These results convey that naltrexone shows promise in reducing appetitive (and perhaps aversive) salience of drug-related stimuli related to *Preoccupation/Anticipation* and *Negative Reinforcement* stages of addiction. Additional studies are warranted to replicate and extend these findings beyond naltrexone to buprenorphine and various therapy interventions. With respect to sMRI findings, OUD users completing 4 weeks of mindfulness-based treatment display improved striatum-INS and frontocingulate structural network strength than OUD users who received treatment as usual (136).

Limitations and Gaps in Knowledge

Several gaps in the neuroimaging literature preclude development of accurate targets to identify and track treatment in OUD. First, inconsistent results are reported cross-sectionally for individuals with former OUD at various stages of recovery (from weeks to months) who also show wide variability in opioid use chronicity. Although testing interactions between drug use recency and chronicity may clarify inconsistent findings, this analysis has rarely been attempted (39). Longitudinal within-subjects designs provide increased statistical power to detect dynamic brain signal changes as a function of prolonged abstinence within each individual; however, few longitudinal neuroimaging studies tracking both brain and behavior change within OUD individuals exist, particularly accounting for both opioid use chronicity and recency. In addition, longitudinal designs can track changes in psychological symptoms related to negative mood states (e.g., depression and anxiety) that in conjunction with brain changes may distinguish OUD who relapse vs. those who are able to remain abstinent. Second, small sample sizes limit statistical power to detect potentially meaningful differences as a function of OUD status, and the majority of OUD studies are comprised of male participants [e.g., (50, 55, 57, 72, 74, 95, 101, 103, 107–109, 126)], limiting generalizability. Although more men use opioids than women, heroin use is increasing at a faster rate and prescription opioid use is decreasing at a slower rate among women than men, contributing significantly to the OUD crisis (137). In addition, research suggests that stress predicts opioid use in women but not men, pointing to the idea that *Negative Reinforcement* processes may be more crucial to target in women's recovery programs (138). Third, only a few OUD studies integrate neuroimaging methods with high temporal (EEG, ERPs) and spatial (sMRI, fMRI) resolution, limiting conclusions that can be drawn regarding precisely when and where brain processes change with abstinence. Longitudinal multimodal (EEG/ERP paired with sMRI, fMRI, and/or fNIRs) neuroimaging studies of OUD recovery are warranted to map temporal and spatial brain changes as a function of early vs. late stages of opiate abstinence and treatment outcome, while mapping changes in individual differences in psychological symptoms [e.g., depression and anxiety; (12, 13)] and co-use of other substances (e.g., alcohol, nicotine) (139). Lastly, despite the fact that processing during the *Negative Reinforcement* stage of addiction is theorized to drive users to relapse (140), few neuroimaging studies of OUD have evaluated how aversive or stressful stimuli, alone or in conjunction with opioid cues, transform brain circuitry to hijack intended abstinence efforts and drive relentless capitulation to drug use despite increasingly dire consequences. The following sections highlight two promising avenues of research that can evaluate aversive sensitization in individuals with OUD.

Operant Conditioning and Interoception

Interoception, the perception and awareness of bodily signals, is thought to be dysregulated as a function of addiction, contributing to drug craving and urges (26, 141–144), but only two studies have examined interoceptive processing in OUD, demonstrating impaired interoceptive awareness as measured by heartbeat tracking accuracy (145), and greater stress-related physiological arousal and craving in response to paired pain-opioid stimuli as a function of pain-driven opioid misuse (146). However, no neuroimaging studies have probed the integrity of brain circuitry implicated in aversive interoceptive processing in OUD. Work by our research team demonstrates that, within the context of an aversive interoceptive manipulation (inspiratory breathing load), stimulant use disorder is characterized by exaggerated trait anxiety paired with attenuated striatum, INS, IFG, and ACC responses during decision-making (147–149). These findings point to increased arousal mismatched with blunted processing of bodily signals in the absence of drug-related stimuli, a pattern that could translate into impaired awareness of or attention to negative consequences during real-world decision-making consistent with the *Preoccupation/Anticipation* and *Negative Reinforcement* stages of addiction. Future studies could attempt to replicate this brain-based pattern of blunted aversive interoceptive processing in OUD and then extend this work by pairing aversive interoception with the presence vs. absence of drug cues to test the role of opioids in aversive sensitization.

Classical Conditioning and Extinction

Fear conditioning is a process where individuals learn which cues are associated with aversive outcomes (shocks, sounds, odors). With repetitive cue-outcome pairings, the cue alone can trigger the same response as the aversive outcome (conditioned fear). A recent meta-analysis demonstrates that fear-conditioned cues consistently elicit greater INS, striatum, and frontocingulate responses than unconditioned cues (150). Heightened AMG signaling for fear-conditioned cues is present across several studies, but may vary across tasks as a function of stimulus duration, predictability, and presentation modality [e.g., (151–156)]. Exaggerated physiological arousal during fear conditioning is specifically associated with AMG-INS signaling and connectivity (157, 158). Fear extinction, in contrast to conditioning, is the process wherein individuals learn to dissociate cues from their previously paired aversive outcomes, involving INS and ACC across studies (159) as well as AMG, particularly within early extinction (153, 160, 161). No studies have examined whether brain mechanisms of classical conditioning and extinction are intact in OUD within the context of aversive stimuli, but given behavioral impairments in decision-making as a function of punishment in OUD (64, 79–82), it is possible that associative learning and unlearning involving negative stimuli is disrupted in opioid users. Future research could identify whether brain circuitry impairments to fear-conditioned and extinguished-stimuli characterizes OUD in the presence vs. absence of drug cues.

SUMMARY AND CONCLUSIONS

Delineating neuroimaging targets for recovery from OUD is a difficult task, given that the majority of studies investigating abstinence are cross-sectional, comprised of opiate users with heterogeneous patterns of use chronicity and recency that may complicate results. In particular, methadone maintained individuals with OUD show brain impairments that are more similar to active illicit opioid users than individuals abstinent from opioids altogether. However, longitudinal studies show some promise that other treatments (e.g., rTMS, DBS, and naltrexone) or prolonged abstinence can change brain signals implicated in *Negative Reinforcement* and *Preoccupation/Anticipation* to reduce salience of drug cues, which may attenuate craving and anguish driving individuals to resume opioid use. The pairing of cue-reactive stimuli with established paradigms targeting cognitive control (e.g., flanker, go/nogo, stop signal) and/or emotion regulation [cognitive reappraisal of negative stimuli; e.g., (162)] may be beneficial for tracking the degree of brain resources that continue to be captured by drug cues over the course of recovery. Many more longitudinal investigations, particularly with males and females and within the context of aversive or stress-related stimuli, are warranted to develop individual-difference prediction models of recovery in OUD.

AUTHOR CONTRIBUTIONS

JS wrote the first draft of the manuscript with AM's input and created the figures. AM, RA, and JB provided revisions to further manuscript drafts. AM formatted the manuscript for publication.

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Improvement of Emotional Empathy and Cluster B Personality Disorder Symptoms Associated With Decreased Cocaine Use Severity

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Aims: Chronic cocaine users display impaired social cognitive abilities, reduced prosocial behavior, and pronounced cluster B personality disorder (PD) symptoms all contributing to their social dysfunctions in daily life. These social dysfunctions have been proposed as a major factor for maintenance and relapse of stimulant use disorders in general. However, little is known about the reversibility of social cognitive deficits and socially problematic personality facets when stimulant use is reduced or ceased. Therefore, we examined the relation between changing intensity of cocaine use and the development of sociocognitive functioning and cluster B PD symptomatology over the course of 1 year.

Methods: Social cognition, social decision-making, and cluster B PD symptoms were assessed in 38 cocaine users (19 with increased and 19 with decreased use) and 48 stimulant-naive healthy controls at baseline and at 1-year follow-up. Cocaine use severity was objectively determined by quantitative 6-month hair analyses. The categorization of the two cocaine user groups was based on a combination of absolute (± 0.5 ng/mg) and relative (± 10%) changes in the cocaine hair concentration between baseline and the 1-year follow-up. Social cognition was assessed using the Multifaceted Empathy Test (MET) and the Movie for the Assessment of Social Cognition (MASC). A combined Distribution/Dictator Game was applied for assessing social decision-making. Cluster B PD symptoms were measured by a Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II) PD questionnaire according to *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV).

Results: Increased cocaine use was linked to worsened empathy, while decreased cocaine use went along with improved emotional empathy. Moreover, whereas decreased cocaine use was associated with reduced severity of self-reported cluster B PD symptoms, these symptoms remained largely stable in *increasers*. In contrast to a significant reduction of prosocial behavior at baseline in the combined cocaine user group, specifically *decreasers* were not statistically distinguishable from controls at the follow-up.

Conclusions: Sociocognitive deficits and cluster B PD symptoms of chronic cocaine users are adaptable over time as they covary with the increase or decrease in cocaine use. Hence, abstinence orientation and training of social cognition and interaction might improve social functioning, and should therefore be important therapeutic elements in cocaine addiction treatment.

Keywords: cocaine, stimulants, social cognition, empathy, Theory-of-Mind, social decision-making, cognition, personality disorder

INTRODUCTION

Neurocognitive deficits such as impaired attention, memory, and executive functions related to chronic cocaine use are well documented (1–3) and a risk factor for poor treatment outcomes (4, 5). While some studies investigated the linkage between these neurocognitive deficits and cocaine abstinence (6), only one study yet investigated the longitudinal relationship between cognitive impairments and changing cocaine use (7). In sum, these studies indicate that basal cognitive deficits in cocaine users seem to be largely drug-induced, remain stable during the first weeks of abstinence but likely improve after some months (8).

While nonsocial cognitive functions have been studied well during the last two decades, the systematic assessment of sociocognitive functioning in cocaine users has only recently emerged. Per definition, the concept of social cognition comprises not only abilities enabling the dynamic interaction with our social environments and include emotional and mental perspective-taking functions such as emotion recognition, emotional empathy (EE), and *Theory-of-Mind*, but also interactive abilities such as social decision-making (SDM), moral behavior, and social network behavior (9, 10). As daily-life social functioning strongly depends on intact social cognition and as the deteriorative impact of sociocognitive impairments on development, progress, and prognosis on other psychiatric disorders such as schizophrenia is well known (11), a close relationship between sociocognitive functioning and the origin and course of stimulant use disorders has been proposed (12–15). Accordingly, we previously demonstrated smaller social networks (16), reduced EE (16), altered SDM (17), stronger detachment from social norms (14), and impaired emotion recognition from voices (18) in recreational and dependent cocaine user groups. Moreover, dependent cocaine users made more errors than controls in a video-based *Theory-of-Mind* task, with recreational cocaine users performing intermediate between the two groups (16). Finally, cocaine users show also blunted neuronal responses to implicit and explicit forms of social reward (19, 20). Notably, all these studies were implemented with a cross-sectional design, but no study has investigated the longitudinal development of sociocognitive functioning so far. Thus, it is unclear if sociocognitive impairments are predisposed or drug-induced and if they are reversible upon prolonged abstinence or reduction of drug use.

As social cognition is the sum of those processes that allow individuals to interact in interpersonal contexts (21), disturbed sociocognitive functioning leads to aberrant social behavior and, in excessive forms, to deviant personality characteristics and impaired interpersonal functioning (22, 23). Notably, cocaine-addicted individuals show an increased risk for concurrent cluster B personality disorders (PDs), mainly of the antisocial and borderline types (24, 25). A cluster B PD comorbidity is largely influential for cocaine addiction severity and treatment outcomes including pronounced executive function deficits (26), more intense cocaine intake, lower rates of treatment applications, and decreased probability of cocaine addiction remission (27, 28). Additionally, it was demonstrated that impulsivity and gambling decision-making, which are both closely related to cluster B PD pathologies (22, 29), covary with changes in the intensity of cocaine use over 1 year (30). Nonetheless, the longitudinal relation between cocaine use intensity and cluster B PD symptomatology has also not been investigated to date.

In sum, only little is known about the temporal dynamics between cocaine use intensity and sociocognitive functioning. Hence, in order to investigate whether the described sociocognitive impairments and comorbid cluster B PD symptomatology in chronic cocaine users are modulated by the increase or decrease in cocaine abuse, we performed a longitudinal study with an interval of 1 year. Thereby, we compared 48 psychostimulant-naive controls with 19 cocaine users with decreased use (*decreasers*) and 19 cocaine users with increased use (*increasers*) after a 1-year interval. To objectively assess the severity and change in cocaine use and to control for co-use of other drugs, we performed quantitative hair and urine toxicology analyses at baseline and follow-up. Considering our previous results from the present sample that changes in basal cognitive functions and impulsivity clearly covary with cocaine use intensity over time (7, 30), we hypothesized that escalating cocaine use is also associated with aggravation of sociocognitive impairments and more cluster B PD symptoms within 1 year. *Vice versa*, we also expected that reduced cocaine use is linked to a reduction of sociocognitive deficits and cluster B PD symptomatology. To test these hypotheses, we expect significant time × group interactions specifically between *decreasers* and *increasers*. Given that at baseline cocaine users displayed significant alterations in EE, social network size, prosocial behavior in money distribution games, *Theory-of-Mind,* and cluster B PD symptoms (14, 16, 17), the longitudinal analysis was focused solely on these parameters.

METHODS

Participants

From a baseline sample of 234 participants (96 healthy stimulant-naive controls, 138 cocaine users) (3, 16, 17), 48 healthy stimulant-naive controls and 38 chronic cocaine users were included in the present longitudinal study. This subsample has been published twice previously but with different outcome measures (7, 30). From the baseline sample, 102 participants could not be measured at the follow-up because of unavailability (i.e., not responding to the invitation, loss of interest, lack of time, death), 27 participants had to be excluded from the final analyses as hair analyses revealed drug use not allowed by our exclusion criteria (e.g., polysubstance use, change in drug preferences), and 19 cocaine users did not meet our cocaine use criteria [see also the cocaine user group assignment below; for further recruitment and selection details, please see Ref. (7)].

At baseline, general exclusion criteria were clinically significant somatic diseases, neurological disorders, head injuries, family history of schizophrenia/obsessive-compulsive disorder/bipolar disorder, or any medication affecting the central nervous system. Additional exclusion criteria for controls were *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) axis I psychiatric disorders (excluding nicotine dependence) and regular illegal drug use (>15 lifetime occasions, except for recreational cannabis use). Additional exclusion criteria for cocaine users were a history of heroin use, polysubstance use, or DSM-IV axis I psychiatric disorders (except for cocaine, nicotine, cannabis, and alcohol abuse/dependence, attention deficit hyperactivity disorder, and a previous episode of an affective disorder). At baseline, inclusion criteria for cocaine users were cocaine use of >0.5 g per month, cocaine as primary drug, and an abstinence duration of <6 months. Participants were asked to abstain from illegal substances for at least 72 h and from alcohol for 24 h before the test sessions. Compliance with these instructions was controlled by urine screenings (semiquantitative enzyme multiplied immunoassay method). The study was approved by the Cantonal Ethics Committee of Zurich. All participants provided written informed-consent statements and were compensated for their participation.

Cocaine User Group Assignment

The categorization of the two cocaine user groups was based on changes of cocaine concentration in hair samples as determined by liquid chromatography–tandem mass spectrometry [for technical details, see Ref. (3)]. If possible, 6-cm hair samples were drawn covering the previous drug use of approximately 6 months. Cocaine users were categorized based on a combination of absolute (±0.5 ng/mg) and relative (>10% increase/decrease) changes in the hair concentration of $cocaine_{total}$ between baseline and the 1-year follow-up (7, 30, 31). According to these criteria, cocaine users were divided into three equally sized groups: 19 cocaine *increasers* [mean ± SD: +30.4 ± 61.9 ng/mg (+297%), range: +0.5 to +268.5 ng/mg (+20% to +5,374%)], 19 cocaine *decreasers* [−10.6 ± 26.7 ng/mg (−72%), −116.9 to −0.6 ng/mg (−100% to −12%)]), and 19 users with a relatively low and stable cocaine use pattern who did not meet both criteria [−0.1 ± 0.5 ng/mg (−2%), −1.9 to +0.5 ng/mg (−100% to +720%)], and, thus, were not further analyzed in this study [for further details, see Ref. (7)].

Procedure

At baseline, self-reported drug use was assessed with a structured and standardized Interview for Psychotropic Drug Consumption (32), attention deficit hyperactivity disorder (ADHD) symptoms were assessed with the ADHD Self-Rating Scale (ADHD-SR) (33), and the Structured Clinical Interview for DSM-IV axis I disorders (SCID-I) (34) was carried out by trained psychologists.

The test battery was assessed at baseline and follow-up and included the Multifaceted Empathy Test (MET) (35) assessing EE, the Movie for the Assessment of Social Cognition (MASC) (36) for the measurement of *Theory-of-Mind*, a Distribution/Dictator Game (37, 38) for the determination of prosocial behavior, the Social Network Questionnaire (SNQ) (39) measuring the social network size, and the SCID-II questionnaire (40) in order to ascertain cluster B PD symptoms. More detailed test descriptions published already in our previous work (16, 17) are given in **Methods S1.**

Statistical Analysis

Effect sizes and power analyses were calculated with G*Power 3.1 (41). As our previous analyses showed an effect size of $_p\eta^2 = 0.12$ (Cohen's f = 0.37) and a power of 99% for the significant interaction in the domain of working memory between *decreasers* and *increasers* (two groups, $p < .05$, two measurements) for the present sample (7), we assumed a more conservative effect size of $_p\eta^2 = 0.06$ (f = 0.25) and calculated a still acceptable power of 86% for the detection of significant interactions in sociocognitive functions in the present sample.

In order to reduce data quantity [see also Ref. (17)], we computed an SDM composite score that was derived by averaging z-transformed payoffs for the other player in the Distribution and Dictator Game (payoffs B) according to the means and standard deviations of the control group. Because of a strong correlation of the explicit and implicit EE scores from the MET in the total sample ($r = 0.86$, $p < .001$), we further integrated both parameters by adding them up into a single MET EE score. The SCID-II Cluster B symptom score was calculated by summing up the dimensional values from histrionic, narcissistic, borderline, and antisocial PD.

Group differences in demographic data and drug use patterns were analyzed by means of Pearson's chi-squared tests, analyses of variance (ANOVA), or independent Student's t-tests. For the longitudinal analysis and in order to investigate group differences over all groups, we performed a multiple linear regression (forced entry) with the test score change values ($\Delta = t2 - t1$) as dependent variables and four preselected independent variables: age, sex, ADHS-SR score, and dummy-coded (zero/one) group contrasts. The two demographic variables were included because previous findings suggest a linkage between advancing age and fairness in stimulant users (17) and due to known gender effects in social cognition/functioning (42, 43). Moreover, because ADHD has previously been linked to cognitive and sociocognitive

performance in cocaine users (3, 16, 44), this variable was further included as a predictor into the regression model. To compare the groups, cocaine *increasers* acted as the reference group. To further analyze test score changes within the single groups (value t2 vs. value t1), we applied dependent Student's t-tests (t_{dep}). To compare the effect of changing cocaine use, we applied independent Student's t-tests (t_{ind}) between controls and a combined cocaine user sample (CCU = *increasers* + *decreasers*) at baseline as well as between controls, cocaine *increasers*, and cocaine *decreasers* at the follow-up. Notably, at baseline, cocaine *increasers* and *decreasers* showed comparable baseline values in all reported test parameters (MET, MASC, SDM, SNQ, SCID-II Cluster B) differing only with very small effect sizes ($t_{ind}(32–35)$ = 0.05–0.34, p = .99–.74, d = 0.00–0.11). In the test parameter analysis, frequency data were analyzed by the Fisher–Freeman–Halton Exact Test (FET) (45). To test for test–retest effects, we applied the Pearson product-moment correlation analyses. The confirmatory statistical comparisons were carried out on a significance level of $p < .05$ (two-tailed).

RESULTS

Demographic characteristics and drug use: As shown before (7, 30), the three experimental groups did not significantly differ regarding age, sex distribution, verbal IQ, years of education, length of study interval (**Table 1**), and socioeconomic status (**Table S1**). Still, cocaine-using groups showed significantly higher BDI and ADHD-SR sum scores than controls at baseline (7, 30). Whereas at baseline both cocaine user groups showed comparable cocaine use severity, the $cocaine_{total}$ hair concentrations for *increasers* (~3-fold increase) and *decreasers* (reduction by the factor 3.5) were significantly different at follow-up. Moreover, hair data revealed a clear preference for cocaine use compared to other illegal drugs. Finally, in both user groups, 8 of 19 participants sought psychiatric or psychological treatment during the study interval. The other cocaine users did not report any related treatment between baseline and follow-up.

Emotional empathy: The introduced predictors explained a significant amount of variance of the EE change scores in the multiple regression analysis [$F(5,80) = 2.68$, $p < .05$, $R^2 = .14$; **Table 2**]. The strongest predictors were sex ($\beta = -0.25$, $p < .05$) and the group contrast cocaine *increasers* vs. *decreasers* ($\beta = -0.25$, $p < .05$; **Figure 1**). *Post hoc* analyses showed that controls and the combined cocaine user (CCU) group showed a nonsignificant difference in EE with a small to moderate effect size at baseline [$t_{ind}(84) = 1.78$, p = .08, d = 0.39]. Whereas in the 1-year interval, *increasers* slightly reduced their already hampered EE [$t_{dep}(18) = 1.19$, p = .25 d = 0.27], and cocaine *decreasers* moderately improved their ability to respond empathically [$t_{dep}(18) = 1.80$, p = .09, d = 0.41]. Notably, controls remained largely stable in EE [$t_{dep}(47) = 0.98$, p = .33, d = 0.14]. Accordingly, at follow-up, controls differed significantly from the *increaser* group [$t_{ind}(25) = 2.14$, $p < .05$, d = 0.64], whereas the difference between controls and *decreasers* was strongly reduced [$t_{ind}(65) = 0.40$, p = .69, d = 0.11]. Finally, at follow-up, *increasers* and *decreasers* displayed a nonsignificant group difference of moderate effect size [$t_{ind}(36) = 1.69$, p = .10, d = 0.56].

Theory-of-Mind: The applied multiple regression model could not predict the MASC total error change scores (**Table 2**). At the phenomenological level, both cocaine user groups displayed small test–retest improvements [*increasers*: $t_{dep}(18) = 1.12$, p = .28, d = 0.26; *decreasers*: $t_{dep}(17) = 0.60$, p = .56, d = 0.14], while the control group showed pronounced improvements [$t_{dep}(47) = 4.68$, $p < .001$, d = 0.68; **Figure 2**).

Social interaction: The multiple regression model was also not able to predict the SDM composite change score (**Table 2**). From the phenomenological perspective, controls and *increasers* acted less prosocial (giving less money to the opponent), while *decreasers* remained stable but, with that, came closer to the controls (**Figure 3**). Exploratory *post hoc* analyses confirmed that controls and CCU significantly differed at baseline [$t_{ind}(65) = 2.51$, $p < .05$, d = 0.56]. At follow-up, controls and *increasers* still display a moderate group difference [$t_{ind}(65) = 1.92$, p = .06, d = 0.50], whereas the group difference between controls and *decreasers* was reduced to a small effect size [$t_{ind}(64) = 0.98$, p = .33, d = 0.26]. In addition, we analyzed behavioral changes between baseline and follow-up (more prosocial decisions, more self-serving decisions, similar decision) only in cocaine users and found that about two-thirds of the *increasers* (58% = 11/19) but only one-third of the *decreasers* (33% = 6/18) showed more self-serving decisions at follow-up (p = .40; FET; **Figure S1**).

Social network size: Regarding the SNQ total network size, the multiple regression model could again not substantially predict the change scores (**Table 2**, **Figure 4**). Interestingly, during the 1-year interval, all three groups reported a substantial and moderate social network reduction of about 2.5 contacts [controls: $t_{dep}(47) = 3.75$, $p < .001$, d = 0.54; *increasers*: $t_{dep}(17) = 1.94$, p = .70, d = 0.46; *decreasers*: $t_{dep}(17) = 3.09$, $p < .01$, d = 0.73].

Cluster B PD: The regression model significantly explained the variance in cluster B PD symptom change [$F(5,77) = 3.25$, $p < .01$, $R^2 = .17$; **Table 2**]. This change score was best predicted by the ADHS-SR score ($\beta = -0.32$, $p < .01$) and the group contrasts cocaine *increasers* vs. *decreasers* ($\beta = 0.34$, $p < .01$) and cocaine *increasers* vs. controls ($\beta = 0.31$, $p < .01$). Importantly, the CCU group showed at baseline significantly more cluster B PD symptoms than the controls [$t_{ind}(81) = 4.40$, $p < .001$, d = 0.96; **Figure 5**]. Whereas controls [$t_{dep}(47) = 4.91$, $p < .001$, d = 0.71] and *decreasers* [$t_{dep}(17) = 3.55$, $p < .01$, d = 0.84] had significantly lower symptom scores after the 1-year interval period, the amount of symptoms for the *increaser* group remained largely stable [$t_{dep}(16) = 0.52$, p = .61, d = 0.13]. Accordingly, at follow-up, controls differed strongly from the *increasers* [$t_{ind}(19) = 4.70$, $p < .001$, d = 1.58] and from the *decreasers* [$t_{ind}(22) = 3.11$, $p < .01$, d = 0.96]. Interestingly, already after 1 year of different cocaine use, *increasers* and *decreasers* displayed a moderate to strong group difference in cluster B PD symptoms at follow-up [$t_{ind}(33) = 1.85$, p = .07, d = 0.63]. Of note, approximately three quarters of the *decreasers* (13/18) displayed lower cluster B PD scores, while more than half of the cocaine *increasers* (9/17) showed even more symptoms at follow-up ($p < .05$; FET; **Figure S2**).

Remarkably, the interaction effect on cluster B PD symptoms was mainly driven by changes in the narcissistic and borderline subscores and less by the histrionic and surprisingly also not by the antisocial subscore (see **Figure S3a–d**). Both the narcissistic

TABLE 1 | Demographic data and pattern of cocaine use.

	Baseline (t1)						1-year follow-up (t2)[m]					
	Controls (n = 48)	**Cocaine Increaser (n = 19)**	**Cocaine Decreaser (n = 19)**	**F/χ^2/T**	**df, df_{err}**	**p**	**Controls (n = 48)**	**Cocaine Increaser (n = 19)**	**Cocaine Decreaser (n = 19)**	**F/χ^2/T**	**df, df_{err}**	**p**
Age, years	30.3 (8.9)	31.5 (9.4)	31.4 (8.3)	.20[a]	2,83	.82						
Sex (f/m)	16/32	3/16	5/14	2.11[b]	2	.35						
Verbal IQ (MWT-B)[d]	107.6 (10.0)	102.9 (9.7)	103.8 (7.1)	2.20[a]	2,83	.12						
Education, years	10.8 (1.8)	10.4 (1.8)	10.0 (1.5)	1.30[a]	2,83	.28						
ADHD-SR score (0-22)	7.7 (5.2)	13.5 (9.4)**	14.1 (6.8)**	8.83[a]	2,83	**<.001**						
ADHD DSM IV (y/n)[e]	0/48	4/15	3/16	7.02[b]	2	**.03**						
Weeks between t1 and t2	58.2 (10.1)	59.3 (12.1)	61.9 (14.5)	.69[a]	2,83	.50						
BDI score (0–63)	3.5 (3.3)	7.3 (8.0)*	8.7 (6.5)**	7.53[a]	2,83	**<.001**						
BDI depression (y/n)[g]	0/48	1/18	1/18	2.59[b]	2	.27						
Cocaine												
Times per week[h]	–	1.6 (1.8)	1.0 (1.3)	1.17[c]	36	.25	–	1.1 (0.8)	0.3 (0.3)	3.85[c]	36	**<.001**
Grams per week[h]	–	2.0 (2.5)	1.7 (2.3)	.41[c]	36	.68	–	1.6 (2.5)	0.4 (0.4)	2.18[c]	36	**.04**
Years of use	–	7.0 (5.5)	8.2 (5.4)	.68[c]	36	.50	–	8.9 (5.4)	9.7 (5.2)	.45[c]	36	.65
Age of cocaine onset	–	24.5 (8.1)	23.1 (5.2)	.61[c]	36	.54						
Max. dose (g/day)[k]	–	4.7 (4.4)	5.9 (6.4)	.71[c]	36	.48	–	3.7 (2.5)	3.1 (2.8)	.63[c]	36	.53
Cumulative dose (g)[k]	–	1182 (1635)	3698 (8585)	1.25[c]	36	.22	–	91 (119)	49 (89)	1.25[c]	36	.22
Last consumption (days)	–	18.5 (25.1)	16.8 (14.6)	.29[c]	36	.77	–	7.0 (6.3)	81.4 (145.1)	2.23[c]	36	**.03**
Cocaine craving (0–70)[i]	–	19.8 (9.5)	17.7 (7.2)	.79[c]	36	.44	–	20.5 (10.8)	15.8 (6.2)	1.66[c]	36	.11
Hair analysis (ng/mg)[l]												
$Cocaine_{total}$	–	10.3 (29.2)	14.9 (32.2)	.46[c]	36	.65	–	40.7 (76.1)	4.2 (8.2)	2.08[c]	36	**.05**
Cocaine	–	8.2 (23.3)	11.4 (23.9)	.42[c]	36	.68	–	31.7 (56.5)	3.1 (5.9)	2.19[c]	36	**.03**
Benzoylecgonine	–	1.9 (5.5)	3.1 (7.6)	.58[c]	36	.56	–	8.3 (19.6)	1.0 (2.2)	1.62[c]	36	.11
Cocaethylene	–	1.0 (2.8)	0.9 (2.8)	.11[c]	36	.91	–	1.2 (2.1)	0.3 (1.0)	1.56[c]	36	.13
$Norcocaine_t$	–	0.2 (0.5)	0.4 (0.8)	.83[c]	36	.41	–	0.6 (1.4)	0.1 (0.1)	1.71[c]	36	.10
Urine toxicology (n/p)[k]	48/0	14/5	16/3	.63[b]	1	.43	48/0	7/12	18/1	14.15[b]	1	**<.001**
Alcohol[n]												
Grams per week[h]	119.9 (136.8)	169.4 (129.2)	155.3 (146.4)	1.07[a]	2,83	.35	104.3 (88.6)	259.7 (244.5)***	127.4 (141.4)°	7.71[a]	2,83	**<.001**
Years of use	13.3 (8.8)	13.7 (7.6)	12.0 (7.3)	.23[a]	2,83	.79	14.0 (8.7)	14.8 (7.5)	12.6 (7.9)	.34[a]	2,83	.71
Nicotine[n]												
Smoking (y/n)[f]	37/11	14/5	14/5	.13[b]	2	.94	40/8	15/4	13/6	1.83[b]	2	.40
Cigarettes per day[h]	8.7 (8.7)	12.8 (11.2)	9.5 (8.2)	1.38[a]	2,83	.26	8.2 (8.7)	13.4 (12.0)	8.2 (7.8)	2.31[a]	2,83	.11
Years of use	9.3 (8.3)	10.4 (8.9)	12.7 (10.3)	.95[a]	2,83	.39	10.5 (8.8)	12.5 (8.6)	12.6 (9.9)	.56[a]	2,83	.57
Cannabis[n]												
Grams per week[h]	0.6 (1.6)	3.3 (8.9)	1.2 (2.3)	2.38[a]	2,83	.10	0.5 (1.6)	2.1 (4.6)	1.1 (2.7)	2.28[a]	2,83	.11
Years of use	4.5 (4.9)	9.5 (8.5)*	10.1 (9.7)*	5.92[a]	2,83	**.004**	4.6 (5.9)	10.5 (9.8)*	8.6 (9.7)	4.64[a]	2,83	**.01**
Cumulative dose (grams)	980 (3985)	3199 (5899)	2606 (6359)	1.61[a]	2,83	.21	53.4 (180)	217.8 (526.5)	84.7 (189.6)	2.15[a]	2,83	.12
Last consumption (days)[j]	39.3 (1.6);n = 22	10.0 (0.4);n = 14	25.4 (1.1);n = 12	2.19[a]	2,45	.12	36.5 (1.5);n = 22	9.7 (0.4);n = 13	50.8 (2.1);n = 10	1.20[a]	2,42	.31
Urine toxicology (n/p)[k]	42/6	15/4	14/5	2.03[b]	2	.36	42/6	7/12	15/4	18.61[b]	2	**<.001**
Amphetamine[n]												
Grams per week[h]	0.0 (0.1)	0.1 (0.1)**	0.0 (0.1)	5.18[a]	2,83	**.008**	0.0 (0.0)	0.1 (0.2)**	0.0 (0.1)	5.89[a]	2,83	**.004**
Years of use	0.0 (0.0)	3.3 (4.0)***	1.3 (3.1)°	13.73[a]	2,83	**<.001**	0.1 (0.5)	3.2 (4.9)**	2.7 (5.5)*	7.46[a]	2,83	**.001**
Cumulative dose (grams)	0.0 (0.1)	56.0 (177.6)*	16.2 (35.9)	2.99[a]	2,83	.06	0.0 (0.1)	4.4 (8.9)**	1.4 (3.5)	6.47[a]	2,83	**.002**
Last consumption (days)[j]	121.6 (5.1);n = 1	73.6 (3.1);n = 10	90.9 (3.8);n = 3	.29[a]	2,11	.75	17.5 (0.7);n = 1	35.7 (1.5);n = 8	99.8 (4.2);n = 4	1.48[a]	2,10	.27
Hair analysis (ng/mg)	0.0 (0.0)	0.1 (0.2)*	0.0 (0.0)	4.35[a]	2,83	**.02**	0.0 (0.0)	0.1 (0.2)	0.1 (0.2)	2.89[a]	2,83	.06

(Continued)

TABLE 1 | Continued

	Baseline (t1)						1-year follow-up (t2)[m]					
	Controls (n = 48)	**Cocaine Increaser (n = 19)**	**Cocaine Decreaser (n = 19)**	**F/χ^2/T**	**df, df_{err}**	**p**	**Controls (n = 48)**	**Cocaine Increaser (n = 19)**	**Cocaine Decreaser (n = 19)**	**F/χ^2/T**	**df, df_{err}**	**p**
MDMA[n]												
Tablets per week[h]	0.0 (0.0)	0.0 (0.1)***	0.0 (0.0)°	7.42[a]	2,83	**.001**	0.0 (0.0)	0.4 (0.9)**	0.0 (0.0)°	5.54[a]	2,83	**.006**
Years of use	0.3 (1.0)	3.5 (4.5)***	2.4 (4.6)*	8.42[a]	2,83	**<.001**	0.2 (1.4)	3.8 (5.5)**	3.2 (5.6)*	7.78[a]	2,83	**<.001**
Cumulative dose (tablets)	1.3 (4.0)	108.8 (249.7)**	18.7 (46.2)	5.71[a]	2,83	**.005**	0.2 (0.8)	17.0 (49.3)*	2.8 (5.2)	3.67[a]	2,83	**.03**
Last consumption (days)[j]	5.0 (0.2);n = 1	89.9 (3.7);n = 7	40.2 (1.7);n = 4	1.63[a]	2,9	.25	91.2 (3.8);n = 3	41.6 (1.7);n = 6	47.8 (2.0);n = 5	1.11[a]	2,11	.36
Hair analysis (ng/mg)	0.0 (0.0)	0.3 (0.7)	0.4 (1.5)	2.23[a]	2,83	.11	0.0 (0.0)	0.5 (0.8)***	0.1 (0.3)	7.87[a]	2,83	**<.001**
GHB[n]												
Cumulative dose (pipettes)	0.0 (0.0)	0.5 (0.7)	0.5 (1.7)	3.36[a]	2,83	**.04**	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	–	–	–
Hallucinogens[n]												
Cumulative dose (times)	0.9 (2.2)	27.9 (72.8)*	9.9 (22.9)	3.92[a]	2,83	**.02**	0.0 (0.0)	1.1 (1.6)***	0.6 (1.5)	8.57[a]	2,83	**<.001**
Methlyphenidate[n]												
Cumulative dose (tablets)	0.0 (0.0)	20.2 (60.4)*	0.5 (2.3)	3.76[a]	2,83	**.03**	0.0 (0.1)	67.7 (239.5)	0.3 (0.6)	2.72[a]	2,83	.07
Hair analysis (ng/mg)	0.0 (0.0)	0.0 (0.1)	0.0 (0.0)	1.80[a]	2,83	.17	0.0 (0.0)	0.1 (0.2)*	0.0 (0.0)	3.62[a]	2,83	**.03**

Means and standard deviations. Significant p values are shown in bold.

[a]*ANOVA (all groups, with significant Sidak post hoc test vs. control group: *p < .05; **p < .01; ***p < .001; vs. cocaine increaser: °p < .05).*

[b] *χ^2-test (all groups/cocaine users only) for frequency data.*

[c]*Independent t-test (cocaine users only).*

[d]*Verbal IQ was assessed by the Mehrfachwahl Wortschatz Intelligenztest (46).*

[e]*ADHD-SR, ADHD self-rating scale (cutoff DSM-IV criteria) (33).*

[f]*Smoking habits were assessed by the Fagerstroem Test of Nicotine Dependence (47).*

[g]*BDI, Beck Depression Inventory (cutoff ≥ 18) (48).*

[h]*Average use during the last 6 months.*

[i]*Craving for cocaine was assessed by the Brief-CCQ (49).*

[j]*Last consumption is averaged only for persons who used the drug in the last 6 months.*

[k]*Urine toxicology (neg/pos) are based on the cutoff value for cocaine = 150 ng/ml and for tetrahydrocannabinol 50 ng/ml (50). The χ^2-test for cocaine includes only cocaine users; the χ^2-test for cannabis includes controls and cocaine users.*

[l]*Hair samples were voluntary and data are missing for three controls.*

[m]*Parameters at follow-up refer to the 1-year period between t1 and t2.*

[n]*At baseline, average use during the last 6 months. Use frequency, duration of use, and cumulative doses are averaged within the total group.*

TABLE 2 | Multiple regression analyses.

	Emotional empathy Δ MET Emotional empathy			Theory-of-Mind Δ MASC total errors			Social interaction Δ SDM composite score			Social network Δ SNQ network size			Personality disorder Δ SCID-II Cluster B		
	B	SE	β	B	SE	β	B	SE	β	B	SE	β	B	SE	β
Constant	1.55	1.14		−1.85	2.02		−0.26	0.45		−0.73	2.72		−1.01	2.80	
Age	0.04	0.03	0.14	0.06	0.05	0.14	−0.01	0.01	−0.08	−0.04	0.06	−0.08	0.02	0.06	0.04
Sex	−1.16	0.50	−0.25*	−0.99	0.86	−0.12	0.09	0.20	0.05	−0.56	1.20	−0.05	−0.71	1.23	−0.06
ADHD-SR score	−0.05	0.03	−0.16	−0.07	0.06	−0.14	0.00	0.01	−0.01	0.04	0.08	0.05	−0.24	0.08	−0.32**
Controls vs. cocaine increaser	−0.26	0.59	−0.05	1.71	1.03	0.20	0.03	0.24	0.01	0.35	1.43	0.03	4.00	1.49	0.31**
Cocaine decreaser vs. cocaine increaser	−1.30	0.66	−0.25*	−0.51	1.17	−0.06	−0.31	0.27	−0.16	0.54	1.63	0.05	4.43	1.69	0.34**
R^2		0.14			0.10			0.03			0.01			0.17	
F		2.68*			1.67			0.57			0.22			3.25**	

Multiple linear regression with the independent variables age, sex, ADHS-SR score, and dummy coded (zero, one) group variables. To compare the groups, cocaine increaser acted as the reference group. Dependent variables are change values (Δ = value at t2 − value at t1).

B, unstandardized regression coefficient; SE, unstandardized standard error; β, standardized beta.

*(*)p < .10; *p < .05; **p < .01; ***p < .001.*

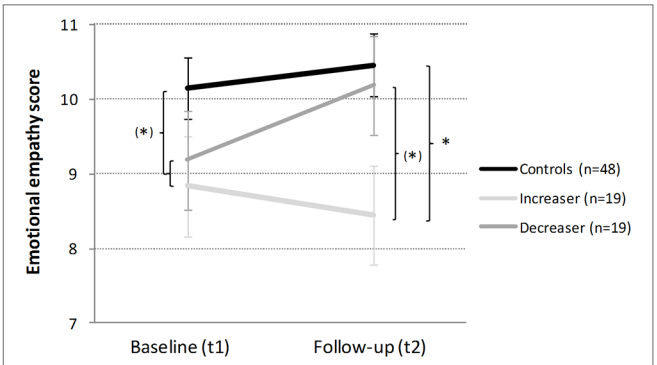

FIGURE 1 | Development of emotional empathy in cocaine *increasers*, *decreasers*, and stimulant-naive controls within 1 year. Mean emotional empathy sum scores and standard errors. At baseline, controls vs combined cocaine user (CCU) (= Ø of increaser and decreaser). Independent Student's t-tests are shown if p < .10. (*)p < .10; *p < .05.

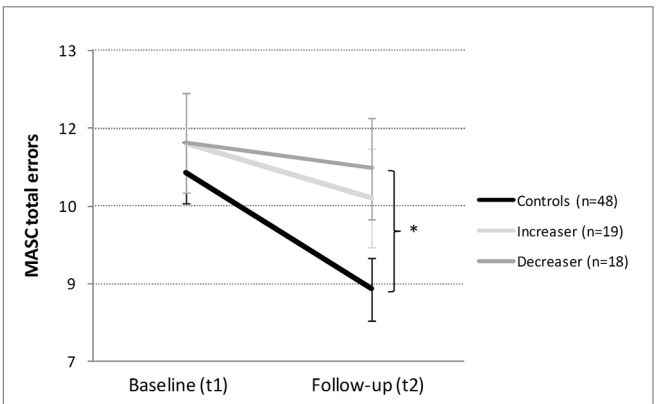

FIGURE 2 | Development of the *Theory-of-Mind* in cocaine *increasers*, *decreasers*, and stimulant-naive controls within 1 year. Mean Movie for the Assessment of Social Cognition (MASC) total errors and standard errors. At baseline, controls vs CCU (= Ø of increaser and decreaser). Independent Student's t-tests are shown if p < .10. *p < .05.

and the borderline subscores revealed significant regression models (**Table S2**), but only the borderline subscore was significantly predicted by the group contrast cocaine *increasers* vs. *decreasers* (β = 0.40, p < .01). Compared to baseline, less symptoms occurred in controls [$t_{dep}(47) = 4.99$, p < .001, d = 0.72] and *decreasers* [$t_{dep}(17) = 3.16$, p < .01, d = 0.75] at follow-up, while symptoms remained stable in *increasers* [$t_{dep}(16) = 0.18$, p = .86, d = 0.04], resulting in a strong group effect between *increasers* and *decreasers* [$t_{ind}(33) = 2.57$, p < .05, d = 0.87] at follow-up.

Change in alcohol use: As not only cocaine but also alcohol intake was increased in *increasers* (see **Table 1**), the change in alcohol consumption was considered in additional multiple regression models. However, alcohol change was not significant in any of the main regression models (p-values ranged from .222 to .659) shown in **Table 2**, while the interaction effects and also the explained variances remained stable, indicating that changes in alcohol consumption have not impacted our main results.

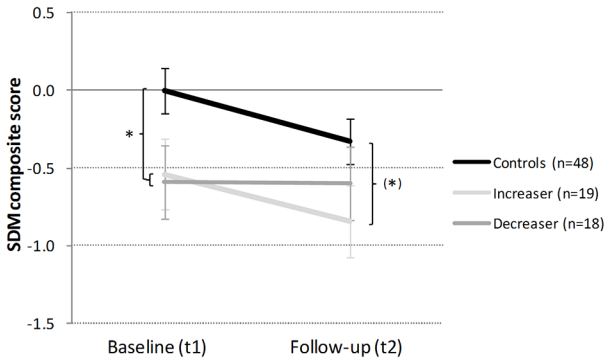

FIGURE 3 | Development of social interaction in cocaine *increasers*, *decreasers*, and stimulant-naive controls within 1 year. Mean social decision-making (SDM) composite z-scores and standard errors. At baseline, controls vs CCU (= Ø of increaser and decreaser). Independent Student's t-tests are shown if $p < .10$. $^{(*)}p < .10$; $^{*}p < .05$.

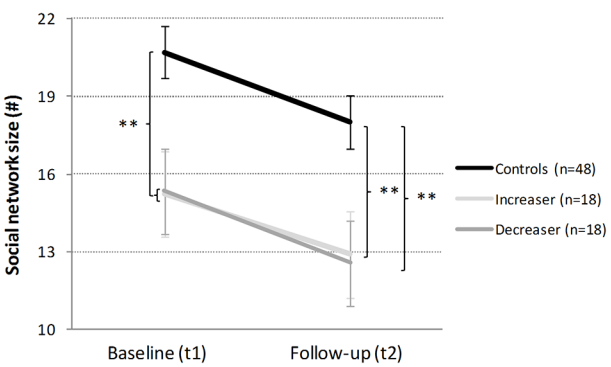

FIGURE 4 | Development of social network size in cocaine *increasers*, *decreasers*, and stimulant-naive controls within 1 year. Mean total network size and standard errors. At baseline, controls vs CCU (= Ø of increaser and decreaser). Independent Student's t-tests are shown if $p < .10$. $^{**}p < .01$.

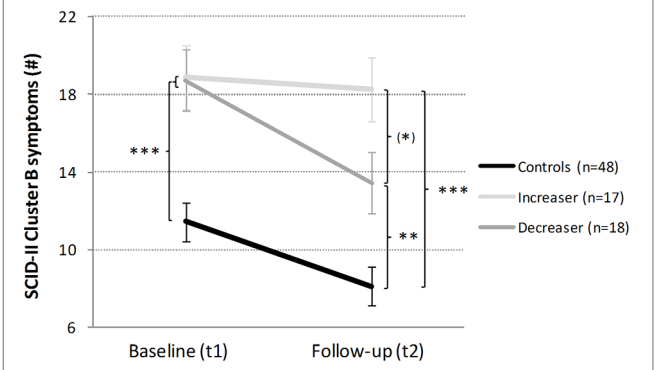

FIGURE 5 | Development of Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II) Cluster B in cocaine *increasers*, *decreasers*, and stimulant-naive controls within 1 year. Mean SCID-II Cluster B symptoms and standard errors. At baseline, controls vs CCU (= Ø of increaser and decreaser). Independent Student's t-tests are shown if $p < .10$. $^{(*)}p < .10$; $^{**}p < .01$; $^{***}p < .001$.

TABLE 3 | One-year test–retest reliability between baseline and 1-year follow-up in controls and cocaine users.

	Controls (n = 48)	Combined cocaine users (n = 38)	Total sample (n = 86)
MET Emotional empathy score	0.66***	0.79***	0.74***
MASC total errors	0.67***	0.60***	0.63***
SDM composite score	0.48***	0.85***	0.70***
SNQ network size	0.75***	0.81***	0.80***
SCID-II Cluster B symptoms	0.68***	0.74***	0.77***

*Pearson's product-moment correlation. Significance level: ***p < .001.*

Test–retest reliability: In the total sample, all dependent variables displayed acceptable to good test–retest reliabilities (**Table 3**). Interestingly, in the SDM paradigm, controls and CCU differed significantly in their test–retest reliability ($z = -3.25$; $p < .001$): While in controls the SDM score showed hardly acceptable reliability ($r = 0.48$; $p < .001$), it was good in the cocaine users ($r = 0.85$; $p < .001$).

DISCUSSION

The present longitudinal study investigated the change of social cognition, social interaction, and socially relevant cluster B PD symptoms in healthy controls and relatively pure and non-help-seeking chronic cocaine users who clearly increased or decreased their cocaine consumption during a 1-year study interval. The most striking findings were that i) improved EE correlated with decreased cocaine consumption, whereas increased cocaine use severity was linked to less EE; and ii) cluster B PD symptom burden was lowered in *decreasers,* whereas *increasers* showed stable severity in these symptoms. Additionally, during the study interval, we found an approximation between controls and *decreasers* regarding their prosocial behavior, while the large gap between *increasers* and controls remained. Moreover, neither the *Theory-of-Mind* Task (MASC) nor the social network size showed interactions with changing cocaine use, indicating that mental perspective-taking (sometimes also interpreted as *cognitive empathy*) and the number of social contacts in the last months were not affected by changing drug use during the study interval.

Importantly, the present analysis of smaller (longitudinal) subgroups from our larger cross-sectional ZuCo²St sample published previously (14, 16, 17) still showed significantly reduced prosocial behavior, a smaller social network, and strongly elevated cluster B personality symptoms in the total group of cocaine users at baseline, indicating that these indicators of social functioning were robustly altered in this population. The EE score of the MET showed only a statistical trend between cocaine users and controls at baseline, but the present effect size ($d = 0.39$) was in the range of the previously

reported effect sizes of the larger cross-sectional sample of recreational and dependent cocaine users (d = 0.39–0.64), suggesting rather a deficiency of power than a lack of reliability. This assumption is further supported by the fact that the MET EE score showed good test–retest reliability scores. Moreover, the MASC did not show any baseline group differences in the present subsample of cocaine users underscoring our previous conclusion that mainly very severe cocaine users with a putative ADHD comorbidity show disturbances in this task (16, 44).

While sociocognitive functions represent basic abilities in perspective-taking and interaction, more conventional psychopathology is aiming at the identification and quantification of symptoms in psychiatric disorders (51). As such, the research on the relationship between PDs and cocaine use is of special interest, as the differentiation between predispositions vs. drug-induced effects merges with the question if these pathologies are reversible or not. In our longitudinal investigation, we found that *decreasers* of cocaine consumption also significantly improved in cluster B PD symptoms during 1 year, whereas the increasers showed a stable PD symptom burden. This is insofar interesting as in both user groups 8 of 19 participants sought psychiatric treatment in the interval, but only *decreasers* improved in some social functions and socially relevant PD symptoms.

In general, PDs are defined as typical constellations of impaired subjective and behavioral traits that result in suffering of the affected individual and/or society (52). These personality traits are regarded as relatively stable across time and consistent across situations (diagnostically mandatory) (53–56). Moreover, cluster B PDs show a higher stability over 12 to 18 years than the other clusters (57). However, studies also found considerable variability of PD symptoms across individuals over time (58, 59), questioning the trait-like character of the disorder. An early study showed changes in PD symptoms related to treatment in substance-dependent patients (60). Interestingly, clusters A and C profited most, while cluster B changes were only observed in patients with borderline PD. In patients with cocaine addiction, cluster B PDs are the most frequent and these patients have the most severe courses of illness including worst treatment outcomes (24, 26–28, 61, 62). Therefore, cluster B PD symptoms are likely personality features that increase the risk for cocaine use and the development of an addiction. However, as seen in the present study, cluster B PD symptom load is nevertheless variable and reduction of consumption leads to a substantial improvement in these symptoms. Consequently, a reduction of cluster B PD symptom burden again increases likelihood of successful treatment, offering the patient an opportunity to leave the vicious circle of addiction.

The suggested consumption-dependent variability of social behavior as well as cluster B symptoms are well in line with our previous analyses from this sample that not only basal cognitive functions such as working memory but also self-reported impulsivity improve with a strong reduction of cocaine use, while they are worsened with increased cocaine consumption (7, 30). The present data and the previous analyses from this sample are also in accordance with our recent results from an independent longitudinal investigation showing that decreased cortical thickness (CT) of several regions within the prefrontal cortex of cocaine users can improve after a strong reduction of cocaine use, while sustained use went along with a further decrease in prefrontal CT during the study interval (63). Importantly, the cortical changes were correlated with cognitive changes, i.e., improved CT as associated with enhanced sustained attention (63). Thus, the overall pattern of change shown by longitudinal data supports our assumption that sociocognitive impairments of cocaine users are at least in part drug-induced and that neuroplastic changes in brain regions and neurotransmitter systems involved in social cognition, social interaction, and social reward processing contribute to a further decrease in social contact and social support leading to an increase in social isolation, aggression, and depressive symptoms. This ends in a further reduction of social reward resources, ongoing social withdrawal, and the establishment of cocaine as the main source of reward resulting in the maintenance of stimulant use and recurrent relapses (15).

While EE is more a perceptive social cognition ability, social decision-making (here assessed with a combined Distribution/Dictator Game) is a form of socially interactive behavior. In our previous cross-sectional analysis sample, cocaine users cared more about efficiency than about fairness compared to healthy controls at baseline (17). This was previously interpreted as predisposition of stimulant use (15), as such fairness preferences and severity of cocaine use were not correlated (17). Intriguingly, utilitarian and opportunistic attitudes assessed with the Machiavellianism Questionnaire (MACH-IV) were also increased in cocaine users compared to controls and were shown to be stable and independent of changing cocaine use (14). However, our data indicated a shift toward improved prosocial behavior in cocaine *decreasers* indicating space for enhancement potential by treatment. Conclusively, SDM deficits in cocaine users likely have both a trait and a state component, and it might be worse to specifically target the state component in therapy in order to improve the treatment outcome.

Limitations

When interpreting the present results, some limitations of our study have to be considered: i) The total sample size is moderate for a longitudinal analysis. Moreover, the test–retest reliabilities of the applied social cognition tasks and questionnaire have a broad range (in controls: r = 0.48–0.75; in cocaine users: r = 0.60–0.85; in the total sample: r = 0.63–0.80). As a consequence of both, the shown interaction effects are not very strong (in terms of p-values). However, to our knowledge, these are the only existing longitudinal samples of chronic cocaine users with objectively verified increasing and decreasing cocaine use (by hair testing). Moreover, the included individuals were preferably pure cocaine users with little axis-I psychiatric comorbidities. We therefore think that the carefully selected and homogeneous sample has nonetheless sufficient explanatory power. ii) In the context of our hypotheses, we attribute the changes in behavior to the changes in cocaine consumption. However, we cannot rule out if other changes in the lives of

our cocaine users (e.g., positive or negative changes in their social environment) not assessed by our test battery may have impacted both drug use and social functioning. Future studies should therefore assess more information on the social life of cocaine users beyond simple parameters such as social network size (e.g., social media use).

Conclusions

The aim of this longitudinal study was to investigate whether cocaine use is associated with permanent or reversible alterations of social cognition and interaction as well as cluster B PD symptoms. We found that specific social dysfunctions and PD symptoms are variable over time as they seem to depend on variations in cocaine use. Thus, strong reduction of cocaine use within only 1 year seems to positively affect social dysfunctions that are assumed to be crucial factor in the maintenance of stimulant addiction (15, 64). From our perspective, the shown positive effects of reduced cocaine use clearly favor abstinence-orientated treatment approaches of cocaine addiction. Furthermore, having the strong impact of social cognitive abilities as well as prosocial behavior and attitudes on the patient–therapist relationships in mind (15), future developments in the psychotherapy of cocaine addictions should consider trainings specifically of social skills and cognitions in order to improve treatment outcome.

ETHICS STATEMENT

The study was approved by the Cantonal Ethics Committee of Zurich, Switzerland.

AUTHOR CONTRIBUTIONS

BQ and MV had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. CE and BQ contributed to the study concept and design. CE, MV, OB, KP, LH, MB, and BQ contributed to the acquisition, analysis, or interpretation of data. OB, CE, MV, and BQ contributed to the drafting of the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content. MV and BQ conducted the statistical analysis. ES and BQ obtained funding. KP, LH, MV, and ES contributed to the administrative, technical, or material support. ES and BQ were in charge of supervision.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00213/full#supplementary-material.

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Emotion Processing, Reappraisal, and Craving in Alcohol Dependence: A Functional Magnetic Resonance Imaging Study

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Alcohol dependence has long been related to impaired emotion regulation—including reappraisal—but little is known about the performance and associated neural activity of alcohol-dependent patients (ADPs) on an emotion reappraisal task. This study, therefore, compares reappraisal of negative, positive, neutral, and alcohol-related images at a behavioral and neural level between ADPs and healthy controls (HCs).

Thirty-nine ADPs and 39 age-, gender-, and education-matched HCs performed an emotion reappraisal task during functional magnetic resonance imaging (fMRI), and craving was measured before and after the reappraisal task. During the emotion reappraisal task, participants were instructed to either attend or reappraise positive, negative, neutral, or alcohol-related images, and to indicate their experienced emotion on a visual analogue scale (VAS).

Both ADPs and HCs completed the emotion reappraisal task successfully, showing significant differences in self-reported experienced emotion after attending versus reappraising visual stimuli and in brain activity in emotion processing/reappraisal relevant areas. ADPs were not impaired in cognitive reappraisal at a behavioral or neural level relative to HCs, nor did ADPs indicate any difference in self-reported emotion while attending emotional images. However, ADPs were different from HC in emotion processing: ADPs revealed a blunted response in the (posterior) insula, precuneus, operculum, and superior temporal gyrus while attending emotional images compared neutral images compared to HCs, and in ADPs, higher baseline craving levels were associated with a less blunted response to alcohol-related images than in HCs. These results reveal that ADPs do not show impaired reappraisal abilities when *instructed*, although future studies should assess voluntary reappraisal abilities in alcohol-dependent patients.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier NCT02557815.

Keywords: alcohol dependence, emotion reappraisal, craving, functional magnetic resonance imaging, emotion regulation

INTRODUCTION

The ability to manage emotional information is central to our daily functioning, and adequately managing emotions is achieved through various emotion regulation strategies, including attention shifting and cognitive reappraisal, the process of moderating the emotional impact of a certain thought or stimulus through cognitive reinterpretation (1, 2). Neuroimaging studies using reappraisal tasks in healthy controls (HCs) indicate that the prefrontal cortex, including the dorsolateral prefrontal cortex (dlPFC), is vital for the *regulation* of emotions, whereas the limbic system—including the amygdala and insula—is important for the initial *processing* of emotions (1–4). Other brain areas related to reappraisal include the dorsomedial prefrontal cortex, superior temporal gyrus, dorsal part of the anterior cingulate cortex (ACC), superior parietal lobule, and inferior frontal gyrus (4). These brain regions are part of cognitive–linguistic control networks, associated with effortful (i.e., explicitly applied) reappraisal by cognitively reframing the affective meaning of a negative stimulus in more neutral terms (2, 5).

Impairments in reappraisal are supposed to be related to the development, persistence, and severity of substance dependence (6). Previous studies have indicated that difficulties in coping with negative affect is one of the most prominent clinical factors in substance dependence (7). The induction of negative affect may increase the urge to drink (8, 9), although a recent study failed to show such a relationship between emotional state and craving for alcohol-dependent individuals (10). Impaired emotional reappraisal also predicts negative outcomes, including relapse, in substance use disorder (SUD) patients (11, 12). A recent study showed impaired emotional reappraisal (ER) in Internet gaming disorder patients compared to drug-naïve controls, suggesting that impaired emotion reappraisal might precede neurotoxic effects of alcohol or other substances (13). Together, these studies indicate that emotional reappraisal is central in the etiology of alcohol dependence.

The results from the aforementioned studies on emotional reappraisal in substance dependence are further corroborated by a recent review on the neural circuitry of impaired reappraisal in patients with SUDs compared with HCs. This review showed decreased recruitment of the ACC, dlPFC, and ventromedial prefrontal cortex (vmPFC) during reappraisal, but no differences in amygdala or insular functioning (14). The review therefore concludes that emotion regulation disturbances in substance dependence are related to impaired prefrontal functioning and not to excessive reactivity to emotional stimuli.

Most studies reviewed by Wilcox et al. (14) did not apply an (explicit) reappraisal task, but included emotion reactivity, implicit reappraisal, or behavioral control tasks, and therefore little is known about the neural circuitry of explicit reappraisal in substance use disorders in general and more specifically in alcohol-dependent patients (ADPs). The available studies into emotion regulation in alcohol dependence reveal that impaired emotion regulation is associated with increased craving levels, especially for ADPs who experience increased negative and decreased positive affect (15). Furthermore, interview data demonstrate that ADPs show reduced use of effortful cognitive emotion regulation and tend to apply less beneficial emotion regulation strategies like response modulation and attentional deployment strategies in daily life (16). ADPs also report problems with the identification and regulation of emotions (17), which are linked to the duration of the last heavy drinking episode, as well as higher drinking rates at 1-year follow-up (18). It is currently not clear, however, whether ADPs perform differently on an explicit cognitive reappraisal task and whether related brain activity is different.

The review by Wilcox et al. (14) further concludes that no differences were found in the limbic system, indicating that impaired reappraisal may originate from prefrontal impairments rather than from an excessive response to emotional stimuli. Some studies even point toward lower limbic responsivity to emotional stimuli in SUDs (19, 20), which fits with the findings regarding reduced salience of natural reinforcing stimuli, relative to addiction-relevant stimuli (21).

The current study is the first to assess differences in cognitive reappraisal abilities between ADPs and HCs at the behavioral and the neural level. We hypothesize that ADPs show decreased reappraisal abilities compared to HCs, indicated by self-report scores on a visual analogue scale (state), an emotion regulation questionnaire (trait). Reduced ER-related brain activity in areas such as the dlPFC and ACC is mainly expected for the reappraisal of negative emotion, which has been implicated in substance dependence (22), whereas the ER of alcohol-related images may either result in lower activity [in line with findings from Wilcox et al. (14)] or higher activity (due to increased cognitive load associated with higher salience of these images). We furthermore hypothesize no differences in brain activity during emotional processing of negative and positive images, but greater activations to alcohol-related images in ADPs compared to HCs. Finally, we expect craving levels to increase due to the emotion reappraisal task, and that craving is negatively related to cognitive reappraisal abilities.

METHODS AND MATERIALS

Participants

A total of 39 ADPs (26 males) and 39 HCs (22 males) were included in this between-subjects study and were matched on (mean) age, sex, and education. ADPs were sober for at least 3 weeks and were recruited from addiction treatment centers in the larger city area of Amsterdam, the Netherlands. Sobriety was confirmed with a urine test in the research lab on the test days. None of the participants were active users of psychoactive medication, cannabis, opioids, or stimulants. HCs were recruited through Internet and social media advertisements. All participants were screened for MRI suitability. All subjects were screened (and if positive excluded) for the presence or history of psychiatric disorders, including substance abuse or dependence, using the Composite International Diagnostic Interview (CIDI) (23). The study was approved by the local Medical Ethical Commission of the Academic Medical Center of the University of Amsterdam and participants signed the informed consent form, consistent with the Declaration of Helsinki, before participating in the study. Participants were remunerated for their participation.

Questionnaires

In addition to the CIDI interview, the Alcohol Use Disorder Identification Test (AUDIT) (24), Beck's Depression Inventory (BDI) (25), Beck's Anxiety Inventory (BAI) (26), the Toronto Alexithymia Scale-20 (TAS-20) (27), and the Emotion Regulation Questionnaire (ERQ) (28) were administered to assess levels of depression, anxiety, alexithymia, and emotion regulation, respectively. Finally, craving was assessed with the Alcohol Urge Questionnaire (AUQ) (29) before and after the performance of the emotion reappraisal task.

Emotion Reappraisal Task

Participants viewed 18 negative (e.g., vicious dog, plane crash), 18 positive (e.g., cute puppies, beautiful landscape), 18 neutral (e.g., people at work, neutral landscape), and 18 alcohol-related images (e.g., glass of beer, bottles of wine) on a screen using a mirror attached to the head coil. The negative, positive, and neutral images used in this task were selected from the International Affective Image Set (IAPS) (30). Negative images had a low valence (≤4.0) and high arousal (≥6.0), whereas neutral images had a mildly positive valence ($4.5 < x < 7.0$) and low arousal ($2.0 < x < 4.2$) and positive images had high valence (≥7.0) and arousal (≥5.0), based on the original IAPS scores. The alcohol-related images were selected from Vollstädt-Klein et al. (31) and supplemented by alcohol-related images of popular Dutch alcoholic beverages. All alcohol-related images were separately validated in an independent sample for valence ($3.0 < x < 6.0$) and arousal ($2.0 < x < 4.0$).

The images were paired with one of two different instructions: "attend" and "reappraise." In the attend instruction, participants were told to view and identify themselves with the situation in the image (e.g., "how would you feel in this situation"). In the reappraise condition, participants were told to reappraise their emotions related to these images in such a way that the negative feelings were reduced (e.g., "imagine a less negative outcome or interpretation"). Images were presented in 24 blocks of three images of the same emotion type (negative, positive, neutral, alcohol) with the same instruction (attend, reappraise) and presented in a pseudo-randomized order (see **Figure 1**).

After each image, for both instructions (attend and reappraise), a visual analogue scale (VAS) ranging from 0 to 100 was presented and participants had to rate their emotional state ("How do you feel?" where 0 is very negative, 50 is neutral, and 100 is very positive) by moving a bar to the right or left by pressing a button box multiple times. This moving bar was set in the middle (representing a neutral value of 50) and the range of emotions was indicated by previously validated self-assessment manikins depicting valence (32). Prior to scanning, the assessment was explained and practiced outside the scanner using example stimuli (not used in the experiments) for approximately 5 min. The reappraisal task itself took approximately 25 min.

Analysis

Behavioral Analysis

Data were prepared for analysis by winsorizing extreme values for experienced emotion (mean VAS per condition) and craving

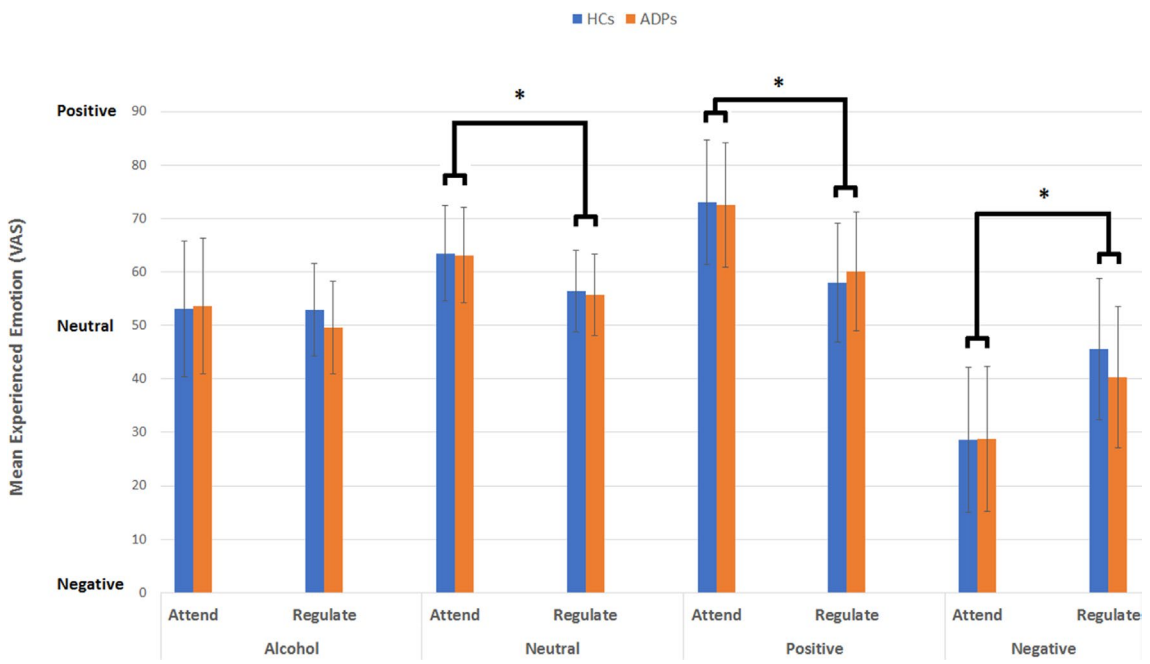

FIGURE 1 | This figure reveals the mean experienced emotion (VAS) per emotion type, instruction, and participant group. Analysis reveals no effect of participant group, but a significant interaction between emotion type and instruction for alcohol-related, neutral, positive, and negative images. Error bars reflect the standard deviation.

(AUQ pre- and post-scores), by replacing values below the 5th and above the 95th percentile by the 5th or 95th percentile, respectively, and by confirming that experienced emotion was normally distributed.

In order to assess effects of emotion type, instruction, and participant group on experienced emotion, a general linear model (GLM) Univariate ANOVA was performed, including experienced emotion (mean VAS) as the dependent variable, and instruction (attend, reappraise), emotion type (alcohol, neutral, positive, negative) and participant group (ADP, HC) as fixed factors. Significant interactions were followed up by Bonferroni-corrected simple effects analyses. Independent sample *t* tests were performed to assess whether gender influenced experienced emotion per condition with results considered significant at a Bonferroni-corrected $p = .006$ (0.05/8).

The AUQ was administered before (pre) and after (post) the reappraisal task. Due to the many mistakes that were made in the second and seventh question—which are reverse coded and were misinterpreted—these were excluded from the analysis. Both pre and post scores were positively skewed and therefore a $\log(x + 1)$ transformation was applied. A repeated-measures ANOVA was performed including AUQ scores as the dependent variable, time (pre/post) as the within-subjects factor and participant group as the between-group factor. Finally, the increases in craving levels (post- minus pre-AUQ scores) were correlated to the means of experienced emotion per emotion type and instruction.

Functional Magnetic Resonance Imaging

Data Acquisition MRI scanning was performed on a Philips Achieva 3T scanner at the Spinoza Imaging Centre, Amsterdam, the Netherlands. Functional MRI [echo time (TE) = 27.63 ms; repetition time (TR) = 2000 ms; field of view (FOV) = 240 × 240 mm, 37 3-mm slices, 0.3-mm slice gap; 80 × 80 matrix; flip angle = 76.1°] was performed to acquire blood oxygenation level-dependent (BOLD) signals using single-shot multi-echo (33) T2*-weighted echo planar imaging (EPI's). These T2-weighted flow-compensated 8 spin-echo anatomical images were oriented axially along the anterior commissure to the posterior commissure (AC–PC) line. During the baseline session, a T1-weighted 3D data set was obtained for anatomical reference; TR = 8.196 ms, TE = 3.73 ms, field of view (FOV) = 140 × 188 × 220 mm, matrix 240 × 187, flip angle = 8°, slice thickness = 1 mm, number of slices = 220.

Preprocessing and First-Level Analysis Preprocessing was performed with SPM8 (Wellcome Trust Centre for Neuroimaging, London, United Kingdom) in MATLAB (version 2012b) and included realignment to the first image, slice timing correction to the middle (18th) slice, co-registration of the anatomical T1 of the subject to the mean functional scan, and warping of this co-registered T1 to standard space. Next, the volumes were normalized to the Montreal Neurological Institute (MNI) template and smoothed with a 7-mm Gaussian kernel in order to increase signal-to-noise ratio. To account for low-frequency drifts, a high-pass filter (128 Hz) was applied. Three subjects (two ADP and one HC) were removed due to the low quality of the fMRI data (e.g., scanner artifacts).

In the first-level model regressors of no interest were Instruction and VAS scoring. Instruction was modeled with a boxcar of 3 s, whereas VAS scoring was modeled with a boxcar for the true duration of the scoring process since this was self-paced. The eight regressors of interest included the onsets of the negative, positive, neutral, and alcohol-related images in either attending or reappraising condition, which were modeled as boxcars (duration, 5 s) and convolved with a hemodynamic response function, in the first-level, single-subject, fixed-effects analysis. First-level contrasts for reappraisal [reappraise > attend] were computed per emotion condition (negative, positive, alcohol, and neutral). For emotion processing, separate contrasts were created for attending emotional images (alcohol, positive, or negative) versus neutral images [attend emotion (positive, negative, alcohol) > attend neutral].

Functional Magnetic Resonance Imaging Data Analysis Separate second-level fMRI analyses were performed for the attend and reappraise conditions. For the attend condition, a 2 × 3 ANOVA was conducted in SPM12, including the [attend emotion > attend neutral] contrast per emotion, in order to assess the interaction between group (ADP, HC) and emotion (alcohol, positive, negative) as well as main effects of group, emotion, and condition. For the reappraise condition, a 2 × 4 ANOVA conducted in SPM12, including the [reappraise > attend] contrasts per emotion, in order to assess the interaction between group (ADP, HC) and emotion (alcohol, neutral, positive, negative) as well as main effects of group, emotion, and condition.

First, the main effects of instruction (attend, reappraise) during the emotion reappraisal task are discussed in order to confirm that the emotion reappraisal task was completed successfully. Then, the group by emotion interactions, as well as the main effects for group and emotion will be discussed. Results are reported at a whole-brain $p < 0.05$ FWE-corrected threshold; furthermore, amygdala Region of Interest (ROI) analyses (based on the BrainMap database) were performed for the attend condition.

In order to assess whether craving is positively correlated to higher brain responsivity during emotion processing and negatively correlated to brain activity during emotion reappraisal, any significant differences in brain activity between ADPs and HCs were followed up by a Pearson correlation analysis, including the extracted individual *b* values from the peak-voxel coordinate, craving levels before the emotion reappraisal task, and the increase in craving levels due to the emotion reappraisal task.

RESULTS

Demographics

ADPs and HCs were successfully matched on age, gender, and years of education. However, ADPs reported significantly higher levels of depression (BDI), anxiety (BAI), and alexithymia (TAS-20). Analyses were not corrected for these differences, because depression, anxiety, and alexithymia levels are well known to be elevated in alcohol dependence (34–37). There were no group differences in the ERQ scores (**Table 1**).

TABLE 1 | Sample characteristics. This table shows the results for the analyses of the sample characteristics. Values are denoted as mean (standard deviation). Total number of participants per comparison may vary due to a small number of missing values. SD, standard deviation; AUDIT, Alcohol Use Disorders Identification Test; TAS, Toronto Alexithymia Scale; DIDF, difficulties identifying and describing feelings; EOT, externally oriented thinking; ERQ, emotion regulation questionnaire. ERQ Reappraisal and Suppression are subscales of the ERQ.

	Possible range (min–max)	Mean ADP (SD) n = 39	Mean HC (SD) n = 39	Significance
Age		41.64 (8.63)	44.05 (10.52)	$t(1,76) = 1.11$, $p = .27$
Years of education		15.31 (3.05)	15.35 (2.98)	$t(1,71) = .64$, $p = .95$
Gender		$M = 26$	$M = 22$	$\chi^2(1,78) = .87$, $p = .35$
AUDIT	0–41	22.11 (10.51)	4.17 (2.51)	$t(1,71) = 9.97$, $p < 0.001$
TAS-20 total	20–100	51.43 (10.83)	43.06 (8.62)	$t(1,67) = 3.54$, $p = 0.001$
TAS-20 DIDF	12–60	31.83 (8.16)	24.86 (7.20)	$t(1,68) = 3.79$, $p < 0.001$
TAS-20 EOT	8–40	11.97 (3.30)	11.36 (2.73)	$t(1,71) = .86$, $p = .39$
ERQ total	7–70	37.81 (7.95)	36.32 (8.56)	$t(1,71) = .77$, $p = .45$
ERQ Reappraisal	6–42	20.22 (5.87)	19.00 (7.80)	$t(1,72) = .76$, $p = .45$
ERQ Suppression	4–28	17.72 (5.01)	17.32 (5.10)	$t(1,72) = .35$, $p = .73$
Beck Depression Inventory	0–63	10.84 (9.58)	4.27 (6.28)	$t(1,72) = 3.39$, $p = .001$
Beck Anxiety Inventory	21–84	30.40 (8.73)	24.18 (4.56)	$t(1,74) = 3.89$, $p < .001$

Task Effects and Group Difference (Behavior)

Negative, Positive, Alcohol-Related, and Neutral Images

The three-way repeated-measures ANOVA with experienced emotion (mean VAS per condition) as the dependent variable, emotion type (negative, positive, neutral, alcohol related) and instruction (attend, reappraise) as within-subject factors, and group (ADP, HC) as between-subject factors did not reveal a significant three-way interaction [$F(3,624) = 1.06$, $p = .36$, $d = .14$]. Two-way interactions between participant group and instruction [$F(1,624) = .53$, $p = .47$, $d = .06$] or participant group and emotion type [$F(3,624) = .19$, $p = .90$, $d = .06$] also did not reveal any significant effect.

Results did reveal a significant interaction between emotion type and instruction [$F(3,624) = 39.11$, $p < 0.001$, $d = .88$], indicating that experienced emotion varied between emotion type and instruction. Simple effects analysis for this interaction revealed a significant difference between attending and reappraising neutral [mean difference = 7.66; $F(1,624) = 17.06$, $p < 0.001$, $d = .33$], positive [mean difference = 13.52; $F(1,624) = 53.24$, $p < 0.001$, $d = .59$], and negative images [mean difference = −13.46; $F(1,624) = 52.79$, $p < 0.001$, $d = .59$]. There was no difference between attending and reappraising alcohol-related images [mean difference = 2.59; $F(1,624) = 1.96$, $p = .16$, $d = .11$]. These results indicate that attending neutral [mean = 64.08, SD = 9.84] and positive (mean = 71.10, SD = 11.31) images resulted in the experience of positive emotions, which were reduced during reappraise condition for both neutral (mean = 56.43, SD = 7.58) and positive images (mean = 59.58, SD = 11.41). Attending negative images on the other hand resulted in the experience of negative emotion (mean = 28.13, SD = 13.04), which were reduced (i.e., less negative) in the reappraise condition (mean = 41.60, SD = 12.77; see **Figure 1**).

Independent-sample *t* tests assessing whether gender influenced experienced emotion during attending revealed no difference in positive, negative, neutral, or alcohol-related images, and also no differences during regulating positive, negative, or neutral images (all $p > 0.006$). However, female participants experienced more positive emotions during regulating alcohol-related images than male participants [mean = 56.15 (SD = 12.85) vs. mean = 47.27 (SD = 13.01), respectively; $t(71) = 2.85$, $p = .006$].

Craving

The repeated-measures ANOVA assessing craving levels revealed no significant interaction between time (pre/post) and participant group [ADP/HC; $F(1,71) = .06$, $p = .81$, $d = 0.06$], but significant main effects for time [$F(1,71) = 29.42$, $p < 0.001$, $d = 1.29$] and group [$F(1,71) = 7.57$, $p < 0.01$, $d = .65$]. These results indicated that the emotion reappraisal task significantly increased craving levels in both ADPs and HCs to an equal extent, but that craving levels in ADPs were overall higher (see **Figure 2**). The increase

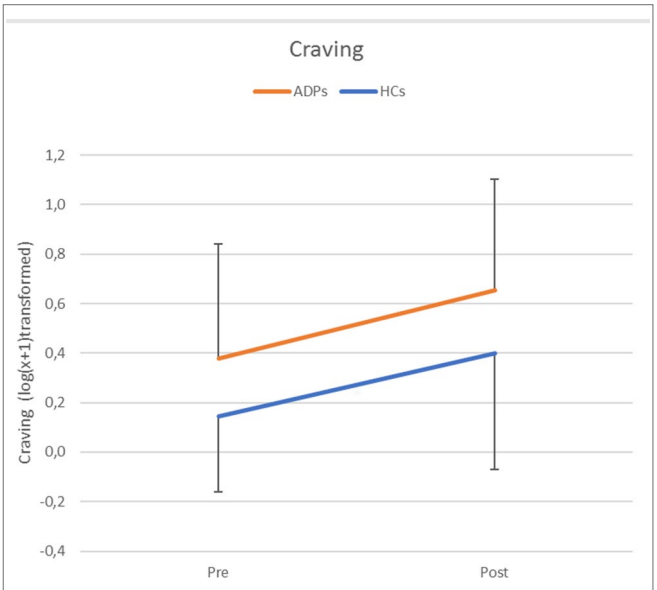

FIGURE 2 | Craving levels per group and time point [pre/post-emotion reappraisal task (ERT)]. Error bars reflect standard deviations. Craving levels were log(x + 1) transformed and refer to self-reported Alcohol Urge Questionnaire (AUQ) scores.

in craving (post/pre) did not correlate with experienced emotion per instruction and emotion type (all p values >0.1) in either ADPs, HCs, or over all subjects.

Functional Magnetic Resonance Imaging Results

Main Task Effects

In order to check the experimental manipulation of the emotion reappraisal task, the main effects of task, i.e., attend [attend emotion > attend neutral] and reappraise [reappraise > attend], were assessed for all emotions and both groups combined (see **Figure 3** and **Supplementary Table 1**). Results revealed that attending emotional images (versus neutral images) increased activity in the visual stream and posterior parietal cortex as well as the precentral gyrus. Our ROI analysis revealed no significant activations in the amygdala.

Reappraising images (versus attending) resulted in increased activation in several cortical structures previously implicated in emotion reappraisal, including the interior frontal gyrus, supplementary motor cortex, and middle frontal gyrus (see **Figure 3** and **Supplementary Table 1**). Furthermore, activity in the visual stream and the medial segment of the superior frontal gyrus was significantly higher during the attend relative to the reappraise condition (see **Figure 3** and **Supplementary Table 1**).

Group Differences in Brain Activation

Emotion Processing

The 3 × 2 ANOVA including the [attend emotion > attend neutral] contrasts per emotion (alcohol, positive, negative) and group (ADP, HC) revealed no significant interaction. The main effect of group showed that HCs have higher activity in the bilateral central operculum, precuneus, and superior temporal gyrus during appraising stimuli (see **Table 2** and **Figure 4A**). Furthermore, there was a significant main effect of emotion within the visual stream, but since these effects are not of main interest, they are reported in **Supplementary Information 2**.

Post hoc correlations between the posterior insula (peak voxel), which was significantly more activated during emotion processing (attend emotion > neutral), and both baseline craving levels and the increase in craving levels due to the emotion reappraisal task indicate a significant correlation for baseline craving levels with the posterior insula only for the APDs [$r(37) = .36$, $p = .03$] and not for the HCs [$r(33) = -.05$, $p = .76$]. This correlation seems to be related to the response to alcohol-related images in ADPs [$r(37) = .43$, $p < .01$, see **Figure 4B**], rather than the response to positive [$r(37) = .28$, $p = .09$] or negative images [$r(37) = .21$, $p = .21$].

Emotion Reappraisal

The 4 × 2 ANOVA for including the [reappraise > attend] contrasts per emotion (alcohol, neutral, positive, negative) and

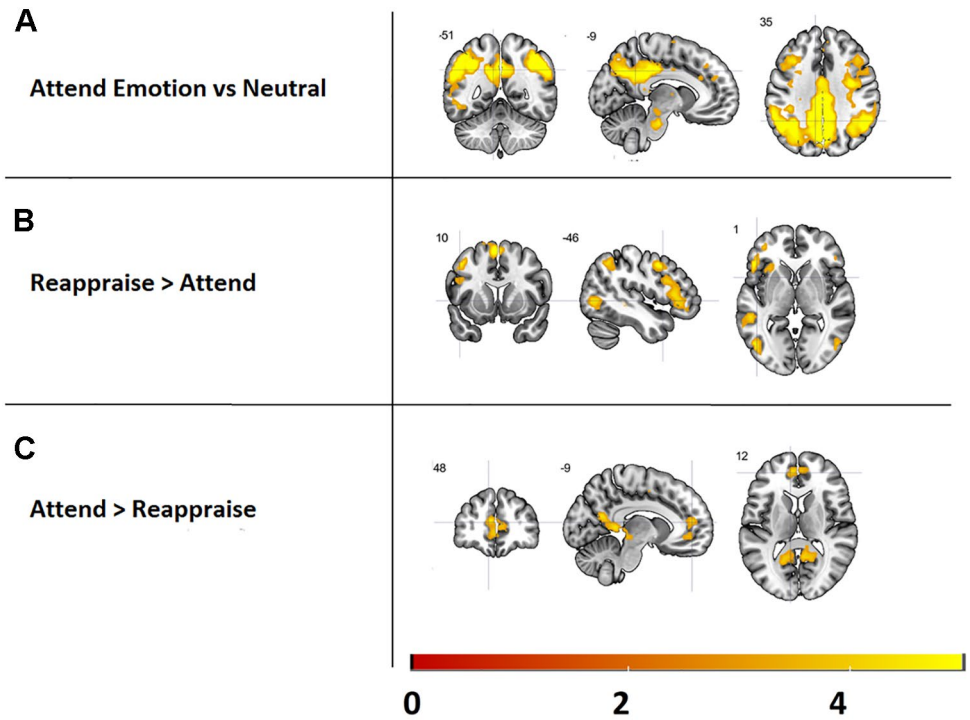

FIGURE 3 | Main effects of the emotion reappraisal task, presented at a threshold of $k > 5$, $p < 0.001$. Top: Brain areas activated while attending emotional images versus neutral images. Middle: activated brain areas during reappraising vs. attending images. Bottom: regions more activated during attending images vs. reappraising images.

TABLE 2 | Main effect of participant group for attending emotional vs. neutral images. *T*, *t* value; *K*, cluster size in voxels; *x*, *y*, *z* are coordinates.

Brain area (attend emotion > neutral)	L/R	*T*	*K*	*x*	*y*	*z*	*p* value (FWE-corrected)
HC > ADP							
Posterior Insula	Left	5.22	70	−36	−10	22	<.001
Parietal Operculum	Right	5.06	100	33	−34	19	0.01
Precuneus	Right	5.00	37	15	−55	28	.013
Central Operculum	Right	4.73	25	42	−7	19	.039
Superior Temporal Gyrus	Right	4.67	18	−21	−7	40	.048
ADP > HC							
n.a.							

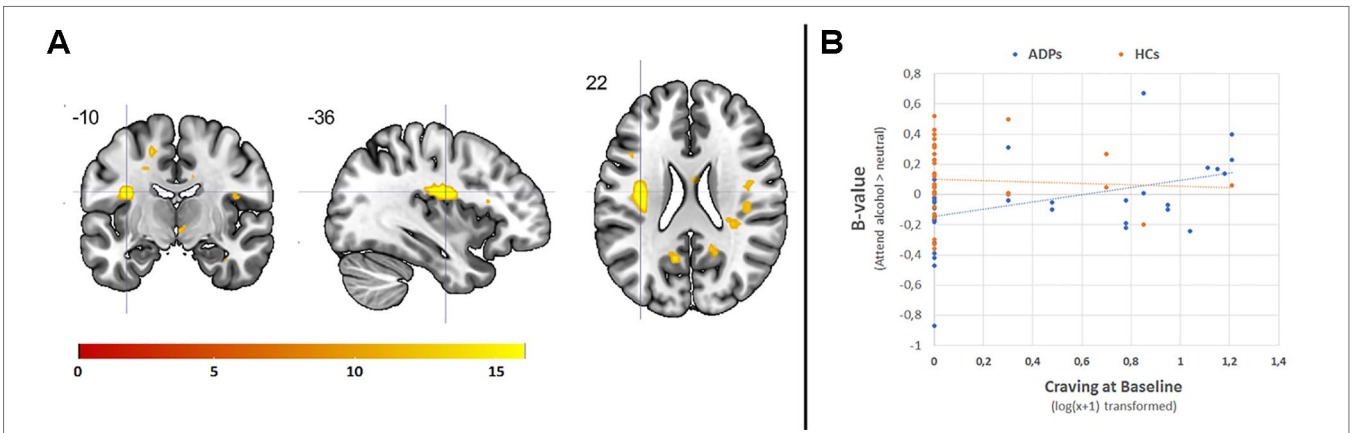

FIGURE 4 | (A) Graphical presentation of the increased activity in healthy controls (HCs) compared to alcohol-dependent patients (ADPs), during emotion processing (attending negative, positive, and alcohol-related images vs. neutral). Crosshair is pointed at the peak voxel in the posterior insula. **(B)** The correlation between the posterior insula and baseline craving levels for the [attend alcohol > neutral] contrast. The threshold for visualization of the results is set at $k > 5$, $p < 0.001$ uncorrected.

group (ADP, HC) revealed no significant interaction or any main effect of group. There was, however, a significant main effect of emotion, indicating a difference in neural response between the neutral, alcohol, positive, and negative images in the visual stream. Since these results are not of main interest, they are reported in **Supplementary Information 2**.

DISCUSSION

This study investigated differences in emotion processing and reappraisal between alcohol-dependent patients (ADPs) and healthy controls (HCs) at the behavioral and the neural level. The emotion reappraisal task was completed successfully as indicated by increased experienced emotion in the attend condition and successful regulation of these emotions in the reappraisal condition. Our results do not show that ADPs have impaired emotion reappraisal based on this paradigm and the emotion regulation questionnaire, nor do they show any difference between ADPs and HCs in neural recruitment during cognitive reappraisal. However, our results do show a reduced neural response to emotional images (in comparison to neutral images) in ADPs versus HCs in the central operculum, precuneus, and superior temporal gyrus. Furthermore, self-reported craving levels increased from pre- to post-testing similarly in both groups, although overall craving levels were significantly higher in ADPs. Finally, self-reported baseline craving levels were correlated to higher neural reactivity to attending alcohol-related images in the ADP group.

The abovementioned results mostly do not correspond with our hypotheses, since we expected reduced emotion regulation ability and decreased associated brain activity in ADPs compared to HCs. These hypotheses were based on a recent review, which indicated reduced emotion regulation abilities and brain function in substance use disorders (14). However, the studies included in this review were mostly studies on emotional reactivity, implicit reappraisal, or behavioral control tasks and are therefore different from our explicit reappraisal paradigm. This may well be a major explanation for our (lack of expected) results, since explicit emotion regulation requires conscious effort, monitoring, and insight, whereas implicit emotion regulation is more automatic. Previous studies also show that ADPs make less use of these effortful emotion regulation strategies in daily life (16). Our results may differ

from these previous studies because our participants were actively instructed to regulate their emotions by applying effortful cognitive reappraisal strategies. The fact that we do not show impaired emotion regulation abilities or differences in related brain function when *instructed* to apply these strategies may point to impairments in the selection of the appropriate reappraisal strategy rather than the ability itself. Of note, the ERQ also did not reveal any differences in emotion reappraisal or suppression between ADPs and HCs. This result is surprising, since the ADP group did self-report higher levels of anxiety and depression. Nevertheless, limited availability and access to emotion regulation strategies has been suggested and found by Khosravani et al. (15) and supports the aforementioned explanation. These results may imply that treatment should focus on selecting the right reappraisal strategy, rather than on reappraisal abilities.

In line with our hypothesis, we show that ADPs and HCs score their experienced emotion (using VAS scores) equally during the attend condition for all emotion types. However, ADPs do show significantly lower brain activity during attending the stimuli in several brain areas, including the posterior insula, central operculum, precuneus, and superior temporal gyrus. These findings are in line with previous studies suggesting a blunted neural response to emotional images in APDs (20) and marijuana smokers (19), participants with excess weight (38), and with studies hypothesizing a blunted response to non-addiction-relevant emotional stimuli (21).

In contrast with our hypothesis, the reappraisal task induced craving equally in both ADPs and HCs. This may be explained by a mismatch between specific preferences from the individual ADPs (e.g., someone who only drinks beer) and the diversity of alcohol-related images that were presented (beer, wine, liquor, bar, supermarket), which may have dampened the craving inducing effect. Future studies should consider a personalized approach, matching the presented images to the subject's specific preference.

Comparing our data to data from the Dutch national monitoring system for drug- and alcohol-dependent patients (39), our ADP group was slightly younger (41 years vs. 46 years), but gender distribution was comparable (67% vs. 72% male). Our ADP participants were in treatment for alcohol dependence but were medication free since the use of psychoactive medication was an exclusion criterion. This is atypical for most treatment-seeking alcohol-dependent patients who are often prescribed anti-craving medication. It is possible that patients who are not prescribed any medication (e.g., our participants) experience less craving compared to ADPs who are prescribed medication since severe craving can be an indication to prescribe medication. Possibly the ADPs included in this study experienced less craving than ADPs who are prescribed psychoactive medication, which may explain the similar effects of the emotion regulation task on craving levels for ADPs and HCs in this study. Our *post hoc* correlations in APDs are in line with this explanation, since they reveal that higher baseline craving levels are associated with more activity within the posterior insula while attending alcohol-related images. In other words, ADPs who experience higher baseline craving levels have a stronger neural response to alcohol-related images in a brain region that has previously been implicated in cue-induced craving in alcohol-dependent patients (22).

Together, these results suggest that ADPs show a blunted response to emotional images when compared to HC, but also that within the ADP group, higher craving levels are associated with a "less" blunted neural response to alcohol-related images. Previous studies indicate that reduced responsiveness to emotional cues could be caused by reduced salience of these cues in comparison to addiction-relevant cues (21) and these findings are in line with our results. Another explanation, which we could not confirm with the available data, is that a reduced neural reaction to emotional images may serve as an implicit protective mechanism. Since a higher response to emotional images has been linked to craving (22), reducing this response may lead to less craving. This explanation, however, is speculative and should be investigated further.

Strengths and Limitations

The current study assessed emotion reappraisal as well as emotion processing in alcohol dependence through a comprehensive study, using both questionnaires, behavioral data, as well as fMRI. Despite the strengths of this study, we only studied one form of emotion regulation (reappraisal), and future studies should incorporate multiple emotion regulation strategies, including, e.g., voluntary emotion reappraisal, avoidance, or distraction. Although the reappraisal task induced craving in ADPs and HCs, it is not possible to clarify which images or conditions caused this effect because craving was measured only before and after the reappraisal task, and this may be an explanation why none of the conditions correlated with the increase in craving levels.

The lack of a clear distinction in emotional reappraisal between ADPs and HCs might be explained by insufficient emotional impact of the images that were used in the task. The IAPS database images may lack ecological validity, thus reducing the impact of these images and thus facilitating the emotion reappraisal process. On the other hand, using a comparable task (without the alcohol-related images), we were previously able to differentiate between HCs and patients with obsessive–compulsive disorder during emotion processing, but not during emotional reappraisal (40). Future studies should consider other ways of inducing emotions with higher ecological validity, including personalized scripts, personalized images, or the use of virtual reality. Additionally, future studies should consider incorporating measurements of personality disorders, including borderline personality disorder, that have previously been linked to impaired emotion reappraisal (41), but were not used in the current study.

CONCLUSION

The current study showed neither impaired reappraisal of emotion in ADPs nor reappraisal-related differences in brain activity in ADPs compared to HCs. The results might have been influenced

by some methodological limitations, although we did demonstrate a blunted neural response in ADPs while attending emotional (positive, negative, alcohol-related) images. Moreover, baseline craving levels were correlated to a less blunted neural response to alcohol-related images in ADPs. Together, these results may suggest a link between emotional reactivity and craving, and impaired natural emotion processing in alcohol dependence, whereas ADPs show unimpaired reappraisal abilities when explicitly *instructed*. Future studies should assess voluntary reappraisal abilities, more ecologically valid ways of inducing emotions, and compensatory mechanisms in ADPs to further understand the differences during natural (re)appraisal of emotional cues.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Medical Ethical Commission of the Academic Medical Center of the University of Amsterdam with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the local Medical Ethical Commission of the Academic Medical Center of the University of Amsterdam.

AUTHOR CONTRIBUTIONS

All authors made a significant contribution to this article, including acquiring funding (AG and WB), study design (AG and WB), development of the emotion reappraisal task (SW, OH, DV, and YD), data acquisition (JJ), data analysis (JJ, DV, and SW), interpretation of results (JJ, AG, SW, OH, YD, WB, and DV) and contributions to this manuscript (JJ, AG, SW, OH, YD, WB, and DV).

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00227/full#supplementary-material

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Increased Neural Activity in Hazardous Drinkers During High Workload in a Visual Working Memory Task: A Preliminary Assessment Through Event-Related Potentials

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Despite equated behavioral performance levels, hazardous drinkers generally exhibited increased neural activity while performing simple cognitive tasks compared to light drinkers. Here, 49 participants (25 hazardous and 24 light drinkers) participated in an event-related potentials (ERPs) study while performing an *n*-back working memory task. In the control zero-back (N0) condition, the subjects were required to press a button when the number "2" or "6" was displayed. In the two-back and three-back (N2; N3) conditions, the subjects had to press a button when the displayed number was identical to the number shown two/three trials earlier. To assess for the impact of alcohol consumption on the updating of working memory processes under various cognitive loads, difference waveforms of "N2 minus N0" and "N3 minus N0" were computed by subtracting waveforms in the N0 condition from waveforms in the N2 and N3 conditions, for the light and the hazardous drinkers. Three main ERP components were noted for both groups: a P200/N200 complex, a P300 component, and an N400/P600 activity. The results show that, to perform the task at the same level as the light drinkers, the hazardous drinkers exhibited larger amplitude differences, mainly around the P300 and P600 components. These data may be considered, at the preventive level, as vulnerability factors for developing adult substance use disorders, and they stress the importance, at a clinical level, to consider such working memory processes in the management of alcohol dependence.

Keywords: heavy social drinking, alcohol, working memory, cognitive workload, *n*-back task, event-related potentials

INTRODUCTION

Working memory (WM), the capacity to store information in short-term registers and simultaneously manipulate it online, is required for most key daily living activities such as planning, engaging in active conversation, or solving complex problems (1). At the functional level, three categories covering most of the functions indexing WM have been well-described: storage and processing, executive processes, and coordination (2). Indeed, one of the main characteristics of WM refers to a capacity limited mental workspace used to store and process information for use in ongoing

cognition (3). This WM load is, therefore, a reasonable measure of the cognitive effort dedicated to holding information in mind for short periods of time while performing a cognitive task (4). It was traditionally proposed by Miller (5) as the "magical number seven plus or minus two" items that can be remembered. Neuroimaging studies have shown that when the WM load exceeds the individual short-term memory capacity, the dorsal prefrontal cortex (PFC)—in addition to ventral PFC regions—may be recruited to mediate strategic processes necessary for the maintenance of a high WM load [e.g., Ref. (6)]. In recent years, there has been considerable debate regarding the notion of a capacity limitation in WM as well as on whether mechanisms of interference, rather than capacity limits, might explain performance limitations [e.g., see Ref. (7)]. Also, WM executive processes refer to three main functions identified as mental set shifting (e.g., the ability to shift from one task to another one), inhibition of prepotent responses (e.g., the ability to suppress a dominant motor response), and information updating (e.g., the ability to update relevant information compared to nonrelevant ones in WM) (8). A third important role of WM is to coordinate elements and build new relations to integrate them into structures (e.g., representing different visual objects in a three-dimensional space). These three different functional facets can be isolated and described on their own. Nevertheless, WM functions as a whole, and all these different facets interact for higher level processes (2). The main point we will focus on here is that *individual differences in WM load* correspond to fundamental differences in *executive control skills* [e.g., Ref. (9)] that might impact some dysfunctional behaviors such as impulsive decision-making typically observed in addictive behaviors [e.g., Ref. (10)].

In dual-process neurocognitive models, the persistence of heavy alcohol consumption results from a) an abnormal bottom-up system generating craving and automatic alcohol-approach tendencies; paired with b) an abnormal top-down system generating reduced cognitive control upon long-term prospects [e.g., Ref. (11)]. The underlying neural mechanisms of these phenomena are defined by increased dopamine release in the cortico-striatal reward circuit triggered by drug stimuli [e.g., Ref. (12)], which draws the subject's attention to the drug-related stimulus [e.g., Ref. (13)], while hypoactivation of frontal regions indicates that alcoholics lack the executive resources needed to inhibit the salient and dominant response [e.g., Ref. (14)]. In this view, a lot of empirical research has been devoted to the role of neurocognitive processes such as cue reactivity [e.g., see Ref. (15) for a meta-analysis] or inhibitory skills [e.g., see Ref. (16) for a review] in the onset, development, and persistence of heavy alcohol consumption. Indeed, both of these processes appear to be promising targets for interventions aimed at treating patients with alcohol disorder [e.g., Refs. (17, 18)].

However, WM capacity has also been shown to impact cognitive control of impulsivity by way of keeping future goals in mind when making decisions when faced with rewarding/arousing distractions (19). This fits perfectly with the dual-process model of cognitive control, whereby executive functions are used to regulate bottom-up implicit arousal responses (14, 20). Indeed, a threshold of PFC activation is needed for effective modulation of bottom-up processes, and is associated with WM [e.g., Ref. (21)]. In such a view, low WM capacity can exacerbate the worse impulse control that results from excessive consumption of alcohol [e.g., Ref. (22)], by triggering poor inhibition of immediate behavior as well as poor longer-term planning of future options (10). Chronic heavy users of alcohol often exhibit lower levels of WM capacity [e.g., Refs. (23, 24)]. However, although some of these deficits appear to result from heavy alcohol use [e.g., Ref. (25)], there is also evidence suggesting that low capacity WM problems contribute to the development of alcohol abuse [e.g., Ref. (26)]. WM deficits are then considered to contribute to the core pathology of addiction [e.g., Ref. (14)]. Indeed, Brooks and colleagues conducted a review yielding 93 studies that examined WM and cognitive control, between 2010 and 2017, in patients with substance use disorders (SUD; including stimulants such as nicotine, opioids, and marijuana, and alcohol use). The majority of the studies (72%) reported worse WM performances compared to healthy drug-naive controls or nondrug-taking control groups. From these insights, training WM has been shown to be highly relevant for reducing stimulant (27) as well as alcohol use [e.g., Ref. (28)] by increasing control over automatic impulses, even though different training techniques appear to produce differential impacts on the broader landscape of cognitive abilities (3). Indeed, there is some evidence that suggests that nonsequential and nonadaptive training paradigms should not be effective (29), while "core training programs" using tasks that commonly involve sequential processing and frequent memory updating appear to produce more far-reaching transfer effects, most likely because they target domain-general mechanisms of WM (3). A good illustration of such a training program relates to *the n-back task*, which requires continuous upgrades of the memory store (i.e., a memory updating process) and which is particularly suited for the study of varying levels of WM load (30).

This *n*-back task requires online monitoring, updating, and manipulation of remembered information, and it is, therefore, assumed to place great demands on a number of key processes within WM subtended by widespread neural areas (31). Indeed, frontal regions have been implicated in numerous cognitive functions that are relevant to the *n*-back task, including monitoring and manipulation within WM (32); the parietal cortex is thought to be involved in the implementation of stimulus-response mapping (33) and in the storage of WM contents (34) as a kind of "buffer for perceptual attributes" (35); while activation of the precuneus during the visual WM task is consistent with a recollection process aided by visual imagery (36), and insula activation is considered to be a part of the inferior frontoparietal network, which responds to behaviorally relevant rather than to expected stimuli (37).

This task has been extensively tested in heavy alcohol users to outline WM disturbances linked with high workloads, but it yielded heterogeneous results. Indeed, decreased PFC activation and worse WM were observed, for instance, in adolescent alcohol users [e.g., Ref. (38)] and in youths with a family history of alcoholism (FHA) (39). However, while many functional magnetic resonance imaging (fMRI) studies have reported insignificant differences in behavioral performances between healthy control groups and heavy alcohol users, significant

neural differences can be discerned by including brain imaging measures [e.g., Refs. (40–42)], indexing compensatory neural processing during variation in cognitive load (43). The bulk of the reported data consisted of *reduced* activation of the PFC network (including insula, cerebellar, anterior cingulate, and/or parietal regions) in alcoholic patients [e.g., Refs. (40, 44)] or (conversely) *increased* PFC network activation in heavy social drinkers (i.e., people characterized by excessive alcohol consumption, without a clinical state of dependence) (42, 45, 46). According to a "functional compensation view," decreases or absences in activation reflect deficits in brain function, and the concomitant increases in activation reflect "attempted" or "successful" compensation for these deficits (47). Aside from fMRI studies, differences in electrophysiological [electroencephalogram (EEG)] components are considered to be sensitive indicators of workload (48, 49). Indeed, a decrease in alpha power is associated with an increase in arousal, resource allocation, or workload [e.g., Ref. (50)], and an increase in theta power (most profound over frontal electrodes) has been observed as task requirements increase [e.g., Ref. (51)]. Event-related potentials (ERPs), derived from EEGs, also convey relevant information about an individual's workload. Throughout the information processing stream, ERP components such as the P100 [e.g., Ref. (52)], the N100 [e.g., Ref. (53)], the N200 (54), a positive/negative component between 140 and 280 ms (55), and the P300 [e.g., Ref. (56)] have been shown to be modulated by the WM workload and task difficulty. By using a visual task with a high WM load (57, 44) or through a spatial 2-back task (58), several ERP studies have determined that memory load capacity is affected in heavy users of alcohol.

However, to our knowledge, there has not been a study to date that specifically investigated the impact of *increasing visual memory load* on neural activity in healthy vs. heavy alcohol users based on ERPs. In light of its high temporal resolution, we sought to define whether increasing WM visual load specifically impacts hazardous vs. light drinkers at specific time intervals throughout the information processing stream. To address this, we chose 1) to use a visual WM *n*-back task (N = 0; 2; or 3), forcing subjects to continuously remember the last two or three rapidly changing items, to induce different levels of visual workload; and 2) to compare light versus heavy social drinkers, as done previously in an fMRI experiment (only comparing N2 vs. N0 conditions) suggesting increased pre-supplementary motor area, PFC, and cerebellar activations in heavy drinkers despite similar behavioral performances (42). In the present ERP study, increasing memory load was applied to participants through N2 and N3-back tasks, and this parametric manipulation of the task variable (visual memory workload) was compared in light vs. heavy alcohol drinkers by use of a subtraction method (N2 minus N0; N3 minus N0) that is well-known to index specific WM processes such as storage and manipulation (updating) (34). Light and hazardous drinkers were enrolled in the study as our aim was to show the potential differences induced by different alcohol consumption patterns (rather than between drinkers and nondrinkers). This strategy appears to be congruent with most earlier studies on heavy social drinking (e.g., cited in this paper) (57, 59), where the control group was composed of light drinkers. Moreover, recent studies have shown that control teetotalers appear to represent a specific population that results in unexpected results (e.g., worse executive performance) (60), which constitutes an additional reason to avoid including nondrinkers in the present study. Our main hypotheses are that 1) light and heavy alcohol drinkers will exhibit similar behavioral performances [see Ref. (61) for a review]; and 2) compared to light drinkers, the higher the memory load, the more that heavy drinkers will recruit neural resources. Moreover, as a result of the optimal temporal resolution of ERPs compared to fMRI (62), a precise temporal window can be defined for this enhanced neural activity recruitment. Such results could have the highest relevance at a prevention level, as these under-investigated WM load processes (compared to executive or cue-reactivity ones) in alcohol disorders could index "biological vulnerability factors" that may trigger further onset of alcohol dependence.

MATERIALS AND METHODS

Participants

First, we conducted a general screening of 120 students from the Faculty of Psychology of the University of Brussels (Belgium) in order to ascertain sociodemographic variables (age, gender, education level, and native language) and patterns of alcohol consumption. On the basis of these self-reported data, groups of participants were defined as detailed below. Exclusion criteria for participants included major medical issues, conditions relating to impairment of the central nervous system (including epilepsy and a prior history of brain injury), visual impairments, and past or current drug consumption (other than alcohol and tobacco use). Our main objective was to select two groups of participants who only exhibited differences in terms of their alcohol-drinking patterns (see **Table 1** for the complete descriptive data). Therefore, subjects concurrently consuming cannabis (defined as at least once in the month prior to the study) were not included. Also, a similar number of participants with a family history of alcoholism (FHA) (63) were included in the final groups (only one by group). In line with earlier studies [e.g., Refs. (42, 59, 64, 65)], three variables (self-reported by participants through the use of a timeline follow-back method questionnaire assessing alcohol–drug consumption characteristics) were used to determine control and heavy alcohol user groups: the mean number of drinking occasions per week (DOW: "how many times do you typically consume alcohol in a week?"), the mean number of alcohol doses per drinking occasion (ADO: "how many drinks do you generally consume during one drinking occasion?"), and the mean number of alcohol doses per week (ADW: "how many drinks do you generally consume in a week?"; one dose corresponding to 10 g of pure ethanol). According to the definition of binge drinking used in European countries, participants who drank six or more standard alcoholic drinks (10 g of alcohol) on the same occasion at a rate of at least two drinks per hour and at most two or three times per week were classified as hazardous drinkers. Those who drank 1 to 30 days a month, but never more than five standard alcoholic drinks on the same occasion and at a maximum rate of two drinks per hour,

were classified as controls. This classification was confirmed utilizing the AUDIT-C consumption subscore, which is defined by three items of the complete 10-item AUDIT instrument (66), and which can help identify people who are hazardous drinkers (67). The AUDIT-C is scored on a scale 0–12. A score of 3 for women and 4 for men is considered optimal for identifying hazardous drinkers; the higher the score, the more likely the drinking pattern affects the participants' safety (68). Hazardous drinking, which can significantly impact public health despite the absence of any *bona fide* disorder in the individual users, is defined as a level of alcohol consumption that is likely to result in harm to the user or other individuals (69).

In order to ensure that any potential difference in the ERP data would be due to alcohol consumption and not to other variables, the groups were balanced for age, gender, and level of education (i.e., the number of years of education completed since starting primary school). The participants were also asked to fill out questionnaires assessing psychological measures. These were the State-Trait Anxiety Inventory (STAI A and B) to assess state and trait anxiety (70); the Beck Depression Inventory (BDI-II) (71) to assess depression; and the Urgency Premeditation Perseverance and Sensation Seeking Impulsive Behavior Scale (UPPS) (72), which is a measure of impulsivity as a personality trait. Control of all of these variables is important, as drinkers with depression, anxiety, as well as high impulsivity symptoms have been shown to be at increased risk of developing alcohol dependence (73–75). Therefore, it can be seen that the participants of both groups did not exhibit any difference in terms of these variables (see **Table 1**). Indeed, based on these criteria, 60 undergraduate students were selected for the ERP study and classified as light ($n = 30$) or heavy (hazardous) drinkers ($n = 30$). Among these, 11 participants exhibiting EEG artifact contamination were removed. Therefore, the final groups were represented by 24 light and 25 hazardous drinkers. We obtained informed written consent from the participants after they were fully informed about the study. The local ethics committee of the Brugmann Hospital approved the study ("Comité d'Ethique Hospitalier CE 2010/156"). The participants were instructed to abstain from consuming alcohol in the 24 h before the ERP recording.

Working Memory *n*-Back Task

WM performance and the underlying neural activity were measured using a visual *n*-back task under three different conditions. The stimuli were white numbers (Arial font, size 74) displayed on a black background on the center of the screen, presented successively in a pseudo-random order. In the vigilant/control zero-back (N0) condition, the subjects were asked to press a button with their right hand whenever the number "2" was displayed (block 1) or "6" (block 2). In the WM two-back (N2) and three-back (N3) conditions, the subjects had to press the button when the displayed number was identical to the number displayed two or three trials earlier (see **Figure 1** for an illustration). The subjects were successively administered two blocks in the N0 condition, then two blocks in the N2 and two blocks in the N3 conditions. This order was kept constant across the participants in order to ensure that all of the groups were exposed to exactly the same manipulation of tasks with increasing complexity (from N0 to N2 and then N3). Each N0 block consisted of a sequence of 80 trials (including 20 targets), while the N2 and N3 conditions consisted of a sequence of 86 (104) trials, respectively, also including 20 targets each. Each stimulus was displayed for 1,750 ms with an interstimulus interval of 250 ms. This way, 40 targets were available for each condition across the participants. The pseudo-random order ascertained that, in N0, two targets were not successively presented; and, in N2 and N3, that the same number was not repeatedly used as a target (but instead varied randomly from 1 to 9). All of the participants performed one practice block for each condition (N0, N2, and N3).

EEG Recordings

During the ERP recordings, each participant sat alone in a darkened room, on a chair placed 1 m from the screen. EEG activity was recorded with 32 electrodes mounted on a Quick-Cap and placed in standard (based on the 10–20 system) and intermediate positions (Fpz, Fp1, Fp2, Fz, F3, F7, F4, F8, FC1, FC5, FC2, FC6, Cz, C3, C4, T7, CP5, CP1, CP2, CP6, T8, P7, P3, Pz, P4, P8, POz, O1, Oz, and O2). Recordings were made with a linked mastoid physical reference. The EEG was amplified

TABLE 1 | The light and the hazardous drinkers were equivalent in terms of age, gender, depression [Beck Depression Inventory (BDI)-II scores], anxiety [State-Trait Anxiety Inventory (STAI)-trait and STAI-state scores], and impulsivity [Urgency Premeditation Perseverance and Sensation Seeking Impulsive Behavior Scale (UPPS) total score] (all p's > 0.05). The two groups differed solely on alcohol variables: the Alcohol Use Disorders Identification Test - Alcohol Consumption questions (AUDIT-C) subscore [$t(47) = -10.836$; $p < 0.001$], the mean number of alcohol doses per drinking occasion (ADO), the mean number of drinking occasions per week (DOW), and the mean number of alcohol doses per week (ADW).

	Light drinkers ($n = 24$)	Hazardous drinkers ($n = 25$)	*T* value	*P* value
Age	26.79 ± 9.3	23.96 ± 2.4	1.442	0.161
Gender (M/F)	11/13	13/12	$\chi^2 = 0.186$	0.666
AUDIT-C	2.92 ± 1.2	6.76 ± 1.2	−10.836	<0.001
ADO	0.95 ± 0.6	2.12 ± 1.3	−3.977	<0.001
DOW	1.71 ± 1.2	5.16 ± 2.4	−6.236	<0.001
ADW	1.8 ± 1.5	7.3 ± 4.9	−5.255	<0.001
BDI-II	6.92 ± 4.9	5.36 ± 4.3	1.171	0.248
STAI-trait	46.54 ± 8.8	44.72 ± 9.1	0.712	0.48
STAI-state	46.67 ± 9.6	43.92 ± 6.4	1.177	0.245
UPPS	101.67 ± 12.1	105.36 ± 11.195	−1.108	0.273

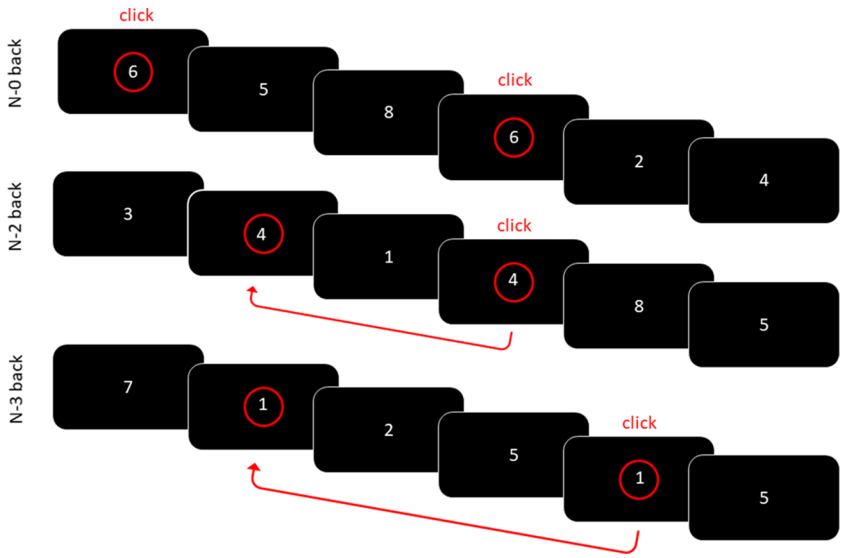

FIGURE 1 | Visual N-back working memory task. In the N0 condition, the participants had to as quickly as possible detect the number 6. In the N2/N3 conditions, the participants had to press the button when the displayed number was identical to the number displayed two/three trials earlier.

with battery-operated ANT® amplifiers with a gain of 30,000 and a bandpass of 0.01–100 Hz. The ground electrode (AFz) was positioned between Fpz and Fz along the midline. The impedance of all of the electrodes was maintained below 10 kΩ during all the experiments. EEG was recorded continuously at a sampling rate of 500 Hz with ANT Eeprobe software. Approximately 20% of the trials were contaminated (a cutoff of 30 mV was used to define trials that were contaminated either by eye movements or muscular artifacts), and they were eliminated offline in order to only analyze the artifact-free trials. Epochs starting 200 ms before the onset of the stimulus and lasting for 800 ms were created. The data were filtered with a 30-Hz low-pass filter. A baseline correction (from −200 to 0 ms) was computed. Only trials that were correctly performed were included in these averages [i.e., correct hits for targets, while hits for nontargets (false alarms) were eliminated]. Two parameters were coded for each stimulus: i) the condition (N0; N2; N3) and ii) the type of response (key press for targets, no key press for the other stimuli). This coding allowed us to compute different averages of ERP target stimuli. The averages were computed for each subject individually. Grand-averages were then computed for the three conditions (N0, N2, and N3) for each group (light vs. hazardous drinkers).

Statistical Analyses

For the behavioral data, three ANOVAs were computed on the correct hits, the reaction times, and the false alarms with level (N0, N2, and N3) as within-subject variables, and group (light vs. hazardous drinkers) as a between-subject variable. The Greenhouse–Geisser correction was applied to all of the ANOVAs when necessary. For the ERP data, we first analyzed the two classical ERP components associated with the control N0 condition: 1) the P100 component, measured as a mean amplitude value over O1, Oz, and O2 electrodes in the latency range [80–140 ms] (55); and 2) the P300 component, measured as a mean amplitude value over P3, Pz, and P4 electrodes in the latency range [280–450 ms] (55). Then, as no group difference emerged on this baseline condition, the main analyses of this study consisted of subtracting it from the WM conditions (N2, N3) in order to isolate specific WM processes such as storage and manipulation (updating) (34, 42, 55). Subtractions "N2 minus N0" as well as "N3 minus N0" were then computed for each participant of each group and were subsequently grand-averaged. Significant effects were calculated at four selected electrode clusters [i.e., Frontal (mean of electrodes F3, F4, and Fz), Central (mean of Cz, C3, and C4), Parietal (mean of P3, Pz, and P4), and Occipital (mean of O1, Oz, and O2)] through Student's *t*-tests (amplitude of the difference wave compared to zero from 0 to 800 ms) (76, 77). These *t*-values were significant at the level $p < .01$ if they were above 2.79/below −2.79 for the hazardous drinkers (significance threshold computed on the basis of a sample size of $n = 25$) or above 2.81/below −2.81 for the light drinkers [$n = 24$; see the critical values (percentiles) for the *t* distribution at https://faculty.washington.edu/heagerty/Books/Biostatistics/TABLES/t-Tables/]. Only spatiotemporal patterns whose *t*-values were significant *for at least 20 ms* were considered as relevant (76–78). All of the analyses were conducted with SPSS 20 software.

RESULTS

Behavioral Data

The light and the hazardous drinkers were equivalent in terms of age, gender, depression (BDI-II scores), anxiety (STAI-trait and STAI-state scores), and impulsivity (UPPS total score; all *p*'s > 0.05). The two groups differed solely on "alcohol" variables, i.e., on the AUDIT-C subscore [$t(47) = -10.836$; $p < 0.001$], and on

the DOW [$t(47) = -6.236$; $p < 0.001$], ADO [$t(47) = -3.977$; $p < 0.001$], as well as ADW [$t(47) = -5.255$; $p < 0.001$] variables. The complete demographic characteristics of the cohort are reported in **Table 1**. The ANOVAs revealed a significant principal effect of level on correct hits [$F(2,94) = 197.549$; $p < 0.001$; observed power = 1], reaction times [$F(2,94) = 171.15$; $p < 0.001$; observed power = 1], and false alarms [$F(2,94) = 89.012$; $p < 0.001$; observed power = 1]. This suggests a "complexity effect," as the more difficult the task (N3 > N2 > N0), the more the participants made errors (fewer correct hits and more false alarms) and had longer response latencies. However, no significant effects of group or significant level × group interactions were found (all p's > 0.05), suggesting that both groups performed the task similarly. Detailed analysis results are presented in **Table 2**.

Event-Related Potential Data

At a technical level, we first ensured that the same number of trials was included in ERP analyses for both groups across conditions. An ANOVA 2 × 3 with group (light vs. hazardous drinkers) as a between-subject variable and condition (N0, N2, N3) as a within-subject variable was computed. As only correct hits for targets were entered in ERP analyses, we were able to show a main condition effect [$F(2,94) = 60.582$; $p < 0.001$; observed power = 1], indexing an increased number of errors as a function of task complexity [mean number of trials ± SD: N0 Light: 29 (7.6), Hazardous: 32 (6.8); N2: Light: 22 (6.9), Hazardous: 25 (7.9); N3: Light: 18 (7), and Hazardous: 20 (7)]. However, this complexity effect was not modulated by the group [no group effect: $F(1,47) = 2.575$; $p = 0.115$; no interaction condition × group: $F(2,94) = 0.231$; $p = 0.779$], suggesting that a similar signal-to-noise ratio was ensured for each condition between groups. Waveforms recorded on target and nontarget trials in each condition (N0, N2, and N3) are shown in **Figure 2**. As expected, the targets involved widespread higher amplitudes than the nontargets [e.g., Ref. (55)].

We then compared P100 and P300 amplitudes on the baseline N0 condition between the light and the hazardous drinkers. We used two ANOVAs with group (light vs. hazardous drinkers) as a between-subject variable. No significant difference emerged (all p's > 0.05). Therefore, as expected [e.g., Ref. (42)], we were able to compute "N2 minus N0" as well as "N3 minus N0" subtractions.

The subtraction "N2 minus N0" revealed three main components in both groups: 1) a widespread positivity (with maximal amplitudes visible at occipital sites) associated with a negativity maximally recorded at occipital sites around 150–250 ms: such a pattern exhibited high similarity with the P200/N200 recorded by Missonnier and colleagues (55); 2) a positive activity around 280–400 ms, mainly visible at frontal sites, that can refer to the well-known P300 component, as in Johnson and colleagues' (79) study; and 3) a large negativity around 300–500 ms associated with a long-lasting positivity starting around 500 ms on all of the electrodes (Fz, Cz, Pz, and Oz) that can be linked to the "old/new" N400/P600 memory effect (80). In the same way, the subtraction "N3 minus N0" also revealed these three main components. This is illustrated in **Figure 3** and **Table 3**.

In order to compare these "subtracted waveforms" (N2 minus N0; N3 minus N0), between groups, we submitted these data to Student's t-tests (amplitude of the difference wave compared to zero from 0 to 800 ms) (76, 77) in order to isolate specific spatiotemporal electrophysiological patterns devoted to the WM processes involved in our task (such as storage and updating) (34, 42, 55). To achieve this, and to deal with the multiple comparisons that we computed, we considered that patterns for which the t-values were above 2.79/below −2.79 ($p < .01$) for the hazardous drinkers ($n = 24$) or above 2.81/below −2.81 ($p < .01$) for the light drinkers ($n = 25$) were significant *only if they lasted for at least 20 ms* (76–78).

For "N2 minus N0," the light drinkers exhibited 1) at frontal sites, no significant difference while the hazardous drinkers exhibited three patterns of significant "difference" activities at ms [306–361], [533–564], and [581–819]; 2) at central sites, a small late difference at ms [751–819], while this difference was more sustained in the hazardous drinkers at ms [532–819]; 3) at parietal sites, a similar pattern to the one described at central sites, i.e., a significant activity around [747–819] ms for the light drinkers and a more sustained one in the hazardous participants around [527–819] ms; and 4) at occipital sites, two significant differences, at [143–180] ms and [379–421] ms intervals, that were not observable in the hazardous drinkers, who always exhibited a sustained later activity around ms [545–819]. The results are shown in **Figure 4A** and **Table 4A**.

For "N3 minus N0," one can observe 1) at frontal sites, no significant difference for the light drinkers while the hazardous drinkers exhibited three patterns of significant "difference" activities at ms [182–211], [544–659], and [676–736]; 2) at central sites, no significant difference for the light drinkers while the hazardous drinkers exhibited three significant intervals at ms [415–467], [632–659], and [668–819]; 3) at parietal sites, a significant activity around [356–475] ms for the light drinkers and two for the hazardous participants around [346–476] and [597–819] ms; and 4) at occipital sites, two significant differences, at [146–178] and [337–443] ms intervals, that emerged for the light drinkers while the hazardous drinkers exhibited four significant patterns of activities at ms [211–231], [300–435], [585–702], and [730–769]. The results are illustrated in **Figure 4B** and **Table 4B**.

TABLE 2 | The ANOVAs revealed a significant principal effect of level on correct hits [$F(2,94) = 197.549$; $p < 0.001$; observed power = 1], reaction times [$F(2,94) = 171.15$; $p < 0.001$; observed power = 1], and false alarms [$F(2,94) = 89.012$; $p < 0.001$; observed power = 1]. No significant effects of groups or significant level × group interactions were found (all p's > 0.05), suggesting that both groups performed the task similarly.

	Level	Light drinkers	Hazardous drinkers
Correct hits (/40)	N0	40 ± 0	39.88 ± 0.3
	N2	33.79 ± 2.6	35.2 ± 2.08
	N3	28.25 ± 5.2	28.04 ± 4.8
Reaction times	N0	422 ± 54.4	423 ± 71.4
	N2	586 ± 110.2	549 ± 98.6
	N3	741 ± 148.3	777 ± 141.4
False alarm	N0	0.13 ± 0.3	0.2 ± 0.5
	N2	3.12 ± 2.3	2.96 ± 1.5
	N3	7.79 ± 4.5	8.28 ± 5.5

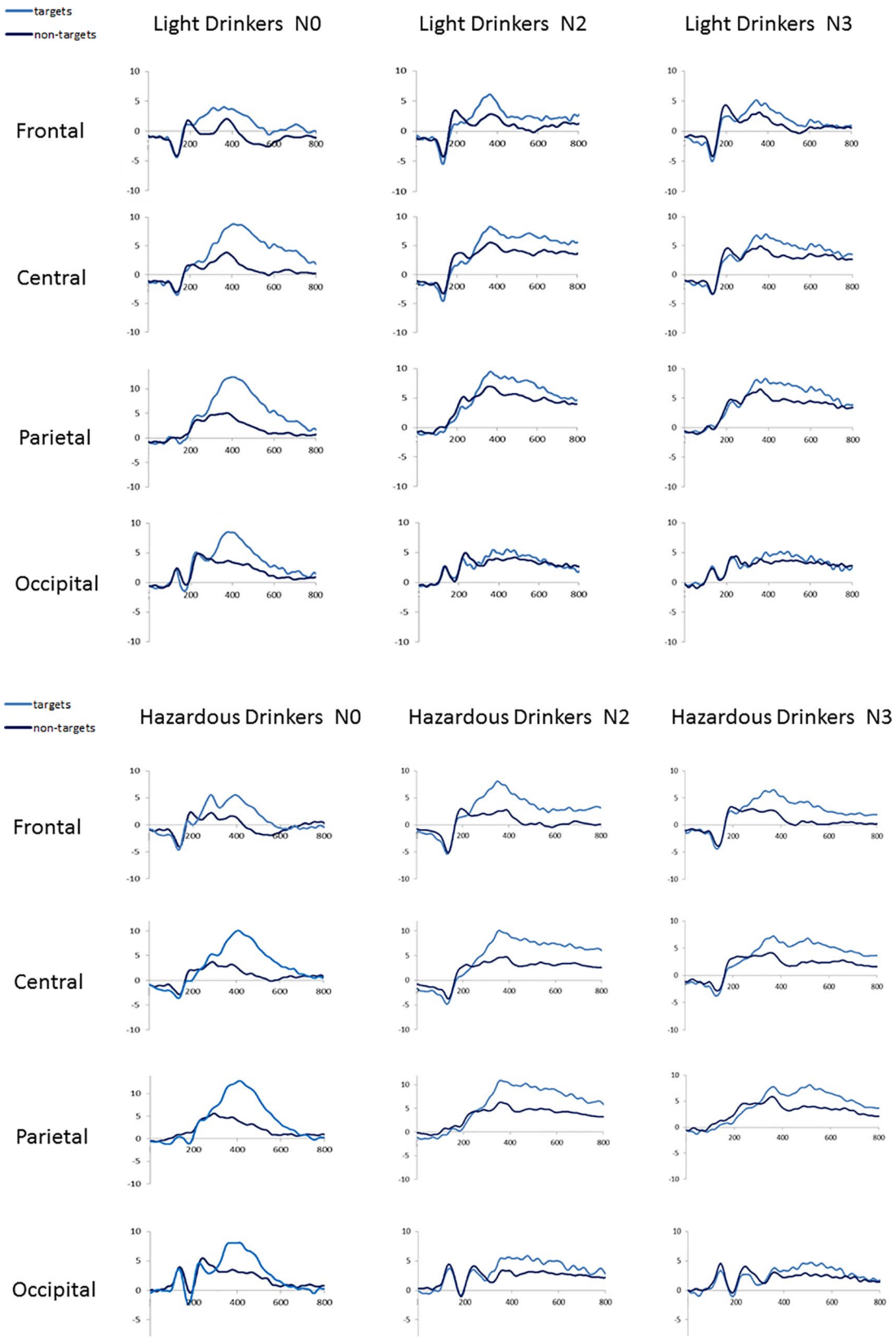

FIGURE 2 | Waveforms recorded at frontal (mean amplitudes for F3, Fz, F4), central (C3, Cz, C4), parietal (P3, Pz, P4), and occipital (O1, Oz, O2) sites for the light (n = 24) and the hazardous (n = 25) drinkers on each condition (N0, N2, N3) for target and nontarget trials.

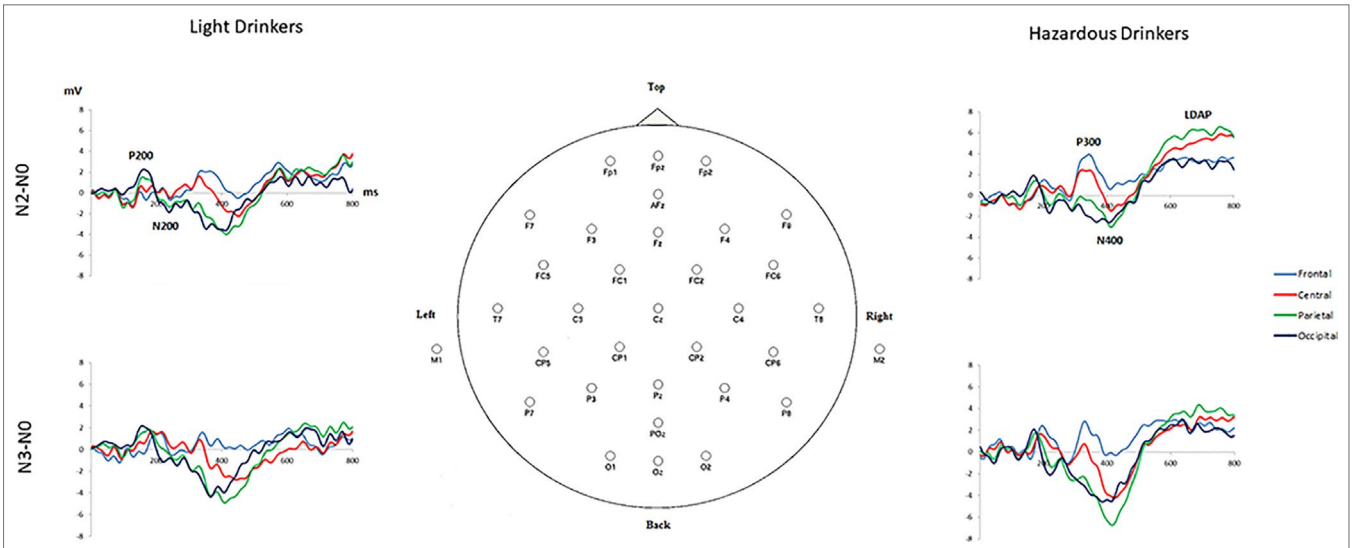

FIGURE 3 | Subtracted grand-average waveforms "N2 minus N0" and "N3 minus N0" at frontal (mean amplitudes for F3, Fz, F4), central (C3, Cz, C4), parietal (P3, Pz, P4), and occipital (O1, Oz, O2) sites for the light (n = 24) and the hazardous (n = 25) drinkers.

Overall, the hazardous drinkers exhibited enhanced amplitude activities compared to the light drinkers, to perform N2 and N3-back conditions. More precisely, the hazardous drinkers exhibited higher amplitude differences, mainly at frontal P300 and widespread P600 components, whereas the light drinkers exhibited enhanced amplitudes around the P200 and N400 components. It should also be noted that, even though the hazardous drinkers exhibited a higher number of significant activities in the N3-back condition compared to the N2-back condition (suggesting incremental activity with task complexity), group differences between the light and the hazardous drinkers were of higher amplitudes for the N2 minus N0 condition than for the N3 minus N0 one. This suggests that the hazardous drinkers exhibited higher processing intensity throughout the information-processing stream, notably around the P300 and the late directing attention positivity (LDAP) components, while the light drinkers can just increase early visual attention (P200) in order to obtain a better memory trace (N400) to deal with the n-back task implying different cognitive loads.

DISCUSSION

Although many n-back studies have not reported any significant difference between healthy participants and excessive alcohol drinkers, significant neural differences have been found indexing compensatory neural processing during variation in the cognitive load (40–44, 46). Moreover, these neural differences appear to be observable throughout the information processing stream when electrophysiological measures (characterized by a better temporal resolution) are used (52–56). In the present ERP study, and for the first time to our knowledge, increasing memory load (N2 and N3-back tasks) has been placed on light and hazardous drinkers.

The main result of the present study is that, even though the performances were equal between the groups, the hazardous drinkers exhibited more intense and widespread activities than the light drinkers. These data are in total agreement with previous data obtained in our lab through an fMRI study (42), in which hazardous drinkers exhibited higher bilateral activity in the pre-supplementary motor area as well as specific positive correlations between the number of alcohol doses consumed per occasion and higher activity in the dorsomedial PFC, and between the number of drinking occasions per week and higher activity in cerebellum, thalamus, and insula while performing the N2 memory task. The present study extended these results, as it showed that 1) these enhanced activities are also present in the N3-back task; and 2) as a result of the optimal resolution of ERPs, it specified the *temporal dynamic* of these increased activities.

At the behavioral level, our results confirmed that the N3 condition was considerably more difficult than the N2-back task,

TABLE 3 | Mean amplitude values (± SD) for the main ERP components resulting from "N2 minus N0" and "N3 minus N0" subtractions on time intervals and on sites of maximally recorded amplitudes for the light and the hazardous drinkers.

			Light (N2–N0)	Hazardous (N2–N0)
P200	100–200 ms	Occipital	1.15 (± 0.82)	0.77 (± 0.68)
N200	200–300 ms	Occipital	–1.16 (± 0.35)	–0.96 (± 0.47)
P300	300–400 ms	Frontal	1.57 (± 0.62)	2.80 (± 0.90)
N400	300–500 ms	Parietal	–2.45 (± 0.97)	–1.19 (± 0.96)
LDAP	500–800 ms	Parietal	1.89 (± 1.03)	5.14 (± 1.52)
			Light (N3–N0)	**Hazardous (N3–N0)**
P200	100–200 ms	Occipital	1.16 (± 0.74)	0.40 (± 0.96)
N200	200–300 ms	Occipital	–1.03 (± 0.30)	–1.57 (± 0.60)
P300	300–400 ms	Frontal	0.76 (± 0.49)	1.36 (± 0.85)
N400	300–500 ms	Parietal	–3.34 (± 1.14)	–4.17 (± 1.62)
LDAP	500–800 ms	Parietal	1.25 (± 1.08)	2.98 (± 1.22)

LDAP, Late Directing Attention Positivity.

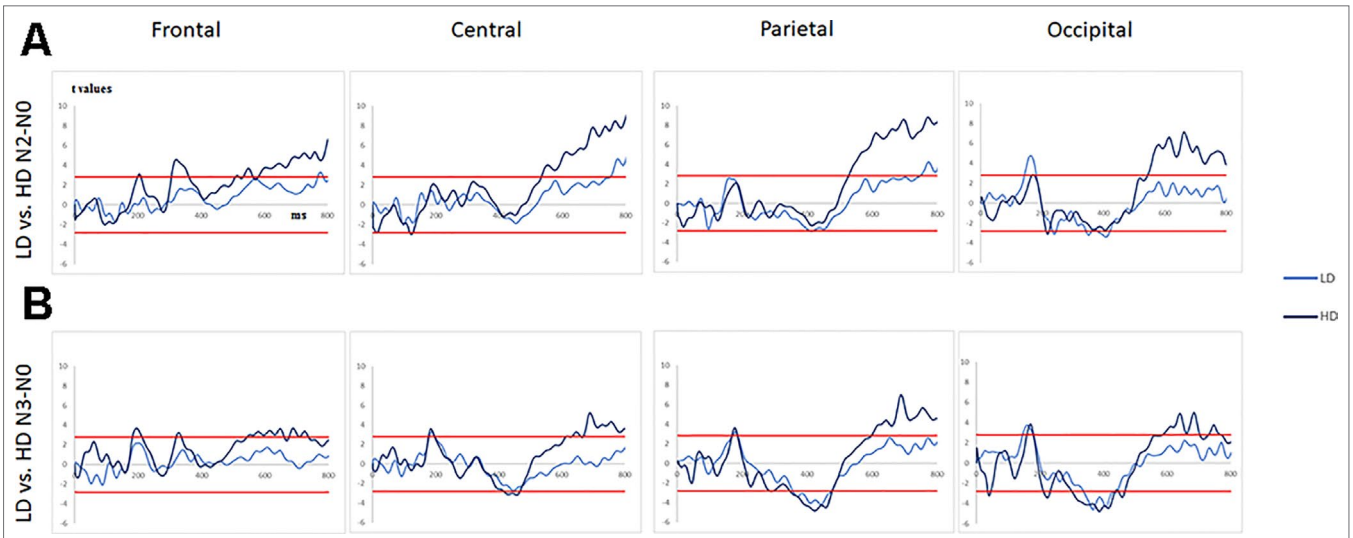

FIGURE 4 | (A) T-values obtained for the subtraction "N2 minus N0" (significance levels are represented by red lines) for the light and the hazardous drinkers at frontal, central, parietal, and occipital sites. **(B)** *T*-values obtained for the subtraction "N3 minus N0" (significance levels are represented as red lines) for the light and the hazardous drinkers at frontal, central, parietal, and occipital sites.

but also that no difference was observable between the groups (as expected) (42). At the ERP level, as the baseline N0 condition was similar across the groups, we computed subtraction "N2 minus N0" and "N3 minus N0" to isolate WM processes (34). By visual inspection, three patterns of activities could be discerned: one around 150 to 250 ms with a maximal activity at posterior sites (P200/N200 complex), one around 300 to 400 ms at frontal sites (P300), and one around 400 to 800 ms as a late positive potential (N400/P600 complex). Therefore, Student's *t*-tests (amplitude of the difference wave compared to zero from 0 to 800 ms) (76, 77) were applied in order to assess statistically significant differences among these three spatiotemporal patterns of activities between the light and the hazardous drinkers.

According to a "functional compensation view," increases in activation reflect "attempted" or "successful" compensation for these deficits during more complex cognitive tasks (47). These changes in cerebral responses may be considered, at the preventive level (particularly for young drinkers), as vulnerability factors for the development of adult SUD (42), but also stressed the importance, at a more clinical level, to consider such WM processes (such as the ability to deal with a high cognitive load) in the management of alcohol dependence. Some studies aiming to train WM efficiency in excessive alcohol users have already been published, disclosing encouraging results (27, 28). Moreover, it has also been shown that prior WM training with a high memory load interferes with the reconsolidation of alcohol-related memories in a sample of nontreatment-seeking heavy drinkers (81). However, more studies tagged dual-process mechanisms [cue reactivity/inhibition; for instance, Refs. (17, 18)]. As WM capacity has been shown to impact cognitive control of impulsivity by way of keeping future goals in mind when making decisions when faced with rewarding/arousing distractions (19), a point that perfectly fits with the dual-process model of cognitive control, further studies aiming to develop cognitive training procedure for alcohol-dependent patients should include the WM process.

Also, it is worth noting that the ERP data we obtained are in line with several previous ERP studies. First, the P200/N200 component has already been described by Missonnier and colleagues (55), by subtracting ERP waveforms from memory-free control tasks (detection) from memory tasks (1-back and 2-back tasks), its amplitude increasing significantly in healthy subjects with higher memory load (2-back vs. 1-back). At the functional level, this complex was interpreted as an *intermediate* phase, as short-term storage should directly follow

TABLE 4A | Statistically significant time intervals (in ms) for the subtracted waveforms exhibited at frontal, central, parietal, and occipital sites for the subtraction "N2 minus N0." A significant interval was considered as relevant (in green) when it lasted for at least 20 ms (76–78). Other intervals (in red) were neither considered nor discussed. P for positive activity; N for negative activity.

	Light drinkers (*n* = 24)	**Hazardous drinkers (*n* = 25)**
Frontal	P [769; 786] P [806; 819]	P [198; 209] P [306; 361] P [508; 520] P [533; 564] P [581; 819]
Central	P [751; 819]	P [11; 15] P [117; 127] P [532; 819]
Parietal	P [406; 419] P [747; 819]	P [527; 819]
Occipital	P [143; 180] N [234; 245] N [343; 361] P [379; 421]	P [167; 174] P [213; 223] P [545; 819]

TABLE 4B | Statistically significant time intervals (in ms) for the subtracted waveforms exhibited at frontal, central, parietal, and occipital sites for the subtraction "N3 minus N0." A significant interval was considered as relevant (in green) when it lasted for at least 20 ms (76–78). Other intervals (in red) were neither considered nor discussed. P for positive activity; N for negative activity.

	Light drinkers (*n* = 24)	Hazardous drinkers (*n* = 25)
Frontal	Ø	P [182; 211] P [320; 335] P [544; 659] P [676; 736]
Central	P [180; 196]	P [177; 196] N [415; 467] P [613; 622] P [632; 659] P [668; 819]
Parietal	P [169; 186] N [356; 475] P [808; 819]	P [168; 187] N [283; 295] P [346; 476] P [597; 819]
Occipital	P [146; 178] N [337; 443]	N [36; 45] P [159; 178] N [211; 231] N [300; 435] N [447; 466] P [585; 702] P [730; 769]

pure sensory-driven processes (such as the P100) and precede execution-related processes (300 ms or later). Therefore, the P200/N200 complex could refer to the visual encoding of the stimulus, translated into its corresponding phonological representations (1), which is created and stored in the posterior parietal cortex, remains active for a few seconds, and constitutes *the storage function of verbal working memory* (82). It needs to be emphasized that the light drinkers exhibited higher responses (for the P200 in the N2-back task) than the hazardous ones. Usually, when task-relevant images are displayed, the early/sustained attention increases, thereby increasing the impact of the stimuli [e.g., Ref. (83)]. This could suggest that the light drinkers generally exhibited an *enhanced early visual attentional process* to ease task performance compared to the hazardous drinkers (consistent with a recollection process aided by visual imagery) (36). Secondly, similarities were also found with a study by Johnson et al. (79), which focused on the *refreshing* process. Refreshing is thought to be a key process for selecting, maintaining, and manipulating information within WM (84), and is, therefore, a critical component in tasks that require manipulation such as updating (e.g., *n*-back) (85). In that study, ERP analyses showed that a typical refresh task does have a distinct electrophysiological response compared to a control condition, and it includes at least two main temporal components: an earlier (∼400 ms) positive peak reminiscent of a P3a/P3b response and a later (∼800–1,400 ms) sustained positivity over several sites reminiscent of the late directing attention positivity (P600 or LDAP) (79). In our study, we found a positive component around 280 to 400 ms, and one around 500 to 800 ms as a late positive potential. These two distinct component cognitive processes are consistent with a two-phase model predicted from fMRI: the first phase referring to the initiation of an appropriate nonautomatic cognitive or motor action based on the interpretation of a cue, and the second reflecting top-down modulation carrying meaningful information about currently active mental representation (79). In this view, it seems reasonable to draw some connections between these two components and the P3 family of responses (typically occurring around 280–500 ms) (86) and the P600 or LDAP (typically arising around 500 ms post-cue) (87). On the one hand, our component around 280 to 400 ms could be related to both the P3a, which is related to the initial orientation to and evaluation of a stimulus, driven primarily by prefrontal regions (88), and the P3b, which appears to be related more to the resolution of uncertainty about stimuli and the concomitant updating of expectancies or context, potentially engaging additional attentional or memory processes, and driven primarily by temporoparietal activity (86, 88). On the other hand, our late positive component from 500 to 800 ms may be seen as similar to a P600 or LDAP, a late positive potential associated with perceptual attention, lasting up to several hundred milliseconds. It has been interpreted as arising from the anticipatory top-down modulation of visual regions in response to the refreshing of a visual representation [e.g., Ref. (89)]. Such WM processes required more intense and sustained activities in the hazardous drinkers compared to the light ones, therefore suggesting a type of vulnerability of these cognitive processes. Thirdly, it is also worth noting that such an LDAP has also been previously linked to an N400 component. Indeed, Finnigan and colleagues (80) recorded ERPs while subjects made old/new recognition judgments on new unstudied words and old words that had been presented in the study either once ("weak") or three times ("strong"). They showed that the N400 component was found to be modulated in a graded manner by the memory trace strength (i.e., an "N400 strength effect") while the amplitude of the LDAP was sensitive to confidence in the decision accuracy. In the present study, the light drinkers exhibited higher amplitudes for this N400 component compared to the hazardous drinkers, suggesting a more intense memory trace.

Overall, one of the main strengths of ERPs is to be able to provide *a dynamic temporal view* of a cognitive process. Using visual *n*-back WM with different cognitive loads (N2-back, N3-back) appears to reveal such an information-processing stream, impacted by alcohol consumption: aside from physical processing of visual stimuli, participants have 1) to translate, encode, and store visual stimuli in short-term verbal memory (i.e., the P200/N200 complex); 2) to orient attention to stimuli (P3a), update short-term memory, and make decisions (P3b); and 3) this decision being impacted by the memory trace strength (N400) and confidence in the decision accuracy (LDAP). *To perform the task at the same level as the light drinkers, the hazardous drinkers exhibited a higher processing intensity throughout the information-processing stream, notably around the P300 and the LDAP components, while the light drinkers could merely increase early visual attention (P200) in order to obtain a better memory trace (N400).* This increment in the neural resources needed to accomplish a more and more complex task can be seen as a compensation strategy. According to a "functional compensation

view," concomitant increases in activation reflect "successful" compensation for these deficits (47). Indeed, due to neuronal loss induced by the neurotoxic effect of alcohol, excessive drinkers need more resources to successfully perform a task. This could imply that 1) once the threshold of available resources is reached (for instance, by making the task more and more complex), a behavioral deficit will appear; and 2) with a less efficient WM load process, excessive drinkers may have fewer resources to plan long-term goals (e.g., be healthy), increasing propensity (i.e., decreasing cognitive control) towards an immediate reward (e.g., a drink). Therefore, it is important to highlight such data for at least two main reasons. First, at a preventive level, it seems important to stress that, *at a stage at which behavioral manifestations are not yet observable,* social heavy drinking is not just trivial social fun, as it induces substantial neural modifications subtending cognitive functions such as WM processes that may impact continuation of excessive alcohol consumption (for instance, by minimizing the impact of long-term consequences). And second, at a clinical level, training WM load capacity may reduce future alcohol consumption by increasing attention toward long-term goals, by increasing control toward immediate rewards that are not relevant to long-term prospects, and by facilitating reconsolidation of alcohol-related memories [e.g., Refs. (27, 28, Kaag et al., 2017)].

Clearly, we are fully aware that our present findings do not allow us to map ERP phenomena directly onto specific cortical areas, and that the relationships that we present above (even though theoretically grounded) are speculative. Such clear associations can, for instance, be obtained through combined ERP-fMRI studies [e.g., Ref. (90)]. We are also aware that it is not possible, from the present study, to completely discount the possibility that the differential effects observed for the hazardous drinkers are pre-morbid in nature, i.e., they existed prior to any alcohol consumption. In this view, further longitudinal studies should be designed in order to verify whether the emergence of brain differences in heavy drinkers did or did not follow the onset of drinking habits. Also, even though the N3-back tasks were more difficult than the N2-back tasks at the behavioral level, electrophysiological group differences between N2 and N0 conditions revealed *higher amplitude differences* than those between N3 and N0 conditions. This could be due to an "order effect," as the participants were always exposed to N2-back tasks *before* N3 ones. This ensured that all of the participants were exposed to conditions that were entirely similar. However, the participants could also develop a strategy to perform the N2-back condition and then apply it in the N3-back tasks so that the latter could require fewer neural resources than if they had been performed first (i.e., when the participants were still "naive" and have to adapt to the task). A fatigability effect cannot be excluded either. Therefore, further studies should alter the order of the presentation of these different conditions in order to be able to directly compare N3-back and N2-back tasks. Indeed, such a comparison would be biased in the present study as neural activities recorded in the N3-back condition appear to be decreased compared to the N2-back ones due to a type of "habituation" effect. This way, one could investigate whether differences between light and hazardous drinkers increase as a function of the cognitive load.

ETHICS STATEMENT

The local ethics committee of the Brugmann Hospital approved the study ("Comité d'Ethique Hospitalier CE 2010/156").

AUTHOR CONTRIBUTIONS

ES and CD contributed equally to the paper (coauthors). They acquired and processed the data and wrote the paper. XN and CK participated to writing the paper. SC participated to task design and paper writing.

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The Effect of High-Frequency Repetitive Transcranial Magnetic Stimulation on Emotion Processing, Reappraisal, and Craving in Alcohol Use Disorder Patients and Healthy Controls: A Functional Magnetic Resonance Imaging Study

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Impaired cognitive–motivational functioning is present in many psychiatric disorders, including alcohol use disorder (AUD). Emotion regulation is a key intermediate factor, relating to the (cognitive) regulation of emotional and motivational states, such as in regulation of craving or negative emotions that may lead to relapse in alcohol use. These cognitive–motivational functions, including emotion regulation, are a target in cognitive behavioral therapy and may possibly be improved by neurostimulation techniques. The present between-subjects, single-blind study assesses the effects of sham-controlled high-frequency neuronavigated repetitive transcranial magnetic stimulation (10 Hz) of the right dorsolateral prefrontal cortex (dlPFC) on several aspects relevant for emotion regulation (emotion processing and reappraisal abilities) and related brain activity, as well as self-reported craving in a sample of alcohol use disorder patients (AUD; n = 39) and healthy controls (HC; n = 36). During the emotion reappraisal task, participants were instructed to either attend or reappraise their emotions related to the negative, positive, neutral, and alcohol-related images, after which they rated their experienced emotions. We found that repetitive transcranial magnetic stimulation (rTMS) reduces self-reported experienced emotions in response to positive and negative images in AUD patients, whereas experienced emotions were increased in response to neutral and positive images in HCs. In the functional magnetic resonance imaging (fMRI) analyses, we found that rTMS reduces right dlPFC activity during appraisal of affective images relative to sham stimulation only in AUD patients. We could not confirm our hypotheses regarding the effect of rTMS craving levels, or on reappraisal related brain function, since no significant effects of rTMS on craving or reappraisal related brain function were found. These findings imply that rTMS can reduce the emotional impact of images as reflected in blood oxygenation level-dependent

(BOLD) response, especially in AUD patients. Future studies should replicate and expand the current study, for instance, by assessing the effect of multiple stimulation sessions on both explicit and implicit emotion regulation paradigms and craving, and assess the effect of rTMS within subgroups with specific addiction-relevant image preferences.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier NCT02557815.

Keywords: alcohol use disorder, emotion reappraisal, craving, functional magnetic resonance imaging, emotion processing, repetetitive transcranial magnetic stimulation

INTRODUCTION

Harmful alcohol consumption ranks among the top five worldwide contributors of disease, disability, and death (1–3), and alcohol use disorder (AUD) is a common mental health disorder with a 12-month prevalence of 2–3% in the United States (4, 5) and 4% in Europe (6).

AUD is often described as a dual process disorder with reduced cognitive control and alterations in the brain reward system (7–9). Alterations in the reward circuitry include hypersensitivity to addiction relevant cues, in combination with hyposensitivity to natural rewards. This reward deficiency may lead to a disbalance in the reward system favoring addiction-relevant stimuli (10, 11). Brain alterations related to cognitive control include impaired (response) inhibition and emotion regulation (12), resulting in diminished ability to effectively control the emotional impact of certain thoughts or stimuli (13, 14). These changes in the reward circuitry and diminished control over emotions increase alcohol craving and relapse in remitted patients (15–17).

Emotion regulation can be described as the process of moderating the emotional impact of a thought or stimulus and may be achieved through various strategies ranging from relatively automatic and implicit (i.e., extinction) to explicit and cognitively controlled (reappraisal) (18). A recent review indicates that impaired emotion regulation is present in AUD based on various studies employing implicit (e.g., non-effortful) emotion regulation tasks such as emotion reactivity, implicit reappraisal, or behavioral control tasks (12). Impairments in reappraisal are supposed to be related to the development, persistence, and severity of substance dependence (19). Difficulties in coping with negative affect is one of the most prominent clinical factors in substance dependence (20), and the induction of negative affect may increase the urge to drink (16, 21), but studies on more controlled and explicit emotion regulation in substance use disordered patients are scarce. Explicit emotion reappraisal has been linked to several prefrontal brain areas: the dorsolateral prefrontal cortex (dlPFC) (for maintaining attentional and manipulating relevant information), ventrolateral prefrontal cortex (vlPFC) (for selecting the goal-appropriate interpretation), and dorsal anterior cingulate cortex (dACC) and dorsomedial prefrontal cortex (dmPFC) (both for conflict monitoring of the intended versus the actual behavioral outcomes) (18).

In our previous study within this special issue, we showed that *explicit* emotion regulation (reappraisal) abilities and related brain functioning were similar in alcohol use disorder (AUD) patients and healthy controls (HCs), but that in AUD patients compared to HCs, reduced brain activity during implicit emotion processing was present (Jansen et al., submitted). Based on these findings and the current literature, it seems that AUD patients are not impaired in explicit emotion regulation when actively instructed to apply these strategies, but that they do show reduced brain activity while watching emotional stimuli. A reduced response to non-addiction-relevant emotional cues in AUD patients may be related to a reduced salience of these non-addiction-related emotional stimuli.

Motivational interviewing and cognitive behavioral therapies are effective treatments for substance use disorders, including AUDs (22). Research suggests not only that psychological interventions should precede pharmacological treatment, but also that both types of treatment are effective (23, 24). After an initially successful period of abstinence, an estimated 50% of patients relapse into alcohol use within the first year (25–28). Similar results have been obtained for the pharmacotherapy of AUDs (25). These high relapse rates indicate that research into new treatment possibilities is warranted.

Noninvasive neurostimulation of the prefrontal cortex, using techniques such as repetitive transcranial magnetic stimulation (rTMS), may offer a new alternative intervention method for substance use disorder patients (29, 30). rTMS and other forms of neuromodulation can reduce acute craving in patients with a substance use disorder (31), especially when stimulating the (right) dlPFC (29) and improve cognitive functions such as attention, memory, and executive functioning in patients with substance use disorders (32, 33). In recent years, increased attention has been directed toward improving emotion processing and emotion reappraisal with prefrontal rTMS, often directed toward the dlPFC, which is central in explicitly controlled emotion regulation strategies, including reappraisal (18). These studies vary in their methodology and reveal contradictory results with high-frequency *right* dlPFC rTMS being associated with an increase in attentional bias toward negative stimuli (34), whereas high-frequency *left* dlPFC stimulation decreased the amygdala response to negative stimuli (35). Additionally, a recent review concludes that rTMS influences cognitive control and the attentional and affective aspects of emotion regulation and that rTMS should be investigated for substance use disordered patients (33, 36).

The five rTMS studies that are discussed by Choi et al. (36) use varying methodological approaches regarding stimulation location (right and/or left dlPFC, cerebellum), stimulation frequency (high and low frequency), and study outcome (autonomic reactions, attention, mood, and affective processing). De Raedt et al. (37) and Vanderhasselt et al. (34) investigated the effects of sham-controlled

high-frequency rTMS of the dlPFC on attentional aspects of emotion regulation, and both conclude that right dlPFC rTMS increased attention toward—or decreased disengagement of—negative stimuli. One study employing sham-controlled high- and low-frequency stimulation of the right dlPFC shows that low-frequency (but not high-frequency) stimulation increased heart rate deceleration in response to negative and neutral, relative to positive, pictures (38). Another study employing low-frequency stimulation of the right dlPFC shows increased responses to fearful faces compared to neutral faces in the right temporal junction (39). Finally, Schutter and van Honk (40) showed that sham-controlled low-frequency stimulation of the cerebellum increased negative mood after an emotion regulation task. Additionally, more recent findings are mixed: high-frequency right dlPFC rTMS stimulation was found not to influence heart rate reactivity to positive or negative images (38) or emotion recognition performance (41). Notzon et al. (42), on the other hand, found high-frequency rTMS of the right DLPFC, compared to low-frequency rTMS, to improve emotion discrimination, leading the authors to conclude that high-frequency rTMS leads to better cognitive control over aversive stimuli. Despite the variety in applied study methods, these studies indicate that rTMS may influence emotion processing and reappraisal in healthy subjects. Other studies suggest that the effect of rTMS may be different in persons with a psychiatric disorder (32), and in a recent study, we have shown that high-frequency *left* dlPFC stimulation may reduce self-reported affect related to negative images in obsessive–compulsive disorder patients and that it reduces dorsomedial prefrontal cortex (PFC) activity relative to sham stimulation, independent of task conditions (43). This study is one of the few studies to investigate the effect of rTMS on both emotion processing and reappraisal at a behavioral and neural level. There are currently no rTMS studies on emotion processing and reappraisal in AUD patients, while these processes are highly relevant for the treatment of this disorder. Cognitive behavioral therapies, for example, often include some form of emotion regulation training (44, 45).

The current study is the first to investigate the effect of high-frequency rTMS on emotion processing and reappraisal in AUD patients and HCs at a behavioral and neural level. Based on previous studies (29), we hypothesize that high-frequency rTMS of the right dlPFC ameliorates reappraisal and the recruitment of the reappraisal-related brain network in both AUD patients and HCs, but this improvement is expected to be greater in the AUD group compared to the HC group [see Ref. (32)]. We expect that high-frequency stimulation will influence (increase or decrease) emotion processing at a behavioral and neural level. Finally, we expect that in AUD patients, high-frequency rTMS decreases reappraisal task-induced craving.

METHODS

This study is part of a larger study, with two fMRI sessions, focusing on differences in emotion regulation performance and related brain activity between AUD patients and HCs during the first (baseline) session and the effect of rTMS on craving, emotion regulation, and related brain activity during the second (rTMS stimulation) session. For a description of the main task effects (e.g., experimental manipulation during the first session), as well as the between-participant group differences at baseline (ADP vs. HC), please see our previous manuscript within this special issue (Jansen et al., submitted). The current manuscript describes the effects of rTMS on emotion processing, reappraisal, craving, and related brain activity.

Participants

A total of 39 AUD patients (26 males) and 36 HCs (20 males) were included in this between-subjects study and were matched on (mean) age, sex, and education. AUD patients were sober for at least 3 weeks and were recruited from addiction treatment centers in the larger city area of Amsterdam, the Netherlands. Sobriety was confirmed with a urine test in the research lab on the test days. None of the participants used psychoactive medication, cannabis, opioids, or stimulants. HCs were recruited through Internet and social media advertisements. All participants were screened for MRI suitability. All subjects were screened (and if positive excluded) for the presence or a history of psychiatric disorders, including substance abuse or dependence, using the Composite International Diagnostic Interview (CIDI) (46). The study was approved by the local Medical Ethical Commission of the Academic Medical Center of the University of Amsterdam and participants signed the informed consent form, consistent with the Declaration of Helsinki, before participating in the study. Participants were remunerated for their participation.

Questionnaires

In addition to the CIDI interview, the Alcohol Use Disorder Identification Test (AUDIT) (47), Beck's Depression Inventory (BDI) (48), Beck's Anxiety Inventory (BAI) (49), the Toronto Alexithymia Scale-20 (TAS-20) (50), and the Emotion Regulation Questionnaire (ERQ) (51) were administered to assess alcohol problem severity, depression severity, anxiety severity, alexithymia, and emotion regulation, respectively. Finally, craving was assessed with the Alcohol Urge Questionnaire (AUQ) (52) before and after the performance of the emotion reappraisal task in both sessions.

Emotion Reappraisal Task

Two matched versions of the task were programmed in E-Prime 2.0 and presented in a counterbalanced order in two different sessions during fMRI scanning. Each session, participants viewed nine negative, nine positive, nine neutral, and nine alcohol-related images on a screen using a mirror attached to the head coil. The negative, positive, and neutral images used in this task were selected from the International Affective Picture Set (IAPS) (53). Negative images had a low valence (≤4.0) and high arousal (≥6.0), neutral images had a mildly positive valence ($4.5 < x < 7.0$) and low arousal ($2.0 < x < 4.2$), and positive images had high valence (≥7.0) and high arousal (≥5.0), based on the original IAPS scores. The alcohol-related images were selected from Vollstädt-Klein et al. (54) and supplemented by alcohol-related images of popular Dutch alcoholic beverages. All alcohol-related images were separately validated in an independent sample of

both HCs and AUD patients ($n = 17$) for valence (mildly positive: $3.0 < x < 6.0$) and arousal (low: $2.0 < x < 4.0$).

The images were paired with one of two different instructions: "attend" and "reappraise." In the attend instruction, participants were told to view and identify themselves with the situation in the image (e.g., "how would you feel in this situation"). In the reappraise condition, participants were told to reappraise their emotions related to these images in such a way that the emotional significance was reduced (e.g., "imagine a less negative outcome or interpretation"). Images were presented in 12 blocks of three images of the same emotion type (negative, positive, neutral, and alcohol) with the same instruction (attend and reappraise) and presented in a pseudo-randomized order.

After each image, for both instructions (attend and reappraise), a visual analogue scale (VAS) was presented. Participants had to rate their emotional state ("How do you feel?") by moving a bar to the right or left by pressing a button box multiple times. A moving bar was set in the middle of a line (representing a neutral value of 50) and the range of emotions on this line was indicated by previously validated self-assessment manikins depicting valence (55). Indicated values ranged from 0 (negative, extreme left of the line) to 100 (positive, extreme right of the line). Prior to scanning, the assessment was explained and practiced outside the scanner using example stimuli (not used in the experiments) for approximately 5 min (for more information, see **S1**). The reappraisal task itself took approximately 25 min.

Repetitive Transcranial Magnetic Stimulation

In the stimulation session, participants received either (single-blind) neuro-navigated (Visor2, ANT) sham or active right dlPFC rTMS using a MagStim Rapid2 Air-film coil with a 70-mm diameter (MagStim Co., UK) immediately before entering the MRI. The active rTMS consisted of sixty 5-s trains of 10 Hz at 110% motor threshold (31). These parameters are within the international safety limits for use of rTMS (56). The stimulation location was defined for each individual separately as the most significant peak voxel in the right dlPFC activated during the reappraisal task in the baseline session for the [reappraise minus attend] contrast, as defined by the BrainMap database (57). Sham stimulation was performed using identical parameters, but the rTMS coil was tilted 90° relative to the skull (58).

Analysis

Behavioral Analysis

Data were prepared for analysis by winsorizing extreme values for experienced emotion (mean VAS per condition and session) and craving (AUQ pre- and post-scores), by replacing values below the 5th and above the 95th percentile with the 5th or 95th percentile, respectively, and by confirming that experienced emotion was normally distributed.

In order to assess effects of stimulation (rTMS/sham), image type (positive/neutral/negative/alcohol), instruction (attend/reappraise), and participant group (AUD/HC) on experienced emotion, a four-way general linear model (GLM) Univariate ANOVA was performed, including experienced emotion after rTMS (condition-specific mean VAS) as the dependent variable, and instruction, image type, participant group, and stimulation as fixed factors. Condition-specific experienced emotion during the first session (before rTMS) was incorporated as a covariate. Significant interactions were followed up by Bonferroni-corrected simple effects analyses.

The AUQ was administered before (pre) and after (post) the reappraisal task during each session. Due to the many mistakes that were made in the second and seventh AUQ question—which are reverse coded and were misinterpreted—these were excluded from the analysis. Pre- and post-scores on both sessions were positively skewed and therefore a $\log(x + 1)$ transformation was applied. A GLM Univariate ANOVA was performed including AUQ scores as the dependent variable, time (pre/post) as the within-subjects factor, and both stimulation (rTMS/sham) and participant group (AUD/HC) as the between-group factor.

Functional Magnetic Resonance Imaging

Data Acquisition

MRI scanning was performed on a Philips Achieva 3T scanner at the Spinoza Imaging Centre, Amsterdam, the Netherlands. Functional MRI [echo time (TE) = 27.63 ms; repetition time (TR) = 2,000 ms; field of view (FOV) = 240 × 240 mm, 37 3-mm slices, 0.3-mm slice gap; 80 × 80 matrix; flip angle = 76.1°] was performed to acquire blood oxygenation level-dependent (BOLD) signals using single-shot multi-echo (59) T2*-weighted echo planar imaging (EPI). These T2-weighted flow-compensated eight spin-echo anatomical images were oriented axially along the anterior commissure to the posterior commissure (AC–PC) line. During the baseline session, a T1-weighted 3D data set was obtained for anatomical reference; TR = 8.196 ms, TE = 3.73 ms, field of view (FOV) = 140 × 188 × 220 mm, 240 × 187 matrix, flip angle = 8°, slice thickness = 1 mm, number of slices = 220.

Pre-Processing and First-Level Analysis

Pre-processing was performed with SPM8 (Wellcome Trust Centre for Neuroimaging, London, United Kingdom) in MATLAB (version 2012b) and included realignment to the first image, slice timing correction to the middle (18th) slice, coregistration of the anatomical T1 of the subject to the mean functional scan, and warping of this coregistered T1 to standard space. Next, the volumes were normalized to the Montreal Neurological Institute (MNI) template and smoothed with a 7-mm Gaussian kernel in order to increase signal-to-noise ratio. To account for low-frequency drifts, a high-pass filter (128 Hz) was applied. Three subjects (2 AUD, 1 HC) were removed due to low quality of the fMRI data (e.g., scanner artifacts).

In the first-level model, regressors of no interest were instruction and VAS scoring. Instruction was modeled with boxcars of 3 s, whereas VAS scoring was modeled with a boxcar for the true duration of the scoring process since this was self-paced. The eight regressors of interest included the onsets of the negative, positive, neutral, and alcohol-related images in either attending or reappraising condition, which were modeled as boxcars (duration, 5 s) and convolved with a hemodynamic response function, in the first-level, single-subject, fixed-effects analysis. First-level contrasts for reappraisal [reappraise > attend] were computed per emotion

condition (negative, positive, alcohol, and neutral). For emotion processing, separate contrasts were created for attending emotional images (alcohol, positive, or negative) versus neutral images [attend emotion (positive, negative, alcohol) > attend neutral].

Functional Magnetic Resonance Imaging Data Analysis

In order to assess the effects of rTMS on emotion processing and emotion reappraisal, separate second-level fMRI analyses were performed.

For the attend condition (emotion processing), a 3 × 2 × 2 ANOVA was conducted in SPM12, including the [attend emotion > attend neutral] contrast per image type (alcohol, positive, and negative), in order to assess the interaction between image type (alcohol, positive, and negative), group (AUD and HC), and stimulation (rTMS and sham). Additionally, two-way interactions (group by stimulation, image type by stimulation, and group by emotion type) were assessed.

For the reappraise condition, a 4 × 2 × 2 ANOVA was conducted in SPM12, including the [reappraise > attend] contrasts per image type, in order to assess the interaction between image type (alcohol, neutral, positive, and negative), group (AUD and HC), and stimulation (rTMS and sham). Additionally, two-way interactions (group by stimulation, image type by stimulation, and group by image type) were assessed. All results are reported at a whole brain $p < 0.05$ family wise error (FWE)-corrected threshold.

RESULTS

Demographics

AUD patients and HCs were successfully matched on age, gender, and years of education. However, AUD patients reported significantly higher levels of smoking, depression (BDI), anxiety (BAI), and alexithymia (TAS-20). Analyses were not corrected for these differences, because depression, anxiety, and alexithymia levels are well known to be elevated in AUD (60–62) and are related to emotion processing and reappraisal, and thus correction for these factors could results in false-negative findings. Remarkably, there were no group differences in the ERQ scores (**Table 1**). Furthermore, there were no significant differences on any of the questionnaires between participants receiving active rTMS or sham rTMS.

Repetitive Transcranial Magnetic Stimulation Effects

Emotion Processing and Reappraisal

The four-way repeated-measures ANOVA with experienced emotion (mean VAS per condition after rTMS) as the dependent variable, image type (negative, positive, neutral, and alcohol), instruction (attend and reappraise) as within-subject factors, and participant group (AUD and HC) and stimulation (rTMS and sham) as between-subject factors—while correcting for baseline experienced emotion (mean VAS per condition) before rTMS—did not reveal a significant four-way interaction [$F(3,559) = .11$, $p = 0.95$, $d < 0.01$]. There was, however, a significant three-way interaction between image type, participant group, and stimulation [$F(3,559) = 7.18$, $p < 0.001$, $d = 0.39$].

To interpret the significant three-way interaction, we conducted separate GLM Univariate ANOVAs per image type (negative, positive, neutral, and alcohol related), including experienced emotion (mean VAS per condition after rTMS) as the dependent variable, and participant group (AUD and HC) as well as stimulation (rTMS and sham) as between-subject factors—while correcting for baseline experienced emotion (mean VAS per condition) before rTMS. The results of these analyses reveal significant interactions between participant group and stimulation for negative [$F(1,143) = 4.86$, $p = 0.03$, $d = 0.37$], positive [$F(1,143) = 18.38$, $p < 0.001$, $d = 0.11$], and neutral images [$F(1,143) = 6.48$, $p = 0.01$, $d = 0.04$], but not for

TABLE 1 | Sample characteristics.

	Mean AUD (sd) *n* = 39	Mean HC (sd) *n* = 36	Significance
Age	41.64 (8.63)	43.75 (10.90)	$t(1,73) = .93$, $p = 0.35$
Years of education	15.31 (3.05)	15.53 (2.85)	$t(1,71) = .49$, $p = 0.62$
Gender	M = 26	M = 20	$\chi^2(1,73) = .97$, $p = 0.32$
AUDIT	22.11 (10.51)	4.23 (2.52)	$t(1,70) = 9.80$, $p < 0.001$
Current smoker	Yes *n* = 29/35 (82.9%)	Yes *n* = 10/32 (31.3%)	$\chi^2(1,67) = 18.30$, $p < 0.001$
TAS-20 total	51.43 (10.83)	42.97 (8.88)	$t(1,65) = 3.48$, $p = 0.001$
TAS-20 DIDF	31.83 (8.16)	24.82 (7.40)	$t(1,66) = 3.71$, $p < 0.001$
TAS-20 EOT	11.97 (3.30)	11.27 (2.78)	$t(1,69) = .98$, $p = 0.33$
ERQ total	37.81 (7.95)	36.58 (8.42)	$t(1,73) = .90$, $p = 0.37$
ERQ Reappraisal	20.22 (5.87)	19.00 (7.53)	$t(1,71) = .76$, $p = 0.45$
ERQ Suppression	17.72 (5.01)	17.58 (5.08)	$t(1,71) = .01$, $p = 0.99$
Beck Depression Inventory	10.84 (9.58)	4.33 (6.36)	$t(1,72) = 3.41$, $p = 0.001$
Beck Anxiety Inventory	30.40 (8.73)	24.25 (4.67)	$t(1,74) = 3.75$, $p < 0.001$

AUD, alcohol use disorder; HC, healthy controls; SD, standard deviation; AUDIT, Alcohol Use Disorders Identification Test; TAS, Toronto Alexithymia Scale; DIDF, difficulties identifying and describing feelings; EOT, externally oriented thinking; ERQ, emotion regulation questionnaire. ERQ Reappraisal and Suppression are subscales of the ERQ. This table shows the results for the analyses of the sample characteristics. Values are denoted as mean (standard deviation). Total number of participants per comparison may vary due to a small number of missing values.

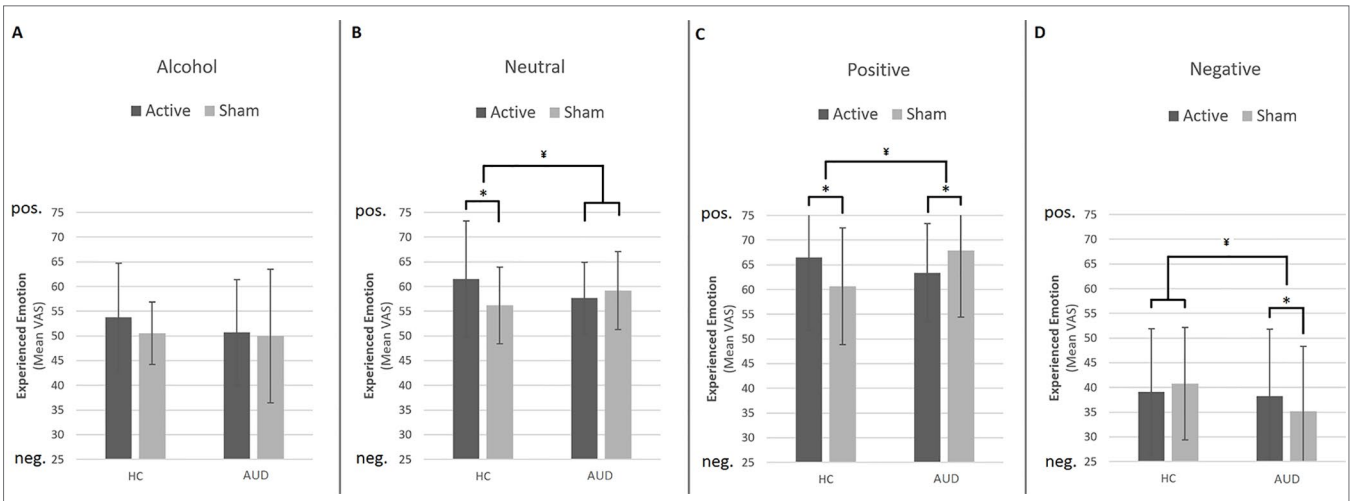

FIGURE 1 | Effect of repetitive transcranial magnetic stimulation (rTMS) on experienced emotion. This figure shows the differential effects of rTMS and sham stimulation on experienced emotion in reaction to alcohol **(A)**, neutral **(B)**, positive **(C)**, and negative **(D)** images. Note that a value of 50 represents "neutral" experienced emotion. Bars represent estimated marginal means, which are corrected for experienced emotion before rTMS. Error bars are standard deviations from the mean. ¥ = significant two-way interaction (group by stimulation), * = significant main effect of stimulation within participant group, pos. = positive, neg. = negative.

alcohol-related images [$F(1,143) = .12$, $p = 0.73$, $d = 0.06$] (see **Figure 1**).

Simple effects analyses show that rTMS dampens experienced emotions in response to positive, neutral, and negative images in AUD patients, whereas in HCs, rTMS intensifies experienced emotions in response to positive and neutral images. For example, experienced emotion in reaction to positive images is more positive after rTMS [mean (m) = 66.50, standard deviation (sd) = 14.66] compared to sham (m = 60.66, sd = 11.82) stimulation in HCs [$F(1,69) = 7.37$, $p = 0.008$, $d = 0.65$], whereas in AUD patients [$F(1,73) = 7.07$, $p = 0.01$, $d = 0.62$], experienced emotion to these images is less positive (e.g., more neutral) after rTMS (m = 63.39, sd = 9.99) compared to sham stimulation (m = 67.87, sd = 13.46). The simple effects analyses for neutral and negative images reveal that rTMS (m = 61.52, sd = 11.77) significantly increases positive experienced emotions to neutral images relative to sham stimulation (m = 56.18, sd = 7.72) in HCs [$F(1,69) = 5.98$, $p = 0.02$, $d = 0.59$], but not in AUD patients [$F(1,73) = 1.00$, $p = 0.32$, $d = 0.24$]. Finally, rTMS (m = 38.26, sd = 13.52) dampens negative emotions in response to negative images in AUD patients relative to sham stimulation [m = 35.18, sd = 13.13; $F(1,73) = 7.07$, $p = 0.01$, $d = 0.62$], but does not affect experienced emotion in HCs [$F(1,69) = .06$, $p = 0.81$, $d = 0.06$].

Craving

The results from the GLM univariate ANOVA with craving levels as the dependent variable, time (pre and post) as within-subjects factor, participant group (AUD and HC), and stimulation (rTMS and sham) as between-subjects factors did *not* reveal a three-way interaction [$F(1,132) = 1.70$, $p = 0.20$, $d = 0.23$]. There was, however, a significant two-way interaction between group and stimulation [$F(1,132) = 4.64$, $p = 0.03$, $d = 0.38$], but not between group and time [$F(1,132) = .36$, $p = 0.55$, $d = 0.11$] or between time and stimulation [$F(1,132) = .90$, $p = 0.34$, $d = 0.17$]. These results indicate that stimulation (rTMS and sham) did not differentially affect the change in craving over time (pre and post) for AUD patients and/or HCs, and therefore do not support our hypothesis that rTMS would reduce craving levels relative to sham stimulation (see **Figure 2**).

Functional Magnetic Resonance Imaging Results

Emotion Processing

Results from the 3 × 2 × 2 ANOVA, including the [attend emotion > attend neutral] contrast per image type, did not reveal a three-way interaction between image type (alcohol, positive, and negative), group (AUD and HC), and stimulation (rTMS and sham). The results do show a significant two-way interaction between group and stimulation within the right dlPFC (see **Figure 3** and **Supplementary Information**), originating from a decrease in dlPFC brain activity after rTMS relative to sham stimulation in the AUD group. The other two-way interactions (emotion by stimulation and group by image type) did not reveal any significant effects.

Emotion Reappraisal

Results from the 4 × 2 × 2 ANOVA, including the [regulate > attend] contrast per emotion, did not reveal a three-way interaction between image type (alcohol, neutral, positive, and negative), group (AUD and HC), and stimulation (rTMS and sham). Although none of the two-way interactions reached significance, there was a trend-significant interaction between image type (alcohol, neutral, positive, and negative) and stimulation (rTMS and sham; $p < 0.1$, FWE corrected). Follow-up analyses revealed that this two-way interaction originated from a difference in the effect of rTMS on brain activity between the reappraisal of positive and negative images in the bilateral superior frontal gyrus for both AUD patients and HCs. rTMS stimulation decreased superior frontal gyrus

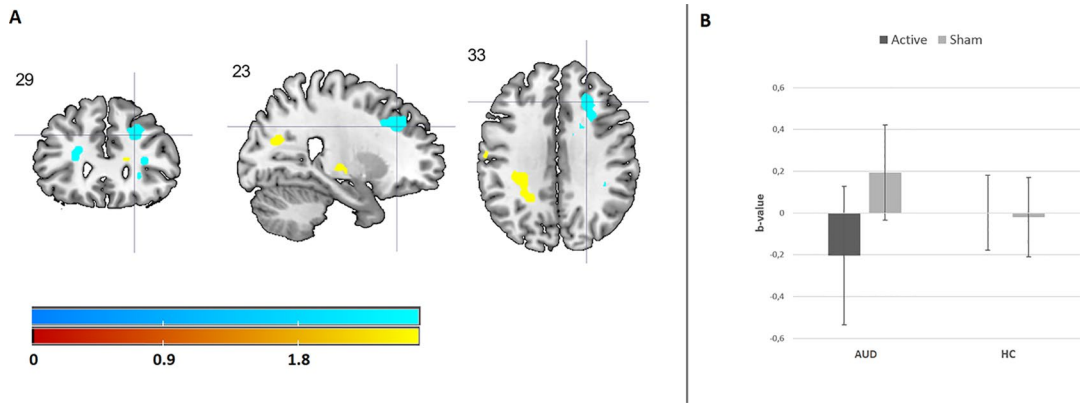

FIGURE 2 | This figure shows the trend-significant interaction between emotion (alcohol, neutral, positive, negative) and stimulation (rTMS, sham) within the superior frontal gyrus. **(A)** This panel shows the location for the interaction in the bilateral superior frontal gyrus. For illustrative purposes, these results are depicted at a $p < 0.001$ uncorrected threshold **(B)**. This panel shows the interaction within the peak voxel in the right superior frontal gyrus, based on the extracted beta weights.

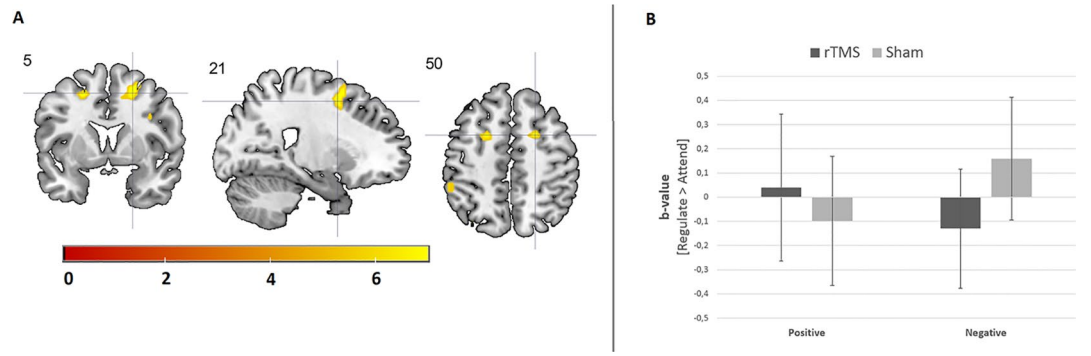

FIGURE 3 | The effect of rTMS on brain activity during emotion processing. **(A)** Cool coloring represents brain activity in the dorsolateral prefrontal cortex (dlPFC), which has decreased due to rTMS relative to sham stimulation in AUD patients. Hot coloring indicates brain activity in the supramarginal gyrus, which has increased due to rTMS stimulation relative to sham stimulation in AUD patients. For illustrative purposes, these results are depicted at a $p < 0.001$ uncorrected threshold. **(B)** This bar chart shows the effect of rTMS and sham stimulation on right dlPFC activity in AUD patients and HCs.

activity in response to negative images relative to sham stimulation, whereas rTMS increased activity in this area in response to positive images (see **Figure 4** and **Supplementary Information**).

DISCUSSION

The purpose of this study was to investigate the effect of sham-controlled high-frequency right dlPFC rTMS on emotion processing, reappraisal ability, and related brain functioning in alcohol use disorder patients (AUD patients) and healthy controls (HCs). We hypothesized that stimulation of the right dlPFC would improve emotion processing and reappraisal—especially in AUD patients—and alter the recruitment of the reappraisal-related brain network. In line with our hypotheses, we found that rTMS reduces self-reported experienced emotions in response to positive and negative images in AUD patients, whereas experienced emotions were increased in response to neutral and positive images in HCs. Instruction (attend or reappraise) did not influence these results. In the fMRI analyses, we found that rTMS reduces right dlPFC activity during appraisal of affective images relative to sham stimulation only in AUD patients. Our results do not support our hypothesis regarding the effect of rTMS on reappraisal-related brain function, since no significant effects of rTMS on reappraisal-related brain function were found. On a lower significance level, however, rTMS—compared to sham stimulation—*decreased* activity during reappraisal of negative images and *increased* activity in the bilateral superior frontal gyrus during reappraisal of positive images in both AUD patients and HCs. rTMS did not influence the change in craving levels compared to sham stimulation.

At a behavioral level, rTMS stimulation reduced the impact of affective (neutral, positive, and negative) images in AUD patients, but increased the impact of positive and neutral images in HCs. No effect of rTMS was found for alcohol-related images in either group, which is not in line with our hypotheses. AUD is characterized by reduced salience of natural stimuli relative to addiction-relevant cues (11), but alcohol consumption has also

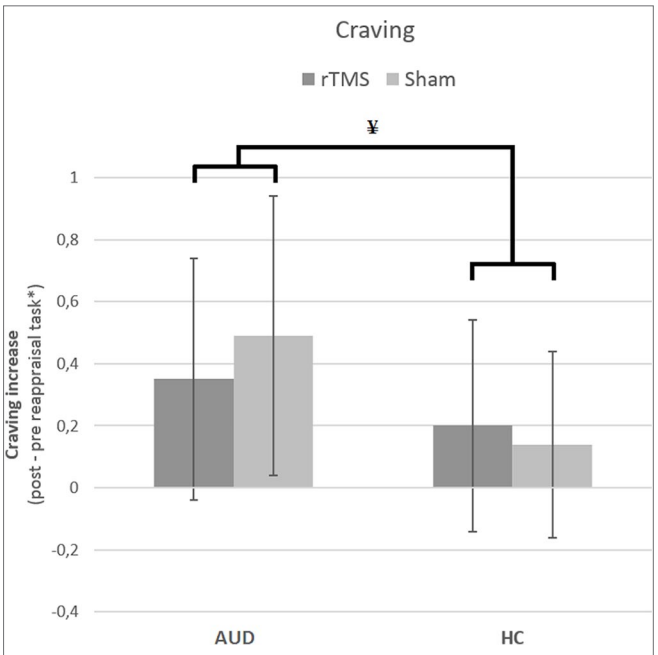

FIGURE 4 | The effect of rTMS and sham stimulation on craving per group. This figure depicts the significant interaction between stimulation (rTMS, sham) and group [alcohol use disorder (AUD), healthy controls (HC)]. * Note that the values are log(x + 1) transformed. ¥ = significant two-way interaction.

been suggested as a self-medication strategy to reduce—relapse-related—stress and negative emotions (63, 64). Therefore, reducing the impact of emotional images in AUD patients through rTMS may be related to reduced emotional impact of affective stimuli, which could possibly reduce stress, craving, and subsequent relapse. This explanation is supported by previous studies, which show positive effects of rTMS on craving reduction (31), cognitive functioning (32, 33), and depressive symptoms (65).

Our results furthermore suggest that rTMS stimulation affects emotion processing and reappraisal in HCs and AUD patients differently, since rTMS reduced emotional experience in AUD patients and reduced right dlPFC activity during emotion processing, whereas experienced emotion was increased in HCs and no effect was found on related brain activity. Although, to our knowledge, there are no other studies on the effect of rTMS on emotion processing and reappraisal in AUD patients, these results are in line with a review that suggests that rTMS effects may differ between healthy and patient populations (32).

These results correspond with previous studies in HCs that reveal that rTMS influences emotion processing (34, 35) and reappraisal (35, 42) in HCs. rTMS increased attentional bias toward negative stimuli in a study in HCs (34) and lead to faster emotion discrimination in HCs (42), which is in line with the strengthened response to (negative) images in HCs after rTMS in our study. Together, these studies imply that high-frequency right dlPFC rTMS impacts emotion processing in HCs, but the neural mechanisms through which these effects occur may partly depend on the paradigm used, which differ between these studies, and are thus in need of further study.

These results are not in line with a recently published multilevel framework on explicit and implicit emotion regulation (18), since the dlPFC is associated with explicitly controlled emotion regulation whereas no effect of dlPFC stimulation on reappraisal was found within this study. The effects on emotion processing reported here may have been caused by (subthreshold) activity changes beyond the site of stimulation that have previously been reported in rTMS studies (66), although none of these effects were found in the fMRI analyses. It is possible that other stimulation targets will render different results; the dmPFC and insula have, for example, been suggested as alternative targets for rTMS stimulation treatment in substance use disorder (67).

Although expected, we did not find any effect of rTMS on experienced emotion, or related brain activity in response to alcohol-related images. This may be explained by the variation in image content, individual preferences for certain alcohol-related contexts, or specific beverage preferences. The images used in the emotion reappraisal task consisted of different variations of alcoholic beverages (beer, wine, and liquor) and alcohol-related contexts (e.g., bar and supermarket). Alcohol-related images may elicit different (e.g., positive and/or negative emotional) responses in AUD patients specifically, due to the psychological burden of having an AUD, and it is possible that these individual differences thus did not result in consistent emotional and brain responses in the AUD group. Increasing the sample size or selecting a subsample of, e.g., beer- or wine-preferring AUD patients, in order to analyze subgroups with specific preferences could clarify these results in future studies.

Finally, in our previous study within this special issue (68), we show that the emotion reappraisal task increases craving levels in both AUD patients and HCs, and that AUD patients have higher overall craving levels. In the current study, we show not only that rTMS affects craving levels differently in AUD patients and HCs but also that the time by stimulation interaction was not significant. These results do not support our hypothesis that rTMS reduces craving levels compared to sham stimulation and are not in line with our meta-analysis on this topic (31), but suggest an accidental preexisting difference in craving levels between the stimulation groups. Furthermore, AUD patients were not eligible for participation when actively using psychoactive medication, including anti-craving medication, due to possible confounding effects on the fMRI data. However, inclusion of non-medicated AUD patients may have resulted in a selection bias. Possibly, these nonmedicated patients are (compared to medicated patient samples) less prone to craving and less susceptible to induction of craving by the emotion reappraisal task. Also, recent reviews (29, 30) suggest that neurostimulation techniques may be more effective in reducing craving for substance use disorder patients when applying more (and longer) stimulation sessions. Finally, although the current study included a larger sample compared to previous neurostimulation and fMRI studies on emotion processing and reappraisal, the sample is still modest, requiring larger effect sizes (or more neurostimulation sessions) to obtain significant results. Future studies should therefore apply more stimulation sessions in a larger AUD sample in order to establish if the rTMS effects reported in this paper are clinically relevant.

Conclusion and Future Directions

This study is the first study that indicates differential effects of sham and high-frequency right dlPFC rTMS on emotion processing, reappraisal ability, and related brain functions in AUD patients and HCs. Subjective experienced emotion during the emotion reappraisal task was reduced after right dlPFC rTMS in AUD patients, but increased the subjective experience in HCs. This possibly indicates an rTMS-related impact on emotion processing of emotional (but not alcohol-related) images in AUD patients. rTMS stimulation changed brain activity in various emotion reappraisal relevant brain areas but did not reduce craving levels in AUD patients. Future studies should replicate and expand the current study, for instance, by assessing the effect of multiple stimulation sessions on both explicit and implicit emotion regulation paradigms and craving, and assess the effect of rTMS within subgroups with specific addiction-relevant image preferences.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of medical ethical committee of the University of Amsterdam Medical Centre, with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the medical ethical committee of the University of Amsterdam Medical Centre.

AUTHOR CONTRIBUTIONS

All authors made a significant contribution to this article, including acquiring funding (AG, WB), study design (AG, WB), development of the emotion reappraisal task (SW, OH, DV, YD), data acquisition (JJ), data analysis (JJ, DV, SW), interpretation of results (JJ, AG, SW, OH, YD, WB, DV), and contributions to this manuscript (JJ, AG, SW, OH, YD, WB, DV).

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00272/full#supplementary-material

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State-Dependent Effects of Ventromedial Prefrontal Cortex Continuous Thetaburst Stimulation on Cocaine Cue Reactivity in Chronic Cocaine Users

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Cue-induced craving is a significant barrier to obtaining abstinence from cocaine. Neuroimaging research has shown that cocaine cue exposure evokes elevated activity in a network of frontal-striatal brain regions involved in drug craving and drug seeking. Prior research from our laboratory has demonstrated that when targeted at the medial prefrontal cortex (mPFC), continuous theta burst stimulation (cTBS), an inhibitory form of non-invasive brain stimulation, can decrease drug cue-related activity in the striatum in cocaine users and alcohol users. However, it is known that there are individual differences in response to repetitive transcranial magnetic stimulation (rTMS), with some individuals being responders and others non-responders. There is some evidence that state-dependent effects influence response to rTMS, with baseline neural state predicting rTMS treatment outcomes. In this single-blind, active sham-controlled crossover study, we assess the striatum as a biomarker of treatment response by determining if baseline drug cue reactivity in the striatum influences striatal response to mPFC cTBS. The brain response to cocaine cues was measured in 19 cocaine-dependent individuals immediately before and after real and sham cTBS (110% resting motor threshold, 3600 total pulses). Group independent component analysis (ICA) revealed a prominent striatum network comprised of bilateral caudate, putamen, and nucleus accumbens, which was modulated by the cocaine cue reactivity task. Baseline drug cue reactivity in this striatal network was inversely related to change in striatum reactivity after real (vs. sham) cTBS treatment (ρ = -.79; $p < .001$; R^2_{Adj} = .58). Specifically, individuals with a *high* striatal response to cocaine cues at baseline had significantly *attenuated* striatal activity after real but not sham cTBS (t_9 = -3.76; $p \leq .005$). These data demonstrate that the effects of mPFC cTBS on the neural circuitry of craving are not uniform and may depend on an individual's baseline frontal-striatal reactivity to cues. This underscores the importance of assessing individual variability as we develop brain stimulation treatments for addiction.

Keywords: addiction, functional magnetic resonance imaging, repetitive transcranial magnetic stimulation, inhibitory, neural circuit, independent component analysis

INTRODUCTION

Substance dependence is a chronic, relapsing brain disease characterized by compulsive drug seeking and use behaviors, despite harmful consequences (1). Cocaine use disorder (CUD) is among the most difficult substance use disorders to treat. The lack of FDA-approved pharmacotherapies, and limited efficacy of conventional psychotherapies, means that as many as 70% of treatment-seeking cocaine users relapse within the first 3 months (1). This leaves cocaine-dependent individuals with limited support for overcoming their chronic illness. Consequently, there is a pressing need for innovative treatment development, including approaches that specifically target the neural circuits associated with continued, habitual use in this population.

One of the strongest precipitants of relapse is drug cue-induced craving (1–4). Craving is associated with activity in reward-motivation brain regions, including the medial prefrontal cortex (mPFC) and striatum (1, 5, 6). Chronic cocaine users exhibit elevated activity in reward-motivation circuitry when exposed to drug-related cues (1, 5, 7). Functional neuroimaging studies have shown that the level of activity in this circuit is related to the intensity of craving (8, 9),and can reliably predict relapse in treatment-seeking substance users (1, 4, 10). Thus, one way to effectively treat CUD may be through a more targeted neurobiological approach, such as by directly modulating activity in this mPFC-striatal craving circuit.

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique that can be used to selectively modulate cortical and subcortical brain activity. Theta burst stimulation (TBS) is a patterned variant of rTMS that mimics endogenous neuronal firing patterns associated with learning and memory (11, 12). Depending on the TBS delivery pattern, either long-term potentiation-like (LTP-like) (intermittent TBS, iTBS) or long-term depression-like (LTD-like) [continuous TBS (cTBS)] effects can be induced in a circuit-specific way (13, 14). A recent study from our laboratory has shown that in cocaine and alcohol users, respectively, mPFC cTBS can lead to a decrease in drug cue reactivity in the mPFC and downstream subcortical targets, including the striatum (15).

However, it is also known that there are individual differences in responses to rTMS treatment, with some individuals responding as expected and others responding less or not at all (16–19). We recently showed that white matter integrity between the mPFC and putamen was one factor that influences individual differences in striatal response to mPFC cTBS (20). In addition, there is some evidence of state-dependent effects, where baseline neural state influences individual differences in response to rTMS (21–23). The objective of the present study was to assess the striatum as a biomarker of treatment response by determining if baseline drug cue reactivity in the striatum influences striatal response to mPFC cTBS. To accomplish this goal, striatal network activity during the cocaine-cue exposure task was extracted using group independent component analysis (ICA) before and after real and sham cTBS, and baseline striatal cue reactivity was related to striatal treatment response.

METHODS

Participants and Procedures

Twenty-five nontreatment-seeking chronic cocaine users [13 females; mean (SD) age = 42 (9) years] were recruited from the Charleston, SC, metropolitan area using digital and print media (i.e., Craigslist, bus ads) to participate in this single-blind, active sham-controlled crossover study. Following informed consent procedures approved by the Medical University of South Carolina Institutional Review Board, participants completed assessments related to protocol safety, mental status, and drug use to determine study eligibility (see **Supplemental Materials, Methods** for detailed inclusion/exclusion information).

Eligible participants completed two MRI/rTMS visits (each ~1 h). A multi-panel urine drug screen (Quikvue 6-panel urine drug screen, Quidel, San Diego, CA) was given to ensure participants were not under the influence of cocaine, [meth]amphetamine, opiates, benzodiazepines, and marijuana during study sessions. A breathalyzer was given to ensure that participants were not under the influence of alcohol. All participants received real cTBS (FP1 landmark based on electroencephalogram (EEG) 10–20 system, 110% resting motor threshold) and sham cTBS (order counterbalanced across participants, six 600-pulse sessions of cTBS on each visit, 60-s break after 1,800 pulses). Functional MRI (fMRI) data were collected immediately before and after exposure to cTBS (see **Supplemental Materials Figure S1** for study design). Visit 2 occurred 7 to 14 days after visit 1. The second cue reactivity fMRI scan was initiated within 10 min of receiving cTBS and completed no later than 30 min after cTBS to maximize presumed effects of cTBS on cortical activity (11). Self-reported cocaine craving was assessed upon visit initiation, before the baseline fMRI scan, before the cTBS session, immediately after cTBS, and immediately after the second fMRI scan.

Clinical Assessments. Self-report assessments included the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders IV (SCID for DSM-IV) (SCID) (24), Timeline Follow-back (TLFB; for cocaine, alcohol, marijuana, and nicotine) (25), Alcohol Use Disorders Identification Test (AUDIT) (26), Fagerstrom Smoking Inventory (27), Beck's Depression Inventory (BDI-II) (28), and Spielberger State-Trait Anxiety Inventory (STAI) (29). TLFB was used to evaluate past week's substance use at screening and both MRI/rTMS visits. In addition, a brief cocaine craving assessment (scale 1–10: 1, no craving; 10, high craving) was administered at five time points during both MRI/rTMS visits to monitor craving levels throughout the study (see **Figure S1**). As typically done in cue-induced craving studies, study personnel ensured craving levels were at or below baseline before participants were dismissed from each visit. Participants received monetary compensation for their time and effort and travel to and from the university.

Cocaine Cue Reactivity fMRI Task. The cocaine cue reactivity task was administered in the MRI scanner as a block design using E-Prime software (Psychology Software Tools, Inc.; 30). The total task time was approximately 12 min and consisted of six 120-s epochs. Each epoch included alternating 24-s blocks of four task conditions: *Drug, Neutral, Blur,* and *Rest*, with each block followed by a 6-s cocaine craving inquiry where participants

were asked to rate their current cocaine craving level on a 1 to 5 rating scale (1, none and 5, high). The task conditions included images of cocaine-related stimuli (e.g., crack pipe; users snorting cocaine), neutral stimuli (e.g., cooking utensils; people eating dinner), blurred stimuli acting as visual controls by matching cocaine images in color and hue, and a fixation cross for alert rest periods. During each task block, five images were presented (4.8 s). Task blocks were counterbalanced across epochs.

Neuroimaging. Participants were scanned using a Siemens 3.0T Tim Trio (Siemens Medical, Erlangen, Germany) MRI scanner with a 32-channel head coil. High-resolution T1-weighted structural images were acquired using a magnetization prepared gradient echo (MPRAGE) sequence (repetition time/echo time = 1,900 ms/2.34 ms; field of view = 220 mm; matrix = 256 × 256 voxels; 192 slices; slice thickness = 1.0 mm with no gap; final resolution = 1 mm^3 voxels). Functional images were acquired with a multislice gradient-echo echo planar imaging (EPI) sequence (repetition time/echo time = 2,200 ms/35 ms; field of view = 192 mm; matrix = 64 x 64 voxels; 36 slices; slice thickness = 3 mm with no gap; final resolution = 3 mm^3 voxels). Each functional run consisted of 328 time points.

cTBS Protocol — Real and Sham cTBS. Coil position was determined using standardized coordinates from the EEG International 10–20 system (with FP1 corresponding to the left mPFC stimulation target). The location and orientation of each participant's coil placement was indicated on a nylon cap that participants wore throughout visit 1 and both MRI/rTMS sessions. Participants' resting motor threshold (rMT; stimulation intensity applied over left motor cortex to produce 50% motor evoked potential response rate in contralateral abductor pollicis brevis) was identified using the standardized PEST procedure (31). The stimulation dose applied to the mPFC was set to be 110% rMT due to the larger scalp-to-cortex distance for PFC versus motor cortex requiring a larger dose to attain equivalent effects (32). The cTBS treatment was administered with a figure-of-eight MagPro Cool-B65 A/P coil (MagVenture, Farum, Denmark). Participants received two 2-min trains of cTBS over FP1 (1 train = 120 s; 3 pulse bursts at 5 Hz; 15 pulses/s; 1,800 pulses/train; 60-s intertrain interval). To enhance tolerability, stimulation intensity was gradually escalated in 5% increments (from 80% to 110% rMT) over the first 30 s of each train.

The Magventure MagPro system includes an integrated active sham. When the coil was oriented in the treatment position, real cTBS was administered, and the scalp electrodes placed on the left frontalis muscle under the coil were not active. When the coil was flipped 180°, the active side of the coil faced *away* from the scalp. In this configuration, the sound and pressure of the coil remained constant and the scalp electrodes became active, thus mimicking the multi-sensory experience of real cTBS, without the CNS stimulation. Previous studies in our laboratory have demonstrated that participants are unable to differentiate real from sham stimulation, with participants exhibiting ~48% accuracy (i.e., ~chance) in identifying whether they received real or sham cTBS in a given session (33). However, for continued assurance, participants were surveyed after each session to routinely assess the integrity of the blinded study.

Cue Recollection During cTBS Administration. Before cTBS administration, participants were asked to recall the last time they used cocaine, and using a series of standardized questions from traditional Narrative Exposure Therapy practice (34), they were asked to describe the place they were using, a visual description of the scene, and a description of the sensory properties of the drug including taste, smell, and sensation. During cTBS administration, the participants were primed every 20 s to "Think about that scene you described wherein you were last using cocaine/crack" (paraphrased such that this was tailored to the participant's description).

Data Analysis

Neuroimaging Preprocessing. MRI data were preprocessed using SPM12 (Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab 7.14 (MathWorks, Inc., Natick, MA; see **Supplemental Materials, Methods** for preprocessing details). Of the 25 recruited participants, 6 participants were excluded for excessive head motion artifact (>3 mm in any plane; x, y, z, roll, pitch, yaw; see **Supplemental Materials, Methods** for details). Data analyses were conducted on the remaining 19 participants [11 males; mean (SD) age = 41 (10) years; range, 21–54 years; see **Table 1** for demographics].

Independent Component Analysis. To accomplish the primary objective of the present study, which was to assess the impact of baseline striatal network drug cue reactivity on cTBS treatment response, the temporal dynamics of the striatal network as a whole were isolated using group-level ICA. Specifically, group spatial ICA was conducted on all 76 cue reactivity task fMRI data sets [4 per participant (pre/post-real, pre/post-sham) × 19 participants] using Matlab's Group ICA of fMRI toolbox (GIFT) (35) (see **Supplemental Materials, Methods** for detailed spatial ICA methods). Briefly, the GIFT ICA procedure uses a two-step data reduction approach. In the first step, principal component analysis (PCA) reduced each subject's data set into 100 subject-specific principal components. For the second step, subject-specific principal components were concatenated and further reduced into 50 group-level principal components, which were then entered into the final group ICA for identification of the 50 group-level independent components. The component reliability was determined by a stability index (20 iterations of ICASSO, Infomax algorithm). Each independent component's subject-specific representation (i.e., unique spatial map and time course) was computed *via* back-reconstruction of the group independent components. These data were normalized to *z* scores to enable comparison across subjects.

General Linear Modeling (GLM) of ICA Network Time Courses. Each subject-specific striatal network time course was entered into a general linear regression [Analysis of Functional Neuroimages' (AFNI's) 3dDeconvolve] with five task conditions (*drug, neutral, blur, rate_craving_drug, rate_craving_other*) and six movement parameters as regressors. For each subject, a mean beta weight value (β) was estimated for the striatal network, which provided a single measure of the level of task-related activity for the network as a whole during each of the task conditions (35–38). Striatal network drug cue reactivity was computed by contrasting network activity during drug cue versus neutral cue conditions. Network drug cue reactivity *after* real/sham cTBS was compared with engagement *before* real/sham cTBS using a factorial design and *post hoc* paired *t* tests.

Linear Regression to Identify Predictors of Neural Response to mPFC cTBS Treatment

Baseline Striatum Drug Cue Reactivity. Robust linear regression was used to determine the association between baseline striatum drug cue reactivity and changes in drug cue reactivity after real (vs. sham) mPFC cTBS. Robust regression was performed in Matlab using iteratively reweighted least squares with a Huber weighting function (default weighting parameter, 1.345). Robust regression was preferred over standard least-squares linear regression due to its minimization of the influence of response variable outliers (39, 40). The regression included baseline striatum network drug cue reactivity as the predictor variable and change in striatum network reactivity after real (vs. sham) cTBS as the outcome variable.

Clinical, Demographic, and Drug Use History Variables. To determine whether clinical and demographic variables influenced or predicted cTBS treatment outcomes, hierarchical multiple linear regressions were conducted with clinical and demographic variables of interest as the predictors and covariate predictors and striatum network reactivity after real (vs. sham) cTBS as the outcome variable.

Scalp-to-Cortex Distance. Given that the effects of TMS on cortical excitability are proportional to the distance between the skull and cortex (32, 41), we calculated the distance from the scalp to cortex on the transverse plane of MPRAGE images for each participant (see **Supplemental Materials, Results**). The average distance from participant-specific placement of FP1 to the cortex was 18 mm (±3.7 mm). These distances were incorporated into the analyses as covariates.

RESULTS

Identification of Striatum ICA Component. Of the 50 components identified by ICA, 17 were classified as noise components (i.e., corresponding to motion and/or other signal artifacts). The 33 non-noise components were comprised of several canonical functional networks commonly associated with sensory, motor, cognitive, and affective processing (42, 43). However, given our focus on evaluating striatum craving circuitry, we focused on the striatum network component, which encompassed bilateral caudate, putamen, and nucleus accumbens (**Figure 1**). Evaluation of the back reconstruction of the striatum component onto the 76 participant data sets confirmed that all participant data sets exhibited a robust striatum network component, including a subject-specific striatum spatial map and time course.

Effect of mPFC cTBS Treatment on Striatum Network Activity During Drug Cue Exposure

Group Analysis. Across all subjects, there was no significant elevation of striatal network activity during drug cue exposure at any time point (**Figure 2A**). Additionally, across all subjects, there was no significant attenuation of striatal network cue reactivity following real versus sham cTBS ($F_{1,68} = 0.17$; $p > 0.05$; **Figure 2A**).

Individual Differences Analysis. Analysis of individual differences, however, revealed that real cTBS *did* strongly alter striatum drug cue reactivity but was modulated by participants' baseline striatum network cue reactivity (**Figure 2B**). Specifically, "cue-sensitive" participants who were responsive to cue induction and initially exhibited *elevated* drug cue reactivity ($t_9 = 4.34$; $p \leq 0.005$), revealed significantly *attenuated* activity after real (vs. sham) cTBS ($t_9 = -3.76$; $p \leq 0.005$; **Figure 2B**, *black bars*). "Cue-insensitive" participants, who were not responsive to cue induction and initially exhibited *suppressed* drug cue reactivity ($t_8 = -4.09$; $p \leq 0.005$), revealed significantly *enhanced* activity after real (vs. sham) cTBS ($t_8 = 4.01$; $p \leq 0.005$; **Figure 2B**, *gray triangles*). These strongly opposing neural responses canceled each other out in the group-level analysis, at both time points, thus causing the group-level analyses to appear non-significant. Conversely, no statistically distinct response patterns were identified for sham stimulation (**Figure 2B**; *striped bars/triangles*). Thus, these data convey a bimodal neural response profile for real (vs. sham) mPFC cTBS (paired *t* test for cue-sensitive vs. cue-insensitive subjects: $t_{17} = -5.36$; $p < 0.005$) and an overall significant three-way interaction between treatment type (real/sham), time (pre/post), and baseline cue reactivity (cue-sensitive/cue-insensitive) ($F_{1,68} = 11.83$, $p = 0.001$). These results are not likely to reflect regression to the mean, as this bimodal

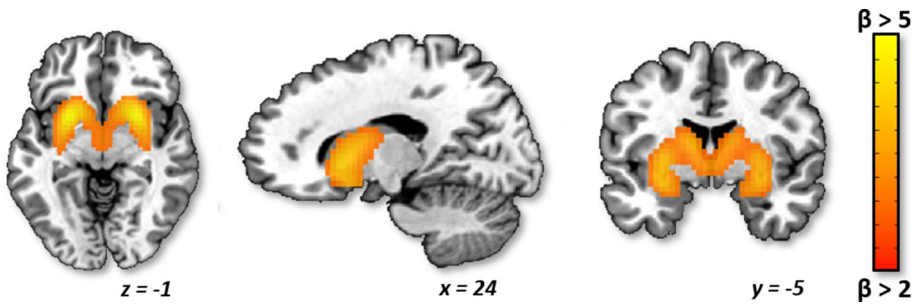

FIGURE 1 | Striatum independent component analysis (ICA) network. Axial, sagittal, and coronal planes are shown, respectively, for the group average striatum network component, which includes the bilateral caudate, putamen, and nucleus accumbens. The network is depicted in neurological convention (left = left) in Montreal Neurological Institute (MNI) coordinate space with cluster-level threshold at β > 2 and minimum cluster size = 50 voxels.

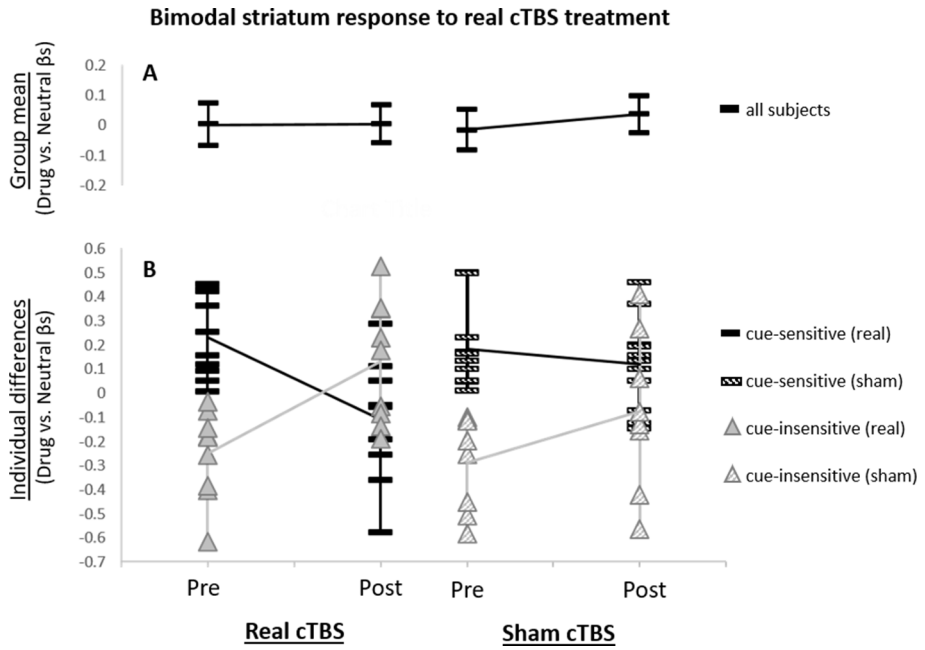

FIGURE 2 | Striatum network drug cue reactivity before and after real and sham continuous theta burst stimulation (cTBS). **(A)** For the group, striatum network did not exhibit significantly elevated drug cue reactivity for any of the functional magnetic resonance imaging (fMRI) scans ($p > 0.05$ for pre- and post-real cTBS and sham, respectively). **(B)** Individual differences analysis revealed a bimodal neural response to real cTBS. Participants, who had initially exhibited elevated striatum network drug cue reactivity ($t_9 = 4.34$; $p \leq 0.005$), revealed significantly attenuated activity after real cTBS ($t_9 = -3.76$; $p \leq 0.005$; black bars). Subjects, who had initially exhibited suppressed network drug cue reactivity ($t_8 = -4.09$; $p \leq 0.005$), revealed significantly enhanced activity after real cTBS ($t_8 = 4.01$; $p \leq 0.005$; gray triangles). No significant differences were found for sham (striped bars/triangles).

response pattern was only seen for the real cTBS condition and not for sham, whereas in the case of regression to the mean, this pattern would be expected for both conditions. In addition, in a *post hoc* analysis, we assessed whether treatment order (real or sham first in this crossover design) influenced treatment response and found no effect.

Baseline Striatum Drug Cue Reactivity Predicts Changes in Striatum Network Response to Real Versus Sham mPFC cTBS. Baseline striatum network drug cue reactivity was strongly inversely related to striatum network reactivity following real (vs. sham) mPFC cTBS ($\rho = -0.79$; $p < 0.001$; $R^2_{Adj} = 0.58$; **Figure 3**).

Influence of Clinical, Demographic, and Drug Use History Variables. Analysis of the influence of clinical and demographic variables on treatment outcomes (see **Table 1** for variables assessed) revealed that only the total years of cocaine use was a significant modulator of striatum drug cue reactivity—for both baseline and treatment-related changes (**Figure 4**). Specifically, hierarchical multiple linear regression showed that the years of cocaine use was strongly positively related to baseline striatum cue reactivity ($\rho = 0.67$; $p < 0.01$; $R^2_{Adj} = 0.45$; when controlling for route of drug administration and Fagerström nicotine dependence; **Figure 4A**) and strongly inversely related to changes in striatum cue reactivity after real (vs. sham) cTBS treatment ($\rho = -0.57$; $p < 0.01$; $R^2_{Adj} = 0.32$; **Figure 4B**). However, despite strong correlations between baseline striatum cue reactivity and years of cocaine use, these variables each explained unique variance in striatum network response to real (vs. sham) cTBS treatment.

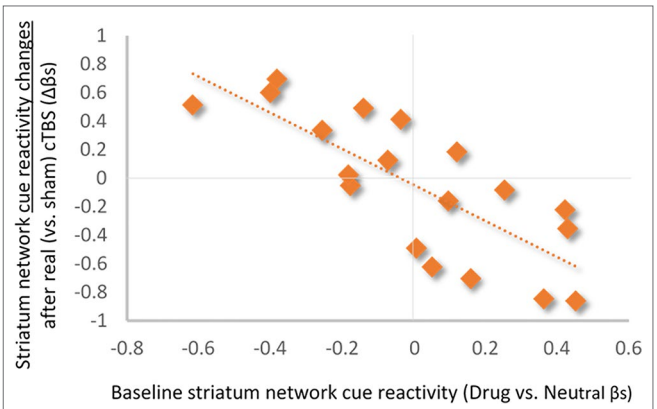

FIGURE 3 | Relationship between baseline striatum network drug cue reactivity and change in drug cue reactivity after real (vs. sham) cTBS treatment. Baseline striatum drug cue reactivity was strongly inversely related to striatum network response to real (vs. sham) cTBS ($\rho = -0.79$; $p < 0.001$; $R^2_{Adj} = 0.58$).

DISCUSSION

In our previous study, we showed that mPFC cTBS could attenuate drug cue reactivity in both the mPFC and striatum in cocaine and alcohol users (15, 20). The present study extends these data by demonstrating that individual variability in the effect of mPFC cTBS on striatal circuitry may be related to baseline

TABLE 1 | Descriptive demographic, clinical, and drug use statistics.

	***n* = 19 Total sample**	***n* = 10 cue-sensitive**	***n* = 9 cue-insensitive**	**Cue-sensitive vs. cue-insensitive**
Demographics				
Sex	11 M, 8 F	6 M, 4 F	5 M, 4 F	χ^2 0.04
Age	41.2 (± 9.5) years	42.7 (± 8.7) years	39.4 (± 10.0) years	*t* 0.72
Ethnicity	18 AA, 1 C	9 AA, 1 C	9 AA	χ^2 0.95
Education	12.2 (± 1.4) years	12.2 (± 1.8) years	12.1 (± 0.7) years	*t* 0.13
Cocaine use				
Preferred drug administration	10 smoke, 8 snort, 1 both	5 smoke, 4 snort, 1 both	5 smoke, 4 snort	χ^2 0.95
Age of first cocaine use	22.4 (± 5.7) years	20.3 (± 4.3) years	24.7 (± 6.2) years	*t* -1.71
Total duration of cocaine use	18.8 (± 9.4) years	22.4 (± 9.8) years	14.8 (± 7.1) years	*t* 1.82
Amount $ spent per week	$136.71 (± $98.70)	$147.80 (± 110.00)	$124.40 (± 82.70)	*t* 0.49
Days used in last 30 days	11.3 (± 6.9) days	10.5 (± 4.8) days	12.1 (± 8.5) days	*t* -0.49
Time since last use (at visit)	2.4 (± 1.0) days	2.3 (± 1.1) days	2.6 (± 1.0) days	*t* -0.51
Other substance use				
Nicotine smokers	17 (89%)	9 (90%)	8 (89%)	χ^2 0.39
Nicotine severity (Fagerström)	3.1 (± 1.9)	2.8 (± 2.1)	3.1 (± 1.9)	*t* -0.32
Marijuana smokers	14 (74%)	7 (70%)	7 (78%)	χ^2 0.15
Days MJ used in last 30 days	4.4 (± 9.0) days	3.4 (± 6.8) days	5.3 (± 10.2) days	*t* -0.37
Alcohol use severity (AUDIT)	9.2 (± 5.3)	10.6 (± 3.8)	7.7 (± 6.2)	*t* 1.18
Age first alcohol use	17.0 (± 3.3) years	17.7 (± 4.5) years	17.1 (± 1.5) years	*t* 0.34
Mental status				
Depressive symptoms (BDI)	10.6 (± 9.1)	12.3 (± 10.9)	8.8 (± 6.0)	*t* 0.82
State Anxiety (STAI-S)	37.4 (± 12.3)	34.0 (± 12.2)	41.2 (± 11.2)	*t* -1.26
Trait Anxiety (STAI-T)	40.7 (± 12.2)[ǂ]	41.4 (± 13.4)[ǂ]	39.9 (± 10.8)	*t* 0.26[ǂ]
Treatment-related measures				
Scalp-to-cortex distance (mm)[¥]	17.9 (± 3.7) mm	17.3 (± 3.9) mm	18.9 (± 3.1) mm	*t* -0.84
Mean absolute cTBS dose[%]	57% (± 9%)	61% (± 9%)	52% (± 8%)	*t* -0.25
Baseline cocaine craving	3.3 (± 2.0)	3.9 (± 2.3)	2.7 (± 1.6)	*t* 1.30
Change in cocaine craving[¤]	-0.6 (± 1.9)	-0.6 (± 1.3)	-0.5 (± 2.4)	*t* -0.11
Baseline striatum reactivity (β)	0.0 (± 0.3)	0.2 (± 0.2)*	-0.3 (± 0.2)*	*t* 5.96**
Change striatum reactivity (Δβ)	-0.1 (± 0.5)	-0.4 (± 0.4)*	0.5 (± 0.3)*	*t* -5.36**

M, males; F, females; AA, African-American; C, Caucasian; MJ, marijuana; AUDIT, Alcohol Use Disorders Identification Test; BDI, Beck's Depression Inventory; STAI, Spielberger State-Trait Anxiety Inventory. Values either indicate mean (± standard deviation) or count (percent%). [ǂ]Missing STAI-T score for one participant. [¥]Scalp-to-cortex distance (mm) for mPFC coil placement at EEG 10-20 FP1. [%]Mean absolute dose of cTBS administered (% total machine output to achieve 110% rMT, averaged over both stimulation sessions). [¤]Change in craving values given by: Δafter real cTBS - Δafter sham. Significance after multiple comparison adjustment (adjusted p < .05; p < .005**).*

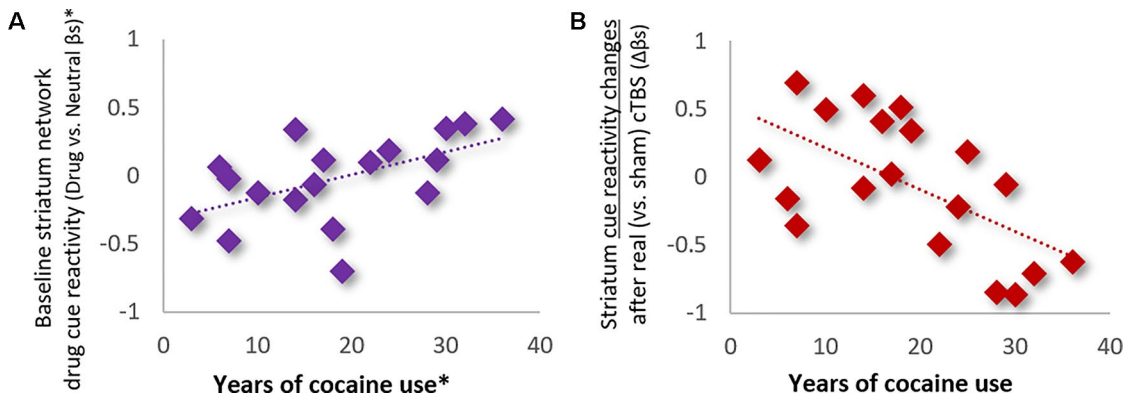

FIGURE 4 | Years of cocaine use was **(A)** positively related to baseline striatum network reactivity to drug cues (ρ = 0.67; $p < 0.01$; $R^2_{Adj} = 0.45$; *Controlling for route of drug administration and nicotine dependence), and **(B)** inversely related to network response to real (vs. sham) cTBS treatment (ρ = –0.57; $p < 0.01$; $R^2_{Adj} = 0.32$).

striatal reactivity to cues. Thus, our preliminary findings in this small data set are a first glimpse into informing treatment by suggesting that cocaine users with the greatest striatum network reactivity to drug cues at baseline may "benefit" most from mPFC cTBS treatment and that individuals with low baseline striatal reactivity to drug cues may not make good treatment candidates.

Individual Variability in Response to Theta Burst Stimulation. Although, to date, there have only been a handful of therapeutic neurostimulation studies implementing mPFC-targeted rTMS [see Ref. (13) for review], individual variability observed in the present study is consistent with studies of dorsal mPFC (dmPFC) rTMS in major depression (17), eating disorders (18), and obsessive-compulsive disorder (19, 44). Using resting-state fMRI, Dunlop et al. (18) demonstrated that in patients with eating disorders, baseline fronto-striatal connectivity discriminated treatment responders from non-responders, with divergent treatment-related alterations in connectivity corresponding to either symptom improvement or worsening, respectively. This divergence has also been observed when rTMS is applied to other cortical targets (16, 17, 19, 45–51). Together, these studies demonstrate that 1) the effects of various rTMS interventions, especially TBS, can be highly variable within a patient population, but 2) baseline levels of neural activity may be useful biomarkers of an individual's predisposition to TMS-induced neuroplastic changes.

Individual variability in neural responsiveness to TBS may be related to differences in plasticity potential (aka metaplasticity) of a given neural circuit across individuals. This concept is often referred to as homeostatic metaplasticity, whereby changes in cortical excitability induced by rTMS depend on the history of neural activation (22, 52). Specifically, the Bienenstock–Cooper–Munro (BCM) theory of homeostatic plasticity (53) posits that a history of lower post-synaptic activity will lower the synaptic modification threshold for LTP and increase the threshold for LTD. Conversely, a history of high synaptic activity will shift the modification threshold toward favoring the induction of LTD and increase the threshold for LTP (54).

Therefore, metaplasticity—or the propensity of a neural circuit to experience a plastic change—may be related to the current state of that circuit's engagement. Several studies involving both animals and humans have provided strong evidence for this phenomenon by showing that the effects of brain stimulation are influenced by prior activation of a given circuit, whether through priming stimulation or physiologic activity (see 21–23 for reviews). Therefore, it is possible that the bimodal neural responses shown across many rTMS studies—where patients with higher baseline neural activity or connectivity show subsequent attenuation, and patients with lower baseline activity or connectivity show subsequent elevation (or facilitation)—are, in fact, evidence of system- or network-level homeostatic metaplasticity (21, 22).

This theory warrants further investigation in human brain stimulation studies (22, 23), particularly in substance abuse populations where other biologic and drug-related factors impact neuroplasticity (5, 13, 20). However, if metaplastic mechanisms do play a significant role in the direction and magnitude of neural response to brain stimulation, then not accounting for or understanding these phenomena may continue to lead to broad variation in rTMS study outcomes (21, 55). It is, therefore, clear that researchers implementing TBS as an intervention in psychiatry should exercise caution in interpreting their study outcomes without considering the role of individual differences in correlates and predictors of response to stimulation. Understanding individual variability and potential mechanisms of metaplasticity in the relevant neural circuits will enable us to optimize the efficacy of rTMS, and TBS in particular, as a treatment tool (22, 23). Therefore, considerations for future implementation of TBS research should involve a focus on identifying the neural, behavioral, and clinical markers that predict clinically relevant outcomes to treatment.

The Utility of fMRI as a Biomarker. In particular, studies like the present, which use functional neuroimaging to inform brain stimulation, are of critical importance to characterizing and developing therapeutic neuromodulation techniques (13, 17, 18). Specifically, the present fMRI task data revealed the neural predictors and correlates of mPFC cTBS response and provided support for homeostatic metaplasticity as a potential neural mechanism for divergent treatment outcomes. Thus, fMRI was of both clinical and neuroscientific relevance, indicating potential treatment candidacy while also illuminating avenues for investigating neuromodulatory mechanisms.

Given that the primary goal of this study was to assess the striatum (the primary projection of mPFC neurons) as a biomarker for treatment response to mPFC-targeted cTBS, we utilized a data-driven ICA to capture changes in the temporal dynamics of striatal network task engagement. ICA was used in the present study versus traditional univariate or Region-of-interest (ROI)-based methods for three primary reasons: 1) the data-driven basis of ICA enabled extraction of the intrinsic spatiotemporal structure of the striatum network in this population without relying on *a priori* input (35, 38, 56, 57); 2) ICA's multivariate statistical approach permitted the measurement of the engagement of the striatum network as a whole, such that the multifocal brain areas simultaneously activated during the cue reactivity task could be captured in their overall patterns of association, rather than being assessed voxelwise or as ROI pairs (38, 57, 58); and 3) increased sensitivity in detecting task-related changes in fMRI signal would result from ICA's ability to diminish noise in the final output by separating artifact from real fMRI signal (36, 59–61). As such, ICA was selected for identification and characterization of the striatum network to enable measurement of network-level task engagement in the subsequent task analysis. However, although focusing on the striatum network was appropriate to address our primary research question, it did not enable us to make conclusions about other brain regions, which may also be affected by the task and mPFC cTBS treatment protocol. As such, these questions could be addressed through further investigation of other relevant cognitive and affective networks, identified through ICA or through a whole-brain, general linear model approach. Although this was beyond the scope of the present research investigation, it would be a valuable approach for future investigation.

The primary limitation of the present study is that it only involves 1 day of cTBS treatment. Although the participants received six 600-pulse sessions of cTBS on that day, there is conflicting evidence as for whether a single day of brain stimulation is sufficient to induce sustainable neural changes (11, 12, 62, 63). Relatedly, we recently showed, in a subset of these subjects, that a single session of mPFC cTBS produced neural changes, but did not produce changes in

drug cue-induced craving (15). However, it is generally recognized that a single day of rTMS is likely not sufficient to produce changes in complex behaviors, such as craving, because rTMS effects are cumulative, and it often takes multiple sessions of treatment for clinically meaningful responses in behavior to emerge (64–67). These data are, however, an important "proof of principle," demonstrating that it is not only possible to shift neural reactivity to cocaine cues in a single day using rTMS but also that individual differences in neural response to rTMS are state dependent, which is an important, foundational step toward determining the efficacy of mPFC cTBS as a treatment for substance abuse. Additionally, the sample size is relatively small compared with many clinical treatment studies in cocaine users. However, it is similar in size to many currently published rTMS studies in cocaine dependence (33, 68)—none of which have used neuroimaging as a predictor of response.

These preliminary findings provide the first demonstration that striatal network activity patterns during drug cue exposure fMRI tasks may be sensitive predictors of response to rTMS treatment and can be used to refine treatment selection and monitor outcomes. However, variability in neural response to treatment and lack of significant changes in cocaine craving indicate the need to further study the neurobiological and technical parameters of successful therapeutic stimulation in substance abuse.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

All subjects gave oral and written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Medical University of South Carolina Institutional Review Board.

AUTHOR CONTRIBUTIONS

CH was responsible for the concept and design of the overall research study. OM and WD were responsible for study administration and data collection. LD preprocessed MRI data. TK-R designed and executed data analyses, interpreted results, and drafted the manuscript. CH and MG provided critical revision of the manuscript for intellectual content. All authors critically reviewed and approved the final version for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00317/full#supplementary-material

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Negative Mood Induction Increases Choice of Heroin Versus Food Pictures in Opiate-Dependent Individuals: Correlation With Self-Medication Coping Motives and Subjective Reactivity

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Acute growth in negative affect is thought to play a major role in triggering relapse in opiate-dependent individuals. Consistent with this view, three lab studies have demonstrated that negative mood induction increases opiate craving in opiate-dependent individuals. The current study sought to confirm these effects with a behavioral measure of heroin seeking, and test whether the effect is associated with self-reported opiate use to cope with negative affect and subjective reactivity to mood induction. Participants were heroin-dependent individuals engaged with treatment services (n = 47) and control participants (n = 25). Heroin users completed a questionnaire assessing reasons for using heroin: negative affect, social pressure, and cued craving. Baseline heroin choice was measured by preference to enlarge heroin versus food thumbnail pictures in two-alternative forced-choice trials. Negative mood was then induced by depressive statements and music before heroin choice was tested again. Subjective reactivity was indexed by negative and positive mood reported at the pre-induction to post-test timepoints. Heroin users chose heroin images more frequently than controls overall (p = .001) and showed a negative mood-induced increase in heroin choice compared to control participants (interaction $p <$ .05). Mood-induced heroin choice was associated with self-reported heroin use to cope with negative affect ($p <$ .05), but not social pressure (p = .39) or cued craving (p = .52), and with subjective mood reactivity (p = .007). These data suggest that acute negative mood is a trigger for heroin seeking in heroin-dependent individuals, and this effect is pronounced in those who report using heroin to cope with negative affect, and those who show greater subjective reactivity to negative triggers. Interventions should seek to target negative coping motives to build resilience to affective triggers for relapse.

Keywords: negative mood induction, coping motives, heroin-seeking behavior, opiate dependence, vulnerability

INTRODUCTION

According to negative reinforcement theory, negative affective states act as powerful triggers for drug use behavior, motivating drug use to cope with those states [e.g., Refs. (1–3)]. Evidence for this proposal comes from lab studies where negative mood induction (including stress) increased various metrics of drug motivated behavior, including craving, choice, demand, consumption, and cognitive bias. Such mood induction effects have been extensively demonstrated for alcohol (4–7), tobacco (8–10), and cocaine (11–14). Furthermore, individual sensitivity to negative mood-induced craving predicts relapse in alcohol- (15–18) and cocaine-dependent individuals (19, 20), suggesting this sensitivity is an important risk factor for relapse.

Three studies have tested whether negative mood induction motivates opiate craving in opiate-dependent individuals. The study by Childress and colleagues (21) recruited 10 opiate-dependent clients who had been abstinent for 30 days, exposed them to guided self-hypnosis of a depressive scene, and found that subjective opiate craving increased from pre- to post-induction. The second study by Hyman and colleagues (22) recruited 14 opiate-dependent individuals who had been detoxified and were undergoing naltrexone treatment. Exposure to guided imagery of a personalized stress situation increased subjective opiate craving from baseline, while exposure to neutral imagery had no effect. Positive correlations were found between stress effects on craving and subjective reactivity (anxiety, fear, and sadness). Finally, the third study by Stathopoulou and colleagues (23) recruited 76 opiate-dependent individuals who had been on methadone maintenance for 4 months and exposed them to short video clips to induce sadness. After excluding 10 participants who showed no increase in subjective negative mood, it was found that the increase in craving from pre to post was related to subjective negative mood, and was moderated by anxiety such that this relationship was only significant in those with high anxiety sensitivity. There was no relationship between mood-induced craving and self-reported opiate use to cope with negative affect. Overall, this work provides preliminary support for the notion that acute negative mood is an important trigger for opiate seeking.

One limitation of the existing literature is that there is no demonstration of negative mood induction increasing a behavioral measure of heroin-seeking behavior. The three prior studies all measured opiate craving which has an unknown relationship to behavior (24). To address this limitation, we employed a pictorial choice procedure in which opiate-dependent individuals had the choice to enlarge heroin versus food thumbnail pictures in a series of two-alternative forced choice trials. Prior studies have validated the pictorial drug choice task by demonstrating that percent drug choice was increased in drug users versus non-users, or as a function of dependence level in the drug user group, in cocaine (25, 26), alcohol (27, 28), and tobacco users (28, 29), and was sensitive to the motivating effects of negative mood induction (10, 27, 30). In the current study, opiate users and control participants completed a concurrent pictorial choice task for heroin versus food pictures before and after mood induction. The first prediction was that heroin users would choose heroin images more frequently than control participants, validating the pictorial choice measure as an index of heroin value. The second prediction was that heroin users would show a mood-induced increase in heroin choice whereas control participants would not, suggesting that acute negative affect is an important trigger for heroin-seeking behavior.

The second limitation of the existing literature is that individual sensitivity to mood-induced opiate craving remains obscure. The two studies by Hyman et al. and Stathopoulou et al. (22, 23) found that mood-induced opiate craving was associated with subjective mood reactivity, consistent with a range of other induction studies [e.g., Refs. (27, 31–34), but see Refs. (35, 36)]. Consequently, the third prediction of the study was that mood-induced heroin choice would be associated with subjective mood reactivity. More interestingly, however, Stathopoulou and colleagues (23) found that mood-induced opiate craving was not associated with self-reported opiate use to cope with negative affect. This finding is at odds with multiple studies that show that coping motives are associated with greater sensitivity to mood-induced drug-motivated behavior [Refs. (5, 7, 15, 16, 27, 37–43); but see Refs. (30, 40, 44)]. The fourth prediction of the current study, therefore, was that mood-induced heroin choice behavior would be greater in opiate users who reported using to cope with negative affect. Sensitivity to negative affect-triggered heroin seeking could be an important mechanism driving relapse (45, 46).

METHOD

Participants and Procedures

Participation was open to males and females aged 18–65 being treated for current heroin addiction by opioid medication at the Royal Prince Alfred (RPA) Hospital Drug Health Clinic in Sydney, Australia. Data were collected from 47 opiate-dependent outpatients (male = 32, female = 15) after they received opiate medication. In total, 2 participants (4.3%) were aged 19–24, 14 (29.8%) were 25–39, 16 (34.0%) were 40–49, and 15 participants (31.9%) were 50+ years of age. Thirty-five participants were receiving methadone (mean dose = 79 mg), 2 participants received buprenorphine (mean dose = 6 mg), and 10 participants were receiving suboxone (mean dose = 21 mg). The majority of these participants were currently unemployed, educated to high school level, and single. Eligibility criteria included: 1) current attendance in treatment for heroin addiction, 2) over 18 years of age, 3) English speaking, and 4) receiving opiate medication for the last 30 days. Healthy controls that did not have a history of opiate addiction were recruited *via* word of mouth from the community. Exclusion criteria included history of substance dependence or any other *DSM-IV* axis I disorders. Participants were matched for gender (opiate users = 33% female; controls = 48% female, Fishers exact $p = .21$), and age, $t(34.26) = 1.66$, $p = .11$. *A* chi-square comparing three categories of educational attainment (below high school, high school, greater than high school achievement) was non-significant, $\chi^2(2, 71) = 4.48$, $p = .11$, suggesting the two groups were matched for educational attainment. One opiate-using participant was excluded for showing an extremely outlying reduction in heroin

choice from pre- to post-induction (>3 times the inter quartile range), leaving 46 opiate users and 25 control participants in the analyzed data set. The study was approved by the Western Sydney University Human Research Ethics Committee, and participants provided informed written consent.

Questionnaires

Participants reported gender and age. Heroin users completed the Reasons for Drinking Questionnaire (RFDQ), adapted for heroin use (47). Instructions stated "The following 16 questions are a list of reasons why people take illicit opiates. Please rate each of these reasons on how important each is for you." Within the questionnaire, the word "alcohol" from the original was replaced with the word "heroin." Responses were scored on a 1–10 scale ranging from "not at all important" to "very important." The RFDQ has three subscales reflecting heroin use to cope with negative affect, social pressure, and cued craving, obtained by averaging relevant items, giving a subscale score range of 1–10. We adapted the RFDQ because the drinking to cope subscale in the original version has been shown to be associated with greater sensitivity to negative mood-induced alcohol choice in two of our prior studies with student drinkers in a task similar to the present (27, 37).

Mood-Induced Heroin Picture Choice Task

The trial structure and timings of the heroin picture choice task are shown in **Figure 1**. At baseline, participants freely chose to enlarge a heroin or food thumbnail picture with a left or right key press, over 32 trials. In each trial, a heroin and food thumbnail was presented randomly in the left or right position, sampled from a set of 28 of each image type (obtained online from non-copyrighted images). Following baseline choice, pre-induction subjective mood was measured by participants reporting the extent to which they currently felt five negative (jittery, upset, distressed, sad, irritable) and five positive emotions (enthusiastic, happy, excited, inspired, alert), randomly ordered, on a five-point scale ranging from "not at all" to "extremely." Sad music was then played through headphones (Barber's Adagio for Strings), and participants were instructed to carefully consider 16 negative statements (e.g., "I don't think things are ever going to get better") randomly ordered [for full list, see Ref. (34)]. The heroin choice test comprised 32 trials identical to baseline, except that the sad music continued to play and a negative statement (randomly selected from the set of 16) was presented prior to each choice (the same picture set was used as at baseline). Post-induction subjective mood was then measured in the same way as before.

RESULTS

Heroin Choice

Figure 2A shows the percentage (and SEM) choice of heroin versus food images, in heroin users and controls. ANOVA on these data, with the variables group (heroin users, controls) and block (baseline, test), yielded a significant main effect of group, $F(1,69) = 19.85$, $p = .001$, $\eta_p^2 = .223$, and interaction between group and block, $F(1,69) = 4.04$, $p = .048$, $\eta_p^2 = .055$, and no

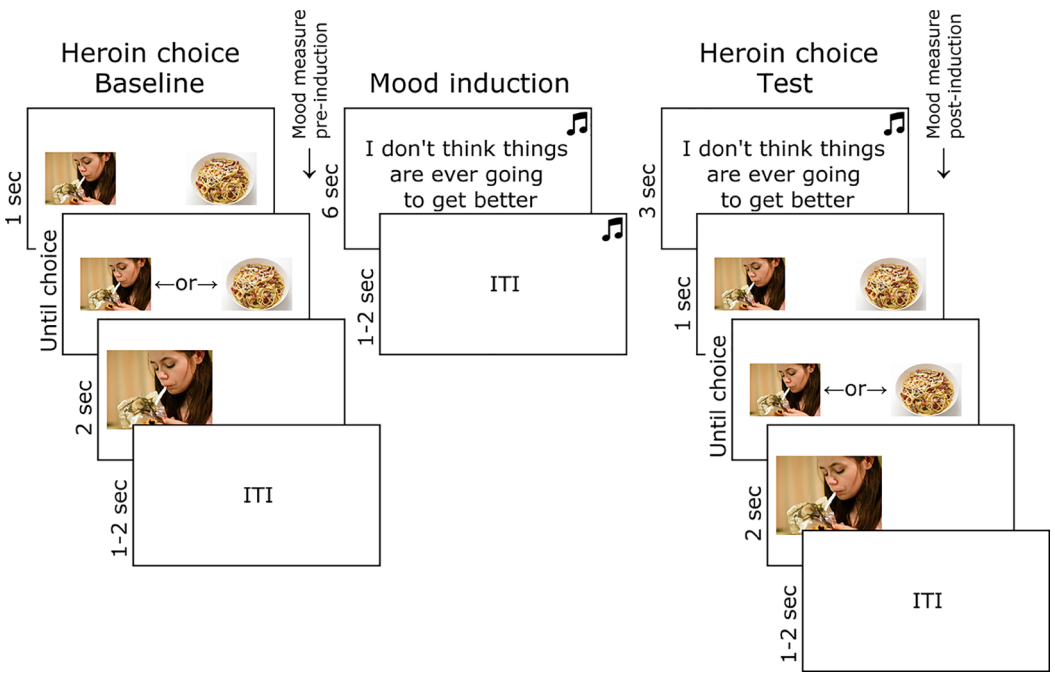

FIGURE 1 | Task used to test the effect of mood induction on heroin choice in opiate-dependent and control participants. Images of heroin and food were obtained online and were not copyrighted.

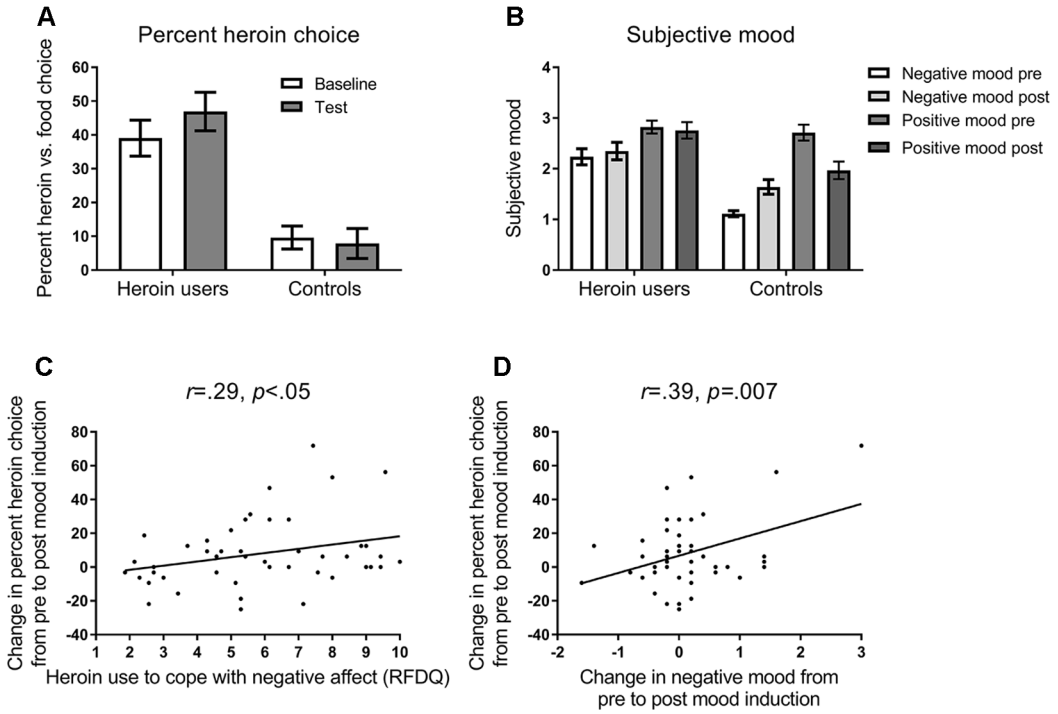

FIGURE 2 | (A) Mean percent (and SEM) choice of heroin versus food pictures in the baseline and test blocks of the task (see **Figure 1**). Opiate-dependent participants showed a higher rate of heroin choice overall compared to control participants, and showed a mood induced increase in heroin choice at test, whereas controls did not. **(B)** Subjective negative and positive mood states reported at pre-induction and post-test timepoints (see **Figure 1**). Opiate-dependent participants showed no overall change in subjective mood states, whereas control participants showed an increase in negative mood and a decrease in positive mood following mood induction. **(C)** Scatterplot and regression slope relating the mood-induced change in percent heroin choice to self-reported opiate use to cope with negative affect in opiate-dependent participants. **(D)** Scatterplot and regression slope relating the mood-induced change in percent heroin choice to self-reported change in negative mood in opiate-dependent participants.

significant main effect of block, $F(1,69) = 1.64$, $p = .21$, $\eta_p^2 = .023$. The main effect of block was significant in heroin users, $F(1,45) = 6.96$, $p = .01$, $\eta_p^2 = .134$, but not controls, $F(1,24) = .26$, $p = .62$, $\eta_p^2 = .011$. These results indicate that heroin users chose heroin images more frequently, and showed increased heroin choice following negative mood induction, compared to controls.

Subjective Mood

Figure 2B shows the mean (and SEM) subjective negative and positive mood reported pre-induction and post-test. ANOVA on these data with the variables group (heroin users, controls), mood state (negative, positive), and timepoint (pre, post) yielded a significant interaction between group, mood state, and timepoint, $F(1,69) = 12.40$, $p = .001$, $\eta_p^2 = .152$. In heroin users, there was a significant main effect of mood state, $F(1,45) = 6.06$, $p = .02$, $\eta_p^2 = .119$, but no effect of timepoint, $F(1,45) = .12$, $p = .73$, $\eta_p^2 = .003$, or interaction between mood state and timepoint, $F(1,45) = .91$, $p = .34$, $\eta_p^2 = .020$. By contrast, in controls, there was a significant main effect of mood state, $F(1,24) = 39.22$, $p < .001$, $\eta_p^2 = .620$, and a significant interaction between mood state and timepoint, $F(1,24) = 26.79$, $p < .001$, $\eta_p^2 = .528$, with negative mood increasing significantly from pre to post, $F(1,24) = 17.23$, $p < .001$, $\eta_p^2 = .419$, and positive mood decreasing significantly from pre to post, $F(1,24) = 16.06$, $p < .001$, $\eta_p^2 = .401$. Thus, heroin users showed no change in subjective mood following mood induction, whereas controls showed the appropriate change in mood states.

Correlations

As shown in **Figure 2C**, the change in heroin choice from the pre to post mood induction correlated positively with RFDQ heroin use to cope with negative affect, $r = .29$, $p < .05$, but not with RFDQ heroin use due to social pressure, $r = -.13$, $p = .39$, or cued craving, $r = .10$, $p = .52$. Furthermore, as shown in **Figure 2D**, heroin users' change in heroin choice also correlated with the change in negative mood from pre- to post-induction, $r = .39$, $p = .007$, but not with the change in positive mood $r = -.19$, $p = .20$. RFDQ heroin use to cope with negative affect did not correlate significantly with the change in negative mood, $r = .28$, $p < .06$. Thus, heroin users' change in heroin choice from baseline to test was amplified in those who reported heroin use to cope with negative affect, and those who reported the greatest increase in negative mood following induction.

DISCUSSION

The study found that opiate-dependent individuals chose heroin over food images more frequently than control participants. This

accords with results from two studies with cocaine-dependent individuals, who chose cocaine over pleasant pictures more frequently than control participants (25, 26). Percent drug choice has also been shown to increase with dependence level within drug user groups (25–29). These findings suggest that the pictorial drug choice task is a valid assay of the relative value ascribed to the drug by drug users. The pictorial choice task may have the advantage over subjective craving as an outcome measure, in being more readily translatable to animal models that also use behavioral measures rather than subjective report (48, 49). This procedure also has an advantage over human concurrent drug self-administration procedures (50–52) in not requiring actual consumption, and so is technically simpler and ethically acceptable for clients who are currently abstinent. Finally, the pictorial drug choice task is superficially similar to attentional bias tasks, but appears more reliable in detecting group differences, and correlations with dependence severity (53).

The second finding was that negative mood induction increased heroin choice in opiate-dependent individuals but not control participants. This extends prior induction studies with opiate users (21–23), by including control participants to demonstrate the specificity of the mood induction effect. The finding also confirms that negative mood acts as a trigger for heroin-seeking behavior (and not just craving), as has been found with other drug classes including alcohol (4–7), tobacco (8–10), and cocaine (11–14).

Sensitivity to mood-induced heroin choice was also found to correlate with subjective changes in negative mood, consistent with two prior opiate studies (22, 23) and induction studies with other drug classes (27, 31–34). These findings accord with the prediction of affective negative reinforcement theory (54) in suggesting that the affective change produced by the induction procedure was responsible for the change in heroin-seeking behavior.

Finally, sensitivity to mood-induced heroin choice was found to correlate with self-reported opiate use to cope with negative affect, but not other opiate use motives (social pressure and cued craving). This finding contradicts the study by Stathopoulou and colleagues (23) which found no association between mood-induced opiate craving and opiate use to cope with negative affect, but corroborates multiple induction studies with other drug classes that have found this same association (5, 7, 15, 16, 27, 37–43). We may therefore accept our association as a true positive. It is possible that coping motives increase the risk of dependence by conferring sensitivity to negative affective triggers for drug-seeking behavior (45, 46).

We might further speculate that individual sensitivity to mood-induced heroin choice is a risk factor for relapse. The basis for this claim is that such sensitivity is associated with relapse risk in alcohol- (15–18) and cocaine-dependent individuals (19, 20). With respect to opiate users, poorer stress tolerance (55) and abnormal cortisol (56) predict poorer treatment engagement or earlier lapse, and preliminary evidence suggests that learning to cope with negative affect may promote abstinence (57). The implication is that sensitivity to negative mood-induced heroin-seeking is also a risk factor for relapse, and that treatments targeting this sensitivity may have efficacy for maintaining abstinence.

One limitation of the current study was that we did not observe an overall change in subjective mood following negative mood induction in the heroin user group, whereas controls did show changes to self-reported positive and negative mood. Despite this, the increase in heroin choice at test for the heroin user group, as well as the correlation between this effect and their change in negative mood, indicated that the mood induction procedure did impact the heroin user group. However, these effects were small and were perhaps reduced by the opiate replacement medications taken shortly before the experiment, similarly to acute alcohol, which has been shown to reduce mood induction effects (58). Future studies may employ a stronger mood induction procedure that produces a reliable change in subjective mood in heroin users, and a larger magnitude of effect on heroin choice behavior.

The second limitation was that we did not employ a control condition to determine whether the change in heroin picture choice was due to the mood induction or time. Previous studies have shown that drug choice remains stable over time then jumps following induction (30). Similarly, percent heroin choice in heroin users of the current study was stable across the two halves of the baseline phase (means = 39% and 39%, respectively), then jumped following induction and was stable across the two halves of the test phase (means = 48% and 46%, respectively). These data, plus the correlation between subjective mood and heroin choice, suggest that the increase in heroin choice was caused by negative mood induction and not by time.

The third limitation was that we could not obtain indices of psychiatric state in the two groups, because we had access to drug-using clients for an extremely short period during their hospital visit. As a consequence, we are unable to test whether the differential mood induction effect between the two groups was due to drug user status, or confounded psychiatric symptoms, such as anxiety or depression, which are known to be associated with greater sensitivity to mood induction effects on alcohol seeking (10, 27).

ETHICS STATEMENT

This study was approved by the Western Sydney University Human Research Ethics Committee.

AUTHOR CONTRIBUTIONS

LHo designed the procedure and wrote the first draft of the manuscript. LHa and AB programmed the task and contributed to the analysis. JM and SC ran the participants and contributed to the analysis. GW and AM oversaw the running of the experiment. All authors contributed to the writing of the manuscript.

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REVIEW
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Prehabilitation in Alcohol Dependence as a Treatment Model for Sustainable Outcomes. A Narrative Review of Literature on the Risks Associated With Detoxification, From Animal Models to Human Translational Research

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In this review paper, we discuss how the overarching concept of prehabilitation is applicable to alcohol dependence. Central to prehabilitation are the concepts of expected harm, risks, and proactive planning to eliminate the harm or cope with the risks. We review the evidence from animal models, psychological experimental studies, as well as pharmacological studies, on the potential risks and harms associated with medically assisted alcohol detoxification and the current treatment paradigm for alcohol dependence. Animal models provide an approximation mostly of the physical aspect of alcohol withdrawal and detoxification process and make predictions about the development of the phenomena in humans. Despite their limitations, these models provide good evidence that withdrawal from chronic ethanol use induces cognitive impairment, which is worsened by repeated bouts of withdrawal and that these impairments are dependent on the duration of alcohol withdrawal. Initial clinical observations with alcohol-dependent patients confirmed increased incidence of seizures. In recent years, accumulating evidence suggests that patients who have had repeated episodes of withdrawal also show changes in their affect, increased craving, as well as significant deterioration of cognitive abilities, when compared to patients with fewer withdrawals. Alcohol dependence is associated with tolerance and withdrawal, with neuroadaptations in γ-Aminobutyric Acid-A Receptor (GABA-A) and glutamatergic *N*-methyl-D-aspartate (NMDA) receptors playing key roles. It is suggested that dysregulation of the NMDA receptor system underpins alcohol-related memory impairments. Finally, we discuss the Structured Preparation for Alcohol Detoxification (SPADe) as an example of how prehabilitation has been applied in clinical practice. We discuss the importance of partial control over drinking as an interim step toward abstinence and early introduction of lifestyle changes for both the patient and the immediate environment prior to detoxification and while the patient is still drinking.

Keywords: alcohol dependence, prehabilitation, withdrawal, detoxification, animal models, human research

INTRODUCTION

The concept of pre-habilitation has been introduced in the field of orthopedics and describes a set of exercises and training routines for certain groups of patients with the aim to maximize physical strength and reduce the risk of expected harm or frequent injuries, therefore taking a proactive rather than a reactive approach. The concept is applied in surgery with the aim of preparing patients for a surgical intervention. It is a strategy for proactive management of risk factors associated with the surgical intervention. The approach is therefore described as a shift away from an impairment-driven reactive model and as an opportunity for introducing proactive sustainable and appropriate lifestyle changes (1).

Central to the successful implementation of pre-habilitation are the concepts of expected harm or risk and proactive planning. Both concepts are considered to be crucial determinants of the interaction between humans and the environment in general, associated with human evolution and the progress from hunting to agriculture, structured communities, and human civilization. Planning is crucial in all aspects of everyday life. The ability to predict or anticipate certain harm or assess certain risks is associated with the human ability of learning from experience, modify behavioral responses, and develop long-term and sustainable response strategies. To that effect, planning in advance of anticipation of risks can be considered as an essential strategy associated with individual survival and progress. Planning should not been viewed as a barrier for improvisation and innovation; on the contrary, it provides a stable environment for progress and positive change to take place.

The term "alcohol dependence" was first introduced in 1976 (2) and was used in both International Classification of Diseases (ICD-10) classification systems (3) and the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) (4). In *DSM-5*, dependence is now conceptualized on a continuum with abuse, such that a single disorder is now called alcohol use disorder (AUD) with mild, moderate, and severe sub-classifications (5). Alcohol withdrawal syndrome is a collection of symptoms that occur after an alcohol-dependent individual stops consumption (6). Withdrawal from alcohol has been associated with cognitive impairments in recovering alcohol-dependent patients and furthermore the risk of relapse after withdrawal is associated with cognitive deficit (7, 8).

In this paper, we introduce the concept of pre-habilitation and its role in the clinical management of alcohol dependence. The approach has many aspects that overlap with other clinical management interventions, such as harm reduction and opioid substitution treatment. The overall aim is to reduce medical and other associated risks in a safe environment and to empower the individual to achieve the psychosocial changes required for recovery and social reintegration. Here, we focus on alcohol detoxification and withdrawal, given that it poses substantial risks to cognitive function. We review the evidence from animal studies, human psychological experimental studies, and imaging studies. We have conducted a narrative review of preclinical and clinical evidence regarding alcohol withdrawal or detoxification using online resources, e.g., PubMed and Google Scholar, and that were published in English prior to September 2018. For the preclinical evidence, we have focused the review on studies using cognitive behavioral paradigms rather than those on physical withdrawal symptoms, e.g., seizures. For the clinical review, we have focused on neuroimaging studies of relevant neurobiological processes. We also discuss the limitations of current pharmacological interventions. Finally, we discuss, in some detail, an example of a clinical implementation of the model. In this paper, we have chosen to use the older and longer established term "patient" rather than client or service user. This choice does not refer to a scientific or philosophical position.

CURRENTLY RECOMMENDED TREATMENT PARADIGM TO MANAGE ALCOHOL DETOXIFICATION

Current clinical guidelines suggest that medically assisted withdrawal or detoxification is generally required for the treatment of moderate to severe alcohol dependence. This should be planned and the importance of providing structured aftercare is emphasized (9). Medically assisted detoxification is required to minimize the risks of withdrawal-related symptoms and complications.

The guidelines suggest that the patient prepares for detoxification by attending sessions at a specialist service to enhance and maintain motivation to change and develop a plan for structured aftercare (9). As described, the latter is considered important to ensure effective treatment. What is delivered however may vary widely with sessions not necessarily providing structured preparation to address issues such as stabilizing the amount of drinking, enhancing partial control over drinking, promoting early lifestyle changes, or empowering changes within the immediate family or social environment.

Detoxification may be medically assisted as an outpatient in the community or as an inpatient in a general hospital or a specialist unit. The choice between these two detoxification settings depends on health risk factors and the availability of social support to mitigate these risk factors during the detoxification process, and it is usually made by the health professionals (9). Medically assisted detoxification is discussed in more detail in Section 6 below.

Structured aftercare (also referred to as rehabilitation) is considered by clinical guidelines as the most important component of the current treatment paradigm, with strong evidence for its effectiveness (9). It is recommended that the structured aftercare that follows detoxification be delivered within a Cognitive Behavioral Therapy approach, either on an individual basis or *via* membership of a Relapse Prevention Group, alongside family interventions. It is highly recommended that patients engage with peer-support or mutual aid groups, such as Alcoholics Anonymous or SMART Recovery. Pharmacological interventions such as acamprosate, naltrexone, or disulfiram are also recommended. The existing evidence does not favor outpatient over inpatient detoxification, or residential aftercare treatment over community treatment, or longer versus shorter duration residential aftercare treatment programs (9). However, access to residential aftercare programs is recommended for

homeless individuals, and efforts should be made to address accommodation issues prior to discharge (9).

Two of the long-term challenges for professionals (both academics and clinicians) involved in the treatment of alcohol dependence are the definition of successful outcome as well as the high relapse rate. For example, statistics from Public Health England for the period 2017–2018 suggest that 61% of clients complete treatment successfully (i.e., are free from dependence, which could mean abstinence but not necessarily), the same proportion as the previous year (10). This number provides an indication of how successful treatment is but is dependent on the definition of successful treatment, the severity of presenting problem, and the time when completion and exit are reported. Other indicators such as maintenance of abstinence for 6 months and 12 months for alcohol-dependent patients could enhance our understanding of the effectiveness of the current treatment paradigm. Our local data suggest that only 60% of patients who have completed planned detoxification have been engaged in aftercare interventions, which are considered to be essential for long-term recovery (11). This ratio has improved to 82% when a pre-habilitation approach has been implemented, such as participation in the Abstinence Preparation Group (see Section 7 below) (12). There may be several explanations for this improvement, including benefits of participating in a group or more specific theory-based factors such as regaining of partial control over drinking and early lifestyle changes (12).

In summary, current treatment guidelines advocate avoidance of unplanned and urgent detoxifications as they do not lead to sustainable outcomes with regard to drinking behaviors (9). They put emphasis on the provision of psychological treatment following detoxification and promotion of participation in peer-support interventions (9). Given the challenges in improving treatment outcomes, we consider that the main shortfalls of these guidelines are that (1) the only therapeutic input prior to detoxification is restricted to motivation enhancement and preparation of an aftercare plan without any theory-based structured intervention to manage the risks expected once alcohol is withdrawn, and (2) a large proportion of patients completing detoxification do not engage with any evidence-based aftercare to reduce the risk for relapse. Given that the majority of psychological interventions may not have an immediate effect, and the high risk of relapse during the first 3 months post-detoxification, we need to consider an alternative approach such as pre-habilitation to reduce the risk of relapse. Furthermore, the fact that these interventions are taking place during a period of mood dysregulation, which is the result of the detoxification itself, might compromise their effect.

LEARNING AND HABIT DEVELOPMENT IN HUMANS

Humans have the ability to test out a new behavior as a solution to a challenge and—depending on the results (e.g., reward)—to either consolidate or abandon this behavior. Consolidated rewarding behaviors then become repeated in similar (or different) situations and, over time, become automatized. This leads to the fast replication of such behaviors—a bypassing of the conscious and careful consideration of pros and cons—since the analysis of their efficacy has already been done, in the past, and proven successful (13). The ability to automatize successful behaviors allows humans to continue with further learning and the accumulation of new skills and expertise. This ability to bypass the conscious decision-making control mechanism confers the advantage of fast and successful responses to dangerous environmental stimuli, but it has a major disadvantage: humans are not able to monitor the appropriateness of the behavior or assess the possible need for behavioral modification (13).

Whenever an automatized behavior requires modification, the learning process must be slowed down, in order to allow for the decision-making process to again become conscious. This does not refer to a meta-cognitive process, but rather to the creation of time and space between the high-risk situation and the behavioral response. In other words, implicit cognitions must again become explicit if the individual is to regain conscious control in order to modify the extant behavior. It is easier to undertake this reversal process (14) in a safe, practice-friendly environment, where those factors necessitating the fast reproduction of a behavioral response may be kept under control. Factors such as stress, threat, or uncomfortable physical symptoms typically provoke instinctive responses of a habitual nature. Humans tend to think more clearly and laterally when they can explore alternative solutions without facing immediate threat or being subject to stress.

The Expected Risk in Alcohol Dependence

In the case of drinking (as well as other substance misuse), this leads to the state whereby habitual drinking dominates all other behaviors and becomes repeated despite the person's awareness of its loss of effectiveness and the accumulation of evidence of the associated harm. This leads the person into the paradox of wanting (implicit activation of need) although not liking (conscious desire and choice) drinking (15). From a psychological perspective, all explicit cognitions—such as positive and negative expectancies of the effect of drinking—which were conscious and under the control of the individual, are rendered implicit, and bypass the conscious decision-making pathway fuelling the continuation of drinking (13). This phenomenon is described as "loss of control", an underlying theme common to 9 out of the 11 criteria of Alcohol Use Disorder in *DSM-5* (5), three out of six criteria for alcohol dependence in ICD 10 (3), and one of three in ICD 11.

In the sections below, we discuss the risks associated with alcohol withdrawal and medication-assisted detoxification interventions. We review the evidence from animal models, pharmacological studies, and psychological experimental studies to explore risks such as cognitive impairment, stress sensitivity, the limitations of medication-based protective roles, as well as limitations of the existing treatment paradigm of planned detoxification and rehabilitation.

ANIMAL MODELS OF ALCOHOL WITHDRAWAL AND DETOXIFICATION ON COGNITIVE IMPACT

Animal models have been used to try and understand the phenomenon of alcohol withdrawal and specifically to determine if repeated withdrawals particularly have an impact on cognitive function. Animal models have several advantages in alcohol research. They may be used to study determinants of alcohol-related behavior where there are ethical issues with carrying out such research in humans due to risks in giving volunteers or patients addictive harmful substances (16).

Further, animal models are used because animals have similar genetic, biochemical, and physiological compositions to humans. Therefore, research using animals can inform the understanding of the human condition and help lead to the development of new therapeutics. Some of the current medications approved for the treatment of alcohol use disorders (e.g., naltrexone and acamprosate) were developed using animal models (16). However, animal models do not represent the entire complex disorder; instead, they allow the study of component features of the condition and help provide evidence for the determinants of such behaviors (17).

There are currently several different methods used to model ethanol (alcohol) dependence in rodents such as forced consumption in drinking water, ethanol containing liquid diet, ethanol vapor inhalation, and repeated intraperitoneal or intragastric administration (18). In addition to route of administration, the length of ethanol exposure varies between models of alcohol use, e.g., from a 4-day chronic intermittent exposure (19) or a 6-month chronic model (20). The variation in both administration and duration of chronic ethanol administration complicates the interpretation of results. All of these models aim to mimic the neuroadaptations in the brain, which lead to tolerance and physical dependence of alcohol. A key issue with these models is the forced exposure to ethanol, which doesn't accurately represent the compulsive element of the human experience of alcohol dependency despite efforts to assess operant re-enforcing and conditioned responses (16). Induction of alcohol dependency in animals is considered to be successful if withdrawal symptoms are present upon cessation of exposure (18). However, this is representative only of a physical dependency and lacks the complexity of all the environmental and psychosocial influences that contribute to the complex human experience of alcohol addiction.

Animal models of alcohol consumption have also been developed to reflect voluntary alcohol consumption such as the two-bottle choice test, using gradually increasing concentrations of ethanol or adding sweeteners (17). Although preference tests are often influenced mainly by taste, some animals show a preference for the pharmacological effects of alcohol, and this has allowed genetic manipulation to produce high or low alcohol preference breeds. Rodents will voluntarily consume up to 40% ethanol (16). For the study of alcohol withdrawal, these voluntary consumption paradigms are often not sufficient because consumption levels are not high enough to induce withdrawal symptoms. Another limitation of these procedures is the difficultly to determine an animal's motivation to seek alcohol. Motivation to consume alcohol can be best demonstrated by an operant task model (such as lever pressing to receive alcohol in which the number of presses required increases) or a conditioned place preference task [for a detailed description, see (21)].

The Impact of Withdrawal on Cognition

Physical withdrawal symptoms are similar in humans and animals and include tremors, agitation, rigidity, spontaneous seizures, audio sensitivity, handling-induced seizure sensitivity, and weight loss (22). However, alcohol withdrawal induces much more than just physical symptoms with low mood and anxiety evident. This negative affective state is thought to contribute to the risk of relapse in alcohol dependence and is therefore a critical area of study (these effects in humans are discussed in detail in Section 5 below). Withdrawal is thought to induce these effects *via* neuroadaptations from chronic ethanol's exposure on brain areas that control fear and memory. For this review, we focused on the studies assessing the impact on withdrawal from chronic alcohol exposure on cognitive function in rodents, which are summarized in **Table 1**. This table shows evidence that cognitive deficits are seen in animal models of withdrawal, that this deficit can worsen with repeated withdrawal, and finally that this cognitive impact varies with the length of the withdrawal period.

The Presence of Cognitive Impact

The experiments in **Table 1** used behavioral paradigms following a variety of chronic alcohol models to assess cognitive function including the elevated plus maze, the T maze, social interaction, and conditioned fear response learning. These have been used to demonstrate withdrawal-induced impairments in learning (19, 31), cognitive flexibility (26), memory (20, 24, 25, 31, 36), sociability (38), as well as increasing anxiety (23, 27) and sleep disruption (35). In addition to the previously described limitations associated with animal models of chronic alcohol consumption and withdrawal, these studies are also subject to the limitations of the behavioral paradigms used. For example, several studies that illustrate the effect of ethanol withdrawal on inducing anxiety in rodents use paradigms such as the elevated plus maze, the light–dark box, and the open field (18). Measures used in these paradigms such as line crossings or % of time spent in the center, can be influenced by impaired locomotion of the animal, as well as anxiety, and therefore these results may lack construct validity. However, taken together, given the multiple cognitive defects assessed, it can be concluded that alcohol withdrawal may induce some cognitive impairment.

The Effect of Multiple Withdrawals

Several of the studies described in **Table 1** indicate the worsening of withdrawal symptoms given multiple withdrawal episodes, which is consistent with the clinical picture. The best documented example of this phenomenon in rodents is the frequency of seizures following several detoxifications: known as the kindling

TABLE 1 | The effects of withdrawal on cognition; a summary of research using animal models.

Reference	Animal	Species	Gender	Age/weight	Chronic alcohol model	Daily alcohol intake	Withdrawal period	Cognitive testing/measure	Cognitive deficit present
(23)	Rat	Lister hooded	Male	250–300 g	Ethanol-containing diet for 24 days 2 × 3-day withdrawal episodes	13–14 g/kg	2 weeks 2 weeks 2 weeks + 1 month	Negative patterning task Contextual fear conditioning via a foot shock Spatial learning in the Barnes maze	YES NO NO
(24)	Rat	Sprague–Dawley	Male	160–180 g	In drinking water as sole source of fluid (20%) 8, 18, and 28 weeks	12.2 to 9.7g/kg	4 weeks	Eight arms radial maze (memory): Spatial Nonspatial	 YES YES
(25)	Rat	Sprague–Dawley	Male	200–250 g	25% ethanol solution as the only source of fluid for 9 months (increasing concentrations from 10%)	53–26 mg%	2 weeks	Memory performance shuttle box: Active avoidance Passive avoidance	 NO YES
(26)	Mouse	C57BL/6	Male	At least 70 days old	Chronic intermittent ethanol exposure ethanol vapor (16 h/day for 4 days with 8-h periods of withdrawal) 3 consecutive cycles, with 3 days of withdrawal IP primer 1.6 g/kg	175–225 mg/dl)	Up to 1 week	Behavioral attentional set-shifting task and reversal learning	YES
(27)	Rat	Wistar	Male	250–280 g	2 g/kg ethanol *via* gavage twice a day for 28 days	BAC up to 120 mg/dl	5 days	Open field (exploratory behavior)	YES (lower frequency of rearing)
(28)	Rat	Hooded Lister	Male	200–240 g	Nutritionally complete liquid diet 7% ethanol Single withdrawal, 24 consecutive days	17.5 g/kg BAC 100 mg/dl	12 days	Seizures (PTZ kindling) Conditioned emotional response	YES NO
					Nutritionally complete liquid diet 7% ethanol Repeated withdrawal, 30 days, with two periods of 3 days, 11, and 21, in which they received control diet		12 days	Seizures (PTZ kindling) Conditioned emotional response	YES (faster than either control or SWD rats) NO ↓
(19)	Rat	Sprague–Dawley	Male	275–325 g	Catheters in the stomach 5 g/kg 25% in diluted nutritionally complete diet Additional ethanol was administered every 8 h for 4 consecutive days	7.6 g/kg	4.5 days	Morris water maze (learning)	YES
(29)	Rat	Hooded Lister	Male	200–240 g	Nutritionally complete liquid diet 7% ethanol Single withdrawal, 24 consecutive days	12.5 ± 0.8 g/kg	2 weeks	Conditioned emotional response (fear conditioning low and high intensity): Suppression Extinction Reversal	 NO NO NO
					Nutritionally complete liquid diet 7% ethanol Repeated withdrawal, 30 days, with two periods of 3 days, 11, and 21, in which they received control diet	12.9 ± 1.0 g/kg	2 weeks	Conditioned emotional response (fear low–high intensity): Suppression Extinction Reversal	 NO YES YES
(30)	Rat	Hooded Lister	Male	200–240 g	Nutritionally complete liquid diet 7% ethanol Single withdrawal, 24 consecutive days	15.0 ± 0.4 g/kg	2 weeks	Pavlovian-to-instrumental transfer	YES

(Continued)

TABLE 1 | Continued

Reference	Animal	Species	Gender	Age/weight	Chronic alcohol model	Daily alcohol intake	Withdrawal period	Cognitive testing/measure	Cognitive deficit present
					Nutritionally complete liquid diet 7% ethanol Repeated withdrawal, 30 days, with two periods of 3 days, 11, and 21, in which they received control diet	15.3 ± 0.6 g/kg			YES
(31)	Mice	CD-1	Male	8 weeks	Only source of liquid increasing concentrations up to 20% ethanol 4 weeks	0.20 ± 0.01 g/dl	3 or 12 weeks after	T-Maze Foot shock Avoidance Greek Cross Brightness Discrimination Step-Down Passive Avoidance Shuttle box Active Avoidance	NO NO NO NO
					Only source of liquid increasing concentrations up to 20% ethanol 8 weeks			T-Maze Foot shock Avoidance Greek Cross Brightness Discrimination Step-Down Passive Avoidance Shuttle box Active Avoidance	YES YES YES YES
(32)	Mouse	C57BL/6J	Male		Vapor exposure 16 h with 8-h break	2.5–3.0 g/kg	32 h	Odor cue conditioning influence on voluntary ethanol consumption 15% presented in a free choice situation with water 5 days	YES
(33)	Rat	Wistar	Male	240–270 g	Nutritionally complete liquid diet as the sole source of nutrients. All rats received the CON liquid diet for an initial 3 days then (6% v/v) for 14 days	8.4–10.4 g/kg BEC 80.3 ± 7.5–132 ± 5.9 mg/dl	8 h, 48 h and 72 h	Elevated plus maze. (anxiogenic-like effect) Contextual fear conditioning (foot shock freezing)	YES (8 h only) YES
(34)	Rats	Lister hooded	Male	130–160 g 350–400 g	Nutritionally complete liquid diet 7% ethanol Single withdrawal, 24 consecutive days	18 g/kg Experiments 2 and 3 12.5 g/kg	8 h	Elevated plus maze (anxiety) Plasma corticosterone	YES YES ↑
					Nutritionally complete liquid diet 7% ethanol Repeated withdrawal, 30 days, with two periods of 3 days, 11, and 21, in which they received control diet			Elevated plus maze (anxiety) Plasma corticosterone	YES but no more than SWD NO
(35)	Mouse	C57BL6/J	Male	90–100 days 24–28 g	4 bouts of 16-h exposure to EtOH vapor separated by 8-h periods of withdrawal	64.76 ± 31.97 mg/dl	4 days continuous	Electrophysiological recording from surgically implanted electrode: Sleep time Sleep architecture	 YES ↓ YES
(36)	Rat	Wistar	Male	250–300 g	Self-administration continuous (24 h/day for 7 days/week) or intermittent (24 h/day for 3 days/week) access to alcohol (20%) using a two-bottle choice procedure 5 months	<80 mg%	24 h to 68 days	Working memory performance in a Y-maze and the delayed nonmatching-to-sample task (DNMS) Elevated plus maze	YES (24–72 h) but not (16–68 days) NO
(37)	Mouse	Swiss	Male	8 weeks	1–8 weeks of intermittent access to 20% 3 days/week 24–48 h between EtOH access days, two-bottle choice	11.10–284.3 mg/dl	6–8 h	Aggressive and nonaggressive behaviors with a conspecific	YES (aggression and decreased social contact)
(20)	Mouse	C57/BL6	Male	4 months at start	Source of liquid, concentrated solutions of ethanol 4% the 1st week, 8% the 2nd week, and 12% for 6 months	15.34 ± 4.3 g/kg	Progressively withdrawn 1 week (1 W)	Working memory task. Spontaneous alternation was tested in a T-maze Elevated plus maze	YES YES

(Continued)

TABLE 1 | Continued

Reference	Animal	Species	Gender	Age/weight	Chronic alcohol model	Daily alcohol intake	Withdrawal period	Cognitive testing/measure	Cognitive deficit present
							6 weeks (6 W)	Working memory task. Spontaneous alternation was tested in a T-maze	YES
								Elevated plus maze	NO
(38)	Mouse	C57BL/6J	Male	At least 10 weeks old	Chronic intermittent vapor inhalation. 16 h separated by 8-h periods of withdrawal ip primer dose	211.2 ± 25.0	3 to 10 days	Social Approach	NO
						208.8 ± 14.3		Novelty-Suppressed Feeding	YES ↑.
						211.2 ± 25.0		Digging	YES ↑
						208.8 ± 14.3		Bottle Brush Tests	YES ↑
		DBA/2J	Male	At least 10 weeks old	Chronic intermittent vapor inhalation. 16 h separated by 8-h periods of withdrawal ip primer dose	253.3 ± 16.0	3 to 10 days	Social Approach	
						173.3 ± 14.7		Novelty-Suppressed Feeding	YES
						169.5 ± 19.9		Digging	NO
						179.5 ± 22.3		Bottle Brush Tests	YES ↑
									YES ↑

effect (39, 40). The kindling effect is defined by Pinel et al. as "the progressive intensification of elicited motor seizures that occurs during a series of convulsive stimulations"; this leads to increased susceptibility to convulsive seizures during alcohol withdrawal due to previous seizure-inducing withdrawals (39). The impact of multiple withdrawals also has a worsening effect on some of the associated cognitive impairments. This was demonstrated using rats fed an ethanol-containing diet (13–14 g/kg/day) for 24 days with two 3-day withdrawals compared with controls and with rats undergoing continuous ethanol treatment (23). These rats performed worse at negative patterning tasks but not spatial learning, which indicates that repeated withdrawals may affect some areas of cognition such as plasticity but not others. This differential effect of repeated withdrawals on only some cognitive defects is consistent with evidence that repeated withdrawals in rats compromised the acquisition of a conditioned fear response without impacting the recall of a previously learned fear association (29). These findings led to a hypothesis that multiple withdrawals induce aberrant neuronal plasticity, which gives rise to interesting predictions. Based on the idea that repeated withdrawal from alcohol results in repeated overactivity within glutamatergic systems (see below), it is possible that hyperactivation of glutamatergic systems would induce synaptic plasticity, leading to synaptic strength. If repeated withdrawals increase synaptic strengths, then stimulation of input pathways will have an enhanced effects on outputs, leading to certain excitability. However, if synapses are already strengthened, then the capacity for further plasticity will be reduced, leading to impaired learning of new associations (41, 42). However, further research is required to determine the underlying mechanism(s) behind multiple withdrawals reinforcing some but not all cognitive defects.

The Duration of the Withdrawal Effect on Cognition

A key consideration is the duration of withdrawal from alcohol treatment. Some studies have looked at immediate effects of withdrawal after 8–24 h (23, 36, 37), while others assess cognitive defects present after a much longer period (several weeks) (25, 31). One key question is whether any cognitive impairment is long-lasting and/or persistent even following a significant period of abstinence. One study found that withdrawal caused significant working memory impairment during acute withdrawal (24–72 h) but not extended abstinence (16–68 days) (36). This contrasts with another study in mice in which short-term memory was not affected by withdrawal but learning and long-term memory were still impaired when tested 12 weeks after cessation of ethanol consumption (31). This suggests that withdrawal, while having a severe acute effect on cognition, may also cause long-lasting impairments. Therefore, the type of cognitive impairment present may also differ depending on the duration of abstinence.

Proposed Mechanisms of Withdrawal-Induced Cognitive Dysfunction

There is much discussion about the mechanism by which withdrawal from chronic ethanol induces cognitive impairments.

Animal models have been used to link alcohol consumption with neurodegeneration and changing brain structure by neurotoxicity, reducing neurogenesis, and reducing the size of existing neurons. This has been related to dysfunctional behavior, which is suggestive of cognitive impairments (19). There have been several studies investigating the processes underlying these neurotoxicities. One such experiment in both rats and mice of both genders found increased levels of corticosterone in the brain tissue and plasma of both acutely (plasma) and prolonged (brain) withdrawn animals (43). Raised levels of corticosterone are known to cause neuronal damage, and it was therefore proposed as a potential mechanism underlying withdrawal-induced cognitive dysfunction. These raised corticosterone levels are thought to increase neuronal damage by potentiating excitatory transmission, inducing neuronal atrophy. Additionally, increased expression of NMDA receptors was found on the synaptic neurones of the medial prefrontal cortex, using a mouse model of chronic intermittent ethanol (26). This was also linked to a behavioral deficit in cognitive flexibility a week after the cessation of ethanol consumption. These findings suggest that the neuro-adaptive changes as a result of chronic alcohol consumption may contribute to withdrawal-induced dysfunction.

Other studies have focused on which brain areas are damaged during alcohol withdrawal, which may further inform how cognitive defects occur. For example, rat performance on a cognitive task was impaired by lesions of the basolateral amygdala (conditioned reinforcement and reinforcer devaluation) and central nucleus of the amygdala (Pavlovian-to-instrumental transfer) to identify which area is affected during single or repeated withdrawals. The result indicated that the central but not basolateral nucleus was affected during withdrawal. Similarity studies of mouse brains found that dendritic spine density was reduced in the lateral orbitofrontal cortex of mice following chronic intermittent exposure to ethanol (43). A comprehensive review of all relevant research is beyond the scope of this article; however, these examples provide evidence that the induction cognitive dysfunction following withdrawal is a complex process involving several brain regions. It is a vital area of research if we are to protect the brain, or at least limit the damage, in alcohol dependence.

Conclusion From Animal Models

Ultimately, there are several different animal models of chronic alcohol consumption that are used to study the impact of withdrawal on cognition. While these models fail to replicate all the complexities of psychosocial and compulsive factors that occur in the human experience of withdrawal, these animal models provide good evidence that withdrawal from chronic ethanol induces cognitive impairment, that this impairment is worsened by repeated bouts of withdrawal, and that these impairments are dependent on the duration of alcohol withdrawal and abstinence. These animal models have led to the identification of neuroadaptations and increased levels of corticosterone as potential modifiers of cognitive deficits caused by withdrawal and which brain regions are vulnerable to or involved in these impairments. Understanding the risks of withdrawal and the underlying neurobiology is vital if we are to develop more effective therapies for reducing the damaging consequences of alcohol withdrawal.

CONSEQUENCES OF REPEATED DETOXIFICATION OF PATIENTS DEPENDENT ON ALCOHOL

There is strong evidence that repeated detoxifications are associated with several cognitive and emotional impairments. Initial observations confirmed increased incidence of seizures (44–46). During recent years, accumulating evidence suggests that individuals who have experienced repeated episodes of withdrawal show changes to their affect, increased craving, as well as significant deterioration of cognitive abilities, when they are compared to patients with fewer withdrawals (47–49).

Several investigators had suggested that repeated episodes of detoxification increase the risk of withdrawal seizures. Further support to their suggestion came with the discovery of the differential response of alcohol-dependent patients to anxiety evoked by the noradrenergic alpha2 agonist, yohimbine, between those with two or more detoxifications compared to those with only one (50). These initial observations were followed by a plethora of experimental evidence showing that repeated experience of repeated detoxifications results not only in increased incidence of seizures and anxiety but also in increased craving and impaired inhibitory control of several behaviors in tasks (50, and in more detail below, e.g., 51, 52). Such tasks are challenging for high-order executive functions within problem solving or emotional evaluation contexts like reward seeking under conditions of incentive conflict, cognitive flexibility in an intra-extra dimensional shift, and reversal task and recognition of emotions in others.

Correspondingly, brain imaging shows that inaccurate performance on the cognitive tasks in alcohol dependence in humans who had experienced multiple detoxifications is associated with loss of gray matter in prefrontal regions; the loss of gray matter is positively correlated with the number of detoxifications. Evidence also suggests that the ability to recognize emotions in others (e.g., fearful faces) is associated with reduced connectivity between insula and prefrontal areas, but increased connectivity between insula and subcortical regions (colliculus) and between amygdala and other subcortical regions [e.g., bed nucleus of stria terminalis (BNST)].

Understanding the mechanisms that underlie the associations between repeated detoxifications and cognitive and emotional impairments as well as brain structure and functions alterations is mainly based on animal models [see previous section and (23)]. Additionally though, binge drinking (a tendency to drink excessively in one session leading to intoxication followed by abstinence) in young human adults has also been used as a model to explore possible predisposition to and early consequences of alcohol drinking in the form of repeated cycles (53–58).

Here, we will summarize the empirical evidence of the cognitive and behavioral deficits and their brain substrates

associated with repeated detoxifications and how such deficits may increase vulnerability to relapse.

Cognitive Control Processes Involved in Relapse

Increased urges to drink alcohol when induced by alcohol-associated stimuli and reduced ability to control the amount are recognized as the two basic processes of alcohol dependence. Inhibitory control is necessary for self-regulation. This is linked to executive function. Individuals who have low executive capacity or have damage to brain substrates subserving executive function display reduced ability for self-regulation and a greater susceptibility to behavior driven by stimulus and relapse (59, 60). Stimuli irrelevant to the present task or in contrast to the individual's current goals can diminish self-regulatory behavior in a stimulus-driven fashion and lead to relapse (61, 62). Other evidence, however, suggests that a stimulus-driven effect may be dependent on search goals driven by the individual's desire to consume alcohol (63). Several cognitive processes are considered to support self-regulation such as working memory and the ability to shift attention from previously relevant (but now irrelevant) stimuli (e.g., alcohol cues) to currently relevant factors (e.g., awareness of drinking consequences).

With the escalation of dependence, alcohol-associated stimuli become more salient and attract attention faster, thus diminishing the ability to inhibit the urge to drink. Such alcohol-associated attentional bias predicts relapse rates and treatment outcomes (64). Neuroimaging studies have provided strong evidence for the increased involvement of stimulus-driven networks (subcortical structures) and reduced involvement of brain substrates associated with cognitive control (65–67). Thus, as dependence progresses, relapse after several efforts to achieve and maintain abstinence becomes increasingly likely as distinct places, people, and paraphernalia associated with the reward offered by alcohol trigger an intense motivation within the addicted person to consume alcohol. As mentioned above, attentional processes (i.e., the ability to shift attention from previously relevant (but now irrelevant) stimuli to currently relevant factors may be crucial for self-regulation. Although impairments of cognitive control are associated with increased incidence of relapse in alcohol dependence, few studies have directly examined the possible impact of repeated detoxifications on cognitive control.

Alcohol-dependent individuals show impaired cognitive flexibility as measured in an intra–extra dimensional shift and reversal task (IED). This is associated with reduced volume of gray matter in a cluster within the inferior frontal gyrus (BA47) and the neighboring anterior insula. This is an area that shows reduced gray matter volume in alcohol-dependent patients and especially in those with a history of multiple detoxifications (52). The inferior frontal gyrus (IFG) is an area involved in inhibitory control. Observed decreased gray matter volume in this area suggests that decreased inhibitory control due to IFG damage may be linked with repeated relapses (68). Therefore, inhibitory control seems to modulate the translation of desire to drink into alcohol consumption and weakening of inhibitory control may lead to addiction (68). To that effect, strengthening inhibitory control may be an important cognitive strategy to prevent relapse (69).

Social Competence as a Cause of Relapse: Brain Mechanisms

The cognitive deficits caused by reduced function of prefrontal brain areas (41, 42) in alcohol dependence, arising from repeated detoxifications, may not only contribute to inflexible behavior and perseveration of drinking but also to the impairments in social cognition, which is crucial for adaptive social interaction (70, 71).

Earlier studies have demonstrated that alcohol-dependent patients generally have reduced ability to recognize emotions expressed by facial expression in others (72–74). Our research has shown that such impairments may increase with greater numbers of detoxifications (75). Emotional recognition deficits are associated with less successful recovery (76, 77). A recent study that examined prospectively objective treatment outcomes found that alcohol-dependent patients who were poor in recognizing emotions in others were also more prone to relapse (78).

Neuroimaging findings have revealed brain changes associated with emotion recognition deficits most commonly in prefrontal cortex, amygdala, and insula brain areas (51, 52). The amygdala is the brain structure involved in processing of emotion (79) including the recognition of fearful facial expressions (80); the insula is associated not only with emotional processing but also with emotion regulation. Imaging the brain of alcohol-dependent patients during fear recognition in emotional facial expression of fear (74) revealed reduced connectivity between insula and prefrontal emotional regulatory regions (81–84). In particular, a reduced connectivity of insula with the anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), and ventrolateral prefrontal cortex (VLPFC) was seen in alcohol-dependent patients with two or more detoxifications compared with either controls or patients with a single or no prior detoxification (51). Increased connectivity, also in patients with two or more detoxifications, was found between insula and a colliculus neuronal cluster, a region representing an important subcortical area for arousal mechanisms (85), as well as between amygdala and bed nucleus of stria terminalis (BNST). BNST has been identified as the key component area of stress-induced relapse in animal models of addiction (86). From these findings, it can be argued that increased connectivity in amygdala-related networks could lead to an increased emotional reactivity (84), whereas decreases in the network integrity of insula-related networks could lead to inappropriate analysis of the emotional input (87).

Importantly, the strength of connectivity between insula and areas involved in control of behavior and regulation of emotion (inferior frontal cortex, frontal pole) was negatively correlated with the number of detoxifications and with the ability to control drinking as evaluated by a self-rating questionnaire (ICQ; 51), suggesting a relationship between repeated detoxifications and the subjective perception of the ability to abstain. These findings further support that focusing treatment in reducing the impact of repeated experiences of detoxifications represents a reasonable approach.

Incentive Conflict and Cognitive Control as a Cause of Relapse: Brain Mechanisms

From the above, it becomes clear that controlling drug taking depends on the ability of higher-level monitoring functions to interrupt the incentive process that is induced by the rewarding properties of the drug, but could also depend on the strengthening of the incentive process as addiction progresses (88).

Drug taking is considered as an impulsive choice for an immediate positive outcome based on previous hedonic experience or relief from pain or stress but on the possible expense of long-term health and social benefits. Alcohol dependence may impair processes that contribute to choice impulsivity (89), so that later consequences of drinking are not taken into account. For the alcohol-dependent patient trying for abstinence, the conflict between the desire to drink and the aim to abstain in order to avoid adverse consequences may be particularly strong, leading to erroneous choice at the time and a lapse.

We have studied aspects of the interaction between incentive learning and behavioral control using the incentive conflict task (ICT) (90). This is a version of negative patterning tasks used in cognitive psychology (91). When performing the ICT, subjects first learn that two independent discrete cues signal reward (money gains), and in this way, they acquire incentive properties. In a second phase, while the individual cues continue to signal reward, when presented together in a compound, they signal punishment (money losses). Participants have to learn to respond appropriately so that they respond to gain money when the stimuli are individually presented, but withhold responding to avoid money losses when the stimuli are presented in compound. The incentive conflict task is thus a task that puts demands on decision-making under conditions requiring conflict resolution. We have proposed that the task creates a conflict between abstaining and responding for reward, which is similar to that experienced by the patient before lapse. Therefore, the impaired ability of patients who have experienced multiple detoxifications to perform the task might reflect the consequences of the detoxification process itself on behavioral control.

As the number of previously experienced detoxifications increases, patients become increasingly impaired in withholding their responses in the condition of no reward, suggesting that the process of detoxification may engender brain changes that affect decision-making to avoid reward losses and lead to loss of control (90). This is consistent with deficits observed in a rodent version of the same task, in rats chronically exposed to alcohol (23). Importantly, in this well-controlled animal study, it was the number of withdrawal events ("detoxifications") that determined the extent of the deficit.

Neuroimaging of the ICT task with human control participants shows activation of several areas but most importantly those of the supplementary motor area, striatum (including putamen), gyrus rectus, ventromedial prefrontal cortex (vmPFC), and superior frontal gyrus areas, which are implicated in cognitive and emotional processing of reward (91–93) and regulatory control over a behavioral response (94, 95). Smaller gray matter volume in alcohol-dependent patients in the areas where dysregulated brain responses are seen during ICT have been reported, such as vmPFC and superior frontal gyrus, even more so in patients who had experienced more detoxifications. This is consistent with suggestions that these smaller volumes are "brain damage" associated with the detoxification experience. Further, the smaller volumes likely are associated with impairments in motivational decision-making, which involves the vmPFC (96, 97), and behavioral control, which involves the superior frontal gyrus (94, 95). Activation changes of vmPFC is shared with the gambling task (97), which resembles incentive conflict in requiring decision-making. Alcohol-dependent patients with several detoxifications also show impairments in this task (98). These findings are further supported by a study (99) that found that resolution of emotional conflict was associated with activation of an area that included the vmPFC.

Blunted response of the vmPFC in alcohol-dependent humans to the presentation of stress cues, a condition that the ICT also possibly generates, has been found to predict the incidence of relapse (100). Higher incidence of relapse with the possibility of trying to detoxify again leads to experience of multiple detoxifications found in our studies to be associated with smaller gray matter volume in vmPFC. Aberrant responsiveness to vmPFC to stress (101) is proposed to be associated with autonomic neural system dysfunction probably induced by the decreased ability of vmPFC to regulate emotional responses to stress or conflict situations. Prefrontal gyrus activation on the other hand may be more associated with the attentional and executive processes involved in inhibitory control that govern responding to ICT (94, 95, 102). Recent work on brain network efficiency of patients with alcohol dependence has identified, among other areas, the superior frontal gyrus area to show reduced nodal efficiency, supporting reduced ability of this area to carry out its functional activity (103).

The damage induced by alcohol—and detoxification—is not restricted to the areas identified in the ICT experiments. For example, the inferior frontal gyrus has been implicated in previous research during cognitive set switching (104) and also when resolving decision conflict during an instrumental learning task (105). Again, decreased inhibitory control due to IFG damage may support the occurrence of repeated relapses.

BRAIN IMAGING OF ALCOHOL DETOXIFICATION IN HUMANS

Alcohol dependence is associated with tolerance and withdrawal with neuroadaptations in GABA-A and glutamatergic *N*-methyl-D-aspartate (NMDA) receptors playing key roles (106). Dysregulation of the NMDA receptor system is thought to underpin alcohol-related memory impairments (107).

Imaging Glutamate in Humans

In humans, magnetic resonance spectroscopy (MRS) can be used to measure glutamate levels in the brain, albeit often with other metabolites and neurotransmitter and metabolic pools that cannot be robustly distinguished (108). A number of studies have reported greater glutamate levels in alcohol-dependent individuals during early withdrawal from alcohol.

One study reported greater MRS glutamate + glutamine (Glx) levels in the anterior cingulate cortex (ACC) at the start (day 1) of alcohol detoxification in alcohol-dependent individuals compared with controls, which normalized over the next 14 days (109). Benzodiazepines were used for treatment. Glx levels were not related to severity of alcohol withdrawal. Complementary preclinical translational studies showed that glutamate levels in the medial prefrontal cortex (mPFC) of ethanol-dependent rats were increased at 12 h of withdrawal compared with controls and during intoxication; the glutamate levels had declined by 60 h. A further study from the same group provided more evidence that a hyperglutamatergic state is associated with brain neurotoxicity. In both humans and rats, hippocampal glutamatergic function was found to be inversely related to volume, although notably, no differences were found with controls in either species (110). This may have been due to different methodology and lack of power to detect a group difference due to smaller hippocampal volume.

However, other studies have reported that human glutamate levels were lower in the ACC, dorsolateral prefrontal cortex (DLPFC), or parieto-occipital cortex (POC) 9 days after stopping drinking compared with "light drinkers" and normalized (i.e., increased) during the following month in ACC only (109). The authors suggested that their first time point may have missed the early elevation in glutamate reported by others and that, altogether, studies suggest that glutamate levels change during alcohol withdrawal and early abstinence. Although glutamate levels at the earlier time point were inversely associated with cognitive task performance, improved cognitive function was not related to any changes in glutamate or indeed other MRS markers [creatine, *N*-acetylaspartate (NAA), choline, and GABA]. Similarly, lower glutamine levels have been found in alcohol-dependent individuals who are still drinking, though breathalyzed negative at the time of the scan, compared with light drinkers (111). An inverse relationship between glutamate, but not glutamine, levels and number of heavy drinking days has been reported in ACC of alcohol-dependent participants but not light drinkers (18).

Higher levels of glutamate + glutamine in the nucleus accumbens and anterior cingulate have also been shown to be positively related to craving in recently detoxified alcohol-dependent individuals (112, 113). However higher levels have not always been reported in the anterior cingulate (112), which may suggest a differential rate of glutamatergic normalization in brain regions. No moderating effect of medication, e.g., diazepam or clomethiazole, was seen on glutamate levels and no relationship was seen with withdrawal symptoms (112). No cognitive measures were described in this study.

Although studies did not necessarily find any relationship of glutamate levels with clinical variables, this is likely due to the clinical heterogeneity of alcoholism in the small number of participants in these imaging studies. Due to the lack of appropriate longitudinal studies, it is not clear whether any differences in MRS-derived markers reflect the neurotoxicity or neuroadaptations from alcohol directly or predate alcohol consumption and increase the risk of an alcohol use disorder.

Modulating Glutamatergic Function

In human alcohol-dependent individuals undergoing alcohol detoxification, those who received acamprosate compared with placebo resulted in a reduction in a glutamate:creatinine ratio between 4 and 25 days in the anterior cingulate (114). Diazepam was allowed if required during detoxification. It appears that any effect of acamprosate took a while to develop as it did not have an effect on alcohol withdrawal symptoms or on glutamate:creatinine ratio in the first few days of detox. Another study reported that glutamate levels were reduced after 4 weeks of acamprosate treatment compared with slight increases in those patients who did not receive acamprosate (113). The evidence from these studies is consistent with acamprosate having an "anti-glutamatergic" effect and that this likely underpins its clinical efficacy including reduction in craving. As no cognitive measures were obtained in the participants in either study, it is unclear if acamprosate did result in any cognitive benefits.

Other MRS Markers

Other MRS markers of neuronal integrity and function have also been studied in alcohol use disorder. For example, evidence is not consistent with lower, higher, or no differences seen in the metabolite *N*-acetylaspartate (NAA), which is seen as a marker of neuronal integrity and function. This likely reflects the heterogeneity of the disorder and methodologies used. Nevertheless, there is evidence that NAA is lower as a result of heavy alcohol consumption, that it increases on stopping drinking, suggesting recovery, and that low thalamic NAA levels have been shown to be associated with poorer treatment outcomes at 3 months (115, 116).

Imaging Inflammatory Response in Alcoholism

The inflammatory burden of alcohol consumption and dependence in regard to cognition is not well characterized in humans though it is likely to be an important target for treatment (115). Such inflammation may also contribute to alcoholism, increasing the risk of Alzheimer's disease (117). Positron emission tomography (PET) imaging studies assessing microglial activity with translocator protein (TSPO) tracers have shown lower, rather than higher, availability in abstinent alcoholics (106, 118, 119). Indeed one study showed that TSPO binding was positively correlated with verbal memory performance (118). Therefore, these studies suggest that lower glial density or an altered activation state with lower TSPO expression may contribute to cognitive impairment in alcoholism.

Treatment of Alcohol Withdrawal/ Detoxification

As described, alcohol withdrawal and its complications develop as alcohol levels decrease and recurrent withdrawals result in increase in severity of symptoms due to kindling (120, 121). Such complications are also more likely in those alcohol-dependent patients who are hypoglycemic, hypokalemic, hypomagnesemic, or with infection or trauma (e.g., subdural hematoma) (120).

Treatment of alcohol withdrawal generally attenuates the risk of such consequences, but too frequently, alcohol dependence is missed due to lack of appropriate questioning or disclosure, so appropriate treatment is not started. Clearly, since delirium tremens and seizures reflect brain toxicity, there may also be an effect on cognition; thus, their prevention is paramount to protect brain function and optimize recovery. The reader is directed to clinical guidelines concerning more information regarding treatment of alcohol detoxification and prevention of complications (9, 122, 123).

Medically assisted alcohol withdrawal is generally treated with a reducing regimen of a benzodiazepine (e.g., chlordiazepoxide, diazepam, and lorazepam) (120, 122, 123). An alternative regimen is "symptom-triggered", where the benzodiazepine is given once symptoms meet a threshold for treatment. This requires regular monitoring of alcohol withdrawal symptoms with a validated scale [e.g., Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar)] by appropriately trained staff and so is not suitable in all circumstances, e.g., a busy admissions unit or nonverbal patients. Other anticonvulsants may be used (e.g., carbamazepine and sodium valproate); however, a Cochrane review did not find evidence in favor of their use to treat alcohol withdrawal (124). It should be remembered that benzodiazepines are also effective anticonvulsants and therefore risk of alcohol-related seizures can be managed with sufficient doses rather than adding in another anticonvulsant (123).

Another important clinical intervention to reduce risk of brain toxicity is consideration of thiamine deficiency as this vitamin is a key co-factor in metabolism. Thiamine deficiency may present with "paresthesia" (pins and needles) in hands and feet with numbness and with Wernicke's encephalopathy (WE), which is a medical emergency. Clinicians are advised to be suspicious as the classic triad of confusion, ataxia, and ophthalmoplegia, suggesting the diagnosis of WE, are rarely seen together, whereas the first two symptoms are very commonly seen in alcoholism (123, 125). Clinically, thiamine deficiency and WE are generally only considered with alcohol detoxification when greater metabolic load increases the risk; however, it may occur at any time and in other addictions with poor diet and absorption. For those with WE or at risk of it, parenteral thiamine is required since absorption from oral thiamine is insufficient to replenish stores (122, 123, 125). Thus, giving thiamine appropriately is a critical intervention to protect brain function and prevent irreversible alcohol brain-related brain disorder.

As described, current clinical treatment with benzodiazepines may not be optimal in attenuating the hyperglutamatergic state of alcohol withdrawal. As described, MRS studies have shown that acamprosate reduces glutamate in the brain. Clinically, acamprosate appears to be well tolerated during alcohol detoxification, when added to benzodiazepines, though there is no impact on alcohol withdrawal symptoms as measured with the CIWA-Ar (114, 126). However, acamprosate during alcohol detoxification has been noted to improve sleep and reduce arousal levels (alpha slow-wave index) when assessed with magnetoencephalography (127). Therefore, it is unclear if acamprosate-related reduction in glutamatergic activity does improve cognitive outcomes either in the short term or in the longer term.

EXAMPLES OF IMPLEMENTATION OF PRE-HABILITATION IN ALCOHOL DEPENDENCE

As described, the concept of pre-habilitation can be applied to the treatment of alcohol dependence, such as our model: "Structured Preparation for Alcohol Detoxification" (SPADe). Although SPADe has been applied on an individual basis, primarily it has been applied as an open, rolling group program, and described initially as Preparation for Alcohol Detox (PAD) and more recently as Abstinence Preparation Group (APG). The intervention may be regarded as a modified Cognitive Behavioral Therapy approach (128, 129), which is offered prior to detoxification and while the person is still drinking. The basic components of this treatment approach include (i) partial control over drinking, (ii) introduction of lifestyle changes for the individual, (iii) and the immediate family and social environment. Existing evaluations of SPADe treatment pathways suggest that about 72% of individuals with alcohol dependence presenting for treatment can engage and complete the pre-habilitation intervention (APG) (12).

Partial Controlled Drinking

When presented as an alternative to lifelong abstinence as the sole treatment outcome (130), the concept of controlled drinking generates intense conflict within the field of addiction medicine. However, within clinical guidelines (9) controlled drinking within "healthy" limits may be considered as an appropriate treatment objective for harmful drinkers. For dependent drinkers, abstinence remains the preferred treatment objective (9).

The main aim of pre-habilitation is to pre-empt clinical withdrawal symptoms and the associated urges to drink. Within the SPADe treatment approach for alcohol dependence, controlled drinking is referred to as "partial" for two reasons: (i) it is an intermediate treatment stage rather than the final treatment aim, which is abstinence; and (ii) the amount and pattern of drinking are not within healthy limits. Therefore, within SPADe, the primary aim of the "partial controlled drinking" stage is to stabilize both the amount of alcohol consumed and the pattern of drinking. Alcohol is considered as "if it were a medication" with frequent and regular dosing to prevent the onset rather than to treat the appearance of withdrawal symptoms. This proactive elimination of symptoms is considered fundamental from a biological perspective, since it protects against acute brain dysregulation, which, in turn, might sensitize the brain, leading to an exaggeration of the negative impact associated with the disturbance of the brain homeostatic system. From a psychological perspective, it empowers the individual by restoring some control over decision-making and reducing the impulsivity associated with the experience and avoidance of cravings and withdrawal symptoms. Furthermore, partial controlled drinking provides a relatively stable environment for the individual—and their social group–to begin implementing lifestyle changes that lead to an increased sense of self-efficacy. This is considered the final mediating factor in social learning theory and cognitive behavioral treatment models (131).

The aim is to avoid substantial and dramatic reductions to the amount of alcohol consumed, which not only will prove

unsustainable but might also lead to the precipitation of withdrawal symptoms, which could be life threatening. Thus, small sustainable changes are implemented, and once stability is achieved, a further gradual reduction of alcohol intake can be safely undertaken. In our experience, about half of the patients following this approach will be able to come off alcohol without the use of detoxification medication (12). This model of detoxification is called "guided self-detox", and alcohol is regarded as if it was a medication that is gradually discontinued.

Early Introduction of Lifestyle Changes

The stabilization of drinking provides for a short period a relatively stable and safe environment for the patient, the immediate family, and the patient's social network to develop and test out lifestyle changes. Such early and gradual changes implemented within the individual's lifestyle are necessary to provide (i) a routine in everyday life that will protect against early relapse, (ii) a response to the void that alcohol detoxification would otherwise leave in its wake, (iii) a distraction strategy against the onset of craving, (iv) an enhancement of personal responsibility, (v) a de-mystification of alcohol and a challenge to the omnipotence of cravings or withdrawal symptoms, and, finally, (vi) protection against the acute sense of stress experienced in the early days of abstinence.

The involvement of family members and the immediate social support system in treatment helps in reframing the environment, modifying unrealistic expectations, and supports the gradual adaptation to the new family dynamics (following the removal of alcohol). It will help in managing the anxiety and difficult feelings/emotions associated with broken trust and promotes a partnership approach. Fundamentally, recovery is easier to achieve and more sustainable within a respectful, stress-free, and supportive environment. It is far easier for the patient to maintain abstinence (in particular during the first few weeks) within a family environment that is also abstinent, thus removing proximal cues/triggers (smell or sight of alcohol) as well more distant cues, such as elevated levels of stress or negative emotional states.

CONCLUSION

In this review, we have described how alcohol detoxification is a neurobiologically challenging time for the brain and is associated with cognitive impairments that contribute to the high risk of relapse. Despite their limitations, animal models have demonstrated that alcohol withdrawals induce impairments in learning, cognitive flexibility, memory, sociability, increased levels of anxiety, and disrupting sleep. The evidence is mixed on the duration of these effects, suggesting that, potentially, in addition to the acute effects, there might be long-lasting impairments. Furthermore, repeated withdrawals may affect some areas of cognition such as plasticity but not all. Evidence supports roles for elevated levels of corticosterone or increased expression of NMDA receptors in neuro-adaptations underpinning alcohol withdrawal.

How does this evidence translate into human patients? There is evidence that with repeated detoxifications, withdrawal seizures, levels of anxiety, and experience of cravings increase, whereas inhibitory control of certain behaviors such as reward seeking, cognitive flexibility, and recognition of emotions in others is reduced. Furthermore, attentional bias towards alcohol-associated stimuli is increased and predicts relapse rates and poorer treatment outcomes.

The evidence from neuroimaging studies is unable to clarify whether any differences observed reflect the neurotoxicity or neuro-adaptations from alcohol directly or predate alcohol consumption and increase the risk of an alcohol use disorder. Nevertheless, it seems that current clinical treatment with benzodiazepines may not be optimal in attenuating the hyperglutamatergic state of alcohol withdrawal.

How could the above evidence guide our clinical practice? The evidence reviewed in this paper suggests that the process of detoxification from alcohol in humans seems to have a negative impact on cognitive functioning and create or worsen mood dysregulation. These effects are temporal, although the exact duration is not specific as multiple factors might have an effect beyond and above the severity of the baseline alcohol intake (chronicity, amount, and pattern). Nevertheless, given that this impact is anticipated, it is prudent to be prepared and proactive into managing the associated risks. To that effect, stabilization of the amount and pattern of drinking, empowerment of the individual patient and the immediate environment to prepare and implement lifestyle changes in advance of stopping alcohol, and furthermore the avoidance, if possible, of detoxification by a gradual withdrawal might prevent or provide protection against or increase the ability of the patient and the immediate environment to cope with them.

There is some evidence that people who had more than two detoxifications do worse than those who had less than two detoxifications. Although some of the cognitive impairment observed might be pre-existing (i.e., as part of increasing vulnerability to addiction), this evidence indicates that there might be an accumulating effect with worsening of outcomes and reduction of the possibility of achieving sustainable outcomes. If this evidence is correct and the hypotheses that repeated detoxifications have a long-term negative impact, then it is crucial to avoid repetition of detoxifications and approach each detox as if it would be the last one. A proactive approach within the spirit of pre-habilitation to maximize the chances of lifelong abstinence following detoxification is even more relevant.

Further, evidence presented suggests that the medication used at the moment does not protect from or necessarily reverse the negative cognitive impact and therefore is not optimal to reduce the risk of relapse and possible long-term accumulative negative effects of detoxifications. Until such medication is developed, active participation with aftercare interventions to maintain abstinence or at least keep drinking at low risk level is crucial and every effort should be made for patients to continue their treatment beyond the end of detoxification. A pre-habilitation approach that exposes and familiarizes patients to psychosocial interventions will enhance their ability to participate in aftercare interventions.

There are several clinical questions for which we require evidence. How many detoxifications should we offer within a specific period of time? How soon after a relapse should we offer another detoxification? Is there a washout period following a detoxification or are these effects permanent? Does this mean that,

following two failed detoxifications, there is no further negative impact and therefore detoxification should be offered at any given opportunity? Given the above clinical uncertainties and the potential risks indicated by the reviewed evidence and until further evidence provides answers, a new treatment paradigm based on the principles of pre-habilitation in addition to rehabilitation seems to have major advantages in providing aspects of the rehabilitation treatment before detoxification. SPADe provides such a model, in which a structured Cognitive Behavior Therapy-based intervention, which aims to stabilize drinking, introduce early lifestyle changes, and involve immediate social system into proactive changes to support the early stages of abstinence, is consistent with pre-habilitation and is supported by preliminary evidence that might be effective (11, 12). It is important though to remind ourselves that one of the primary objectives of a pre-habilitation treatment paradigm is the empowerment of the person with the drinking problem and for the immediate social environment to take responsibility for the problem and be active agents of the solution. Structured interventions prior to detoxification should be offered within the spirit of pre-habilitation and not as a screening process to manage the ever-reducing budgets for inpatient detoxification as suggested in the most recent report of PHE (10). If implemented to screen patients, then such a use of pre-detoxification groups could create barriers into accessing treatment and compromise rather than enhance long-term treatment outcomes (10).

AUTHOR CONTRIBUTIONS

CK: overall coordination of the manuscript with final editing and writing up of sections Introduction, Currently Recommended Treatment Paradigm to Manage Alcohol Detoxification, Learning and Habit Development in Humans, Examples of Implementation of Prehabilitation in Alcohol Dependence, and Conclusion. TD: written section Consequences of Repeated Detoxification of Patients Dependent on Alcohol; EP: written section Animal Models of Alcohol Withdrawal and Detoxification on Cognitive Impact; and AL-H: written section Brain Imaging of Alcohol Detoxification in Humans.

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REVIEW
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Addiction, Anhedonia, and Comorbid Mood Disorder. A Narrative Review

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Background: Recently, anhedonia has been recognized as an important Research Domain Criterion (RDoC) by the National Institute of Mental Health. Anhedonia is proposed to play an essential role in the pathogenies of both addictive and mood disorders, and possibly their co-occurrence with a single individual. However, up to now, comprehensive information about anhedonia concerning its underlying neurobiological circuitries, the neurocognitive correlates, and their role in addiction, mood disorder, and comorbidity remains scarce.

Aim: In this literature review of human studies, we bring together the current state of knowledge with respect to anhedonia in its relationship with disorders in the use of substances (DUS) and the comorbidity with mood disorders.

Method: A PubMed search was conducted using the following search terms: (Anhedonia OR Reward Deficiency) AND ((Drug Dependence OR Abuse) OR Alcohol OR Nicotine OR Addiction OR Gambling OR (Internet Gaming)). Thirty-two articles were included in the review.

Results: Anhedonia is associated with substance use disorders, and their severity is especially prominent in DUS with comorbid depression. Anhedonia may be both a trait and a state dimension in its relation to DUS and tends to impact DUS treatment outcome negatively.

Keywords: anhedonia, disorders in the use of substances, substance abuse, addiction, depression, mood disorder, gambling, internet gaming

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INTRODUCTION

Disorders in the use of substances (DUS) as defined by the *Diagnostic and Statistical Manual of Mental Disorder-5 (DSM-5)* are a set of highly prevalent disorders with an enormous negative impact on individuals, their families, and society as a whole (1). From a neuroscientific perspective, DUS can be conceptualized as complex disorders, i.e., multiple symptom clusters and underlying neurobiological circuitries/systems play a role. In its core lay both a hypersensitivity to drug-related stimuli and an impairment in (executive) control over these impulses. On the other hand, and increasingly as the disorder progresses, a "darker" side has been suggested where an increase of brain-stress system, impaired stress tolerance, negative affect, and anhedonia take the upper hand (2).

From a clinical perspective, anhedonia, i.e., a markedly diminished interest or pleasure in activities that are naturally rewarding, is an essential characteristic for many addicted individuals. Anhedonia-like symptoms have been reported in the context of active chronic substance use,

(protracted) withdrawal, and during sustained abstinence. Also, anhedonia may, for some individuals, act as a pre-existing vulnerability for substance initiation, regular use, and the subsequent development transition to addiction (3). The symptoms characterizing anhedonia may reflect underlying neurochemical changes, typically associated with the "dark side" of addiction, where negative reinforcement drives continuing substance use and the neurochemical picture is dominated by dysregulation of brain-stress systems (2). These may also include peripheric inflammation processes that have been reported in the context of chronic substance use and associated with depression and anhedonia (4). In line with this are the recent findings indicating that antidepressants, i.e., agomelatine, might affect anhedonia, possibly *via* decreasing C-reactive protein and increasing BDNF serum levels (5–7). Furthermore, anhedonia may have specific clinical importance, i.e., for outcome and treatment response. Indeed, anhedonia increases the likelihood of relapse and is associated with craving (3).

Characteristic of DUS is the high prevalence of comorbidity with other psychiatric disorders. This might be the result of the diagnostic vagueness inherent to the currently used diagnostic categorical systems such as DSM and ICD. Alternatively, common underlying factors may drive different behavioral–phenotypical presentations that when diagnosed "categorical" on a behavioral level results in statistical high levels of comorbidity (8). Disorders of mood (MD) are one of the psychiatric disorders that have been reported to co-occur frequently with DUS are mood disorders (MD). The co-occurrence of MD and DUS has been well established with an estimated two- to fivefold increase in odds of having an MD when the other condition is present (9). With respect to the pathogenesis of psychiatric disorders, anhedonia has been considered as a principal, transdiagnostic characteristic, within the phenotypic concept of different mental disorders, e.g., mood disorders, schizophrenia, and also DUS (10). Recent studies suggest that reward hyposensitivity within unipolar depression will be most strongly associated with a state of anhedonia characterized by motivational versus hedonic deficits (11, 12). From this perspective, it might be hypothesized that anhedonia as an underlying neurobiological construct acts as a driver explaining the high prevalence of the DUS–depression comorbidity. Alternatively, anhedonia might be a symptom within both disorders but of which its origin is based on different pathogenetic pathways, e.g., anhedonia as a result of down-regulation of reward pathways in a response of chronic substance (ab)use.

Anhedonia is by far not the only common construct underlying comorbidities between DUS and other psychiatric disorders. Indeed, using the Research Domain Criterion (RDoC) terminology, deficits in threat-related processes (Negative Valence Systems), executive control (Arousal/Regulatory Systems), and working memory (Cognitive Systems) are observed across many psychiatric disorders in both the "internalizing" spectrum (e.g., depression, anxiety) and the "externalizing" spectrum, i.e., DUS (8, 11). However, up to now, the role of anhedonia in both the pathogenesis of addiction and in the comorbidity with mood disorders has been mainly left understudied. This is an essential caveat since an increasing number of studies indicate that anhedonia, e.g., within the context of depression, is a factor that negatively impacts treatment outcome. Indeed, anhedonia is a predictor of poor longitudinal course of symptoms of major depression, suicidality, and suicidal ideation and poor response on pharmacological treatment (13–16).

Within the scope of this review, we first present ideas on conceptualizing and assessing anhedonia. Next, we review the literature exploring the relationship between anhedonia and substance use disorders. In the discussion, we extend on how these findings match with current concepts on anhedonia and how this, potentially, reflect on treatment and future research.

CONCEPTUALIZATION OF ANHEDONIA

Anhedonia refers to a decreased interest or pleasure in response to stimuli that are either by nature or previously perceived as rewarding. As such, anhedonia is inherently associated with reward processing. Reward processing involves multiple components that can be dissected experimentally in animal models but are likely intermingled in real life-situations: sensory detection of a stimulus, affective hedonic reaction, pleasure itself (liking), motivation to obtain the reward and work for it (wanting or incentive salience), and reward-related learning processes (17).

At least two broad dimensions underlying anhedonia have been identified through animal and human research: 1) reward hyposensitivity and 2) reduced approach motivation. Of importance, both aspects can be dissected regarding their underlying neurobiological pathways and neurochemical hallmarks (11).

Reward hyposensitivity has been suggested to be associated with the functionalities related to the "consummatory" part of reward processing, i.e., often reflected by the term "liking." Pleasure experience is suggested to be mediated by the endogenous opioid and endocannabinoid receptor pathways in different brain areas (18). This component could be called the hedonic dimension of anhedonia, i.e., "hedonic anhedonia."

Approach motivation is viewed as the driver that facilitates approach or goal-directed behavior to obtain rewards. Information encoded by dopaminergic transmission within the mesolimbic system is suggested to play a role in reward motivational value and motivational salience (17). The primary system is proposed to be dopaminergic frontostriatal circuitries. Reducing dopaminergic functioning has an adverse effect on the motivation to pursue and work for rewarding stimuli. This dimension could be called the motivational component of anhedonia, i.e., "motivational anhedonia." Of interest, administration of a dopamine agonist (d-amfetamine) produces an increase in the willingness to work for rewards in animal models (11, 19).

Taken together, growing evidence from self-report, behavioral, and neurophysiological studies suggest that reward hyposensitivity and reduced approach motivation reflect anhedonia (11). From this perspective, two distinct neural circuits underlying motivational (anticipation, wanting; i.e., associated with dopamine signaling within the frontostriatal circuitry) versus hedonic (consumption, liking; i.e., associated with endogenous opioids signaling) reward-related states can be hypothesized (11). For this review, we conceptualize anhedonia to these two basic dimensions (**Figure 1**).

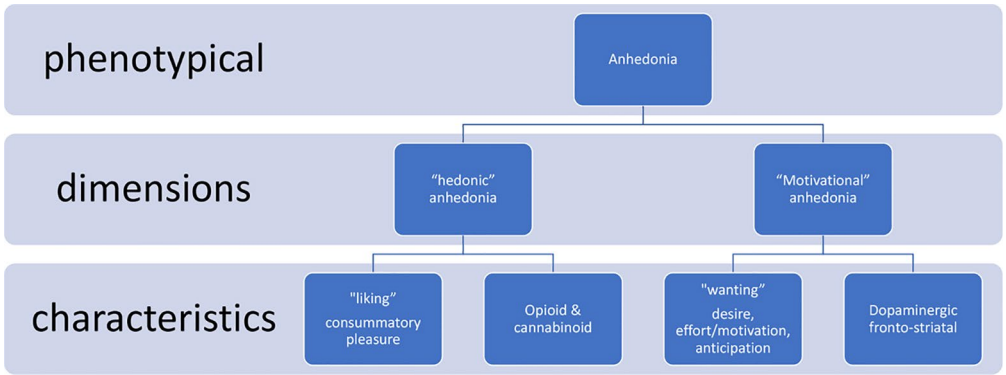

FIGURE 1 | Anhedonia dimensions (11, 18).

REVIEW: AIM AND QUESTIONS

Within the scope of this explorative–narrative review part of this manuscript, we aim to explore the following questions:

- What is the prevalence of anhedonia within human DUS individuals?
- What types of measurement instruments of anhedonia are used in human studies within DUS samples?
- Is there a differentiation according to hedonic versus motivation anhedonia?
- How does anhedonia relate to DUS–depression comorbidity?
- What is the role of anhedonia in DUS course and treatment response?

METHOD

The most recent systematic review on the relation between substance use disorders (SUD) and anhedonia reviewed the literature up to 23 May 2013 (3). So, with this review, we aimed at expanding this body of work by reviewing the literature published after this date, i.e., last 5 years. A search was performed in PubMed using the same search terms as in this latter publication (3). We included pathological gambling and internet gaming in this search because they recently were included in the DUS chapter of the *DSM-5* (and will be in the next ICD11) as addictive disorders.

In order to obtain original studies investigating the link between anhedonia and DUS, a PubMed search (May 2013–November 2018) for English language articles was conducted using the following search terms: (Anhedonia OR Reward Deficiency) AND ((Drug Dependence OR Abuse) OR Alcohol OR Nicotine OR Addiction OR Gambling OR (Internet Gaming)). The papers were filtered for human studies only. An overview of the inclusion process can be found in **Figure 2**. The PubMed search yielded 171 results; abstract screening led to the exclusion of 136 papers, leaving 35 papers. Of these, one full paper could not be retrieved, and two validation studies were excluded, so 32 articles were included in the review.

RESULTS

The majority of studies (n = 13) focused on tobacco smoking compared to alcohol (n = 4), cannabis (n = 4), cocaine (n = 5), benzodiazepines (n = 1), and opioids (n = 4). Behavioral addictions remain poorly studied, i.e., one study on gambling and none on online gaming. See **Table 1** for an overview of all studies.

Types of Measures of Anhedonia Used Within DUS Studies

Self-report measures were, by far, the most used instruments, i.e., all studies included self-report measures. Of these, the Snaith–Hamilton Pleasure Scale (SHAPS) (50) was most frequently used, i.e., in 15 of the 32 studies. Within the depression research, the SHAPS has been validated and remains the gold standard. It measures the consummatory pleasure (51) typically. However, given the recommendation that any scale should be validated in the population of interest prior to use, it needs to be noted that none of the self-report scales found in this review was ever validated within DUS populations. This particularly warrants interpretation of the current results.

Of interest, three studies used ecological momentary assessments (EMAs) during four times a day in a smoking cessation trial (25, 28, 34). It was questioned how much pleasure the participants experienced during the day on three domains (social, recreation, and performance/accomplishment). EMA might be a promising methodology providing data better covering the actual evolution of symptoms than (retrospective) self-report and is increasingly used in both depression and addiction research (52, 53). However, as yet, no validated set of EMA-implementable questions on anhedonia have been developed.

Few studies (n = 4) used behavioral tasks. Guillot et al. used the Picture Rating Task, which is a measure of affective valence related to positive, negative, and smoking cues (27). In this task, participants were instructed to rate the pleasantness of each stimulus by pressing keys corresponding to seven-point Likert scale from −3 (very unpleasant) to 3 (very pleasant). Positive,

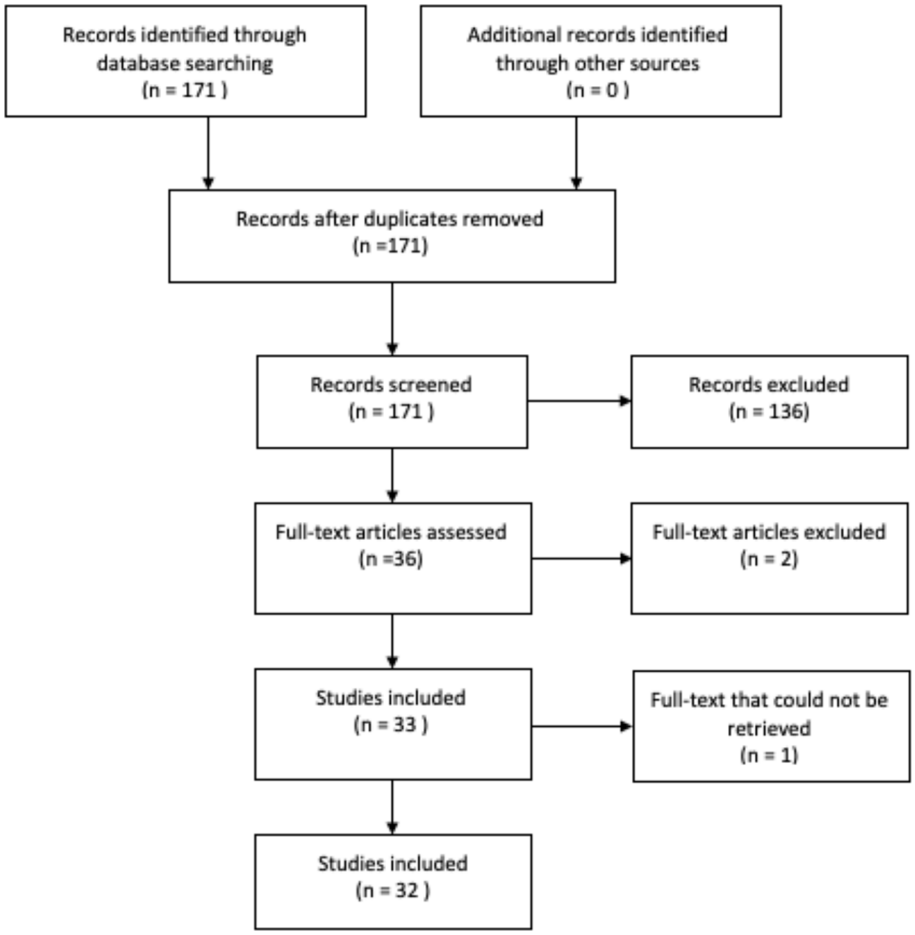

FIGURE 2 | Search strategy for research papers in PubMed.

negative, smoking, and neutral images are shown. In this task, anhedonia has been inversely related to pleasantness ratings of positive or reward-related stimuli.

Liverant et al. (33) used a signal detection task designed to assess modulation of behavior in response to rewards, which was already used in trials with MDD and bipolar disorders (54). In the latter studies, an inverse relationship between response bias and anhedonia was already demonstrated.

Leventhal et al. used a behavioral task measuring the relative reward value of smoking (36). This task yields objective behavioral measures of the relative value of a) initiating smoking versus delaying smoking for money and b) self-administering cigarettes for money when given the opportunity to smoke.

Wardle et al. used a progressive ratio procedure as a behavioral measure of anhedonia (19). Participants can choose two options in which option A results in greater rewards in exchange for greater effort while option C results in less reward but requires less effort. Fewer key presses for A indicates motivational anhedonia. It has to be noted that this type of behavioral measure is not strongly related to the SHAPS (55).

Taken together, the four studies using behavioral tasks all used a different paradigm. It remains unclear as to which aspect/dimension of anhedonia they tap in and how they relate with self-reported anhedonia.

Seven studies used neurobiological, i.e., neurophysiological or imaging, measures of anhedonia. First, an functional magnetic resconance imaging (fMRI) study in young cannabis users implemented a two-card guessing game that assessed response to anticipation and receipt of monetary reward (38). In this paradigm, anhedonia was associated with a pattern of negative Nucleus Accumbens (NAcc)–medial Prefrontal Cortex (mPFC) connectivity.

Parvaz et al. used a gambling task predicting whether they would win or lose money on each trial, while ERP data were required (40). Reward Positivity component (RewP) in response to predicted win trials was extracted from the ERPs. RewP is attributed to the same brain regions that are also implicated in anhedonia (i.e., ventral striatum and mPFC). The results showed that RewP amplitude in response to rewarded trials correlated with anhedonia severity in CUD.

Morie et al. performed two ERP studies in cocaine abusers and healthy controls (41, 42). In Morie et al. (41), a speeded response task with varying probabilities of reward is used. Cocaine users showed blunted response to reward-predictive cues and to feedback about task success or failure. Anhedonia measured by

TABLE 1 | Results from the literature review.

	Author	Sample	Anhedonia measure			Comorbidity	Result
			Self-report	Behavioral task	Neuro-biologic		
Alcohol	(20)	MDD (n = 4,339) MDD+AUD (n = 413)	MINI	/	/	MDD	Anhedonia is associated with alcohol abuse
	(21)	Trauma-exposed US military veterans (n = 913)	PCL-5	/	/	PTSD symptoms	Anhedonia associated with past-year alcohol consequences
	(22)	18- to 25-year Hispanic emerging adults (n = 181)	CES-D	/	/	/	Higher levels of anhedonia were associated with higher alcohol use severity
	(23)	College students (18–22 years) (n = 820)	MASQ-SF	/	fMRI while participants completed a card-guessing task, which elicits ventral striatum reactivity	/	Reduced ventral striatum reactivity to reward is associated with increased risk for anhedonia in individuals exposed to early life stress. Such stress-related anhedonia is associated with problematic alcohol use
Nicotine	(24)	Non-daily cigarette smokers (18–24 years) (n = 518): smoking more than 1/m more than 6m	SHAPS online after 3, 6, and 9 months follow-up	/	/	/	Anhedonia is not predictive for other tobacco products use (OTP), but those with anhedonia used hookah more frequently
	(25	Adults in a smoking cessation clinical trial (n = 1,122), min 10 sig/d min 6 m: placebo (n = 131), bupropion (n = 401), or NRT (n = 590)	Ecological momentary assessments 4 times a day 5 days prior and 10 days after target quit day	/	/	/	Anhedonia is associated with dependence and was suppressed by agonist administration
	(26)	Ninth-grade students (13–15 years) (n = 3299): ever-smokers (n = 343), never-smokers (n = 2,956)	SHAPS	/	/	/	Anhedonia is associated with smoking initiation in the overall sample and higher initiation susceptibility in the subsample never-smokers
	(27)	Non-treatment-seeking smokers (more than 10 sig/d, more than 2 years) (n = 125) attending 2 counterbalanced experimental sessions (abstinent (for 16 h) vs. none abstinent)	SHAPS	Picture Rating Task	/	/	Greater anhedonia associated with less negative affective reactivity to negative pictures
	(28)	Smoking participants in a double-blind cessation clinical trial (n = 1,236): nicotine patch (n = 216), nicotine lozenge (n = 211), bupropion (n = 213), patch + lozenge (n = 228), bupropion + lozenge (n = 221), placebo (n = 147)	Ecological momentary assessments 4 times a day 5 days prior and 10 days after target quit day	/	/	/	High craving anhedonia group reported higher dependence, were less likely to have received combination nicotine replacement, reported lower week 8 abstinence rates and relapsed sooner
	(29)	Smokers (more than 5 sig/d) (n = 1125)	MASQ-S	/	/	/	Urgency is associated with smoking at average or higher levels of anhedonia; it was unrelated to smoking when few anhedonia symptoms were endorsed

(Continued)

TABLE 1 | Continued

Author	Sample	Anhedonia measure			Comorbidity	Result
		Self-report	Behavioral task	Neuro-biologic		
(30)	Adult smokers (n = 525) (more than 10/d) from a cessation clinical trial on 21 mg/day nicotine patch therapy during 8 weeks	SHAPS	/	/	/	70 participants (13%) were anhedonic, men were more anhedonic, anhedonic smokers were more likely to be abstinent
(31)	Ninth-grade students (n = 807): 294 no history of SUD, 166 lifetime history of drug/alcohol use without tobacco, 115 lifetime history of drug/alcohol use with tobacco	SHAPS	/	/	/	Teens with lifetime alcohol/drug use without tobacco had higher anhedonia
(32)	Ninth-grade students (n = 3,310): 2,557 neither conventional nor e-cigarettes, 412 e-cigarettes only, 152 conventional cigarettes only, 189 conventional and e-cigarettes	SHAPS	/	/	/	Anhedonia was higher in e-cigarette only vs. non-users. An ordered effect of dual-use vs. e-cigarette use only vs. non-use was found for anhedonia
(33)	Veterans with MDD or dysthymia (n = 80): 36 depressed smokers and 44 depressed non-smokers	MASQ-S BIS/BAS	Probabilistic reward task that measures reward-learning	/	MDD-dysthymia	Depressed smokers reported higher trait anhedonia and reduced BAS reward responsiveness compared to non-smokers. Depressed smokers demonstrated greater acquisition of reward-based learning
(34)	Adults from smoking cessation clinical trial (n = 1,175) (min 10 sig/d last 6 months): bupropion, nicotine lozenge, nicotine patch + lozenge, bupropion + nicotine lozenge or placebo	Ecological momentary assessments 4 times a day from 5 days prior to 10 days after target quit day	/	/	/	Anhedonia showed an inverted U- pattern of change in response to tobacco cessation and was associated with the severity of withdrawal symptoms and tobacco dependence. Post-quit anhedonia was associated with decreased latency to relapse and with lower 8-week point prevalence abstinence. NRT suppressed the increase in abstinence-related anhedonia
(35)	Adults recruited *via* announcements (n = 275) (more than 10 sig/d): participants attended a baseline visit that involved anhedonia followed by 2 counterbalanced visits after 16 h smoking abstinence and non-abstinent	SHS TEPS CAI	Behavioral smoking task measuring relative reward value of smoking	/	/	Higher anhedonia predicted quicker smoking initiation and more cigarettes purchased, partially mediated by low and high negative mood states. Abstinence amplified the extent to which anhedonia predicted cigarette consumption among those who responded to the abstinence manipulation, but not the entire sample
(36)	Smokers enrolled in a smoking cessation treatment study (n = 1,469) (more than 10 sig/d more than 6 m): bupropion (n = 264), nicotine lozenge (n = 260), nicotine patch (n = 262), bupropion + lozenge (n = 262), placebo (n = 189)	Life time anhedonia *via* CIDI	/	/	depression	Anhedonia predicted cessation outcome

(Continued)

TABLE 1 | Continued

	Author	Sample	Anhedonia measure			Comorbidity	Result
			Self-report	Behavioral task	Neuro-biologic		
Cannabis	(37)	Cannabis users between 15 and 24 years (n = 162): 47 early onset, before 16 years; 115 late onset	Online OLIFE	/	/	Schizotypy	Early-onset cannabis use is associated with higher levels of anhedonia in females only
	(32)	Student at the age of 14 (n = 3,394) at baseline, 6-, 12-, and 18-month follow-up	SHAPS	/	/	/	Anhedonia is associated with subsequent marijuana use escalation amplified by cannabis-using friends, but baseline marijuana use is not related to the rate of change in anhedonia.
	(38)	20-year-old men (n = 158), recruited at the age of 6–17 m	SHAPS	/	fMRI during a 24-trial slow event-related card-guessing game that assesses response to anticipation and receipt of monetary reward		The escalating trajectory group displayed a pattern of negative NAcc–mPFC connectivity that was linked to higher levels of anhedonia
	(39)	MDD subgroup from a national survey (n = 2,348): users with CUD vs. users without CUD	*DSM-IV* criteria	/	/	MDD	Level of cannabis use is associated with anhedonia
Stimulants	(19)	Treatment-seeking adults with cocaine dependence: on contingency management (n = 85): 40 placebo, 45 levodopa	SHAPS	PR task	/	/	L-dopa did not improve outcomes of CM, nor was the effect moderated by anhedonia; anhedonia may be a modifiable individual difference associated with poorer outcome of CM
	(40)	CUD participants (n = 46)	CSSA	/	RewP of ERP	/	RewP is correlated with anhedonia, and anhedonia explained a significant amount of variance in the RewP amplitude
	(41)	Current cocaine abusers (n = 23) and participants with no drug history (n = 24)	SHAPS	/	ERP after reward receipt	/	Anhedonia is associated with reward motivation, diminished reward feedback, and diminished monitoring
	(42)	Current cocaine abusers, outpatients (n = 23) and controls with no drug history (n = 27)	SHAPS CPCSAS	/	Go/NoGo task while EEG was recorded. Valenced pictures from the International Affective Picture System	/	Cocaine users performed more poorly than controls on the inhibitory control task. Cocaine users were more anhedonic. Higher levels of anhedonia were associated with more severe substance use. Inhibitor control and anhedonia were correlated only in controls
	(43)	Cocaine-dependent patients, free from cocaine during the last 3 weeks (n = 23) and healthy controls (n = 38)	Chapman psychosis-proneness scales (with revised physical anhedonia and revised social anhedonia)	/	A paired-stimulus paradigm to elicit three mid-latency auditory evoked responses (MLAER), namely, P50, N100, and P200	Psychosis proneness	Social anhedonia scores accounted for the largest proportion of variance in P200 gating. Poorer P50 gating is related to higher scores on the social anhedonia scale in healthy controls and across mixed samples of cocaine-dependent patients

(Continued)

TABLE 1 | Continued

	Author	Sample	Anhedonia measure			Comorbidity	Result
			Self-report	Behavioral task	Neuro-biologic		
Opioids	(44)	Heroin-dependent participants on opioid maintenance (n = 90): on methadone (n = 55) or on buprenorphine (n = 35); and recently abstinent (up to 12 months) opioid-dependent participants (n = 31); and healthy controls (n = 33)	SHAPS TEPS	/	/	/	Elevation in anhedonia in opioid-dependent participants
	(45)	Patients (mostly inpatients) with opioid dependence (n = 306): 1,000 mg naltrexone implant + oral placebo (n = 102), placebo implant and 50 mg oral naltrexone (n = 102), both placebo (n = 102)	FAS CSPSA	/	/	/	Anhedonia was elevated at baseline and reduced to normal within the first 1–2 months for patients who remained in treatment and did not relapse, no difference between groups
	(46)	Opioid-dependent patients 10–14 days after withdrawal (PODP) (n = 36) and healthy controls (n = 10)	SHAPS	Affect-modulated startle response (AMSR)	Cue reactivity task during which participant's RPFC and VLPFC were monitored with functional near-infrared spectroscopy	/	PODP reported greater anhedonia on self-report, reduced hedonic response to positive stimuli in the AMSR task, reduced bilateral RPFC and left VLPFC activity to food images and reduced left VLPFC to positive social situations compared to controls. Patients with anhedonia showed reduced response to positive social stimuli and food
	(47)	Detoxified heroin-dependent patients recruited from addiction-treatment centers (n = 12) 2 weeks after detoxification starting extended-release naltrexone (XRNT) and healthy subjects (n = 11)	SHAPS	/	[^{123}I]FP-CIT SPECT-scan imaging striatal DAT binding: 1 before and 1 2 weeks after injection with XRNT	/	XRNT does not affect anhedonia, but with a significant reduction of depressive symptoms
Gambling	(48)	Outpatients with Parkinson's disease (n = 154): 34 fulfilled criteria for impulse control disease (ICD), of which 11 met criteria of pathological gambling (PG)	SHAPS	/	/	Parkinson's disease	PG had a higher incidence of anhedonia
Internet gaming		/	/	/	/	/	/
Benzodiazepines	(49)	MDD outpatients of the MDPU database (Mood Disorder Psychopharmacology Unit) (n = 326): 79 benzodiazepine users, 247 nonbenzodiazepine users	MADRS	/	/	MDD	Anhedonia was greater in the benzodiazepine group, and anhedonia was the strongest predictor of regular benzodiazepine use

OLIFE, Oxford-125 Liverpool Inventory of Feeling and Experiences; PCL-5 = PTSD Checklist for DSM-5; SHAPS, Snaith–Hamilton Pleasure Scale; TEPS, Temporal Experience of Pleasure Scale; REI, Rewarding Events Inventory; CES-D, Center Epidemiological Studies Depression Scale; PR task, progressive ratio task; FAS, Ferguson Anhedonia Scale; CSPSA, Chapman Scale of Physical and Social anhedonia; MASQ-S, Mood and Anxiety Symptoms Questionnaire-Short Form (with Anhedonic Depression subscale); CSSA, Cocaine Selective Severity Assessment Scale; RewP, Reward Positivity component; TEPS, Temporal Experience of Pleasure Scale; BIS/BAS, Behavioral Inhibition/Behavioral Activation Scale; CPCSAS, Chapman Physical and Chapman Social Anhedonia Scales; SHS, Subjective Happiness Scale; CAI, Composite Anhedonia Index; MINI, Mini International Neuropsychiatric Interview; CIDI, Composite International Diagnostic Interview; MADRS, Montgomery–Asberg Depression Rating Scale.

the SHAPS was also associated with diminished monitoring and reward feedback in cocaine users. The measures of anhedonia were associated with reward motivation in both cocaine users and healthy controls (41). Morie et al. (42) used a Go/NoGo task in response to valenced pictures. Though this is more a measure for executive functioning, i.e., inhibition and performance monitoring, a correlation was found between inhibitory control and anhedonia, but only in controls.

In a small group of detoxified heroin-dependent patients, striatal dopamine transporter binding was assessed by [^{123}I]FP-CIT single photon emission computed tomography (SPECT) before and 2 weeks after injection with extended-release naltrexone (47). Although depression scores were higher for patients at baseline and depression scores were lower after extended-release naltrexone (XRNT) treatment, no associations could be found for anhedonia.

Finally, a large fMRI study with 820 college students used a ventral striatum reactivity task, a blocked number-guessing paradigm, consisting of three blocks of positive feedback, three blocks of negative feedback, and three control blocks (23). Reduced ventral striatum reactivity to reward is associated with increased risk for anhedonia in individuals exposed to early life stress. This interaction is linked to other depressive symptoms and problematic alcohol use.

In only one study were self-report, behavioral, and neurobiological measures combined (46). Thirty-six opioid-dependent patients and 10 healthy controls filled in the SHAPS and performed the affect-modulated startle response (AMSR), a psychophysiological measure of emotional valence, that was used before to assess hedonic responses to standardized reward-related stimuli. Four categories of stimuli can be derived: positive, negative, neutral, and drug-related. Meanwhile, acoustic startle probes were presented at variable points and the eye-blink component of the startle reflex was recorded by EMG. All participants completed a standard visual cue activity paradigm while being monitored with functional near-infrared spectroscopy (fNIRS). Stimuli consisted of three hedonically positive categories (highly palatable food, positive social interaction, and emotional intimacy) as well as emotionally neutral stimuli. Opioid-dependent patients reported greater anhedonia on self-report, reduced hedonic response to positive stimuli in the AMSR task, and reduced bilateral RPFC and left VLPFC to food imaged and reduced left VLPFC to positive social situations compared to controls.

Taken together, although more studies used a neurobiological measure as compared to behavioral task only, again all of them used a different paradigm, making a comparison of the results difficult. Also, it remains de be defined what dimensions/aspects of anhedonia are captured by these different paradigms, although some studies provide indications for the motivational component (e.g., fronto-striatal connectivity).

Anhedonia Within DUS Populations

Very few studies compared anhedonia between a sample of DUS patients with non-DUS controls. Other studies focused on the relationship between substance abuse and severity-related variables in relation with anhedonia in samples of DUS individuals.

Studies with a healthy control group showed consistently that cocaine abusers, heroin-dependent individuals, and benzodiazepine-dependent individuals were more anhedonic versus controls. Also, higher levels of anhedonia associated with more severe substance use (42, 44, 46, 47, 49).

Studies within DUS samples without control revealed a similar result; i.e., anhedonia was associated with substance use variables. Three studies on alcohol showed a positive association between anhedonia and alcohol use severity and related consequences (20–22). Within cigarette smokers, most studies provide indications of an adverse effect of anhedonia on smoking: initiation, smoking susceptibility, and severity (24, 26, 29, 35). Finally, early onset of cannabis use, subsequent escalation of marijuana use, and level of use have been associated with higher levels of anhedonia (32, 37, 39). One study on gambling showed higher levels of anhedonia in a gambling subsample of Parkinson's disease patients (48). However, this study included only 11 gamblers, warranting careful interpretation.

Taken together, across different substances, indications are consistent that 1) DUS individuals have higher levels of anhedonia than controls and that 2) anhedonia might be related with early onset of substance use and subsequent severity of DUS.

Time Course of Anhedonia: Trait or State?

For nicotine-dependent individuals, there is evidence that anhedonia is both a state and a trait factor. First, in a longitudinal study with 518 young participants, the presence of anhedonia predicted the use of hookah (24). Evidence for anhedonia as a trait can also be found in the study of Leventhal (36), which is already described above (36). The trait anhedonia predicted quicker smoking initiation and more cigarettes purchased, and 16-h smoking abstinence amplified the extent to which anhedonia predicted cigarette consumption. In addition, a recent study showed that 1) anhedonia is associated with smoking initiation and 2) adolescents with higher (vs. lower) anhedonia who have never tried smoking may be more susceptible to smoking initiation perhaps due to stronger pro-smoking intentions or willingness to smoke (26).

Data supporting trait anhedonia for other substances are few. For cannabis, anhedonia has been associated with both early onset of cannabis use and marijuana use escalation in early adolescence (32, 37).

On the other hand, anhedonia can be a part of smoking withdrawal. Cook et al. (34) demonstrated an inverted U-pattern in response to tobacco cessation, which was associated with the severity of withdrawal symptoms and tobacco dependence (34). In the 6-month follow-up study with opioid-dependent patients (mostly inpatients), elevated anhedonia levels at baseline reduced to normal after 1 to 2 months for patients who did not relapse (45). In the study of Garfield et al. (44), elevation of anhedonia was found in opioid-dependent participants compared to healthy controls (44). Among participants on opioid pharmacotherapy (i.e., methadone and buprenorphine), a significant association was found between the frequency of recent illicit opioid use and anhedonia scores, which supports the hypothesis that opioids can

cause anhedonia. On the other hand, no association was found between duration of abstinence and anhedonia in the group of abstinent opioid-dependent participants.

Anhedonia and DUS and Depression Comorbidity

Two out of four studies concerning alcohol use disorder (AUD) focused on comorbidity as well. In an major depressive disorder (MDD)-subsample of the Mental Health in the General Population (MHGP), 4,339 subjects met the criteria for MDD (20). In the MDD population, 413 AUD subjects were identified, including 138 subjects with alcohol abuse and 275 with alcohol dependence. Anhedonia was associated with alcohol abuse in the group with MDD and AUD compared to the group without AUD (OR 1.66).

A sample of 916 trauma-exposed US military veterans was drawn from a larger dataset from the National Health and Resilience in Veterans Study (NHRVS, 21). A subsample was chosen that endorsed a "worst" traumatic event on the Traumatic History Screen. In this nonclinical sample, associations between the seven-factor hybrid model of PTSD symptoms and alcohol consumption and consequences were found. Lifetime anhedonia, together with dysphoric arousal and negative affect, was most strongly associated with past-year alcohol consequences.

MDD comorbidity is studied in nicotine papers as well. In an MDD/dysthymia subsample of veterans from a large VA Healthcare System in the Northeast United States, 36 depressed smokers were compared to 44 depressed non-smokers (28). Depressed smokers reported more anhedonia and reduced reward responsiveness. However, on a probabilistic learning task, depressed smokers showed a stronger preference for the more frequently rewarded stimulus, which suggests that depressed smokers demonstrated more robust acquisition of reward-based learning.

Leventhal et al. (36) adjusted the relation between anhedonia and depressed mood with relapse in nicotine for lifetime depressive disorder based on the CIDI. Depressed mood did not predict cessation outcome, while anhedonia did (36).

For cannabis, only one study focused on comorbidity between CUD and MDD. Feingold et al. (39) selected an MDD subgroup from a national survey and concluded that the level of cannabis use was associated with more symptoms at follow-up, notably anhedonia, while remission rates did not differ between MDD with or without CUD (39).

Rizvi et al. (49) demonstrated that anhedonia was more significant in MDD patients using benzodiazepines, with anhedonia being the strongest predictor of regular benzodiazepine use (49).

One fMRI study showed a decreased ventral striatum reactivity to the (monetary) reward associated with an increased risk for anhedonia, especially for those participants who were exposed to early life stress (23). This might suggest that for these individuals specifically, motivational anhedonia is impaired.

Anhedonia and Effect on Treatment of DUS

Most studies showed an adverse effect of anhedonia on treatment effect. In a large randomized, double-blind placebo-controlled smoking cessation trial, four distinct types of quit-day withdrawal were identified: the moderate withdrawal class were the least likely to report high levels of any individual symptom for hunger and anhedonia. The high-craving anhedonia group reported high levels of craving and anhedonia. The affective withdrawal group was scoring high on poor concentration and negative affect. The hunger group reported high quit-day hunger, but low on other indicators. The high-craving anhedonia group reported lower week 8 abstinence and relapsed sooner but were also less likely to have received combination nicotine replacement in this trial (28).

In another smoking cessation treatment study with 1,469 participants, lifetime anhedonia predicted increased odds of relapse after 8 weeks and 6 months (36). Moreover, post-quit anhedonia was associated with decreased latency to relapse and with lower 8-week point prevalence abstinence. Similar findings were demonstrated in the study of Piper using the same design and method (28). They reported lower abstinence after 8 weeks for the high craving anhedonia group.

Wardle et al. (19) demonstrated that anhedonia was associated with poor treatment outcome (i.e., cocaine-negative urines) for cocaine-dependent participants following contingency management. Also, a dopamine-agonist (L-DOPA) did not improve outcomes in this study, nor was the effect of L-DOPA moderated by anhedonia (19).

Only in one study did anhedonia have a positive effect on treatment (30). In the clinical cessation trial on 21-mg nicotine patch a day for 8 weeks, 70 participants were anhedonic based on the SHAPS. The anhedonic smokers were more likely to be abstinent on a nicotine patch.

DISCUSSION

In this exploratory–narrative review, we identified 32 original research papers exploring anhedonia and its relationship with substance use disorders. Results provide indications that 1) anhedonia is associated with substance use problems/disorders and their severity, 2) anhedonia is especially prominent in DUS with comorbid depression and early life stress experiences, 3) anhedonia may be both a trait and a state dimension in its relation to DUS, and 4) anhedonia tends to negatively impact DUS treatment outcome. Finally, most evidence points to motivational anhedonia as the most involved subdimension of anhedonia within its relationship with DUS.

Overall, the findings in this review, focusing on articles over the last 5 years, are in line with the earlier review of Garfield et al. (3). Across the different substances of abuse, findings in this review provide indications that anhedonia—as a broad concept—is associated with DUS and DUS severity. However, these findings need to be looked upon prudently. Indeed, the number of studies using a control group remains very limited. Also, the severity measures used throughout the different studies are very variable, leaving consistent interpretation difficult. Altogether, the number of studies remains very limited especially when compared to the number of studies published on impulse/executive control in SUD. This is remarkable. Indeed, in a recent

consensus paper, RDoC Positive Valence System (Reward Valuation, Expectancy, Action Selection, Reward Learning, Habit) was put forward as an essential domain with respect to the pathogenesis of addictive disorders, implicated in vulnerabilities for initiation, continuation, and chronicity of the disorder (8). Anhedonia can be positioned on the bridge of both negative and positive Valence Systems, but associates close to Reward Valuation, Reward Expectancy, and Reward Learning. This theoretical ground and the findings of our review indicate that anhedonia deserves more attention.

Moreover, anhedonia is looked upon as an important "transdiagnostic" concept underlying many different psychiatric disorders, e.g., depression, bipolar disorder, and schizophrenia (11). All these disorders relate, in different ways, to altered reward processing. Finally, anhedonia might have relevance bridging with a growing literature on the role of inflammation in the pathogenesis of psychiatric disorders such as mood disorders or addictive disorders (56). From this perspective, it can be hypothesized that a neurobiological vulnerability to inflammatory stimuli may drive the link between chronic substance use (early life stress) and anhedonia.

A sizable number of (large) studies in this review focused on comorbidity and provided indications that DUS patients with a comorbid mood disorder had higher levels of anhedonia as compared to single diagnosis groups. These findings give some ground for the hypothesis that anhedonia might be a common factor underlying both types of disorder or at least a subtype of each. Subtypes in depression with anhedonia being the prominent feature have recently been suggested. Specifically, an "inflammatory" subtype has been proposed with a neurobiological vulnerability to inflammatory stimuli that drive the link between stress and anhedonic symptoms (56). Of interest, early childhood adversity may be one of the most critical factors modulating this neurobiological vulnerability. It is remarkable that two studies in this review showed a clear association between anhedonia and substance use severity, specifically in a population of individuals exposed to trauma (21, 23). Given the high prevalence of early childhood adversity within individuals with DUS, future studies need to explore whether this subgroup is associated with anhedonia.

Research on anhedonia in other psychiatric disorders, e.g., depression, can also help to provide more insight into how research on anhedonia in SUD needs to be done. As mentioned above, self-reports are the most used instrument, while they are mostly unable to distinguish the different aspects of reward processing and reward learning. In depression literature, however, various aspects of reward in relation to anhedonia could be disentangled based on numerous studies combining behavioral tasks and neurobiological measures, mainly event related potential (ERP) studies. Neuroimaging studies could be useful as well, taking into account the idea that fMRI paradigms are mostly unable to dissect into anticipatory, consummatory, and learning components of reward processing (23). A multimodal approach using the same paradigms in future research projects is recommended.

Data from this review show mixed results as to the trait versus state characteristic of anhedonia within the context of substance use. Some studies give support to the hypothesis that anhedonia might be a trait that underlies a vulnerability for early substance use initiation and early escalation. This is in line with the self-medication theory whereby substances are used to mediate mood disorders or innate reward deficiencies (9). Also, adolescents with high stress and amygdala reactivity are more likely to consume a full standard alcoholic drink, are more likely to experience early intoxication, and are at a heightened risk for the onset of an alcohol use disorder (57). In line with this, anhedonia can be hypothesized as a vulnerability trait for early substance use trajectories and subsequent increase of DUS risk. A hypothesis is also in line with the reward deficiency hypothesis (58). Inversely, different studies in this review indicate that anhedonia is associated with ongoing substance use and withdrawal while improving over time in abstinence. This is in line with earlier studies showing improvement in reward responsiveness during treatment and abstinence (59). These findings are indicative of a state characteristic. However, longitudinal studies remain very scarce, i.e., in this review, only one study followed the course of anhedonia over a 6-month abstinence period showing improvement over time (45). So, any conclusion concerning trait or state is at best preliminary.

Several studies in this review showed a negative influence of anhedonia on DUS course and treatment effect, i.e., shorter posttreatment abstinence and higher relapse rates. This is confirmation of findings presented in the earlier review on this topic showing that anhedonia increases the likelihood of relapse and is associated with craving (3). In the depression research, anhedonia negatively influences disease course. This has also been documented within the context of treating depression (13–16). It can be hypothesized that anhedonia as a transdiagnostic characteristic modulates disease course and outcome.

Within the context of depression treatment, existing psychological and pharmacological treatments have proved to be rather ineffective for treating anhedonia. Some of the more commonly used antidepressants, e.g., fluoxetine, may even worsen anhedonic symptoms (60–62). Of importance, newer treatments such as ketamine are shown to have improvement of anhedonia, even in treatment-resistant depression (63, 64). This is of interest, also from the perspective of indication that ketamine can be used within the context of treatment of DUS (65). Although, at this point, no study has been published exploring the effectiveness of ketamine as a treatment for patients with DUS and depression/anhedonia comorbidity, this is an exciting idea. Of interest in this review is the finding that substitution treatment (i.e., nicotine patch) might be beneficial specifically for smokers scoring high on anhedonia. Powers et al. (30) showed an increased likelihood of short-term abstinence using a 21-mg/day nicotine patch therapy. Cook et al. (34) observed that administering nicotine replacement therapy suppressed abstinence-induced anhedonia and alleviated nicotine withdrawal symptoms during short-term abstinence. Moreover, depressed non-smokers show significant declines in depressive symptoms during nicotine patch treatment, suggesting that NRT (and nicotine patch in particular) may have antidepressant-like effects (66). It has been hypothesized that nicotine exposure ameliorates the hypoactivation in crucial structures of the reward pathway (including caudate, nucleus accumbens, putamen) among depressed smokers, with data showing increased activation after nicotine administration in the

dorsal striatum during anticipatory reward responding and in the medial prefrontal cortex associated with sensitivity to reward (67). It has to be noted that the sample of anhedonic participants in the study of Powers et al. (30) was small, and the lack of a placebo condition made it difficult to draw inferences about the impact of nicotine patch therapy on pretreatment anhedonia or depression more generally. Finally, there is preliminary evidence that aripiprazole might promote alcohol abstinence and reduce anhedonia, possibly *via* dopaminergic and serotonergic modulations at the fronto-subcortical circuitries (68). However, this needs future replication.

Taken together, although anhedonia is notably challenging to treat and can negatively impact disease course, these preliminary studies hold promises for developing future—pharmacological—treatments.

Findings in this review need be looked upon critically. Several limitations need to be taken into account. First, the vast majority of studies focus on tobacco smoking. Other substances of abuse remain largely understudied, and regarding behavioral addictions, the information is zero. Next and most importantly, throughout the studies, a variety of anhedonia measures has been used. For none of these measures it is known what exact anhedonia dimension they measure, neither is enough information available on how these measures relate. This makes a comparison between studies impossible and may be responsible for sometimes contradictory findings. Third, different study designs and samples are used, which makes it difficult to draw general conclusions about the temporal and causal relationships between anhedonia and DUS. Finally, ours is an explorative, narrative review highlighting the broad field of the anhedonia–DUS relationship. Future hypothesis-driven studies are needed both on the clinical consequences and on elucidating the exact underlying mechanisms and neurocognitive dimensions.

CONCLUSIONS

Findings from this review provide indications that anhedonia might be of relevance for a better understanding of the pathogenesis of addictive disorders and their comorbidities. Anhedonia might prove to be an unimportant transdiagnostic dimension underlying many disorders in their relationship with different reward processing impairments. Within the National Institute of Mental Health's (NIH) Research Domain Criteria (RDoC), anhedonia is conceptualized as an RDoC Element (behavior) within the following Domains and Constructs: 1) Domain: Negative Valence Systems; 2) Construct: Loss and Construct. However, anhedonia might also be linked to other domains, i.e., Positive Valence Systems (11), so anhedonia might be important in bridging these systems and/or reflect different subgroups/mechanisms.

However, in contrast to the field of impulsivity, the study of anhedonia in the relationship with DUS is only nascent. Reflective of this is not only the relatively small number of studies but also the variability of measures and concepts used in the different studies. There is a great need of consensus in defining the neurocognitive dimensions and best measurement instruments/paradigms to help the field move on more quickly. Within this context, the recent international consensus paper identifying the most critical cognitive domains within neuroscience of addictions is a vital initiative (8). Let us see how and when anhedonia finds a place in this model.

AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript conception design and writing.

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REVIEW
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Integrating Preclinical and Clinical Models of Negative Urgency

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Overwhelming evidence suggests that negative urgency is robustly associated with rash, ill-advised behavior, and this trait may hamper attempts to treat patients with substance use disorder. Research applying negative urgency to clinical treatment settings has been limited, in part, due to the absence of an objective, behavioral, and translational model of negative urgency. We suggest that development of such a model will allow for determination of prime neurological and physiological treatment targets, the testing of treatment effectiveness in the preclinical and the clinical laboratory, and, ultimately, improvement in negative-urgency-related treatment response and effectiveness. In the current paper, we review the literature on measurement of negative urgency and discuss limitations of current attempts to assess this trait in human models. Then, we review the limited research on animal models of negative urgency and make suggestions for some promising models that could lead to a translational measurement model. Finally, we discuss the importance of applying objective, behavioral, and translational models of negative urgency, especially those that are easily administered in both animals and humans, to treatment development and testing and make suggestions on necessary future work in this field. Given that negative urgency is a transdiagnostic risk factor that impedes treatment success, the impact of this work could be large in reducing client suffering and societal costs.

Keywords: negative urgency, animal model, delay discounting, Impulsive behavior, internalizing disorder, transitional, UPPS Impulsive Behavior Scale

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INTRODUCTION

Negative urgency is an impulsive personality trait reflecting the tendency to act rashly when experiencing extreme negative emotional states, included in the UPPS-P Model of Impulsive Behavior (1, 2). Overwhelming evidence suggests that negative urgency is robustly associated with rash, ill-advised behavior, and this trait may hamper attempts to treat patients with substance use disorder [e.g., Refs. (3, 4)]. However, a systematic investigation of negative urgency in the context of treatment has been limited, in part, due to the lack of a valid objective, behavioral, and translational model of negative urgency. The goal of the current paper is to review the current human and animal approaches to the measurement of negative urgency and to make suggestions on how an objective translational model could be developed. We review the existing literature and make suggestions for prime models that can be explored as translational approaches in negative urgency. We also review the neural and psychopharmacological correlates of negative urgency, suggesting potential novel targets of intervention within a translational model. We suggest that the development of a translational

model easily administered in animals and human would allow for better characterization of the neuroscientific correlates of negative urgency, determination of prime neurological and physiological treatment targets, and the validation of an objective measure of treatment effectiveness in the preclinical and clinical laboratory.

NEGATIVE URGENCY IN THE BROADER CONSTRUCT OF IMPULSIVITY AND PERSONALITY

Impulsivity is broadly defined as traits and behaviors that predispose individuals to rash action (or ill-advised inaction) (5–7). The UPPS-P model integrated existing personality-based measures of impulsivity into five traits, using the Five-Factor Model as a theoretical framework. The five traits include negative urgency, positive urgency (i.e., a tendency to act rashly in response to extreme positive emotional states), lack of premeditation (i.e., a tendency to act without thinking), lack of perseverance (i.e., an inability to stay focused on a task), and sensation seeking (i.e., tendency to seek novel and exciting experiences). These traits are best described as separate, though related, tendencies toward rash action (8). Research supports a multidimensional nature of impulsivity, and extensions of the UPPS-P model have been suggested (9). There is increasing consensus that impulsive personality consists of traits that are affect-free and traits that have a strong affective component (9, 10). The distinction between affect-based and affect-free impulsigenic traits is further supported by the fact that they share little common variance (0–13%) (10).

Negative urgency is well placed in the personality literature. It shares conceptual overlap with the Impulsiveness facet of the NEO-PI-R (11); however, a factor analysis by Peterson and Smith (2008) found that negative urgency loaded onto the Neuroticism, Conscientiousness, and Agreeableness factors, suggesting that negative urgency is not represented by one domain or facet of the NEO-PI-R, but rather assesses a trait characterized by high distress, low conscientiousness, and low agreeableness (2). Some have suggested that negative urgency (along with the positive mood variant of positive urgency) is quite similar to one of the two higher-order dimensions of the Five-Factor Model (alpha, representing high levels of emotional instability, disagreeableness, and disinhibition) (12, 13).

What differentiates negative urgency from other constructs pertaining to responses to emotions, such as emotion regulation and emotional lability, is that it reflects a disposition to reflexive reactions in response to intense negative emotion. Emotion regulation involves efforts, either reflexive or effortful, to modify the intensity of the experienced emotion that varies across situations and across time, and emotion dysregulation can occur in the absence of intense emotion (14, 15). Negative urgency captures the between-person variability in the capacity to control intense emotion-driven urges (10). Effects of negative urgency are not explained by additive or interactive combinations of negative affective traits (e.g., neuroticism, emotional lability) combined with general disinhibition (2, 8). Similarly, negative urgency is only moderately correlated with measures of emotion regulation, which signifies that these are related, but separate, constructs with distinct contributions to psychopathology (16). In fact, the majority of the reliable variance in negative urgency is not explained by other related traits (2).

NEGATIVE URGENCY AS A TRANSDIAGNOSTIC RISK AND TREATMENT FACTOR

Accumulating evidence suggests that negative urgency is one of the most robust predictors of a wide range of maladaptive behaviors and psychopathology, including alcohol use and dependence (3, 5, 17, 18), tobacco use and dependence (19–21), and problematic cannabis use (22–24). The fact that negative urgency developmentally precedes substance use and addictive disorders (25, 26) indicates that negative urgency is likely a contributor to the development and maintenance of addictive disorders. This is further bolstered by empirical evidence showing that decreases in impulsivity are associated with decreases in substance use across the lifespan (27). This accumulating evidence supports the notion that negative urgency is a transdiagnostic endophenotype for problematic levels of behaviors associated with risk (28). This includes not only addictive behaviors, but also disorders highly comorbid with these conditions, such as depression, anxiety, and bipolar disorders (5, 28, 29). Negative urgency is represented in broad diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) (29).

Despite the substantial amount of research implicating negative urgency in the development and maintenance of addictive behaviors, only a small body of empirical work has systematically studied its application to treatment (29, 30). There are no specific behavioral or pharmacological treatments for negative urgency, although some have been suggested (31). A meta-analysis conducted by Hershberger et al. (30) examined the effect of negative urgency on substance use disorder psychotherapy outcomes and how this trait changes during treatment. The findings showed that increased levels of negative urgency at baseline are related with poorer treatment outcomes, suggesting that this trait potentially inhibits substance use symptom improvement (30). Additionally, the authors identified only small decreases in negative urgency ($g = -0.25$) from the beginning to the end of treatment. This suggests that current substance use treatments are not changing negative urgency notably, which increases the risk for subsequent substance use re-initiation or relapse (30). They explain one way in which negative urgency lowers treatment efficacy: Most existing therapies for addictive disorders are focused on the modification of proximal factors related to addiction, such as substance use motives or environments that facilitate use, rather than the distal factors, such as negative urgency, that underlie them (32, 33). For example, negative urgency is a predictor of the development of substance use motives (34) and likely contributes to individuals seeking out and selecting environments that facilitate use, consistent with personality–environment transaction theories (35).

Although addressing proximal risk factors of addiction might improve current symptoms, if distal risk factors remain unchanged, relapse or treatment nonresponse becomes more likely (29), as the distal factors can impart risk independent of the modified proximal factor. The authors suggest that the integration of negative urgency in case conceptualization, treatment planning, and goal setting would significantly improve substance use treatment outcomes (30).

Although negative urgency-targeted interventions have not been systematically developed or investigated, there is promising evidence for their potential success. Zapolski et al. (31) provided recommendations for strategies to target negative urgency in treatment. Their recommended strategies include training in emotion regulation, distress tolerance, interpersonal effectiveness, training in modifying emotional reactions based on the context, relaxation techniques, identification of precipitating events and triggers to emotional reactivity and use of adaptive alternatives, and the use of medications, such as selective serotonin reuptake inhibitors (31, 36). Many of these strategies have been successfully incorporated in several clinical interventions in different contexts, including substance use, and their effectiveness has been tested and supported (5, 26, 36–40) with some exceptions (41, 42). Because negative urgency increases the risk of a wide range of addictive behaviors and other clinical disorders, negative-urgency-targeted interventions could have wide and broad benefit. Additionally, such interventions are easily adopted by addiction medicine practitioners and would improve their daily practice in prevention, treatment, and rehabilitation of addictive disorders and accompanying conditions.

We propose that an important and viable long-term goal is to design and test pharmacological, psychological, behavioral, and physiological treatments that specifically aim to reduce negative urgency. This would allow the application of these treatment strategies transdiagnostically, which would be fruitful to reduce not only the target disorder (e.g., alcohol use disorder), but also maladaptive coping related to comorbid disorders (e.g., depression). Thus, one intervention could be effective for treatment of multiple disorders or behaviors. In the current paper, we focus specifically on the role of negative urgency in addictive disorders, although the implications would likely apply to any disorder in which negative urgency is implicated (29).

CURRENT MEASUREMENT OF NEGATIVE URGENCY IN HUMANS

Negative urgency is most commonly measured using the UPPS-P Impulsive Behavior Scale. The UPPS-P is a 59-item self-report questionnaire originally created by Whiteside and Lynam (1) with four subscales (negative urgency, lack of premeditation, lack of perseverance, and sensation seeking). The positive urgency subscale was added later (43, 44). Individuals rate their general tendencies on a four-point scale from *Agree Strongly* to *Disagree Strongly.* Individual item scores are reverse coded (as needed) and averaged together to approximate a mean level of each trait, with higher scores indicating higher levels of rash action. The negative urgency subscale includes items assessing the disposition of respondents to act without careful consideration of the consequences when faced with negative affect. Example items for the scale include "When I feel bad, I will often do things I later regret in order to make myself feel better now" and "When I am upset, I often act without thinking." The UPPS-P has been shown to produce valid and reliable data across men and women, different age groups, and clinical and community samples (43, 45–47).

Although there are no behavioral tasks developed specifically to assess negative urgency, there are many behavioral tasks measuring state-like rash action in general (48, 49). Both self-report and behavioral task measures of rash action are strongly correlated with risky behaviors, but research has shown little overlap *between* these two types of measures. A meta-analysis conducted by Cyders and Coskunpinar (48) found that effect sizes for the relationship between self-report and behavioral task measures of rash action are small, ranging from $r = 0.097$ to 0.134, suggesting that at least 99% of the variance between these types of measures is unshared. This indicates that self-report and behavioral measures of rash action assess complementary, but separate, constructs. In some ways, this lack of overlap is not surprising, as these different task domains assess separate aspects of rash action. Self-report measures likely represent stable tendencies toward general behaviors (trait-like impulsivity) reflecting predominately emotional/motivational mechanisms of rash action, whereas behavioral tasks are more likely snapshots of behavior (state-like impulsivity) in response to stimuli, reflecting predominately cognitive mechanisms of rash action (9).

Self-report measurement of negative urgency has important strengths in the context of psychopathology. First, it has content and ecological validity as it reflects the individuals' subjective experience of patterns of thoughts, emotions, and behaviors in daily life, which can easily be generalized to the real world (50). Second, it has strong face validity, in that questions and results can be easily interpreted without making assumptions since they are based on direct and clear questions to the respondents (29, 48). Finally, it is inexpensive and easy to administer to a large group of people (48). However, this type of assessment has some limitations that make it less ideal in designing or testing the efficacy of treatments. Self-report measurement is limited by self-awareness, openness, and social desirability (48, 51), making the assessment only as good as what a person knows and is willing to report about the self. For example, in a clinical trial, individuals might not report on less socially desirable aspects of the self, and thus baseline levels might be underestimates of the true level of negative urgency, making measuring change over the trial more difficult. Relatedly, measuring negative urgency repeatedly in short succession might lead to participant fatigue or might influence an individual's responses in undue ways, further contributing to error in the measurement. For example, in a clinical trial, individuals might report a reduction in negative urgency after treatment, because they assume such a reduction is expected and not due to any true changes in the trait in response to treatment. Additionally, because the UPPS-P evaluates general tendencies, changes that do occur in shorter time frames might not be accurately assessed *via* this measure (i.e., it is not designed to assess shorter fluctuations in behavior). Finally, self-report

measures are difficult to translate into animal models. Behavioral tasks designed to measure the behavioral expression of negative urgency in lab settings would be an excellent complementary approach to address these limitations and to better design and assess treatment effectiveness.

ANIMAL MODELS OF NEGATIVE URGENCY

The use of animal models would greatly enhance the capability to deconstruct possible underlying neural mechanisms of negative urgency and allow for greater manipulation of testing variables to determine new therapeutic targets. There are numerous papers describing external validity, including the specific criteria animal models must meet and how different facets of external validity simulate conditions, neurobiology, and behavior seen in clinical populations (e.g., 52–55). The earliest characterization of these criteria included the requirement for animal models to demonstrate the same etiology, symptoms, response to treatment, and biochemistry seen in human populations (54). These criteria were the foundation for decades of work establishing a well-defined framework for animal models. The traditional framework, proposed by Willner (55), included three types of validity: *predictive validity* (i.e., the model predicts some criterion of interest), *face validity* (i.e., the model looks similar to the human condition), and *construct validity* (i.e., the animal model measures what is intended to measure) (55). Expansions and modifications of these criteria provide a more granular method for establishing reliable, translatable animal models, taking into account several factors that represent critical points for similarity. Geyer and Markou (53) emphasized the additional importance of *etiological validity* (i.e., the model has the same etiology as human condition) and *convergent/discriminant validity* (i.e., the model is associated with other related models but unrelated to models that are disparate with the underlying condition). Belzung and Lemoine (52) further emphasized *induction validity* (i.e., etiological effects on observable behaviors in animals have similar effects in humans) and *remission validity* (i.e., similarity in response to treatment across animal and human conditions).

Any animal model of negative urgency must fulfill these validity requirements; we evaluate existing and potential models in terms of these criteria (**Table 1**). For the sake of simplicity, we have not included every measure, but rather those we believe most strictly comply to a model of negative urgency. We also highlight the types of validity each model satisfies, where applicable, which aids in determining translatability.

At present, studies investigating negative urgency in animals are sparse. One proposed method for generating negative urgency (utilized in both animal and human models) involves unexpected reward omission (56–58). In one study, humans or rats were trained to perform an operant task (button pressing or lever pressing, respectively) and were rewarded with either money or a food pellet, respectively (56). Increases in response rates and decreases in response latencies were dependent variables constituting measures of negative urgency. This task has many strengths, including that it can and has been applied across human and animal models and that it appears to have adequate predictive and face validity for the emotional change. The task is especially analogous in clinical and preclinical administration (56); however, this task lacks the "rash action" component necessary to accurately assess negative urgency. For the model to have good external validity, there must be some procedure in place to assess the effect of this induced negative urgency on impulsive behavior. In short, this model does not provide any negative consequences of impulsive behavior generated through negative affect. Therefore, although this task shows some promise, further research is required for better, more representative models.

SUGGESTIONS FOR OBJECTIVE TRANSLATIONAL MODELS OF NEGATIVE URGENCY

Affective State

Clinical designs for incitement of negative affect in humans include the International Affective Picture System (IAPS), the Paced Auditory Serial Addition Test (PASAT), and social rejection, although there are no analogous methods in animal models (59, 60). The IAPS involves presentation of positive, neutral, or negative images (61). Numerous studies have shown that the administration of the IAPS is effective in producing transient negative emotion with resultant changes in brain activity or behavior (62–66). However, none of these studies has demonstrated increased impulsive, rash behavior associated with that negative affect. The PASAT is a procedure in which subjects must serially add a quickly vocalized list of numbers and is a demonstrated lab-induced stressor (67). Implementation of a social rejection protocol has generated changes in response inhibition during a Go/No-Go task (64, 68), thus linking negative affect with rash action. A meta-analysis by Westerman (69) outlines numerous other mood induction paradigms (including video clips, writing, etc). and describes the strengths and drawbacks of each. For example, the Imagination mood induction procedure requires the subject to imagine an emotion-laden experience from their past, and the Velten mood induction procedure requires the participants to make negative self-references (69). Unfortunately, these methods are not conducive to reproduction with animal models.

Although these findings suggest usefulness of these methods in humans, translatability to animals is questionable at best. There is no comparable method to many of these procedures (IAPS, PASAT, Imagination, Velten) in preclinical studies. While social isolation models in rodents can elicit behavioral modifications, these are typically utilized to produce depressive states and may instigate neurobiological alterations that have little connection to impulsivity and may hinder the ability to interpret results (54, 70, 71). For greatest translatability, the methods by which negative urgency are elicited should be as similar as possible in human and animal subjects.

TABLE 1 | Methods for induction of negative affect and measurement of impulsive responding. This table lists several possible suggestions for induction of negative affect in animals and humans and impulsivity assessment. It also outlines which types of validity (which describes translatability) are fulfilled with each task. NEO-PI-R: NEO Personality Inventory, revised; IAPS: International Affective Picture System; na: no available data.

TASK	APPLICABLE IN HUMANS	APPLICABLE IN ANIMALS	TYPES OF VALIDITY					
			FACE	CONSTRUCT	ETIOLOGICAL	CONVERGENT	INDUCTION	REMISSION
INDUCTION OF NEGATIVE AFFFECT								
REWARD OMMISSION TASK	+	+	+	+	+	+	+	na
IAPS	+							
Paced Auditory Serial Addition Test	+							
IMAGINATION Mood Induction Procedure	+							
VELTEN Mood Induction Procedure	+							
SOCIAL REJECTION (humans)	+							
SOCIAL ISOLATION (animals)		+		+			+	na
FOOT SHOCK		+		+				na
FOOD DEPRIVATION		+		+			+	na
ACUTE RESTRAINT STRESS		+		+			+	na
MEASURES OF IMPULSIVITY								
DELAY DISCOUNTING	+	+	+	+	+	+	+	+
GO/NO-GO	+	+	+	+	+	+	+	+
STOP SIGNAL	+	+	+	+	+	+	+	na
CONTINUOUS PERFORMANCE TASK	+	+	+	+	+	+	+	na
BALLOON ANALOGUE RISK TASK	+			+				na
ERIKSEN FLANKER TASK	+							
SELF-REPORT MEASURES								
UPPS-P	+					+		
NEO-PI-R (Impulsiveness facet)	+					+		

Currently, there are several animal models capable of inducing stress, anxiety, and depression, such as restraint stress, foot shock, and the forced swim test (72–75). Many of these suffer from limited translatability to clinical models, due to ethical or feasibility restraints. Additionally, these models typically result in long-term effects (including downstream effects on neurotransmitter systems), in addition to immediate, negative states. For an animal model to have good face and etiological validity, there must be some instigating event that engenders a transitory negative state without conferring semi-permanent or permanent change. Given the effects of corticosterone on numerous brain regions, including the hippocampus (76, 77), the task should avoid chronic stressors and focus on events that primarily lead to depressive-like states. Additionally, it is important to limit exposure to the negative stimulus to avoid creation of a disposition to depression often seen after repeated administration (78). This distinction permits researchers to narrow investigations to discrete elicited state-like behavior rather than long term, trait-like behavior.

Impulsive Choice

Delay discounting is based on the premise that reinforcer influence on behavior decreases as a function of the delay to its delivery (79). In one version of this task, the adjusting amounts version, subjects complete several trials in which they must choose between a small, immediate reward and a larger, delayed reward and every choice of the immediate reinforcer decreases the amount of reinforcer available upon choice of the immediate reinforcer on the next trial (80, 81). In this manner, repeated choice of the immediate reinforcer results in overall suboptimal levels of reinforcer across the session. Although delay discounting is typically thought to assess levels of cognitive impulsivity (82), the design of the task is such that impulsive-like responding is rewarded immediately (immediate reinforcer) and is then consequently paired with decrease in immediate reinforcer volume. Through manipulation of the length of the delay to the larger reward and the use of the hyperbolic discounting equation, we are able to generate a "discounting curve" that describes the steepness or "impulsivity" of each individual. This curve can be

thought of as a measure of how long the subject is willing to wait for a specific reward, a measure of "cognitive impulsivity."

Previous work has demonstrated the translatability of delay discounting. The delay discounting model has considerable face validity (52). The basic premise is identical in both human and animal models, particularly in the Experiential Discounting Task for humans, which requires the participant to experience the delay during the task, rather than afterwards, eliminating the need for the subject to "imagine" the delay while continuing to respond (83). In the animal version, subjects are also required to experience the delay during the session. Furthermore, one of the proposed mechanisms of external validity is the requirement that the task must measure the same changes in behavior upon treatment (remission validity) (52). Although this version of delay discounting most closely resembles the version administered in animals, there are possible limitations in test–retest reliability and conflating the delay and probability of receiving reward (84). A more common administration (the adjusting amounts version) involves presenting a delayed choice that will be accessible at some point in the future rather than implementing the delay during the task itself. The adjusting amounts version is also efficient at generating discounting curves and there is no demonstrable difference in effect between delayed rewards during the task and those imagined in the future (85). The animal version of delay discounting described here is accurate enough to detect the same decreases in impulsivity after stimulant (methamphetamine/amphetamine) administration observed in clinical applications (86–91). Given the demonstrated ability of the delay discounting task to evaluate changes in impulsive, rash behavior, and the translatability of those results, it may provide a valid mechanism to analyze behavior motivated by a negative emotional state.

Impulsive Action

In the Go/No-Go task, the subject is required to respond on a specified manipulandum upon presentation of some stimulus during "Go" trials and must inhibit that response upon presentation of some stimulus during "No-Go" trials (92, 93). This method is used to measure action restraint in a number of animal models of disease, including alcohol use disorder (94). A meta-analysis found a significant correlation between results on clinical applications of the task with self-report measures of negative urgency (48). A recent study examining the association between induced negative urgency and performance on the Go/No-Go task revealed that greater activation in brain regions involved in inhibitory processes was correlated with higher levels of urgency (64–66, 68). An investigation into the effects of social rejection on impulsivity found that subjects reporting higher levels of negative affect completed significantly fewer successful No-Go trials (95). There is also evidence that responding in the Go/No-Go task predicts relapse rates in abstinent alcoholics (96). Administration of this task in an animal model of negative urgency could pave the way toward understanding what neural correlates underlie this association.

Conclusions on Translational Tasks

In conclusion, although the literature on animal models of negative urgency is sparse, there are some interesting and promising attempts to model negative urgency preclinically. The very nature of negative urgency centers upon behavioral reactions to emotional states, suggesting an internalizing primary aspect of the trait that is integrated with an externalizing behavioral outcome. Therefore, any reliable, translatable model of negative urgency must include a method for inducing negative affect in addition to the demonstration of an externalizing behavior of some interest. Unfortunately, the design of preclinical models of internalizing affective disorders is inherently problematic. Emotional states, such as depression, are not easily represented in non-human subjects, which limits the ability to devise translational, behavioral measures (52, 78, 97–99). Any animal model seeking to evaluate affectivity must demonstrate the capacity not only to induce a specific emotional state, but also to effectively identify alterations in that state under manipulation. Since evaluating the subjective experiences of animals is difficult, this is a challenging prospect; however, the translatability of the model is necessary for the generation of meaningful results (52).

Ideally, the behavior evoked by the induction of negative affect should be immediately reinforcing, yet ultimately yield suboptimal results. Cyders and Smith (100) proposed that rash or ill-advised actions during times of negative arousal, such as consuming alcohol upon receipt of bad news, provide immediate relief, reinforcing the behavior (100). Alternatively, more adaptive coping mechanisms are not implemented, limiting the reinforcement of these responses. For example, then, engagement in repeated alcohol intake to alleviate negative affectivity is reinforced and the behavior becomes more frequent, despite being detrimental in the long term. The key in an animal model is to devise a task that provides an opportunity to access a preferred reward (food, sucrose, mating), paired with loss of a highly valued resource or punishment, such as excessive lever pressing, resulting in smaller amounts of reward over time.

NEURAL AND GENETIC CORRELATES OF NEGATIVE URGENCY AND POTENTIAL TREATMENT TARGETS

There are numerous excellent reviews outlining human brain structures and systems believed to contribute to the experience of negative urgency (2, 101) and other emotion-related constructs (9, 102–104). Given the implicit obstacles associated with neuroimaging in rodents and the lack of definitive homologous prefrontal regions in rodent brains, there has been limited information gleaned from animal neuroimaging studies.

Human Neuroimaging

Research concerning the neurobiology underlying negative urgency follows two primary tracts: structures and systems that represent bottom-up processing and structures and systems that are associated with top-down regulatory control. Regions representing bottom-up processing, such as the amygdala, have connections to regions regulating top-down control, including the orbitofrontal cortex (OFC), the ventral medial prefrontal cortex (vmPFC), and the dorsolateral PFC (dlPFC).

These connections constitute a reciprocal system by which both systems integrate to detect negative affect, determine the salience of that affect, and initiate or inhibit behavior in reaction (2). For instance, the amygdala is greatly involved with the experience of negative emotions (105) and projects to, and receives back projections from, the OFC (106). The OFC and its medial sector, the vmPFC, play a role in modulating emotion-based behavior and reactivity (105) and can inhibit behavior that is emotion-based (107). The ability of top-down regulatory systems to control emotion-based behavior is essential for preservation of long-term goals. There is emerging evidence that negative urgency relates to variations in neural activity in these and other subcortical [ventral striatum (VST) and caudate nucleus (CAU)] and frontal (dlPFC) brain regions (57, 64, 68, 108, 109).

There is a wealth of information concerning the function of these brain regions from neuroimaging studies, implicating the association of various structures in negative-urgency-mediated ill-advised behaviors, particularly in alcohol use disorder populations and social drinkers. The insula (INS), which plays a role in emotional processing, shows greater activation during negative urgency in adolescent binge drinkers (110). The caudate (CAU) demonstrates greater activation in response to alcohol cues in social drinkers (64, 68). The mOFC/vmOFC, primarily engaged in evaluation of rewarding stimuli to determine action, is activated more strongly to alcohol odor cues, while activation of the lOFC, which evaluates punishing stimuli, was related to negative urgency in social drinkers (63). The PFC, particularly the dlPFC, is heavily recruited during cognitive tasks in subjects high in negative urgency (111, 112). Finally, the amygdala, which is specifically involved in processing negative emotions (113) and is an important hub in negative urgency (101), shows greater activation in response to negative mood images and during negative mood evaluation in cocaine users with personality disorders (114, 115). Taken together, these findings imply a dysregulation in this interconnected system of regions associated with emotional processing and emotion-based behavioral control, which is likely contributing to maladaptive actions in pathological populations.

Emerging evidence from functional connectivity studies indicates that these structures interact to direct emotional lability and drive behavior. Dysfunction in the vmPFC impacts its association with the amygdala, resulting in potentiated response to emotional cues (116). Non-treatment-seeking alcoholics have aberrant anterior insular cortex connectivity, a region associated with assignment of emotional states to interoceptive bodily stimuli (117). There is evidence of increased cortico-limbic connectivity in cocaine-dependent subjects, associated with emotion-based impulsivity (118). A model-free, resting-state study of alcohol-dependent subjects found increased within-network connectivity in salience, orbitofrontal, and default mode networks and increased between-network connectivity associated with higher self-reported ratings of negative urgency (119). These findings indicate interconnected, functionally coupled sets of brain regions associated with emotional activation and responding, which must be better understood to further development of more targeted treatment strategies. There are numerous avenues for further exploration using connectivity tools, which would immeasurably enhance insight into underlying mechanisms of behavior. Unfortunately, neuroimaging techniques are inherently difficult to conduct in animal models and may be confounded by agents used to anesthetize subjects, limiting investigations at the preclinical level.

Human Neurotransmitter Systems

Function in many of the above brain regions is largely mediated by dopamine (DA) and serotonin (5HT) transmitter systems. These systems interact to influence emotion-based decision-making. Researchers have reported that low levels of 5HT are associated with greater incidences of rash or maladaptive behavior involving risk and increases in negative affect (120–125). Conversely, subjects with lower mono-amino oxidase, responsible for the breakdown of 5HT, display higher levels of aggression and negative urgency (126), which suggests that it may be the dysregulation of serotonin that influences emotional lability rather than simply a depletion. Interestingly, high 5HT levels in the PFC are correlated with socially adept behavior in monkeys (127), while low levels of 5HT in the anterior cingulate cortex are correlated with inhibited emotional regulation (124). It is important to note that these associations are receptor-dependent. The 5HT system is composed of several types of receptors and transporters, which may infer opposite effects upon activation. For instance, a reduction in 5HT available at $5HT_{2c}$ and $5HT_{1a}$ receptor sites increases likelihood of impulsive, rash behavior, while low 5HT at $5HT_{2a}$ receptor sites reduces risky behavior (128, 129). This dichotomy in receptor effects is important when determining possible pharmacological treatments. Although $5HT_{2c}$ and $5HT_{1a}$ receptors are more common, any prospective treatment targeting this system would be better served to attempt pharmacological effects specified for these receptors.

Alternatively, greater levels of DA activity are associated with a higher tendency to act (130), greater behavioral disinhibition (131), and greater reward-seeking and risk-taking behaviors (132, 133). DA is highly influential in the OFC–amygdala circuit (considered to be the "reward" circuit), particularly at D2 and D4 receptor sites, and it is theorized that DA effects on rash action may stem from D2 activation decreasing the value of delayed rewards (134). A recent study evaluating DA availability using positron emission tomography (PET) found that increased levels of DA in the putamen were associated with greater levels of impulsivity on the delay discounting task (135). The DA system in the OFC–amygdala circuit is modulated by serotonergic input through both direct and indirect mechanisms (136, 137). 5HT systems that subsume information processing influence DA pathways that underlie approach behavior (120, 138); therefore, decreased 5HT levels would result in diminished suppression of rash, ill-advised behavior.

Human Genetics

Overall, it is well-established that behavior consistent with negative urgency is associated with depleted 5HT levels in the PFC and overactive DA in the OFC–amygdala circuit. There are a number of genetic polymorphisms possibly contributing to the imbalances observed in populations endorsing elevated negative

urgency. Certain alleles of the serotonin transporter gene (5HTTLPR) and DA receptor genes (DRD2, DRD3, and DRD4) have all been associated with fluctuations in 5HT and DA levels and, thus, frequency of emotion-based rash behaviors (139–144). Associations between DA and 5HT are also present in an animal model of negative urgency. Yates et al. found that increased DA transporter function in the nucleus accumbens and greater 5HT transporter function in the OFC are mediated by higher exhibited negative urgency in a reward omission task (57). This neurobiological similarity highlights the usefulness of animal models to further elucidate the correlation between negative urgency and risky behavior, such as alcohol consumption.

There is limited information regarding the association between these neurotransmitter systems and negative urgency in alcohol use disorder populations. There are numerous lines of evidence indicating that decreased levels of 5HT are strongly associated with increased alcohol consumption and risk for future alcohol problems (145–147). One recent study reported that negative urgency (as measured by UPPS-P) mediated the relationship between alcohol abuse and genetically driven decreases in 5HT availability (148). In this study, higher polygenic 5HT scores (indicating lower 5HT function) were positively correlated with higher self-reported negative urgency and greater levels of alcohol consumption. At this time, there are no preclinical investigations evaluating the relationship between these transmitter systems, alcohol overconsumption, and negative urgency, although one study did report an increase in negative affect during cocaine withdrawal in rats in the reward omission task (58).

In addition to the influence of the DA and 5HT systems, there is evidence that polymorphisms of the GABRA2 gene, which codes for the $GABA_A$a2 receptor, are also associated with both alcoholism risk and negative urgency (149). Villafuerte (150) identified an association between impulsiveness and alcoholism with genetic variants of the GABRA2 gene in a family strongly endorsing alcoholism (150). This same study reported that this association was mediated by activation during reward or loss. Further research uncovered that impulsiveness, particularly negative urgency, mediates the association between the GABRA2 gene and alcoholism (151). In addition, lower levels of gamma-Aminobutyric acid (GABA) in the dlPFC are correlated with greater reports of negative urgency (152). This region is implicated in the effortful control of behavior and is heavily activated during behavioral inhibition tasks in subjects high in negative urgency. Lack of GABA in this brain region may inhibit function, decreasing the ability of the dlPFC to efficiently regulate behavior.

Implications for Treatment

Taken together, these findings provide excellent opportunities for translation to animal models, with the ultimate goal of improving clinical treatment. Translation of negative urgency to preclinical models would improve treatment in three main ways.

First, it allows for more precise identification of the neural correlates of negative urgency in human neuroimaging studies. Examining these regions translationally allows for more precision in the identified regions, circuits, and neurotransmitter systems. For example, identified neural substrates mediating negative urgency may be manipulated in animal models, and support of those hypotheses would provide data suggesting potential mechanisms through which those substrates may be manipulated to aid in treatment. Thus, this would help determine if these brain correlates are simply associated with negative urgency or are a causal mechanism in these maladaptive behaviors. This could lead to novel neurological and physiological targets.

Relatedly, animal models provide a unique opportunity to further elucidate neural underpinnings of behavior through manipulation of genetic predispositions. There are several lines of mice and rats selectively bred to prefer alcohol, including alcohol-preferring rats, high alcohol-drinking rats, and high alcohol-preferring mice (153, 154). Behavioral models can be used to compare responding to negative urgency in these subjects to responding observed in low alcohol-preferring subjects. These methods have demonstrated the ability to identify behavioral characteristics inherited alongside the predilection to prefer and consume alcohol, including impulsive-like responding in a delay discounting task (81, 155). Furthermore, they increase understanding of contributions of specific brain regions, networks, and neurotransmitter systems on alcohol consumption and associated risky behavior (156–160). Manipulation of brain region function in selectively bred animals through lesion studies, or neurotransmitter systems through pharmacological agents, grants researchers the ability to assess how each component affects behavior and determine what modifications may be employed to alter that behavior. Importantly, upon development of an animal model of negative urgency, researchers can better understand the relationship of negative affect and alcohol consumption. Although research implies that trait negative urgency contributes to the progression of alcohol use disorder, is it possible that prolonged heavy alcohol use increases the influence of negative affect? As noted above, research in humans suggests that the immediate relief from negative emotions provided by alcohol consumption increases the likelihood of repeated pairings. Animals that are selectively bred to prefer alcohol grant researchers the ability to evaluate this premise and manipulate factors, such as neurotransmitter systems, which facilitate this association. The use of selectively bred animals is recommended when investigating the interaction of two traits (alcohol preference and negative urgency).

Second, it enables the testing of novel compounds and their ability to reduce negative urgency-like behaviors, which, if successful, could then be applied and tested in clinical models. This treatment may be pharmacological, as in a drug purported to reduce anxiety (targeting the affective aspect), or behavioral, such as training the subject to reduce excessive lever pressing in times of stress (targeting the rash behavior aspect). Examining these treatments in animals first allows for testing of initial feasibility, safety, and effectiveness prior to implementing such interventions in humans. These treatments may produce objective, quantifiable outcomes that can then be administered in a clinical setting. Given the demonstrated influence of negative urgency on increased alcohol consumption in alcohol use disorder populations and the increased elucidation of neural mechanisms underlying this association, developing novel therapeutic targets through animal models should constitute the next step

toward more efficacious treatment options. Upon design of a translational, externally valid animal model, there are numerous possible targets of investigation. In particular, administration of agents designed to boost 5HT availability, specifically in the PFC, could generate a cascading effect downstream in the DA system of the OFC–amygdala circuit. Alternatively, increasing levels of GABA in the dlPFC may heighten the ability of this region to function efficiently, alleviating the heavy cognitive load required by subjects with high negative urgency to inhibit behavior.

Translation to animal models in this way has provided greater understanding of neural correlates of behavior in several domains. For instance, the symptoms of bipolar disorder are often alleviated through lithium administration, which also serves to decrease incidents of suicidal behavior (161–163). Valproate, an alternate method for bipolar disorder treatment, is also efficacious in relieving symptoms, but has no effect on suicidal behavior (164). A study evaluating the effects of these drugs on impulsivity using the delay discounting task revealed that lithium was more effective at reducing impulsive behavior in that paradigm, which may underlie the decrease in suicide attempts in that population (165). Models of Parkinson's and Alzheimer's disease have provided valuable information on the neural deterioration or malfunctioning that accompany the symptoms of those disorders (166–170). Animal models of depression have helped identify brain network and neurotransmitter systems associated with negative affect (171–174). One of the most useful tools of the animal model is to administer pharmacological therapies to attempt to identify what neurobiological mechanisms underlie symptoms and behavior.

Third, it allows for the manipulation of negative urgency in human studies and how changing the immediate expression of the trait can be clinically applied. Such studies would help test the viability of potential interventions in changing negative urgency in the human laboratory. It would also allow the use of a behavioral task of negative urgency as an objective marker of change for clinical trials of negative-urgency-based interventions, avoiding limitations related to self-report, as described above. Therefore, it is clear that the use of objective translational paradigms of negative urgency would be conducive to advancing research concerning the treatment of addictive disorders, as well as other comorbid disorders related to negative urgency.

CONCLUSIONS, LIMITATIONS, AND SUGGESTIONS FOR FUTURE WORK

We propose two important gaps in research on negative urgency that should be filled as next steps in the long-term goal of intervening on negative urgency. First, existing translational approaches for negative urgency only assess negative affect or impulsive behavior, but not both. We suggest that only by combining these two aspects of negative urgency into one model can we increase the validity of the model in both animal and human subjects. There is still some work to do to figure out the most valid way to create such a translational model. In devising a translatable method to accurately evaluate negative urgency, and more importantly to develop a model that is sensitive enough to detect changes in behavior, investigators should seek to preserve as many aspects of validity as possible (**Table 1**). Of course, other potential methods could be developed, but should meet minimal validity criteria. Importantly, many of the methods of inducing negative emotions in humans have limited translatability, hindering the design of a truly translational task. The reward omission task may be a prime place to start to induce negative emotion across human and animal models. However, other approaches to induce negative affect translationally may need to be species specific. For example, food restriction might be effective and useful in animal models, but these methods have feasibility and ethical restraints in human work. In an animal model, acute restraint stress, food deprivation, and foot shock are demonstrably effective at inciting negative affect; however, these methods may lead to increased corticotrophin levels or persistent depressive-like symptoms, so exposure should be minimal. Any combination of these methods should be thoroughly vetted and rigorously tested to establish both construct and predictive validity. In contrast, several of the impulsivity methods are highly translatable (**Table 1**) and serve as good starting points in designing a new model. Of these impulsivity tasks, the delay discounting task would be the most effective for use of cognitive impulsivity inquiries, while the Go/No-Go task would be most informative for measures of motor impulsivity.

One limitation of investigations of negative urgency is the difficulty in parsing specific emotional reactions for evaluation. There is inherently a great deal of overlap in experience of emotion; anger, fear, and sadness often co-occur and the neural underpinnings of singular emotions are highly interconnected. An excellent review from Price (175) on the neurocircuitry of mood disorders describes this phenomenon very succinctly, identifying several structures, including the primary structures of the limbic system and hippocampal regions, which contribute to various emotions and how those structures interconnect. Although the ability to efficiently unravel such closely related emotions (sadness, stress, etc). would be ideal, it has not yet been successfully accomplished and negative urgency has been shown and theorized to relate to multiple different negative emotions, including sadness, stress, and anger. Unfortunately, the inability to untangle specific emotions may hinder the ability of animal research to completely model the human experience.

Another important caveat of developing a translational model of negative urgency is the distinction between state and trait behavior, which show little overlap (46). This might limit the feasibility of developing a translational model. Current self-report evaluations of negative urgency in humans are effective at assessing trait levels of negative urgency; a similar trait-like construct may be modeled in animals through selective breeding. For example, the high alcohol-preferring mouse lines have demonstrated higher impulsive behavior in the delay discounting task (76), making them an ideal model for investigations of trait impulsivity. State behavior is successfully measured in both human and animal models, allowing for the potential of strong concordance between these groups. Although state and trait approaches do not overlap strongly, researchers propose that increased overlap would likely occur through increased specificity in the measures (46). For example, performing a behavioral task under a negative emotional

state would theoretically lead to larger correlations between the state measure and the trait of negative urgency.

Second, research has yet to examine identified human neural and genetic correlates of negative affect in animal models. There are numerous avenues for exploration that are well supported in the field and should be manipulated in animal models to test their potential treatment value. Abundant research implicates dysfunction of the serotonin and dopamine systems in regulation of the OFC–amygdala circuit may contribute to behavioral disinhibition during negative emotional states. There is also evidence of the contribution of GABA unavailability in the PFC, which may account for the excessive activation during response inhibition in subjects high in negative urgency. Identifying agents that efficiently reduce impulsive behavior during negative urgency in an animal model provides a basis for potential applications in a clinical setting. Future work should aim to further elucidate the influence of the OFC–amygdala circuit (emotional processing) and regions of the prefrontal cortex (behavioral control) in negative urgency. Novel pharmacological treatments can be discovered through manipulation strategies only available in animal models, which can then be applied in a clinical setting. It should be noted that although several lines of research have identified rodent brain regions as homologous to the human prefrontal cortex regions, there is no definitive nomenclature that accurately confirms these regions (169), which may limit translatability of neural data across preclinical and clinical models, although this type of work has been successful in related disorders (for review, see Ref. 93).

In conclusion, we suggest that future studies should seek to devise and test a valid translational model of negative urgency that is easily administered in both animals and human subjects. We hope that our review not only answers some questions about how to do this, but also creates new questions that can improve and advance this work more in the future. The long-term goal of such work will be to bring together basic research on negative urgency and clinical practice of addiction medicine, for more effective prevention, treatment, and rehabilitation of addictive disorders. We suggest that development of this model will allow for determination of prime neurological and physiological treatment targets, the testing of treatment effectiveness in the preclinical and the clinical laboratory, and, ultimately, improvement in negative-urgency-related treatment response and effectiveness. Given that negative urgency is a transdiagnostic risk factor that impedes treatment success, the impact of this work could be large in reducing client suffering and societal costs.

AUTHOR CONTRIBUTIONS

All authors contributed to the overall direction and goals of this review. The original concept was generated and broadened by MC, who was also responsible for edits and comments. EA wrote the introduction to urgency, outlined research in clinical subjects using the UPPS self-report measure, and contributed to editing and comments. MH wrote the bulk of the paper, including sections on animal models and possible neural correlates for investigation and contributed to overall edits and comments.

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Network Alterations in Comorbid Chronic Pain and Opioid Addiction: An Exploratory Approach

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The comorbidity of chronic pain and opioid addiction is a serious problem that has been growing with the practice of prescribing opioids for chronic pain. Neuroimaging research has shown that chronic pain and opioid dependence both affect brain structure and function, but this is the first study to evaluate the neurophysiological alterations in patients with comorbid chronic pain and addiction. Eighteen participants with chronic low back pain and opioid addiction were compared with eighteen age- and sex-matched healthy individuals in a pain-induction fMRI task. Unified structural equation modeling (SEM) with Lagrange multiplier (LM) testing yielded a network model of pain processing for patient and control groups based on 19 *a priori* defined regions. Tests of differences between groups on specific regression parameters were determined on a path-by-path basis using *z*-tests corrected for the number of comparisons. Patients with the chronic pain and addiction comorbidity had increased connection strengths; many of these connections were interhemispheric and spanned regions involved in sensory, affective, and cognitive processes. The affected regions included those that are commonly altered in chronic pain or addiction alone, indicating that this comorbidity manifests with neurological symptoms of both disorders. Understanding the neural mechanisms involved in the comorbidity is crucial to finding a comprehensive treatment, rather than treating the symptoms individually.

Keywords: chronic low back pain, opioid addiction, fMRI, pain induction, unified structural equation modeling, vector autoregressive modeling, automated search strategy

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INTRODUCTION

There is a high prevalence of comorbid chronic pain and opioid addiction, presenting a serious healthcare challenge that has become an epidemic in the United States (Rosenblum et al., 2003; Clark et al., 2008; Barry et al., 2013; Salsitz, 2016). Independently, chronic pain and opioid addiction are difficult to treat, and the comorbidity only increases the difficulty with diagnosis and treatment of the disorders. Patients with a substance use disorder (SUD) and co-occurring physical pain have

increased cravings (Tsui et al., 2016) and are more likely to misuse opioids than SUD patients without pain (Potter et al., 2008; Dennis et al., 2015). Impulsive tendencies in chronic pain patients indicate a high risk of illicit opioid use (Vest et al., 2016). As well, opioid use is anticorrelated with pain acceptance and lower pain acceptance rates were associated with higher opioid use rates, but pain intensity had no relationship with opioid use (Lin et al., 2015). Chronic pain is positively associated with substance use disorder severity, psychiatric disorders, psychological distress, medical comorbidities, general physical health problems, medical care utilization, and poorer psychosocial function (Jamison et al., 2000; Rosenblum et al., 2003; Potter et al., 2004; Trafton et al., 2004; Arnow et al., 2006; Tunks et al., 2008; Dominick et al., 2012; Burke et al., 2015; Howe et al., 2015). These comorbid factors are associated with relapse into substance use (Potter et al., 2010) and poor treatment outcomes.

The above challenges are compounded by the fact that opioids are often prescribed as treatment for chronic pain conditions. The effect sizes for opioid treatments are negligible, the associated risks, especially for those of dependency, are high (Ballantyne and LaForge, 2007; Noble et al., 2010). Additionally, chronic opioid use can result in opioid-induced hyperalgesia, increasing pain sensitivity (Lee et al., 2011; Stoicea et al., 2015). Thus, there is a great need for further research addressing the comorbidity of chronic pain (Noble et al., 2010; Chou et al., 2015; Dowell et al., 2016; Volkow and McLellan, 2016). The Centers for Disease Control and Prevention recently released a report providing a set of guidelines for clinicians on prescribing opioids for chronic pain, and the first guideline states that non-pharmacologic and non-opioid pharmacologic treatments should be considered before opioids. If opioids are prescribed, it should be at the lowest effective dose for the shortest duration, and non-pharamcologic therapies, such as mindfulness-based or behavioral therapy approaches, and follow-up monitoring should be used in conjunction (Dowell et al., 2016).

In regard to the brain, pain sensation is not only a peripheral physical phenomenon. Acute pain sensation induces widespread activation spanning regions including the anterior cingulate cortex (ACC), insula, somatosensory cortices, thalamus, basal ganglia, and prefrontal cortices (Tracey, 2005; Chen et al., 2008; May, 2008; Schweinhardt and Bushnell, 2010; Davis and Moayedi, 2013; Schmidt-Wilcke, 2015; Jensen et al., 2016; Morton et al., 2016). Chronic pain disorders often manifest altered processing in and interactions between many of those regions during pain tasks and at rest (Apkarian et al., 2001; Gracely et al., 2002; Moisset and Bouhassira, 2007; Napadow et al., 2010; Baliki et al., 2011; Cifre et al., 2012; Davis and Moayedi, 2013; Schmidt-Wilcke, 2015; Jensen et al., 2016; Martucci and Mackey, 2016; Morton et al., 2016), and chronic pain patients exhibit activation in pain-related structures at lower stimulation levels than healthy controls (Gracely et al., 2002; Giesecke et al., 2004). A recent meta-analysis showed healthy individuals have increased activation likelihood due to painful stimulation in the ACC, insula, and thalamus than chronic pain (Jensen et al., 2016). In addition, gray matter volume and cortical thickness are also decreased in many of the same regions, primarily the ACC, thalamus, basal ganglia, insula, and dorsolateral prefrontal cortex (DLPFC) (Apkarian et al., 2001; May, 2008, 2011; Schmidt-Wilcke, 2008; Davis and Moayedi, 2013; Ivo et al., 2013; Smallwood et al., 2013; Alshuft et al., 2016; Yang et al., 2017). In individuals with CLBP, 1 month of oral morphine consumption resulted in gray matter increases and decreases in pain and reward-related structures (Lin et al., 2016).

Opioid dependence and addiction also affect brain structure and function. Differences in regional dynamics in drug-cue task fMRI have been observed in the ACC, insula, prefrontal cortices, caudate, thalamus, putamen, hippocampus, and amygdala (Langleben et al., 2008; Yang et al., 2009; Wang et al., 2010, 2011, 2014; Lou et al., 2012; Li et al., 2013; Schmidt et al., 2014, 2015b). These regions and the nucleus accumbens exhibit altered functional connectivity at rest in opioid-dependent subjects and heroin addicts (Ma et al., 2010, 2015; Upadhyay et al., 2010; Schmidt et al., 2015a; Zhang et al., 2015). Structurally, opioid-dependent subjects have significantly less gray matter volume bilaterally in the amygdala and nucleus accumbens (Upadhyay et al., 2010; Seifert et al., 2015; Lin et al., 2016) and in frontal and temporal areas (Qiu et al., 2014; Lin et al., 2016; Wollman et al., 2016) and increased gray matter volume in the cingulate (Lin et al., 2016). Administration of oral morphine to healthy subjects undergoing pain stimulation caused the pain-related activations to have smaller spatial extent (Hansen et al., 2015).

Treatment for these disorders must be driven by principles of neural plasticity. Specifically, positive treatment outcomes are linked to targeting neural structures that support a given function. This is known as the "specificity" principle because it has been shown that neural plasticity must specifically target those brain regions or networks that have changed from their normal state (Kleim and Jones, 2008; Cramer et al., 2011). Hence, extensive knowledge of both healthy and abnormal brain structures involved in pain processing and reward circuitry is necessary. While knowledge of the neural substrates of chronic pain or opioid addiction alone is substantial, there are no data on the comorbid disorders, hampering treatment development. It is likely that pain and SUD comorbidity causes complex and unique effects on neural organization. We hypothesize that the comorbidity will result in similar changes but with larger magnitudes than in either of the two disorders alone, and that these synergistic effects will extend to unique brain regions.

Complex functions are supported by a connected network of brain regions, and understanding the function of each region of the network and network connectivity properties is important in determining the underlying neural substrates of disorders. The comorbidity of pain and SUD along with other usual symptoms (e.g., depression, anxiety, and sleep disturbances) makes the typical approach to imaging analysis (e.g., group analysis of conditional contrasts) difficult to use since each impairment contributes distinct neurophysiological response patterns. Hence, this study uses a connectivity approach to understanding this comorbid disorder. Because this clinical population has not been investigated with neuroimaging until now, in this experiment we used an exploratory approach to connectivity analysis that is ideal given the vast possibilities for regional changes. This approach allows for a large number of regions to be entered into the analyses. Further, exploratory

connectivity analyses allow for study of neural networks without the bias of preconceived hypotheses and can drive more detailed analyses that focus on the specific neural systems implicated in a disorder.

In this study, the first aim was to identify an optimal network of brain regions and study their connectivity based on coherence of regional activities for patient and healthy control groups. Given that the brain data on the individual comorbid conditions are not available, we argue that we are justified in using a healthy control group in this first study. Much is known about the neuroscience of chronic pain and addiction independently, however, the comorbid patient population is yet unstudied. To accomplish this, we used a unified structural equation modeling (SEM) approach (Kim et al., 2007) that provides a framework for estimating contemporaneous and temporal or lagged relationships through a multivariate vector autoregressive model in conjunction with an automated Lagrange multiplier (LM) model testing strategy (Gates et al., 2010). Our second aim was to determine if statistical differences in magnitude existed between groups based on regional alterations. The network structure identified in aim one was evaluated to determine if statistical differences existed between patient and control groups for each path specific to the magnitude and sign of the regression weights.

MATERIALS AND METHODS

Eighteen (39.2 ± 12.8 years; 10 males) opioid-addicted individuals with chronic low back pain were recruited from methadone clinics in San Antonio, TX. Eighteen healthy (39.5 ± 12.4 years) individuals were recruited as sex and age (within ±3 years) matches to the patients. Patients met the requirements for current DSM-IV opioid dependence, were currently enrolled in opioid replacement therapy (i.e., methadone maintenance or buprenorphine therapy) for more than 30 days, and had been experiencing chronic low back pain for at least 12 months at a level of 5 or greater on a 0 to 10 rating scale. Control participants had no drug use within the past 30 days, had no drug dependence within the past year, rated their pain-related functional interference as less than 2 on a scale from 0 to 10, and considered themselves healthy. This study was carried out in accordance with the recommendations of the University of Texas Health Science Center San Antonio's Internal Review Board with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

Participants completed a battery of paper questionnaires to assess pain and addiction severity, including the Acceptance and Action Questionnaire II (AAQ-II; Bond et al., 2011), the Mindfulness Attention Awareness Scale (MAAS; Brown and Ryan, 2003), the Roland Morris Disability Questionnaire (RMDQ; Roland and Morris, 1983), and the visual analog scale for opioid craving, interference, and intensity (VAS; McMillan and Gilmore-Thomas, 1996). All demographic and assessment data have been included in **Table 1**. While outside of the scanner, participants also underwent a threshold test to determine their individualized pain stimulation levels. Pain stimuli were delivered via pressure to the right thumbnail with a pneumatic device.

TABLE 1 | Participant demographics and assessment results.

	HC	CPOA matched
Subjects (N)	18	18
Gender	10 males, 8 females	10 males, 8 females
Age (years)	39.5 ± 12.4	39.2 ± 12.8
Acceptance and action questionnaire II (AAQ-II)	62.0 ± 9.0*	39.2 ± 9.0
Mindfulness Attention Awareness Scale (MAAS)	4.8 ± 0.9*	3.6 ± 0.9
Visual analog scale (VAS), opioid craving	0.0 ± 0.0	2.4 ± 2.6
Visual analog scale (VAS), interference	0.0 ± 0.0*	3.7 ± 2.0
Visual analog scale (VAS), intensity	0.0 ± 0.0*	3.8 ± 2.1
Roland Morris Disability Questionnaire (RMDQ, %)	–	53.0 ± 24.5

*Averages and standard deviations listed; HC, healthy controls; *healthy controls significantly different from matched patients, $p \leq 0.001$.*

Patients underwent a 16-min pain induction fMRI task containing 8 triplets of 5-s painful pressure blocks (pressure the subjects rated as 40/100 on a pain scale) and 8 triplets of 5-s innocuous pressure blocks (pressure that was not rated as painful), each followed by rest periods. An anatomical scan for registration was also collected. Data were collected using a 3T Siemens TIM Trio scanner (fMRI TR/TE/tip angle/slices/voxel size = 2500 ms/30 ms/90°/36/1.72 × 1.72 × 3 mm; aMRI TR/TE/TI/flip angle/voxel size = 2200 ms/2.8 ms/766 ms/13°/1 × 1 × 1 mm). The pain task fMRI data were pre-processed and analyzed using SPM8. To begin, motion parameters were observed across the entire time series of the scan. If a subject had a large spike in motion (≥1 mm/TR), the ArtRepair toolbox was used to interpolate signal from the preceding and following volumes. Then either the raw data (if no motion correction was needed) or the artifact-repaired data were realigned and resliced, coregistered to the anatomical image, transformed into MNI standard space using the transformation derived from the segmented anatomical image, and then smoothed with an 8 mm FWHM kernel. The functional time series for each volume of interest (VOI) was extracted, normalized, and adjusted for motion. Each VOI was centered on the coordinate specified in **Table 2** and was spherical with a 6 mm radius. The 19 regions subjected to analyses are included in **Table 2**. The effective sample size was N = 1153 in the control group (pain condition) and N = 1153 in the patient group (pain condition). The effective sample size was N = 6912 for the control group under all experimental conditions (pain + innocuous + rest) and N = 6903 for the patient group under all experimental conditions.

ANALYTIC STRATEGY

In functional connectivity studies, the goal includes modeling the temporal effect of neural activation in one region in relation

TABLE 2 | Volumes of interest included in model 2.

Region	X	Y	Z	Abbreviation
Left insula	−40	6	2	lIns
Right insula	41	15	1	rIns
Dorsal anterior cingulate cortex	3	36	22	dACC
Left amygdala	−23	−3	−17	lAmyg
Right amygdala	23	−4	−16	rAmyg
Left dorsolateral prefrontal cortex	−31	43	22	lDLPFC
Right dorsolateral prefrontal cortex	41	39	24	rDLPFC
Left putamen	−25	0	5	lPut
Right putamen	25	7	2	rPut
Left caudate	−12	4	13	lCaud
Right caudate	15	9	14	rCaud
Left thalamus	−13	−11	16	lThal
Right thalamus	9	−11	7	rThal
Left primary somatosensory cortex	−57	−24	23	lS1
Right primary somatosensory cortex	58	−24	21	rS1
Left precuneus	−18	−57	34	lPrecun
Right precuneus	19	−57	35	rPrecun
Left nucleus accumbens	−9	6	−4	lNAcc
Right nucleus accumbens	9	6	−4	rNAcc

Center coordinates in MNI space of 6 mm radius spheres provided.

to another region. However, each observation (single fMRI volume) is partly a function of the previous within-subject observation due to the multiple volumes collected for each subject. The interdependence among the observations within subjects is manifested in the within-subject residual error of regression for one observation at time *t* (contemporaneous component) correlating with the previous measurement at time *t*-1 (temporal component). The autoregressive effect is typically positive thereby biasing the standard errors of regression estimates downward, yielding *F*-statistics with inflated statistical significance (Bingenheimer and Raudenbush, 2004). Kim et al. (2007) provided a unified SEM approach that allows for estimation of contemporaneous relations (e.g., at time *t*) among ROIs controlling for sequential dependencies present in fMRI data structures. The unified SEM approach also provides a framework for estimating vector autoregressive parameters (i.e., lagged relationships – time *t*-1) after controlling for contemporaneous effects. For example, interest may lie in the effect of region *X* at time *t*-1 on region *Y* at time *t* (current time). This autoregressive analytic approach is then expanded throughout the multivariate regression (network) model to estimate the path loadings throughout the network (Kim et al., 2007; Price, 2012).

Thus, the unified SEM approach advances current techniques by providing a flexible, dynamic approach for simultaneously estimating contemporaneous and lagged relationships between ROIs. Although Granger Causality Modeling can be used to estimate lagged relationships, biased estimates may result from failing to consider contemporaneous relations (Gates et al., 2010). Dynamic causal modeling (DCM) is another approach that can be used to study event-related data. However, DCM is limited to modeling contemporaneous change, whereas the unified SEM is appropriate for simultaneously modeling contemporaneous and lagged effects. Additionally, DCM is used for confirmatory analysis, while the unified SEM approach is appropriate for either confirmatory or exploratory analysis. Because it is entirely data-driven, the unified SEM offers a substantial degree of flexibility when compared to alternative approaches (Gates et al., 2010, 2011; Guàrdia-Olmos et al., 2018).

Identifying the Network Structure

Prior to analyses, we conducted data screening to evaluate the time series properties of the data. Data screening included evaluating (a) the stationarity or non-stationarity of the time series, (b) the time period between observations to determine the lag structure (e.g., lag-1, lag-2, or lag-3) and (c) the autocorrelation and partial autocorrelation functions. Results of the data screening (i.e., autocorrelation and partial autocorrelation plots of residuals) revealed a stationary, white noise process with a lag-1, the time series best representing the series (Box et al., 2015).

The present study was exploratory given the lack of previous research on the comorbidity of chronic pain and opioid addiction. Therefore, although the regions of interest were selected *a priori*, no network model of functional connectivity between those regions was posited *a priori*. Consequently, we employed a search strategy involving LM testing with forward selection starting with a null model (no regression paths among regions) then sequentially added additional parameters one step at a time (Chou and Bentler, 1990; Gates et al., 2010). This process continued until the first non-significant path loading was observed. This search algorithm was conducted using Linear Structural Relations (LISREL), version 9.2 (Jöreskog and Sörbom, 2015). **Table 3** provides the fit statistics for the final model for the patient and control groups. **Supplementary Tables S1, S2** show all the connections present in the optimal models in all subjects for all conditions and the pain condition, respectively. To compare connections between groups, a *Z*-test was employed on the Fisher's Z for each connection for each group.

RESULTS

Almost every connection in the model was significantly different between groups because there was such a large sample size;

TABLE 3 | Summary fit statistics pain condition, all conditions.

	Control	Patients	Controls	Patients
X^2	2520.64	4594.89	11341.75	23431.75
df	590	590	590	590
p	<0.001	<0.001	<0.001	<0.001
CFI	0.93	0.90	0.92	0.92
RMSEA	0.05	0.07	0.05	0.07
Stability Index	0.46	0.51	0.53	0.53

X^2-test of overall model fit; df, degrees of freedom; p, probability level; CF, comparative fit index; RMSEA, root mean square error of approximation; Stability Index is a measure of system stability in a non-recursive structural equation model (Fox, 1980; Bentler and Freeman, 1983). Pain condition, left; all conditions, right.

therefore, an effect size (Cohen's q; Cohen, 1988) was calculated to distinguish the most relevant and meaningful differences. The results and discussion will focus on the connections that were significantly different between patients and controls with at least a moderate effect size ($q \geq 0.3$). The between group differences for all connections (regardless of effect size) can be seen in **Supplementary Tables S1, S2**. All of the significantly different connection strengths with large or moderate effect sizes were greater in patients than in control subjects. Although there were some connection strengths that were greater in controls than patients, as indicated by a negative z-score, effect sizes for these comparisons were small ($q \leq 0.21$ for all conditions, $q \leq 0.19$ for pain condition only).

For the time series with all conditions included, the connections that differed significantly with large or moderate effect sizes were the connection between the right thalamus and dACC (effect size $q = 0.58$, lag $q = 0.70$), the right S1 and left caudate ($q = 0.59$, lag $q = 0.58$), the right insula and left NAcc ($q = 0.57$, lag $q = 0.34$), the right amygdala to left amygdala ($q = 0.53$, lag $q = 0.57$), the right insula and right caudate (lag $q = 0.40$), the right insula to left caudate ($q = 0.38$), the right caudate and left caudate ($q = 0.37$), and the right insula and left insula ($q = 0.31$). See **Figures 1**, **2**.

During the pain conditions, there were only connection strength differences with moderate effect sizes. These connections were between the right S1 and left caudate ($q = 0.34$, lag $q = 0.43$), the right insula and right caudate (lag $q = 0.41$), the right caudate and left caudate ($q = 0.38$), the right insula and left NAcc ($q = 0.35$), right insula and left caudate ($q = 0.34$), right S1 and right thalamus (lag $q = 0.34$), right thalamus and dACC (lag $q = 0.33$), and the right caudate and right precuneus (lag $q = 0.32$). See **Figures 3**, **4**.

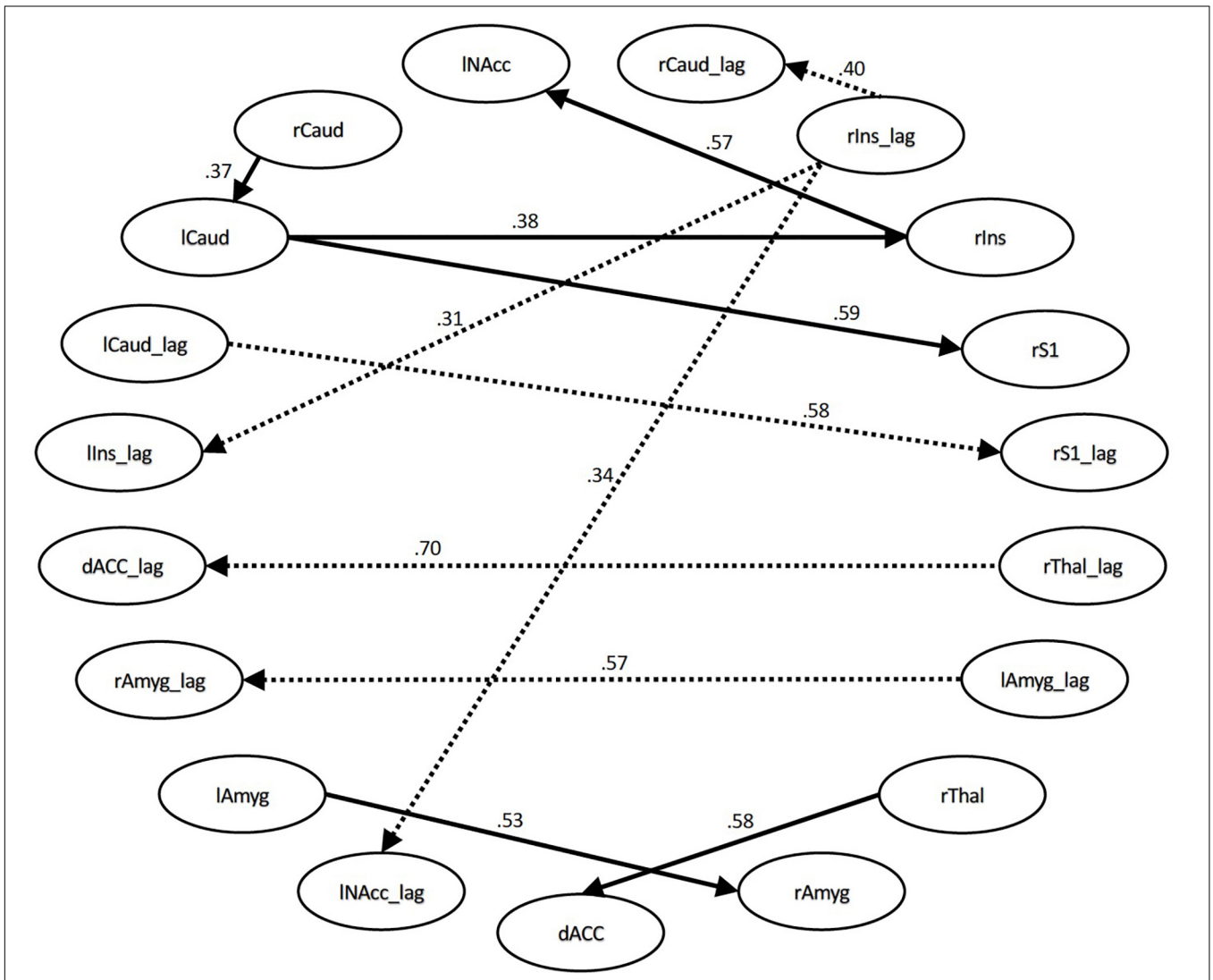

FIGURE 1 | Structural equation modeling network model – all. Patient and Control Groups, All Conditions. Numbers on paths are effect sizes representing the difference between Controls and Patients under all conditions.

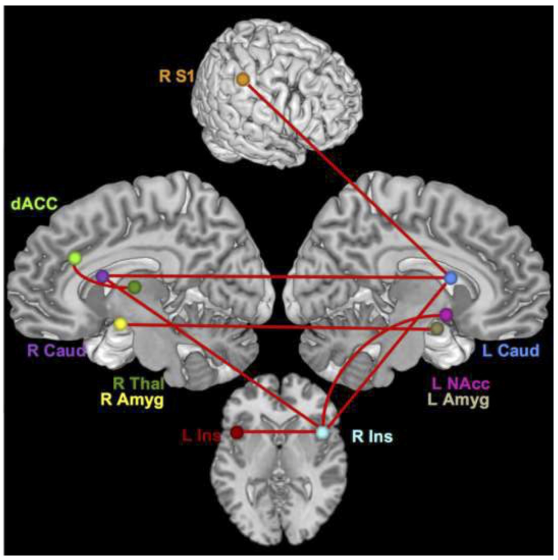

FIGURE 2 | Brain network regions – all. Connections that differed significantly between groups with a moderate or large effect size for all conditions.

DISCUSSION

This study is to our knowledge the first to characterize the neural networks underlying comorbid chronic pain and opioid addiction. Our results indicate that the network changes occurring in patients with this comorbidity reflect a combination of the changes observed in chronic pain and addiction alone. Because of the novelty of the population we used an exploratory analysis to determine the network model via SEM using an automated search algorithm that implements LM testing. Group differences were quantified based on this network model. Hence, the critical analysis from these data is the quantification of coupling properties between model regions. Specifically, higher connection values denote stronger connection strengths, with the inference being two regions with similar temporal activity fluctuations are working in concert during the processing of stimuli. The connections that varied between groups, demonstrating a medium or greater effect size ($|q| \geq 0.3$), reflected *higher connection strengths* in patients compared with controls (positive q). This indicates an increase in coherence of activity between seed regions during painful stimulation in opioid- addicted patients with CLBP compared to healthy subjects.

Previous studies in chronic pain have also reported altered connectivity in patients at rest, showing differences in the default mode network (DMN) (Baliki et al., 2008, 2014; Napadow et al., 2010; Bolwerk et al., 2013; Otti et al., 2013; Kucyi et al., 2014; Hemington et al., 2016; Mansour et al., 2016; Letzen and Robinson, 2017; Yang et al., 2017), executive attention network (Napadow et al., 2010), salience network (Otti et al., 2013; Hemington et al., 2016), in the insula, ACC, and basal ganglia (Malinen et al., 2010; Cifre et al., 2012; Schwedt et al., 2013;

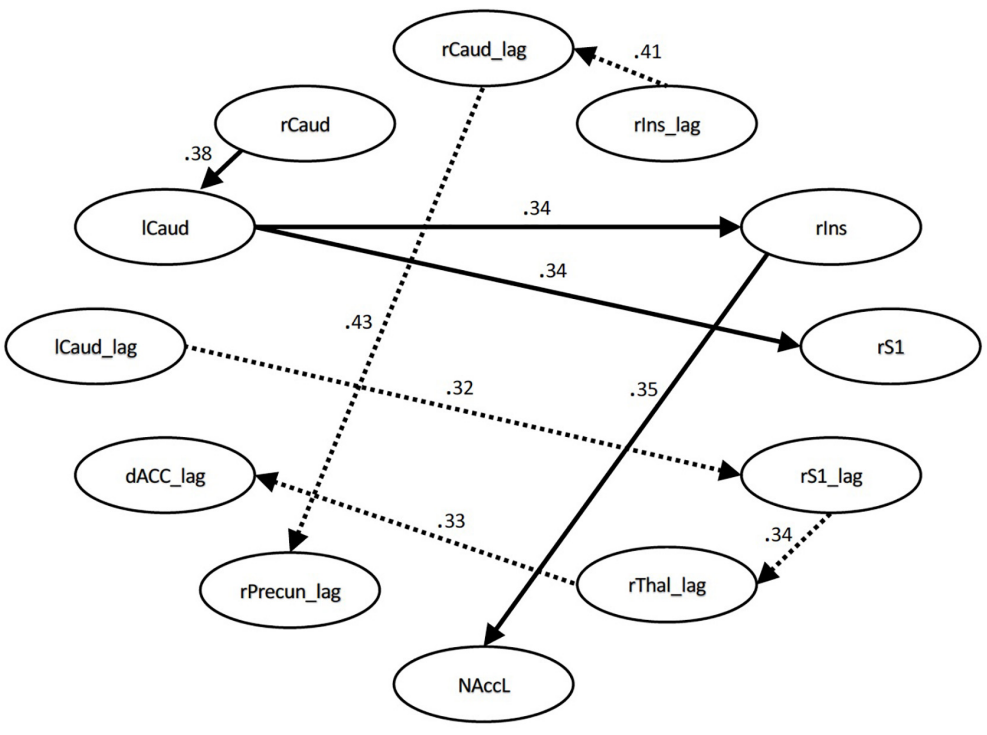

FIGURE 3 | Structural equation modeling network model – pain. Patient and Control Groups, Pain Condition. Numbers on paths are effect sizes representing the difference between Controls and Patients under pain condition only.

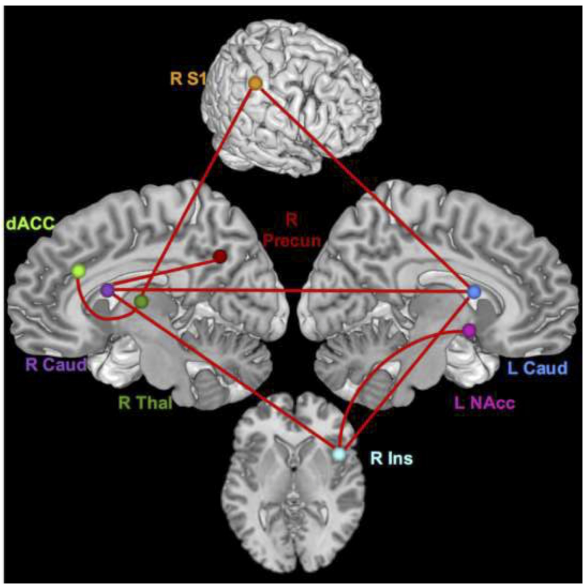

FIGURE 4 | Brain network regions – pain. Connections that differed significantly between groups with a moderate effect size for the pain condition.

Yang et al., 2017), during spontaneous back pain (Hashmi et al., 2013), and during painful stimulation (Baliki et al., 2010; Jensen et al., 2013). Similar connectivity alterations have been observed in opioid-dependent and -addicted populations, with the alterations occurring in amygdala, insula, NAcc, prefrontal cortex (Ma et al., 2010; Upadhyay et al., 2010; Zhang et al., 2011; Schmidt et al., 2014, 2015b), orbitofrontal cortex, caudate, parahippocampus, lingual gyrus, precuneus, middle temporal gyrus (Chang et al., 2016), putamen, posterior cingulate (Schmidt et al., 2015a), and anterior cingulate (Zhang et al., 2015). Our results, coupled with existing literature, indicate both conditions likely contribute to connectivity alterations and that patients' neurophysiological responses to induced pain are characterized by stronger connections between regions than normal controls' responses. This increased synchronicity between regions in patients could reflect an increase in communication with more information being passed between the regions; it could also be indicative of an alteration in a common upstream or regulatory region that is passed to its downstream effectors. Whatever the mechanism, these patterns are consistent with central sensitization (Ng et al., 2017); the neuroplastic changes that occur in chronic pain could lead to regions being more functionally connected than necessary for typical pain processing.

The regions with differing connections are not only regions associated with sensory discrimination of pain (S1, thalamus, insula), but also regions that are involved in the emotional response to pain (insula, caudate, amygdala, dACC) and higher-level regulation and integration of pain signals (caudate, nucleus accumbens, dACC) (Tracey, 2005; Chen et al., 2008; May, 2008; Baliki et al., 2010; Schweinhardt and Bushnell, 2010). If individuals with chronic pain and opioid addiction simply had lower pain thresholds, we would expect to see differences primarily, or even exclusively, in sensorimotor regions. The increased coupling strength of sensory regions with others could partially underlie differences from normal. However, the diverse functional nature of regions with stronger connectivity signifies that this population likely has a heightened multi-dimensional response to pain (i.e., sensory, affective, and cognitive), not just in pain sensation. This is in agreement with a finding that chronification of back pain coincides with a shift of processing from more sensory/acute pain circuits to affective circuits (Hashmi et al., 2013), and CLBP patients appear to have more alterations in regions associated with emotion and cognition than in nociceptive regions (Woolf, 2011). Another interesting trend was many of the significant connections with moderate effect sizes were interhemispheric, indicating that although the painful stimulation was only applied on the right thumb, pain processing in this clinical population seems to be characterized by increased bilateral engagement. This is an intriguing consideration in the context of a recent study of normal pain processing that revealed higher pain stimulus levels resulted in increased interhemispheric DLPFC connectivity (Sevel et al., 2016). Perhaps the constant state of pain in the patients causes these plastic changes in bilateral connections.

Additionally, considering the task used in this study highlights an important trend in the regional connectivity. A pain induction paradigm would assume activation and coordination of thalamus and S1 which primarily encode the sensory aspects of pain. However, another important feature to note in the difference network is that, other than thalamus and S1, all of the regions are altered in both diagnoses independently. The observable differences manifesting in regions that overlap between chronic pain and opioid addiction is consistent with the suggestion of chronic pain and addiction following similar neuroadaptation patterns based on a common neural substrate foundation (Elman and Borsook, 2016). It could be that these are regions where the two disorders work synergistically to cause alterations. This finding provides strong support for the development of treatments that simultaneously treat the two disorders, rather than treating one and/or the other independently. Though there have only been a couple of clinical studies with this approach, they have promising results for patients with comorbid chronic pain and opioid addiction (Ilgen et al., 2016; Smallwood et al., 2016).

The observed increases in connectivity likely are not only related to the actual pain stimulus, but evince aberrant connectivity due to addiction. The NAcc is a central part of reward circuitry (Martin-Soelch et al., 2001) and is altered in opioid-dependent subjects (Ma et al., 2010; Upadhyay et al., 2010). It was also predictive of the effect of pain stimuli on chronic pain in a pain induction study in chronic back pain (Baliki et al., 2010). Its role here suggests its participation could be part of a mechanism underlying the emotional response to pain in the form of a trigger for the substance dependence-related response. This is consistent with the between-group difference in its connection with the insula. The insula has a key role in pain processing, being responsible for both sensory and affective aspects of pain (Tracey, 2005; Chen et al., 2008; Schweinhardt and Bushnell, 2010). In painful stimulation of healthy subjects, it was shown that its connectivity shifted with

modulation of attention and emotion (Ploner et al., 2011). The insula is also one of the regions commonly activated in tasks when heroin addicts are shown heroin cues in the scanner (Langleben et al., 2008; Lou et al., 2012). Naqvi and Bechara (2010) proposed a drug cue-induced model of processing that includes a connection between the insula and NAcc. They hypothesized that observing a cue previously associated with partaking of a particular addictive substance would activate a network in which the insula acts as a gate to allow previous experiences of the substance's effects to intensify the urge use, represented by the nucleus accumbens within the reward system. Perhaps in this population painful sensations and their affective sequelae trigger the association of the analgesic effect of opioids, thus increasing the individual's craving for pain relief and the high experienced from the opioids. This highlights a unique challenge to treating addiction and dependence in patients with comorbid chronic pain: if the presence of the pain creates an additional drive for substance use, these individuals could be fighting an even stronger impulse to use. Furthermore, qualitative research suggests that patients with comorbid chronic pain and SUD perceive that healthcare providers are not treating their pain and addiction in an integrated manner (St. Marie, 2014), thereby generating heightened cravings and perpetuating substance misuse.

The caudate is hypothesized to be responsible for regulating the affective response to pain (Borsook et al., 2010), so the connection between S1 and caudate is likely a pathway for transduction from a sensory-only experience to a multi-dimensional experience that includes affective and higher order cognitive/regulatory components. The increased connectivity in patients between the caudate and the precuneus during the pain only condition could be indicative of an increased affective response to pain in patients due to increased pain sensitivity (Goffaux et al., 2014). The amygdala receives nociceptive inputs from the brain, but also encodes a plethora of affective processes (Veinante et al., 2013) and has been linked with craving-relating activation in response to drug cues in opioid-dependent subjects (Murphy et al., 2017). The bilateral amygdala connection differing significantly could imply an increase in the emotional response to pain, but since the difference was observed only in the time series with all conditions (including rest and innocuous pressure) and not during pain induction alone, perhaps it signifies patients having an increased fearful response or negative anticipation of the coming pain compared with controls.

It is important to underline here that since we are not reporting longitudinal or structural MRI data, we cannot conclude on the neural network and morphological changes that may have occurred in the patient group after withdrawing from opioids. All patients had been enrolled in an opioid replacement therapy program for at least 30 days prior to data collection. Fingelkurts et al. (2009) reported that measures of local and remote electroencephalogram (EEG) functional connectivity of opioid-dependent patients treated with methadone for 6 months did not differ significantly from normal values observed in healthy controls. Studies of medication-overuse headache (MOH), which has also been associated with psychiatric comorbidities, report that in some patients gray matter volume changes reverted to normal state after a period of drug withdrawal. Namely, an increase in gray matter in the orbitofrontal cortex and a decrease in periaqueductal gray region of the midbrain were observed and these changes positively correlated with treatment response (Riederer et al., 2013; Lai et al., 2016). To address this issue, future studies should include both longitudinal and voxel-based morphometry (VBM) data.

Our study provides a novel approach to modeling network structure and connectivity patterns, though we address a few limitations here. First, the population of opioid-addicted individuals with chronic pain was very heterogeneous. Ideal exclusion criteria should include a variety of psychiatric disorders. However, this population included participants with a range of comorbid psychiatric conditions such as depression, anxiety, bipolar disorder, and schizophrenia. Nearly every participant self-reported some type of psychiatric condition, often more than one. This is consistent with data reported in a review by Kelly and Daley (2013), stating that 27% of people with SUD have at least one psychiatric disorder and 45% of people with psychiatric conditions actually have two or more disorders (Kessler et al., 2005). These conditions were self-reported, and had they been excluded there would not have been a large enough population to conduct a study with this comorbidity. Second, another constraint that plagues studies of comorbidities is that it is unknown how two (or more) comorbid disorders interact and whether they interact uniformly in all patients. This introduces the potential for more heterogeneity, and these sources of heterogeneity are one of the primary impetuses for using an exploratory approach. Additionally, any differences observed cannot be ascribed to one diagnosis or the other, as we only have the comorbid patient population and a negative control population. Future studies should have positive control groups including subjects with only chronic low back pain and only opioid addiction. However, we feel strongly that although we cannot specifically attribute any of these differences or characteristics to one diagnosis, the other, or the comorbidity, these results still provide essential knowledge about a pragmatic clinical population (Ford and Norrie, 2016) that represents one of our current significant healthcare challenges.

CONCLUSION

The results presented here show that in a network determined via an exploratory SEM analysis, opioid-addicted chronic pain patients had increased connectivity in regions that are affected in both disorders independently. These increases likely indicate altered emotional responses to pain as well as addiction-related neurophysiological reactions, signifying that this comorbidity may act in a synergistic way to exacerbate neural alterations.

This analytic approach represents a novel and interesting way to examine connectivity data. The SEM allowed for defining and refining an optimal network for all subjects. The feature of the SEM that allowed for a large number of regions to be included in the model was invaluable from the exploratory side of the analysis. Because this is a novel population for neuroimaging

study, having few restrictions on the number of regions (nodes) of interest included in the model and requiring no *a priori* hypotheses about model structure allowed a broader investigation of the potential relationships and alterations between brain regions in this cohort.

ETHICS STATEMENT

This study was approved and carried out in accordance with the recommendations of the University of Texas Health Science Center San Antonio's Internal Review Board with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

RS conducted all the study aspects, development, implementation, interpretation, and wrote the manuscript. LP developed the connectivity models, assisted in model interpretation, and ran all the statistical tests on model connections and wrote the manuscript. JC, SAA, TM, SWA, and AG contributed to proofreading, provided the input into final document, assisted with writing and interpretation of the data, and contributed pertinent supporting references. JP assisted in study design, interpretation of data, and wrote the manuscript. DR supervised and was invovled in all aspects of study development, implementation, analysis, and interpretation.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2019.00174/full#supplementary-material

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Learning From Loss After Risk: Dissociating Reward Pursuit and Reward Valuation in a Naturalistic Foraging Task

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A fundamental feature of addiction is continued use despite high-cost losses. One possible driver of this feature is a dissociation between reward pursuit and reward valuation. To test for this dissociation, we employed a foraging paradigm with real-time delays and video rewards. Subjects made stay/skip choices on risky and non-risky offers; risky losses were operationalized as receipt of the longer delay after accepting a risky deal. We found that reward likability following risky losses predicted reward pursuit (i.e., subsequent choices), while there was no effect on reward valuation or reward pursuit in the absence of such losses. Individuals with high trait externalizing, who may be vulnerable to addiction, showed a dissociation between these phenomena: they liked videos more after risky losses but showed no decrease in choosing to stay on subsequent risky offers. This suggests that the inability to learn from mistakes is a potential component of risk for addiction.

Keywords: risk, regret, foraging, decision-making, externalizing

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INTRODUCTION

Many choices, like starting a new relationship or accepting a job out of state, involve some level of risk that can be expressed as a win or loss relative to baseline (1). Such decisions can lead to negative affective experiences, particularly if an individual chooses to take a risk and then receives an unfavorable outcome (2). While some individuals learn to make choices that minimize future negative outcomes (3, 4), the inability to learn from such losses may be integral to certain externalizing psychopathologies like addiction (5, 6). In this study, we examined relations between risky losses and externalizing tendencies by modifying a newly established human foraging paradigm (the *Web-Surf Task*) (7).

An earlier version of the Web-Surf Task was based on a rodent neuroeconomic task (*Restaurant Row*) (8). These parallel tasks entailed serial stay/skip choices regarding offers of real-time delays and primary rewards (food from four feeder sites in Restaurant Row, video clips from four galleries in the Web-Surf Task). On each encounter in the Web-Surf Task, the subject was informed of a required delay before the reward would be delivered, indicated by a download bar and numeric text instruction. The subject could either accept the deal and *stay* through the delay for the reward, or *skip* the deal and try his or her luck at the next reward site (video gallery). Reward kind (genre of video) remained constant at each gallery. Subjects had a limited time to spend on the task, thus creating

delay-related trade-offs between galleries. Delay was random (selected uniformly from 1 to 30 s) on each offer encounter.

In our earlier work, we observed comparable decision valuation processes across species using these analogous tasks (9). Each subject revealed different, but reliable, delay-dependent preferences (i.e., thresholds) for each restaurant/gallery, taking delays below that threshold and skipping delays above. We also observed a high correspondence between choices and consummatory responses among humans (delay thresholds related to video enjoyment ratings), and between choices and stated preferences (delay thresholds related to rankings of video galleries assessed at the end of the task) (7).

Our initial work using the original Web-Surf Task bridged cross-species models of decision-making while also demonstrating the task's capacity to parse different valuation processes (7). A critical next step is to understand whether foraging task parameters predict meaningful individual differences, like those observed on the externalizing psychopathology spectrum (including addiction). We were motivated to use the Web-Surf Task to assess externalizing tendencies for two reasons: 1) the rodent analogue (Restaurant Row) has been used to assess the effects of different substances (i.e., cocaine and morphine) on deliberation and post-decisional commitment (6), highlighting the value of this paradigm for understanding substance use disorders. 2) Recent theories suggest that foraging models of decision-making are a promising approach for studying addiction, as these tasks measure how a subject allocates scarce resources (e.g., time) when searching for valuable goods (e.g., food, drug) (10). For instance, drug users can be conceptualized as foraging for resources in a patchy environment, e.g., smokers looking for the cheapest cigarettes (11).

To better assess for behavioral markers of addiction vulnerabilities using the Web-Surf Task, we added a risk component to the task, given accumulating evidence that risky decisions represent a vulnerability for substance use disorder (12). We then characterized risky outcomes according to prospect theory (13), which raises the possibility that subjects might reframe their enjoyment with regard to post-decisional outcomes. That is, they might reframe the outcome of an incurred risk (e.g., a win or loss) relative to the mid-point of the option, independent of whether the choice was the right option to take given the information at the time. For instance, the act of losing on a risky decision may impact video enjoyment regardless of whether their choice to stay and wait for that video was consistent with the offer's value.

Our overarching goal for the current study was to test whether an experiential foraging task can measure addiction-relevant behaviors, following from theories that conceptualize risky substance use within foraging models (14). More specifically, we aimed to determine 1) whether subjects showed differential responses to risky losses with respect to their enjoyment of reward and acceptance of subsequent risky deals, and 2) whether individual differences in response to risky losses predicted variation in trait-level externalizing, a risk factor for substance use disorders (15–17). We expected bad outcomes to reduce one's likelihood of accepting subsequent risky offers and for this pattern to be reversed among high-externalizing subjects (suggesting continued risk-taking despite negative outcomes).

METHODS

Subjects

One hundred five undergraduate students (81% female, average age 20.2 years) from the University of Minnesota completed the current study and received compensation in the form of extra credit towards psychology courses. We targeted a sample size of around 100 subjects for our individual differences analyses (i.e., relations with externalizing scores), given an *a priori* power analysis indicating the need for 84 subjects to have 80% power for detecting a moderate effect size of $r = 0.3$ when employing a 0.05 criteria for statistical significance (based on a meta-analysis indicating small to moderate effect sizes for risk-taking and externalizing trait correlations) (18). The racial/ethnic breakdown of the sample was as follows: 63% Caucasian, 26% Asian, 4% Black/African American, 3% Hispanic, 1% American Indian/Alaskan Native, 1% Native Hawaiian/Pacific Islander, 2% other. The University of Minnesota Institutional Review Board approved the study procedures, and all subjects provided written informed consent.

Experimental Design

In the risk variant of the Web-Surf Task (**Figure 1A**), subjects had 40 min to travel between galleries that provided video rewards from the four galleries described in Abram et al. (7): kittens, dance, landscapes, and bike accidents. As in the original Web-Surf and Restaurant Row tasks, subjects had a fixed amount of time to forage; this means that subjects should have made economically maximizing decisions and stayed when the subjective value of an offer exceeded its cost.

Subjects encountered serial offers that presented a set of possible delays (**Figure 1B, C**): on entry into a gallery, the subject was shown a gallery icon, a textual representation of the offer, a pair of web-page like delay bars showing the maximum and minimum delays that could be received on that trial (possible delays ranged from 3 to 30 s), and the option to wait through the delay for a video from that gallery or move on. If the subject chose to wait, the actual delay was revealed, the delay counted down, and a 4 s video was shown; the subject then rated the video from 1 to 4 as an indicator of how much he or she liked it (4 = highest). Enjoyment ratings were made with key presses, and the task did not proceed until subjects input a rating (thus, there were no missing ratings). Importantly, in this version of the task, punishment was inescapable: subjects were locked in after making a stay choice (after which the delay began to count down). After each trial (regardless of the choice to stay or skip), the subject had to perform a short "travel" task, which entailed clicking the numbers 1 to 4 (presented in a darker shade of gray) as they randomly appeared around the screen (shown in a lighter gray). This travel task produced a cost to leaving an offer before getting to the next offer and was analogous to the travel time required as rats move between feeders during Restaurant Row.

Risky and non-risky trials were intermixed. Risk level was reflected by the variance of an offer and was either 0 (non-risky) or greater than 0 (risky, see **Figure 1**). *Risky trials* consisted of an offer with a range of delays (e.g., 5, 10, or 15 s), and each offer varied according to the set of possible delays and spread between

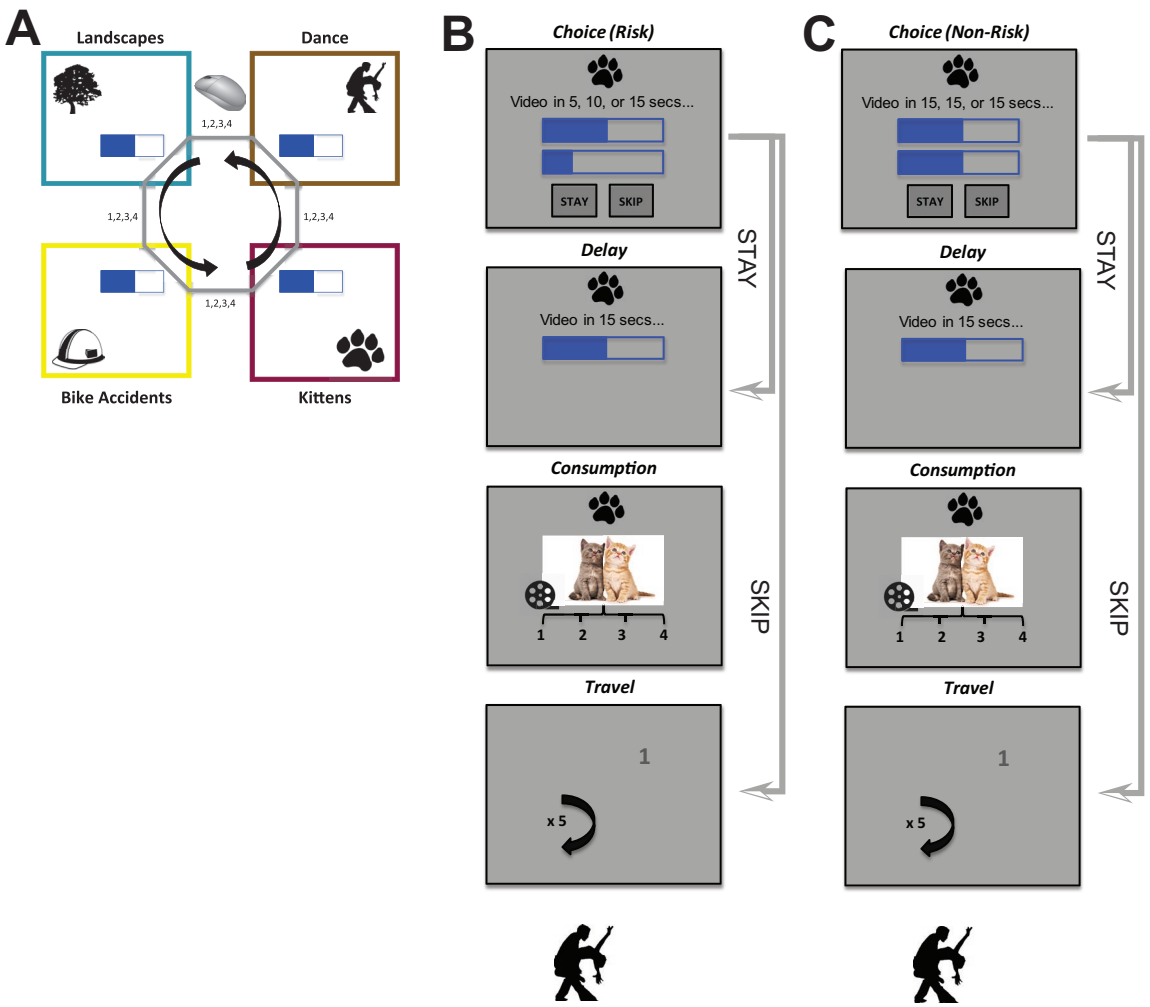

FIGURE 1 | Overview of task layout. **(A)** Schematic representation of the Web-Surf Task. Subjects cycled between four video galleries (kittens, dance, landscapes, bike accidents) in a constant order. **(B, C)** Flow diagram illustrates sequencing between risky **(B)** and non-risky **(C)** trials. For a risky trial, the true delay was only revealed if the subject stayed. If they instead skipped, they advanced directly to the travel task before encountering the next offer. The travel task entailed clicking the numbers 1–4 as they appeared around the screen (traveling required five random number selections).

the shortest and longest delay. (We did not allow for non-integer mid values in the risky trials, e.g., "Video in 5, 5.5, or 6 secs…" could not occur.) Critically, for risky trials, the true delay was only revealed if the subject elected to stay. Subjects were not informed of the probabilities associated with receipt of the different delays on risky trials. In comparison, *non-risky trials* presented offers with three identical delays, e.g., "Video in 7, 7, or 7 secs…"

We further classified risky trials as good or bad based on their outcome: receipt of the low delay on a risky trial was a "good" outcome, while receipt of the high delay was a "bad" outcome. (Following the framing effects from prospect theory, our definitions derive from an offer's outcome *type* but not *value*, meaning that a bad outcome could have a delay below one's threshold.) We were particularly interested in situations where the subject accepted a risky offer and received the bad outcome, i.e., the subject took a risk and "lost." We contrasted these trials with a control condition, in which the subject accepted a non-risky offer of equivalent value, and with situations characterized by relief, where the subject received the good outcome on a risk trial, i.e., the subject took a risk and "won". Importantly, the decision to *stay* or *skip* the offer on a non-risky trial, in which the true offer delay is known, can be assumed to be economically valid (i.e., correctly judged, not a mistake).

All subjects first underwent a training phase that entailed eight practice trials (two cycles through all four galleries, presented in the same order as the main task). After completion of the training phase, the subject had the opportunity to ask questions of the examiner before advancing to the main test phase.

Trait-Level Externalizing Measure

Subjects completed the 100-item version of the Externalizing Spectrum Inventory (ESI; 19), which has been employed in several studies of undergraduate students (20–23). This

inventory captures a range of traits and behaviors associated with the externalizing spectrum of psychopathology, including general disinhibition processes (e.g., theft, irresponsibility), substance use/abuse, and callous aggression.[1] Total ESI scores were acquired by summing across all items in the inventory (20) and then applying a log-transformation to improve normality.

To assess whether behavior on the risk variant of the Web-Surf Task was related specifically to substance abuse tendencies versus externalizing behavior more broadly, we computed the three ESI subfactors: *general disinhibition* (which captures impulsivity and irresponsibility), *substance abuse* (which captures recreational and problematic substance use), and *callous aggression* (which captures physical/relational aggression and lack of empathy) (21, 24). Lastly, we computed three subscales from the substance abuse subfactor that measure problems associated with substance use: *alcohol problems*, *marijuana problems*, and *drug problems*; here, our aim was to further explore whether task behaviors predicted substance-related consequences or harms. Examples of questions in these subscales are: "My drinking led to problems at home," "I've broken the law to get money for drugs," and "At times, marijuana has been more important to me than work, friends, or school." Because many subjects were non-responders on the problem scales, we encountered a zero-inflation problem. We thus isolated subjects who endorsed at least one item on the subscale, as individuals already experiencing negative consequences (evidence of behavioral disinhibition) are at greater risk for developing an alcohol or substance use disorder (25); 22 subjects (21%) were retained for the alcohol problem subscale analyses, versus 18 subjects (17%) for the marijuana problem subscale analyses, and 19 subjects (18%) for the drug problem subscale analyses.

Analyses

Specialized Procedures

Heaviside step function: a piecewise function denoted $H(x)$, where $H(x) = 0$ for $x < 0$, $H(x) = ½$ when $x = 0$, and $H(x) = 1$ for $x > 0$. This function captures the point at which a signal switches from 0 to 1. We used this function to identify the point at which subjects reliably began to skip offers (which we refer to as *delay thresholds*; see below for details). We used a Heaviside step function as an alternative to the logistic fit function described in Abram et al. (7), as the Heaviside approach is better equipped to handle extreme cases (i.e., when a subject stayed or skipped all offers in a gallery). In such instances, the Heaviside step function produces a reasonable value (e.g., the minimal or maximal delay offered), whereas the logistic function can produce values approaching infinity.

Subject-specific delay thresholds were computed separately for each trial using a leave-one-out approach; this yielded four thresholds, one per gallery. Thresholds were indicative of revealed preferences, reflecting the delay time at which a subject reliably began to skip offers for a particular gallery. To obtain the threshold for trial *i*, we fit a Heaviside step function to all trials in gallery *x* excluding trial *i*. This produced a vector of thresholds with length equal to the number of trials in gallery *x*. Importantly, thresholds were computed using the mid value of each offer for risky trials only. Non-risky trials were then assigned a threshold equal to the mean of the threshold vector for the respective gallery.

Expected value for non-risky trials (with a given delay): defined as the difference between the gallery-specific threshold and the offered delay. **Expected value for risky trials:** calculated as the average expected value of the three delays, assuming an equal likelihood for each delay (low, mid, high; see **Figure 1C**). For simplicity, we assumed a linear difference. Values ranged from −27 to 27, with a value of 0 meaning that the delay offer was equivalent to the revealed threshold.

Mixed-effects models: We used linear mixed-effects models to assess for group-level effects; all reported models include original p-values as well as false discovery rate (FDR)—adjusted p-values using Benjamini and Hochberg's FDR control algorithm (26). We fit models using the MCMCglmm package in R (27), which uses Markov chain Monte Carlo techniques (see below), and lmer and lsmeans, which provided nearly identical estimates, for plotting (28, 29). The tilde (~) in all regression models can be read as "is modeled as a function of" (30).

Markov chain Monte Carlo (MCMC) techniques: an approach that uses random sampling to approximate the posterior distribution of a variable of interest within a probabilistic space.

Validity Analyses

We evaluated the *external and face validity* of the risk variant of the Web-Surf Task using methods described in Abram et al. (7). For each subject, for each gallery, we averaged the vector of delay thresholds produced using the leave-one-out method described above; this yielded four thresholds per subject. We measured external validity by correlating delay thresholds with stated preferences (i.e., average gallery ratings and post-test gallery rankings) and obtained two validity correlations per subject.

Group-Level Choice, Rating, and Reaction Time Models

Our *primary choice/rating models* evaluated the impact of framing (i.e., good/bad outcome) on risk seeking (i.e., subsequent choices) and reward valuation (i.e., immediate video enjoyment ratings).

The *primary choice model* evaluated whether the type of outcome on the previous trial influenced subsequent risk seeking or aversion. This model included choice at the current trial as the dependent variable, actual value received and outcome type at the previous trial as fixed-effect independent variables, and subject as a random effect: [$Choice_t \sim actual\ value_{t-1} + outcome\ type_{t-1} + (1|subject)$]. This model included risky trials where the subject stayed and also received a risky offer at the next trial.

The *primary rating model* assessed the impact of framing effects on immediate reward valuation and included mean-centered rating as the dependent variable (i.e., centered to the average of the respective gallery), actual value and outcome type at the previous trial as fixed-effect independent variables, and subject as a random effect: [$Rating_t \sim actual\ value_t + outcome\ type_t + (1|subject)$]. This model included risky trials for which the subject stayed.

[1] Missing self-report data for 1 subject.

Lastly, we computed a *secondary group-level model* to examine direct relations between risk seeking/aversion and reward valuation, while considering the effects of framing and risk. In particular, we were interested in whether affective responses interacted with actual value or offer type when predicting subsequent decisions (building off the prior choice model detailed above). This model included choice at the current trial as the dependent variable; actual value, mean-centered rating, and outcome type of the previous trial, and two interaction terms as fixed-effect independent variables; and subject as a random effect: [$Choice_t \sim actual\ value_{t-1} + rating_{t-1} + outcome\ type_{t-1} + actual\ value_{t-1}{:}rating_{t-1} + actual\ value_{t-1}{:}outcome\ type_{t-1} + (1|subject)$]. In this model, outcome type coded good outcomes, bad outcomes, and non-risky offers; this metric then reflected the framing and risk manipulations.

To assess whether bad outcomes influenced the speed at which subjects made subsequent decisions, we tested a *supplemental reaction time model* that included logged reaction times as the dependent variable, actual value received and outcome type at the previous trial as fixed-effect independent variables, and subject as a random effect: [$logRT_t \sim actual\ value_{t-1} + outcome\ type_{t-1} + (1|subject)$].

Global Risk-Aversion Trend and Control Models

We also constructed a set of models to investigate global trends in risk seeking/aversion and reward valuation, i.e., address the possibility that any trial-by-trial effects were better explained by cross-session effects. The *global risk-aversion model* included choice as the dependent variable; number of videos viewed (i.e., consumed up to trial *t*), expected value, a risky/non-risky categorical indicator, and a video consumption × risky/non-risky interaction term as the fixed-effect independent variables; and subject as a random effect: [$Choice_t \sim number\ videos\ consumed_t + expected\ value_t + risky/non\text{-}risky_t + number\ consumed\ videos_t{:}risky/non\text{-}risky_t + (1|subject)$]. All trials were included in the choice model.

The global risk-aversion rating model was structurally equivalent to the first but included mean-centered ratings as the dependent variable: [$Rating_t \sim number\ videos\ consumed_t + expected\ value_t + risky/non\text{-}risky_t + number\ consumed\ videos_t{:}risky/non\text{-}risky_t + (1|subject)$]. Only stay trials were included in the rating model, as subjects only rated videos during stay trials.

Based on the results of the global trend models above, we constructed a *control model* to assess whether any trial-by-trial effects were better explained by other risk-aversion patterns. Within this model, we controlled for global risk-aversion trends (number of videos consumed), as well as categorical (high, low, mid) and continuous (0–30 s) risk dimensions. Our intention was to determine if cross-session declines in accepting risky deals and/or the general tendency to prefer offers with lower risk, i.e., a more narrow offer window, could better account for the sequential choice effects seen. The control model was structured as follows: [$Choice_t \sim actual\ value_{t-1} + outcome\ type_{t-1} + number\ videos\ consumed_t + risk_t + (1|subject)$].

Subject-Specific Choice and Rating Models

To examine individual differences, we fit subject-specific models based on the main choice and rating group-level models. For the *subject-specific choice models*, we included choice at the current trial as the dependent variable and actual value and outcome type of the prior trial as the independent variables: [$Choice_t \sim actual\ value_{t-1} + outcome\ type_{t-1}$]. We extracted the unstandardized outcome-type coefficient that reflected the subject's likelihood to stay following receipt of the good versus bad outcome, with higher values indicating an increased tendency to stay after receiving the bad outcome.

For the *subject-specific rating models*, we included mean-centered ratings as the dependent variable and actual value and outcome type of the prior trial as independent variables: [$Rating_t \sim actual\ value_{t-1} + outcome\ type_{t-1}$]. We again extracted the unstandardized outcome-type coefficient for good versus bad outcomes, with higher coefficients reflecting better ratings for the bad versus good outcome.

We correlated the subject-specific coefficients with trait-level externalizing, using robust partial correlation methods to reduce the influence of outliers and control for age, sex, and ethnicity. We included the age and sex demographic covariates based on prior research linking these variables with self-report and behavioral impulsivity measures (31), and more broadly with externalizing tendencies (32–34). We also included race/ethnicity, as substance use trajectories through young adulthood may differ by this factor (35). Our *primary partial correlations* related the two subject-specific coefficients with total ESI scores (distributions shown in **Figure 7**), and *follow-up partial correlations* assessed for associations with the substance abuse subfactor and subscales.

Delay-Discounting Comparison Models

Given the extensive literature using traditional binary choice tasks to evaluate externalizing and impulsivity (36–38), we tested whether metrics from a computerized monetary delay- and probability-discounting paradigm better explained individual differences in externalizing.[2] This entailed subjects making a series of binary choices between hypothetical monetary rewards of different reward magnitudes associated with different temporal delays (e.g., "Would you prefer $5 now or $10 in two weeks?") or probabilities (e.g., "Would you prefer $5 for sure or $10 with a 75% chance?"). Offers ranged from 50 cents to $10. The task lasted approximately 10 min.

A discounting rate (or k-value) was computed for the delay and probability trials separately using a hyperbolic function (39), yielding two k-values per subject. Higher k-values reflect more rapid discounting of delayed rewards and have been linked with impulsivity and addiction (40). For each subject, we checked for nonsystematic data using criteria outlined by Johnson and Bickel (41), and an R^2 value was calculated to determine how well the data points fit the hyperbolic function.[3] The median R^2 was 0.86 and 0.91 for the delay- and probability-discounting rates

[2] Missing delay- and probability-discounting data for three subjects.

[3] We excluded nine subjects with invalid k-values (discounting rates of 0), one subject with a k-value more than 4 standard deviations above the mean, and one subject with nonsystematic data.

(i.e., logged k-values), respectively. Logged parameter distributions of k from the delay-discounting experiment showed median = −5.26 days^{-1}, SD = 2.05, and from the probability experiment showed median = 0.28% chance^{-1}, SD = 0.84. These results are comparable to those reported in a large sample of healthy adults (31) and suggest that, for our sample, a $10 reward would be generally worth $9.52 after a 10-day delay or $8.75 when equated with a 90% chance.

RESULTS

Subjects Were Willing to Wait for Videos and Showed Individual Preferences

Subjects performed similarly on this task to what was seen in the original Web-Surf Task (7). As shown in **Figure 2D** and **E**, subjects showed reliable thresholds that were generally correlated with ratings (median r = 0.66) and with rankings (median r = 0.60). The decision curves of both risky and non-risky decisions depict the expected sigmoid shape, where subjects typically skipped low-valued offers (i.e., expected value < 0) and stayed for high-valued offers (i.e., expected value > 0).

Loss After Risk Influences Choice and Reward Valuation

To address questions of how subjects responded to loss after risk, we examined how risky outcomes impacted decision behaviors and video ratings. Here, a given delay was framed as good, bad, or in-between (mid) depending on its placement within an offer on a risky trial. Note that the true delay was known at the outset of the non-risky trials but was only revealed after the decision to stay on risky trials. Our *primary choice model* shows that, when controlling for actual value, subjects were less likely to accept a successive risky offer if they previously received a bad outcome than if they had previously received a good outcome (p-adj = 0.01; **Figure 3A**; **Table 1a**). Subjects were also slower to make decisions following receipt of the bad outcome (**Figure 4**; **Table 2**), suggestive of post-error slowing in response to risky losses.

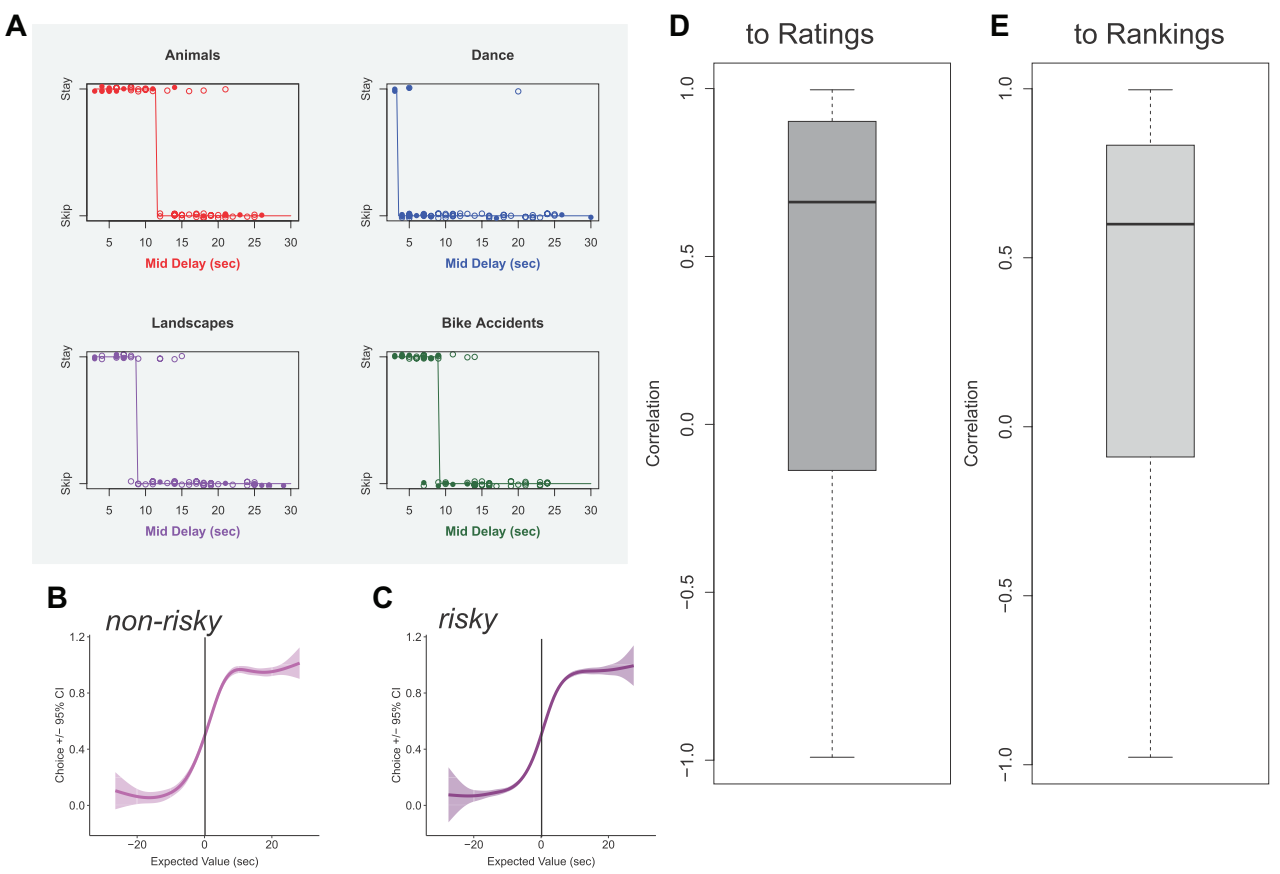

FIGURE 2 | Thresholds reveal valuations. **(A)** Example thresholds identified for a typical subject. Open circles show risky trials; closed circles show non-risky trials. Threshold marked with solid line. **(B)** Average psychophysics curve for non-risky decisions, aligned to threshold for each video gallery for each subject. **(C)** Average psychophysics curve for risky decisions, aligned to threshold for each video gallery for each subject. Panels **(B)** and **(C)** are aligned to the same threshold, calculated for each gallery for each subject. **(D)** Distribution of observed correlations between revealed thresholds and video ratings. **(E)** Distribution of observed correlations between revealed thresholds and post-task stated rankings.

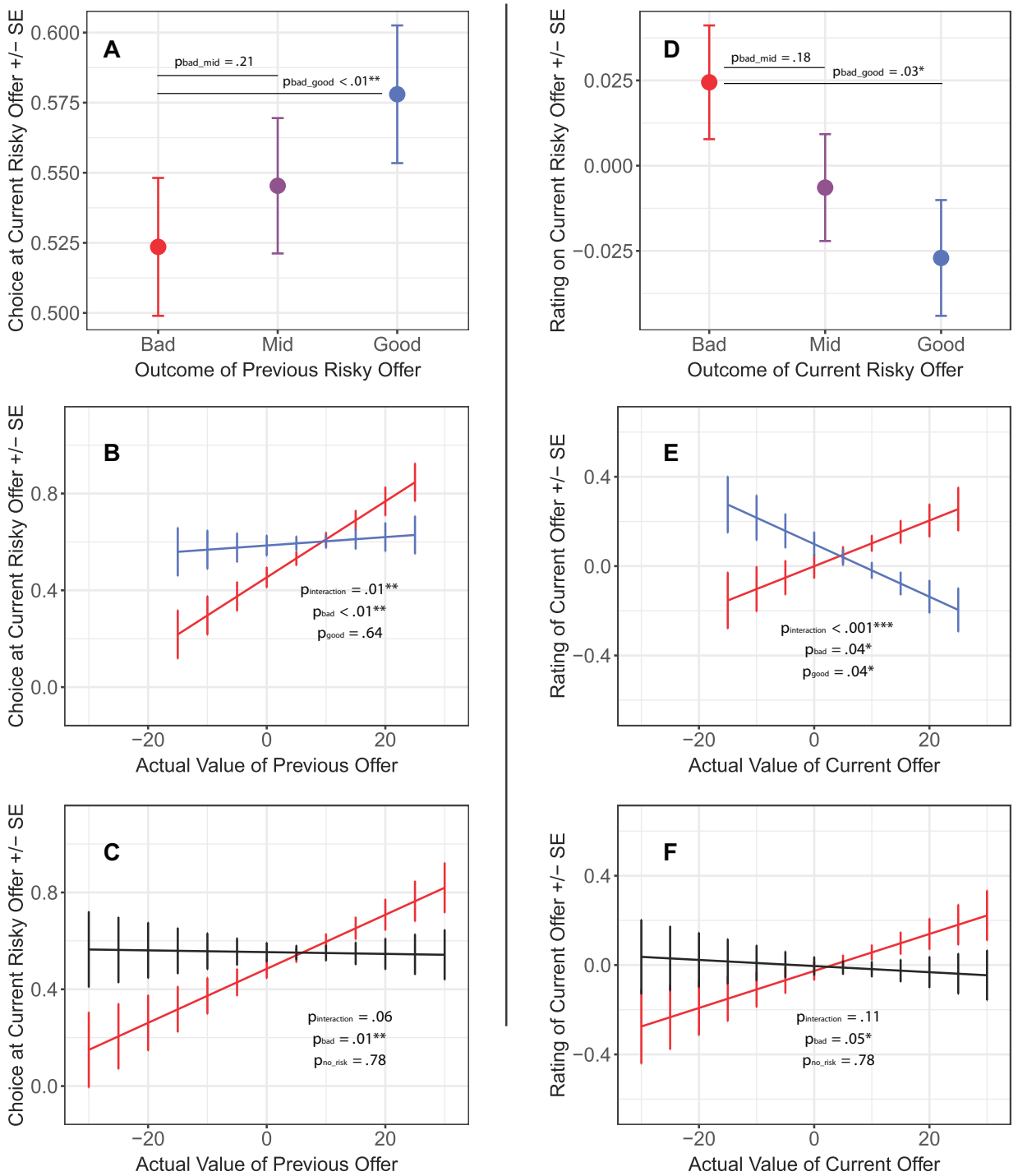

FIGURE 3 | Group- and individual-level effects of risky losses on deliberation and reward likability. **(A)** Proportion of stay choices on current risky offers following receipt of the good, bad, or mid outcome on the previous risk trial. Red represents a bad outcome after accepting a risky offer; blue indicates a relief-inducing situation (good outcome after accepting a risky offer), with higher values indicating an increased likelihood of staying. Subjects were more risk-averse after risky losses. **(B, C)** Interactions between previous outcome type and actual value when predicting choices on subsequent risky offers. Black represents the control condition (equivalently valued non-risk offers). Subjects became risk-averse following risky losses of low value, versus risk seeking after risky losses of high value (whereas no associations between value and choice were detected for the relief and control conditions). **(D)** Mean-centered likability ratings following the receipt of the good, bad, and mid outcomes on the current risk trial. Subjects rated videos that followed bad outcomes more highly than those that followed good outcomes. **(E, F)** Interactions between previous outcome type and actual value when predicting immediate likability ratings (mean-centered). After a risky loss, subjects tended to rate videos that followed a low-value offer worse than those that followed a high-value offer; the inverse pattern was found for videos linked to good outcomes. A similar pattern emerged when comparing bad outcomes and control trials. Error bars indicate within-subject standard errors. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

TABLE 1 | Choice/rating by framing models.

Predictor variable	B	CI	*P*-value	*P*-adj
(a) Choice by framing (main)				
Actual value	−.006	[−.008, −.004]	**.001**	**.002**
Outcome type (bad vs. good)	−.055	[−.098, −.020]	**.008**	**.01**
Outcome type (mid vs. good)	−.033	[−066, .005]	.10	.10
(b) Choice bad vs. good framing (follow-up)				
Actual value	.013	[.004, .023]	**.004**	**.008**
Outcome type (bad vs. good)	.134	[.010, .236]	**.02**	**.02**
Actual value × outcome type	−.014	[−026, −.002]	**.01**	**.02**
(c) Choice by bad vs. non-risk framing (follow-up)				
Actual value	.011	[.002, .019]	**.02**	**.03**
Outcome type (bad vs. non-risk)	.056	[−.048, .144]	.24	.24
Actual value × outcome type	−.010	[−.020, .000]	.06	.08
(d) Rating by framing (main)				
Actual value	.002	[.000, .004]	**.04**	**.05**
Outcome type (bad vs. good)	.051	[.005, .100]	**.03**	**.05**
Outcome type (mid vs. good)	.020	[−.022, .065]	.38	.38
(e) Rating by bad vs. good framing (follow-up)				
Actual value	.010	[.000, .020]	**.04**	.08
Outcome type (bad vs. good)	.100	[-.046, .244]	.17	.23
Actual value × outcome type	−.022	[−.038, −.009]	**<.001**	**.004**
(f) Rating by bad vs. non-risk framing (follow-up)				
Actual value	.008	[.000, .016]	**.04**	.37
Outcome type (bad vs. non-risk)	.021	[−.087, .128]	.68	1.00
Actual value × outcome type	−.010	[−.021, .004]	.11	.48

B, unstandardized coefficient; CI, confidence interval; P-adj, FDR-adjusted p-values.
Bolded text indicates p-values that are below 0.05.

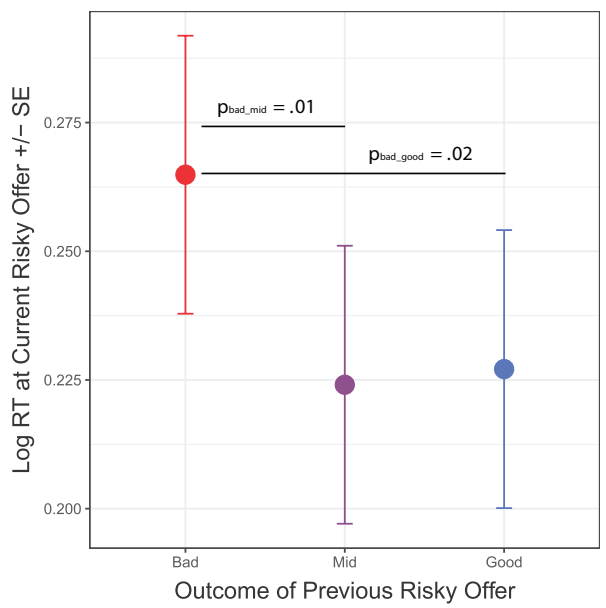

FIGURE 4 | Loss after risk influences reaction times. Receipt of the bad (long-delay) outcome (red) resulted in slower reaction times (log RT) on subsequent trials, as compared to other risky conditions. Error bars represent within-subject standard errors.

Follow-up models clarified these sequential choice effects using subsets of trials matched by the actual value of the previous trial. The first subset included trials for which subjects stayed and received the good or bad outcome on a risky trial and encountered risk on the following trial. The second subset included trials for which subjects stayed and received the bad outcome or stayed on a non-risky trial and encountered risk on the subsequent trial. Trials were matched on a subject-by-subject basis and then combined for the group analysis. Because each subject's contributing trials only included a portion of the possible values, we included actual value as a nested variable in the following model: [$Choice_t \sim actual\ value_{t-1} + outcome\ type_{t-1} + actual\ value_{t-1}$:$outcome\ type_{t-1} + (actual\ value_{t-1}|subject)$]. We included the interaction term to test whether framing effects differentially shaped value-by-choice sequencing effects.

TABLE 2 | Logged choice reaction time by framing model.

Predictor variable	B	CI	*P*-value	*P*-adj
Actual value	.001	[−.001, .003]	.33	.44
Outcome type (bad vs. good)	.041	[.008, .071]	**.02**	**.04**
Outcome type (mid vs. good)	.001	[−.028, .032]	.95	.95

B, unstandardized coefficient; CI, confidence interval; P-adj, FDR-adjusted p-values.
Bolded text indicates p-values that are below 0.05.

For the subset that matched bad- with good-outcome trials, we observed a significant outcome-by-value interaction (p-adj = 0.02; **Table 1b**); further analyses revealed that the negative framing of the previous outcome impacted relations between value of the previous trial and choice on the current trial (β = 0.014, CI = [0.004, 0.023], p = 0.004; **Figure 3B**). That is, subjects became risk-averse after receiving a bad offer of lower value and risk seeking after a bad offer of higher value. In contrast, we did not detect an association between the previous trial's value and successive choice after receipt of a good outcome (β = 0.002, CI = [−0.007, 0.011], p = 0.64). We identified a similar (but trend-level) effect for the subset that matched bad outcome with equivalent non-risk offers (outcome-by-value

interaction, p-adj = 0.08; **Table 1c**); follow-up analyses indicated a positive association between value and choice following receipt of a bad outcome (β = 0.012, CI = [0.004, 0.020], p = 0.012; **Figure 3C**), versus no association for non-risky decisions (β = 0.001, CI = [−0.007, 0.009], p = 0.78). Together, these results suggest that receipt of negatively framed outcomes (or losses), in particular, changed subsequent reward pursuit and decision-making.

But to what extent do losses after risk impact the liking of a reward? Experiments have suggested that subjects take expended costs into account when making valuations (42, 43). To address this question, we tested the impact of framing on ratings. We observed an opposite pattern in the *primary rating model* as compared to the *primary choice model*: where subjects rated videos that followed a *bad* outcome more highly than those that followed a good outcome (p-adj = 0.05; **Figure 3D–F**; **Table 1d**). We clarified these rating effects using *follow-up* matched-trial *models* that compared ratings that followed good versus bad outcomes and ratings that followed bad outcomes versus non-risky offers. We then fit the following model: [$Rating_t \sim actual\ value_{t-1} + outcome\ type_{t-1} + actual\ value_{t-1}$:$outcome\ type_{t-1} + (actual\ value_{t-1}|subject)$].

These follow-up analyses revealed an interaction between actual value and rating for bad versus good outcomes (p-adj = 0.004; **Figure 3E**; **Table 1e**), with bad outcomes yielding a positive association between value and rating (β = 0.010, CI = [0.000, 0.020], p = 0.04) and good outcomes a negative association (β = −0.012, CI = [−0.022, −0.001], p = 0.04). Although not significant (interaction term in **Table 1f**), we saw a similar pattern for the interaction between risky and non-risky trials, with risky trials having a more substantial impact on the relationship between bad outcomes and ratings than non-risky trials (bad outcomes: β = 0.008, CI = [0.000, 0.017], p = 0.05; non-risky: β = −0.001, CI = [−0.010, 0.007], p = 0.78; **Figure 3F**).

Global Trends Impacted Choices But Not Ratings

We found that subjects were less likely to accept a risky offer versus a non-risky offer as they consumed more videos (significant number of consumed videos × risk interaction, p-adj = 0.004; **Figure 5A**; **Table 3a**); that is, subjects became more risk-averse across the session. This interaction remained significant if the consumption variable was replaced with the number of good outcomes or bad outcomes, suggesting that this effect was not solely driven by accumulated negative experiences (but rather, risky rewards became progressively less effective in eliciting reward seeking with ongoing exposure). In comparison, we did not observe a consumption history x risk interaction (p-adj = 0.67) for the rating model (**Figure 5B**; **Table 3b**), suggesting that ratings were less impacted by these factors.

Sequential Choice Effects Remained When Accounting for Global Trends

Based on the evidence that subjects grew risk-averse across the session, we built a *control model* to test whether the global risk-aversion trends (noted above) confounded trial-by-trial framing effects. The control model indicated that trial-by-trial choice effects were not better explained by consumption history (i.e., number of videos consumed) or risk level (i.e., spread of delays on a risky offer; **Table 4**).

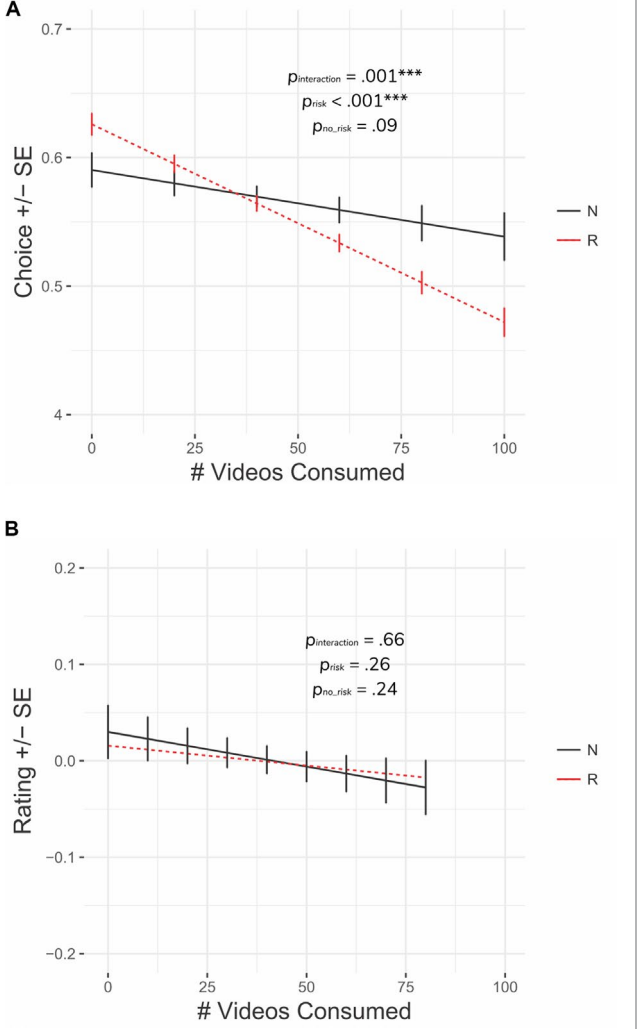

FIGURE 5 | Global risk trends. **(A)** Subjects became more risk-averse as the task progressed. **(B)** Subjects' likability ratings decreased over time but did not differ between risky and non-risky offers. Error bars represent within-subject standard errors. ***p < 0.001.

Is the Effect Simply Due to Seeking Gains and Avoiding Losses?

The analyses above showed that the effect of risky trials on subsequent choices depended on the unexpected costs of the trial: a bad outcome meant spending more time than expected and was therefore a loss (worse than expected), while a good outcome meant spending less time than expected and was therefore a gain (better than expected). To test whether this was a general property of unexpected gains and losses, we turned to variability in the ratings within each gallery. While all the videos within a gallery were similar (e.g., cute videos of kittens), each individual video was different. Thus, subjects had an expectation of video quality based on their gallery preferences, but observed a specific video on completion of the delay that might have been better or worse than the average. This produced variability in the post-video ratings: for example, seeing a video rated worse

TABLE 3 | Choice/rating by consumption models.

Predictor variable	B	CI	*P*-value	*P*-adj
(a) Choice				
# videos consumed	−.001	[−.001, .000]	**.07**	.17
Expected value	.032	[.031, .033]	**.001**	**.004**
Risk/non-risk	.036	[.007, .061]	**.006**	**.02**
# videos consumed x risk/non-risk	−001	[−.002, .000]	**.001**	**.004**
(b) Rating				
# videos consumed	−.001	[−.002, .001]	.25	.62
Expected value	.002	[.000, .004]	**.02**	.11
Risk/non-risk	−014	[−.086, .048]	.67	.67
# videos consumed x risk/non-risk	.000	[−.001, .002]	.66	.67

B, unstandardized coefficient; CI, confidence interval; P-adj, FDR-adjusted p-values. Bolded text indicates p-values that are below 0.05.

TABLE 4 | Choice by consumption and risk confound model.

Predictor variable	B	CI	*P*-value	*P*-adj
Actual value	−.007	[−.008, −.005]	**<.001**	**.002**
Outcome type (bad vs. good)	−.055	[−.092, −.017]	**.006**	**.01**
Outcome type (mid vs. good)	−.036	[−.068, −.001]	**.04**	**.05**
# videos consumed	−.001	[−.002, −.001]	**<.001**	**.002**
Risk	−.002	[−005, .000]	.07	.07

B, unstandardized coefficient; CI, confidence interval; P-adj, FDR-adjusted p-values. Bolded text indicates p-values that are below 0.05.

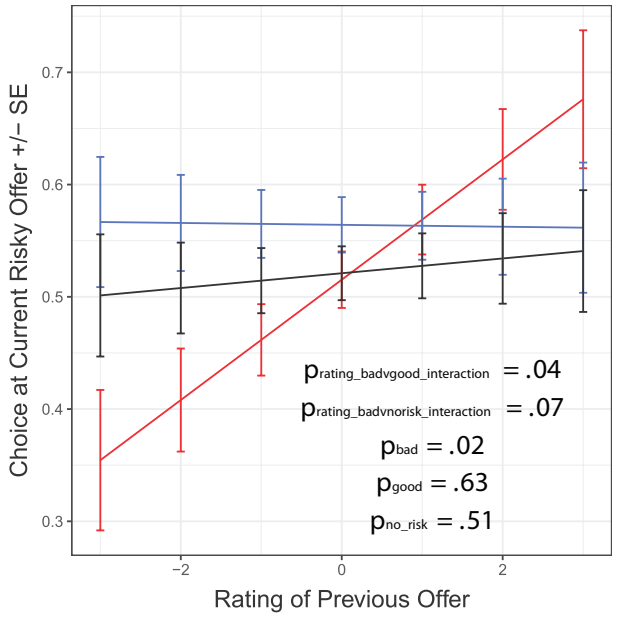

FIGURE 6 | Interaction between previous outcome type and rating when predicting choices on subsequent risky offers. Following receipt of the bad outcome, subjects were more risk-averse after lower-rated videos and more risk seeking after higher-rated videos; no association was detected for the other conditions; ratings are mean-centered. Error bars represent within-subject standard errors.

than average was effectively a loss, while a video rated better than average was effectively a gain. In general, we can consider video ratings themselves as a measure of gain/loss.

We used a *secondary model* to test whether video ratings directly guided future choices under the different conditions of interest (**Figure 6**; **Table 5**). We found trend-level interactions between outcome and rating (p-adj = 0.06, p-adj = 0.09): following risky losses, relatively lower ratings predicted risk aversion, whereas relatively higher ratings yielded risk-seeking behaviors (β = 0.040, CI = [0.005, 0.071], p = 0.02). We did not detect associations between video ratings and subsequent choice following good outcomes (β = 0.009, CI = [-0.028, 0.039], p = 0.63) or non-risky trials (β = 0.011, CI = [-0.017, 0.043], p = 0.51). Thus, ratings only produced changes in risk seeking if in the context of bad outcomes on risky trials (akin to a win–stay/lose–shift strategy) (44). This implies that there was something different about risky losses that went beyond the mere experience of a less enjoyable reward (since a good outcome of the risky trial leading to a poorly rated video was still a loss but did not impact subsequent reward pursuit). We note that these effects remained when accounting for the number of prior videos consumed.

Failure to Learn from Loss After Risk Correlated With Externalizing Traits

To explore the importance of personality traits to risky decision-making, we investigated whether individuals scoring high on the Externalizing Spectrum Inventory (ESI, 19, which measures a range of impulsive, substance use, and aggressive behaviors) were less influenced by risk when making choices. **Figure 7A** and **B** shows the distribution of observed ESI values. Many subjects who typically score high on externalizing inventories, such as chronic smokers and individuals at risk for addiction, have been seen to be less influenced by risk when making choices (45, 46). We examined whether such individuals exhibited similar risk-induced effects on reward valuation (i.e., video ratings).

Informed by the group-level model, we computed a parameter that compared a subject's likelihood of accepting a risky offer after receipt of a good versus bad outcome on the prior trial. Individuals scoring high on the ESI showed an inverse pattern to that observed

TABLE 5 | Choice by rating integrated model.

Predictor variable	B	CI	*P*-value	*P*-adj
Actual value	−.006	[−.008, −.004]	**<.001**	**.004**
Rating	.040	[.005, .073]	**.03**	.06
Outcome type (good vs. bad)	.049	[.015, .090]	**.01**	**.03**
Outcome type (non-risk vs. bad)	.006	[−.028, .039]	.74	.74
Actual value × rating	.002	[.000, .004]	.12	**.14**
Rating × outcome type (good vs. bad)	−.055	[−.110, −.004]	.04	.06
Rating × outcome type (non-risk vs. bad)	−.047	[−.102, .001]	.07	.09

B, unstandardized coefficient; CI, confidence interval; P-adj, FDR-adjusted p-values. Bolded text indicates p-values that are below 0.05.

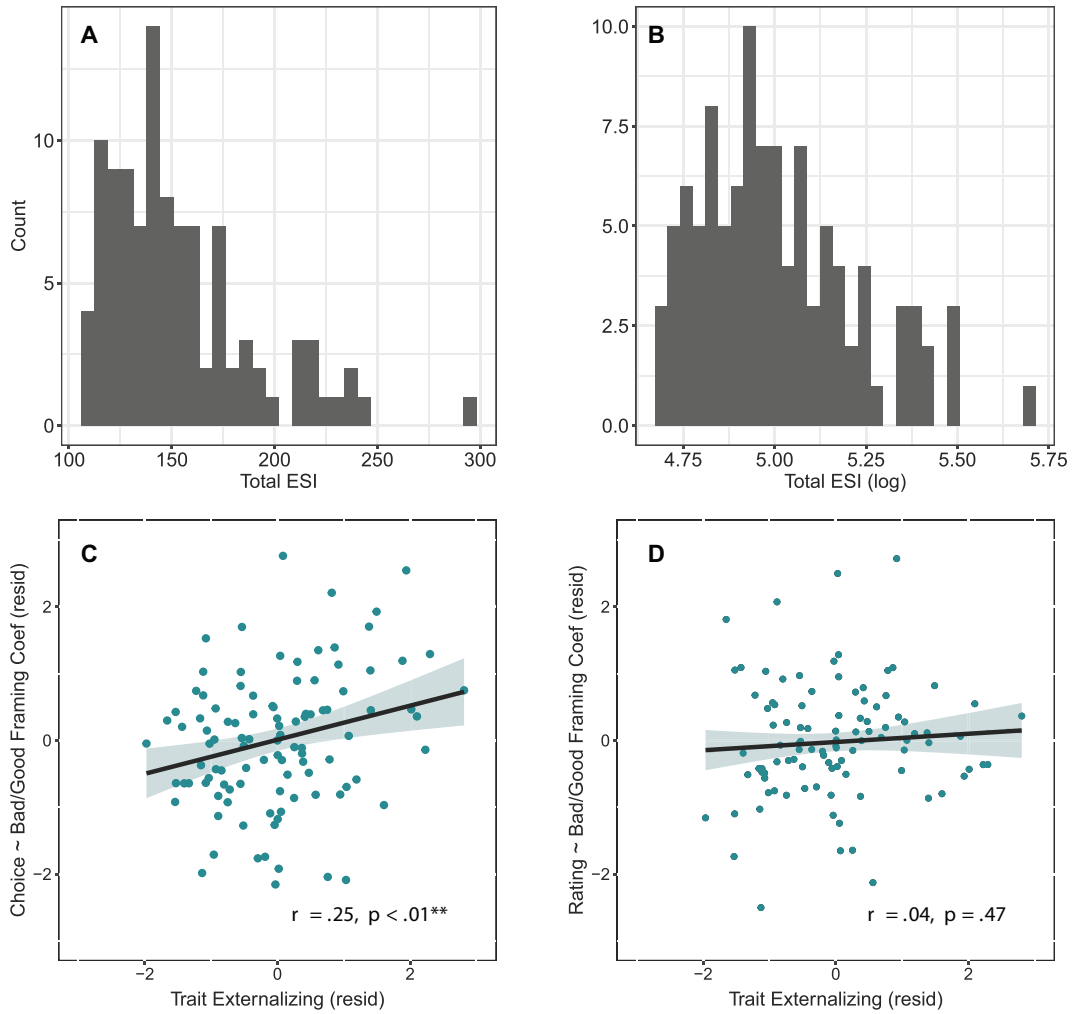

FIGURE 7 | Externalizing Spectrum Inventory distributions and risky loss associations. Distribution of scores from the Externalizing Spectrum Inventory (ESI), shown as raw values **(A)** and logged values **(B)**. **(C)** Relationship between trait-level externalizing and the likelihood of accepting a risk offer after previously receiving the bad outcome. Impulsive subjects showed less risk aversion in response to bad outcomes. **(D)** Relations between trait-level externalizing and immediate likability ratings (mean-centered). Impulsive subjects did not differ in their ratings following bad outcomes. $^{**}p < 0.01$.

at the group level (partial $r = 0.25$, $p = 0.008$; **Figure 7C**); these individuals were more likely to accept a risky offer after having just received a bad outcome, signifying a potential deficiency in learning from risky losses. In contrast, the association between outcome type and ratings was unrelated to ESI scores (partial $r = 0.04$, $p = 0.47$; **Figure 7D**).[4] Together, these results indicate that these externalizing traits affected individual differences in reward pursuit but not reward valuation.

Based on the group-level results above, we used *follow-up partial correlations* to probe whether reward pursuit was related to the broader *substance abuse* subfactor (versus *general disinhibition* and *callous aggression)*, as well as its underlying problem subscales (i.e., *alcohol problems*, *marijuana problems*, *drug problems*. We computed one-tailed robust correlations (i.e., assuming more risk seeking after bad outcomes) and report original and FDR-adjusted p-values that account for the six follow-up correlations.

Our results revealed that two of the three ESI subcomponents were correlated with reward pursuit when accounting for multiple comparisons (general disinhibition partial $r = 0.16$, $p = 0.05$, p-adj = 0.08; substance abuse partial $r = 0.24$, $p = 0.005$, p-adj = 0.01; callous aggression partial $r = 0.20$, $p = 0.02$, p-adj = 0.05; **Figure 8A–C**); however, only substance abuse remained a significant predictor when accounting for the other two subcomponents (partial $r = 0.18$, $p = 0.03$). Further, for individuals endorsing alcohol problems, we found a positive association between reward pursuit after risk and the alcohol problem subscale ($r = 0.59$, $p = 0.004$, p-adj = 0.01; **Figure 8D**), versus no association with the marijuana ($r = -.22$, $p = 0.14$, p-adj = 0.17; **Figure 8E**) and drug problem ($r = 0.19$, $p = 0.75$, p-adj = 0.75; **Figure 8F**) subscales.

[4] We excluded one subject with a coefficient less than 4 standard deviations below the mean.

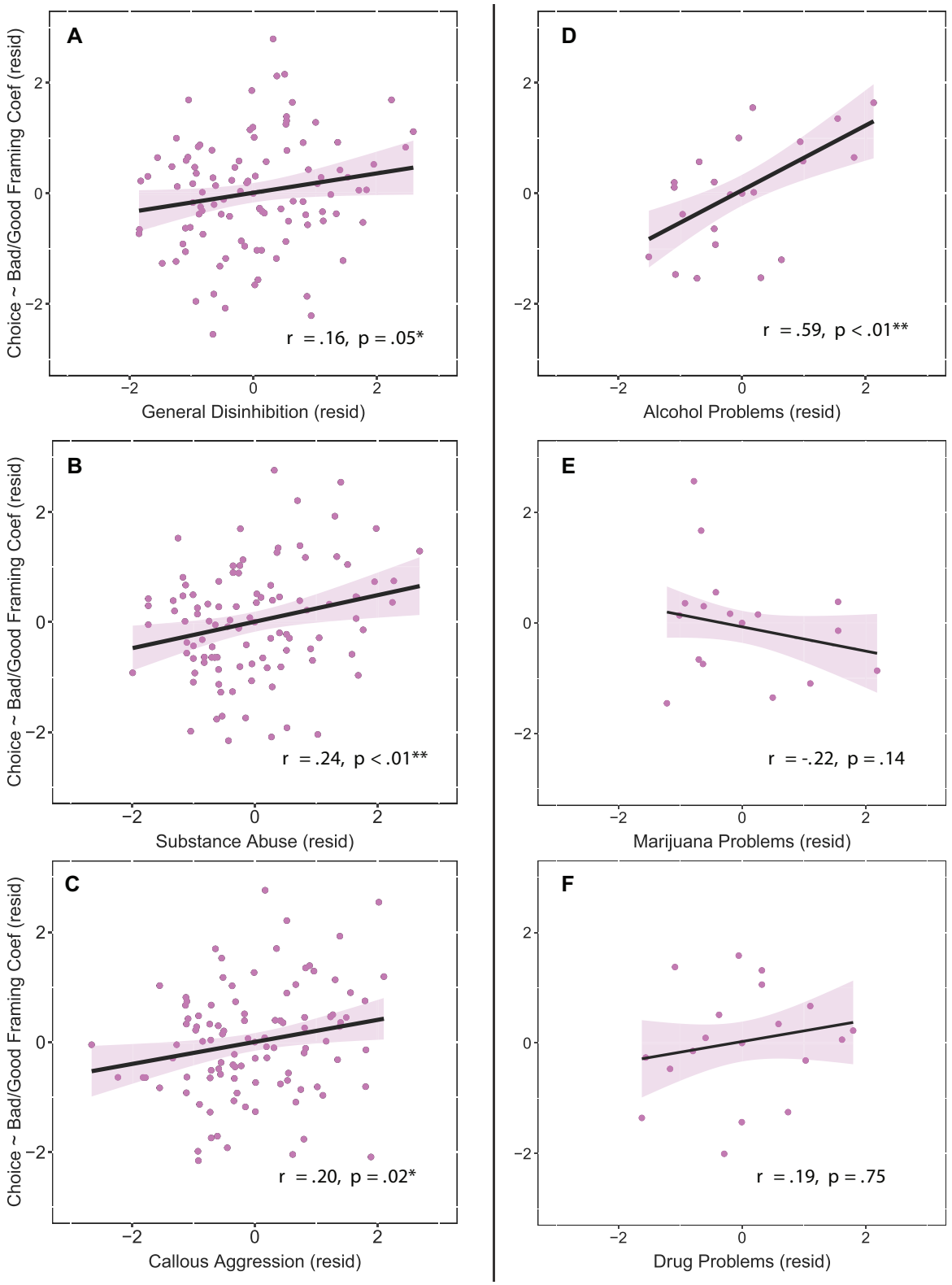

FIGURE 8 | Risky losses influence each ESI subfactor and alcohol problems. The left trio of panels **(A, B, C)** shows the correlation between each ESI subfactor and the likelihood of accepting a risk offer after previously receiving a bad outcome. More externalizing subjects showed less risk aversion in response to bad outcomes for each subfactor. The right trio of panels **(D, E, F)** shows correlations with the three problem subscales of the substance abuse subfactor; more problematic alcohol use was associated with less risk aversion after a bad outcome. $^{*}p < 0.05$; $^{**}p < 0.01$.

Discounting Rates Did Not Explain the Effects of Externalizing Traits on Reward Pursuit

We computed a series of follow-up robust partial correlations to compare Web-Surf Task–derived metrics with those from a traditional discounting task. The first two correlations predicted total ESI scores from the log-transformed delay and probability k-values, while controlling for age, sex, and ethnicity. Here we found that discounting rates did not significantly predict externalizing (delay k-value: partial $r = 0.08$, $p = 0.46$; probability k-value: partial $r = 0.02$, $p = 0.88$). We then checked whether k-values were related specifically to the substance abuse subfactor, given null associations with the total score and our interest in addiction liability. Similarly, k-values were unrelated to substance abuse (delay k-value: partial $r = 0.05$, $p = 0.68$; probability k-value: partial $r = -.07$, $p = 0.57$). Lastly, we tested whether the subject-level coefficient from the Web-Surf Task that indicated sequencing responses following receipt of a good versus bad outcome still predicted ESI scores, after controlling for the two k-values and additional covariates. Importantly, the Web-Surf Task parameter capturing reward pursuit following risk still predicted ESI scores, even when accounting for the two k-values (partial $r = 0.25$, $p = 0.03$).

DISCUSSION

We assessed the effects of wins and losses on reward valuation and reward pursuit in a new risk variant of the Web-Surf Task. We found that receipt of the bad outcome on a risky gamble influenced both reward valuation and reward pursuit, but in opposite directions; that is, bad outcomes after risk led to reduced reward pursuit and higher reward valuation. Follow-up analyses showed that offer value impacted these effects, whereby low-value risky losses led to risk aversion and lower-than-normal reward valuations, while high-value losses led to risk seeking and higher-than-normal reward valuations. Subjects were also slower to make decisions after bad outcomes, which points to a post-error slowing effect. There was no impact on willingness to take risks following wins after risk situations (better than expected) or after non-risky control trials. Thus, there was something unique about situations in which subjects lost after deciding to take a risk that increased plasticity in risk-seeking behaviors. Importantly, we also found that trait-level externalizing, particularly substance use tendencies, tracked whether these situations influenced future decisions. Externalizing behaviors were not better explained by performance on a traditional discounting task, highlighting the value of foraging behaviors in capturing substance use disorder vulnerabilities.

In line with our hypotheses and prospect theory (13), the *framing* of an offer relative to the mid-point (versus its absolute value) impacted subsequent reward pursuit and reward valuation. That is, whether an outcome was good or bad relative to the mid-point influenced a subject's performance regardless of whether he or she took the correct action, as determined by comparing risky and non-risky offers of equivalent value, where non-risky outcomes did not influence performance. Framing effects were also not better explained by global trends in risk aversion. Global trend analyses showed that subjects accepted fewer risky deals as the session progressed, which could suggest that subjects become more sensitive to punishment over time and/or that they experienced reward satiety from ongoing reward exposure. Regardless, the tendency to turn down risky deals following bad outcomes remained when accounting for global risk-aversion trends, highlighting the impact of framing effects on risky choices above and beyond other influences.

Choosing to accept a risky deal and finding oneself in the bad outcome, i.e., with a longer delay than expected, may also be seen as a regret-inducing situation. Constructs of regret suggest that regret occurs at the intersection of agency and mistake (47, 48), where a subject recognizes that an alternate choice (counterfactual) would have led to a better outcome (49). Counterfactually, the subject could have "just skipped it" if only they had known they were going to get the bad deal. A similar phenomenon has been found in mice running the Restaurant Row task, in which mice show regret-related behaviors after accepting a deal and then quitting out of it, but not after spending the same amount of time deliberating over the offer before skipping it (50).

The finding for slowed reaction times after risky losses is consistent with observations in humans of post-error slowing (51–53) but contrasts with findings that rats and mice respond more quickly to the next trial after making a mistake of their own agency (8, 50). There remain several differences between these tasks: 1) the human task presented here included chance and risk, while the rodent tasks were deterministic; 2) humans had brief pre-training, while rodents had months of training; and 3) humans were working for luxury items (videos), while rodents were working for their basic necessities (food intake for the day). And because rodents had a fixed amount of time to consume their meal, there was potentially more impetus to move quickly and consume more food before time ran out. Of course, it is also possible that there could be a species difference in how humans and rodents respond to these tasks, e.g., cross-species divergences in self-evaluation processes following loss could contribute to the observed reaction time differences, although given the similarities recently seen in their response to deliberation and sunk costs (9), this may be less likely. Whether this post-error response inconsistency arises from cross-species differences in response to regret or unique task attributes remains unknown and will have to be left for future study. One possibility is that "regret" is more complicated and that there are differences between realizing that you made a mistake in a situation in which you had all the necessary information to make a better decision versus taking a risk only to find that the answer is not what you hoped for.

Our analyses also revealed that risky losses had an opposite impact on reward valuation, whereby subjects liked videos that followed a bad (long-delay) outcome more than those following a good (short-delay) outcome on risky trials, though we note that the effects of reward valuation were less robust than those for reward pursuit and should be interpreted with caution. These reward valuation results are consistent with economic observations that humans rate outcomes higher when they have spent more on them (54). This suggests that subjects have

a backwards-looking view when rating videos that is consistent with explanations of sunk-cost effects seen in human and non-human subjects (9, 55, 56) and with economic explanations for the effect of anticipation on subsequent reward valuation (57). A desire to reduce cognitive dissonance, an aversive mental state that occurs when there is a discrepancy between behavior and attitude (58), could also explain higher ratings following bad outcomes. That is, subjects may have been trying to alter their attitude as a means to reduce psychological discomfort (59).

A key result from this study is that individuals exhibiting greater externalizing disorder vulnerability were more likely to accept a risky offer after receipt of a bad outcome. Critically, our findings were strongest for the substance abuse subfactor, and largely, the alcohol problem subscale, which could reflect the nature of an undergraduate sample. This risky decision–externalizing association is consistent with notions that addiction involves continued reward pursuit despite negative outcomes (60), and could reflect an inability to learn from mistakes (61). These results also speak to dimensional models of psychopathology, given that behavior is correlated with externalizing problems even in the absence of clinical diagnoses.

Compared to reward pursuit, we saw no relation between externalizing and reward evaluation following regret, suggesting that externalizing may have different associations with different facets of the decision process. One hypothesis is that high externalizers do not show differentiation in reward valuation because of a tendency to respond in a socially conforming manner. For instance, prior research suggests that striatal dopamine availability is a common link between the tendency to "fake good," i.e., respond in a socially desirable way (62, 63), and impulsivity (64). It is then possible that high-externalizing subjects may conform to the socially expected pattern when evaluating rewards. Similarly, externalizing problem behavior is highly related to cognitive distortions, which is an umbrella term that includes the rationalization (or neutralization) of deviant behavior (65). Here, high-externalizing subjects may rationalize their bad decisions with positive ratings. Future research could directly test these theories by including scales that measure socially desirable responding (e.g., the Marlowe–Crowne Social Desirability Scale; 66) or pre-conscious rationalization (65).

Our data could be explained in part by differences in temporal attention, whereby reward valuation is done by looking backwards, while changes in reward pursuit are done by looking forwards. This leads to a key question of whether these two processes are linked. We found them linked in typical subjects, but our individual-differences analyses revealed that these effects occur through separable processes: more externalizing individuals showed comparable effects of risk on reward valuation but did not subsequently modulate their reward pursuit following regret. In fact, **Figure 4** suggests that people scoring high on the ESI may even show the opposite effect, becoming risk seeking after regret-inducing instances. These results are consistent with application of the temporal attention hypothesis to delay discounting, in which a preference for immediate rewards among individuals with addiction is due to a narrowing of temporal attention (67); perhaps high-externalizing subjects have a narrowed attention window that leaves valuation of recent consummatory experiences intact but reduces their capacity to evaluate distal outcomes.

As noted above, externalizing tendencies were not associated with performance on a traditional discounting task. This result diverges from established links between substance abuse and discounting (68, 69). One possible explanation is that steeper discounting is more strongly tied to *current* substance abuse versus a *liability* towards substance abuse. For instance, while steeper discounting rates are observed in chronic nicotine users, discounting rates have been shown to normalize among ex-smokers (70, 71). Gowin et al. (69) observed similar results, where individuals with current alcohol use disorder (AUD) had steeper discounting rates than healthy controls, but individuals with past AUD showed no difference from controls. The fact that our sample includes both individuals with a substance use/abuse history and individuals who are prone to substance use may have reduced our likelihood of capturing such a link. This explanation is in line with Isen et al. (72), who found that hypothetical delay-discounting behaviors did not predict latent trait-externalizing tendencies as similarly measured with the ESI. This again suggests that there may be weaker relationships between discounting behaviors and externalizing liability.

Limitations

A recognized limitation of the current study is the use of an undergraduate sample that was not specifically recruited based on substance use history. However, the fact that we still detected foraging–substance use relations suggests that the task is sensitive to behaviors that are likely present even at the lower end of the externalizing spectrum; this study also provides a set of foundational findings that can be tested in a confirmatory manner to clarify whether reward pursuit during foraging similarly tracks recreational and problematic substance use in the broader community and among individuals with varying levels of usage. Another limitation is the lack of consumption or craving measurements, as these factors could moderate the observed effects. We also acknowledge that the consequences of a risky loss on the Web-Surf Task is small relative to real-life consequences like filing for bankruptcy, losing transportation options following a DUI, or being imprisoned; but if we find substance use associations when the stakes are low, we might expect greater effects as substance use becomes more chronic and/or problematic.

Conclusions

Our results suggest a dissociation among individuals with greater substance use disorder vulnerability: costly experiences serve to enhance reward value but did not impact subsequent reward pursuit following regret. Taken together, a blunted sense of regret may result in an overvaluation of risky losses that in turn drives the continued pursuit of risky endeavors. Future work will assess the impact of risky losses while foraging in clinical samples.

ETHICS STATEMENT

The University of Minnesota Institutional Review Board approved the study procedures, and all subjects provided written informed consent.

AUTHOR CONTRIBUTIONS

SA, AR, and AM designed the experiment. AR and AM supervised the project. SA carried out the experiments and analyzed the data. SA, AR, and AM wrote the manuscript.

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An Examination of Motivation to Change and Neural Alcohol Cue Reactivity Following a Brief Intervention

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Background: Brief interventions represent a promising psychological intervention targeting individuals with heavy alcohol use. Motivation to change represents an individual's openness to engage in a behavior change strategy and is thought to be a crucial component of brief interventions. Neuroimaging techniques provide a translational tool to investigate the neurobiological mechanisms underlying potential mediators of treatment response, including motivation to change. Therefore, this study aimed to examine the effect of a brief intervention on motivation to change drinking behavior and neural alcohol taste cue reactivity.

Methods: Non–treatment-seeking heavy drinkers were randomized to receive a brief drinking intervention (n = 22) or an attention-matched control (n = 24). Three indices of motivation to change were assessed at baseline and after the intervention or control session: importance, confidence, and readiness. Immediately following the intervention or control session, participants also underwent an functional magnetic resonance imaging (fMRI) during which they completed an alcohol taste cues paradigm.

Results: There was a significant effect of the brief intervention on increasing ratings of importance of changing drinking behavior, but not on ratings of confidence or readiness to change. Ratings of importance after the intervention or control session were associated with neural alcohol taste cue reactivity, but notably, this effect was only significant for participants who received the intervention. Individuals in the intervention condition showed a positive association between ratings of importance and activation in the precuneus, posterior cingulate, and insula.

Conclusions: The brief drinking intervention was successful at improving one dimension of motivation to change among non–treatment-seeking heavy drinkers. The brief intervention moderated the relationship between ratings of importance and brain activation in circuitry associated with interoceptive awareness and self-reflection. Together, findings represent an initial step toward understanding the neurobiological mechanisms through which a brief intervention may improve motivation to change.

Keywords: brief intervention, mechanisms of behavior change, motivation to change, alcohol, functional magnetic resonance imaging

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INTRODUCTION

An increasing number of individuals engage in heavy alcohol use, putting themselves at risk of myriad health, psychological, and social consequences (1). Brief interventions represent a promising psychological intervention targeting individuals with heavy alcohol use who have not yet progressed to moderate or severe alcohol use disorder (AUD). Brief interventions are short (5 to 60 min), traditionally one to five sessions, interventions designed to increase motivation for behavioral change and encourage self-monitoring of high-risk situations for heavy drinking (2). Although specific therapeutic techniques vary, many of these interventions seek to increase motivation by providing individuals normative feedback about individualized risk of developing AUD, inquiring about the desire to change their drinking, and working collaboratively to explore and develop behavior change options (3). Meta-analyses have identified small yet robust effects of brief interventions on alcohol consumption that can be flexibly administered in multiple settings, including hospital emergency departments, primary care, and *via* digital/tele-therapy (2–4). Brief interventions have also been shown to sustain drinking reductions at 12-month follow-up (4).

Motivation for change is conceptualized as a multi-dimensional, dynamic construct representing one's openness to engage in a behavior change strategy (5), and is thought to be a crucial component of brief interventions (6, 7). High levels of motivation for change have been considered a prerequisite for successful treatment response. For instance, among individuals with comorbid substance use disorders and serious mental illness, high motivation was associated with reporting greater cons and fewer benefits to using substances, and taking steps to reduce substance use (8). Motivation for change was also associated with higher client reports of therapeutic alliance with therapists among treatment-seeking problem drinkers (9). Among homeless individuals placed in a housing intervention program, motivation for change was a stronger predictor of alcohol outcomes than treatment attendance (10). Many brief interventions for AUD have, therefore, focused on enhancing motivation for change given its importance in treatment engagement and outcomes.

To advance the literature on behavior change applied to alcohol use, current scientific efforts have focused on elucidating the specific mechanisms of behavior change, including underlying neural-level substrates that subserve changes in alcohol use. To that end, neuroimaging techniques provide a translational tool to investigate the neurobiological mechanisms underlying potential moderators of treatment response. Several studies to date have used neuroimaging to probe the underlying neurobiological mechanisms of psychosocial interventions (11–14). Three studies have examined the mechanisms of motivational interviewing interventions in alcohol-using populations (11, 14, 15). These studies investigated the importance of client and therapist speech as components of motivational interview interventions. The first study found that client change talk was effective in attenuating neural reward response to alcohol cues (11). The second study found that the origin of client change language is crucial for motivational interventions; self-generated change talk and counter-change talk were associated with increased activation in brain regions associated with introspection and self-awareness, when contrasted with experimenter selected language (14). The third study found that therapist statements designed to encourage complex reflections were associated with neural response in brain regions associated with reward and self-reflection, when contrasted with closed questions from therapists (15). Together, these studies provide evidence that neuroimaging can be successfully used to investigate the neurobiological mechanisms of brief interventions for alcohol use.

Although motivation for behavioral change has been identified as a critical component of behavioral interventions, no translational studies have yet explored how the relationship between psychological interventions and motivational change are represented neurobiologically. Identifying a neurobiological substrate of a behavior change target, in this case motivation for change, is critical for understanding the mechanisms of behavior change (16, 17). There are several brain regions that may be involved in these processes, particularly those that are associated with incentive salience and introspection. Brain regions implicated in incentive salience processing in addictive disorders include the ventral striatum (nucleus accumbens), dorsal striatum (caudate and putamen), and the orbitofrontal cortex (18, 19). Brain regions involved in self-reflection and introspection include the posterior cingulate cortex, precuneus, and insula (12, 14).

We recently conducted a study designed to examine the effectiveness of a brief intervention on improving drinking outcomes and modulating neural alcohol cue reactivity (20). This study randomly assigned non–treatment-seeking heavy drinkers to receive a single-session brief intervention or to an attention-matched control condition. The brief intervention was designed to help participants understand their individual level of drinking risk and help initiate changes in their alcohol use. Participants completed an alcohol taste cue reactivity paradigm during a functional magnetic resonance imaging (fMRI) scan immediately following the intervention. Participants completed a follow-up visit one month after the intervention to report on their drinking behavior. There was no significant effect of the brief intervention on drinking outcomes at follow-up or on modulating neural alcohol taste cue reactivity.

A better understanding of the neurobiological mechanisms of how brief interventions work through motivational change may help improve treatments for alcohol using populations. Therefore, this secondary analysis (20) aimed to examine the effect of a brief intervention on motivation to change drinking behavior and neural alcohol taste cue reactivity. To do so, we first tested whether the brief intervention had an effect on proximal outcomes of motivation to change (i.e., readiness rulers). We hypothesized that participants in the brief intervention condition would exhibit greater motivation to change compared to the control group. We also examined the association between motivational readiness and alcohol taste cue reactivity and assessed if the brief intervention moderated this association. We hypothesized motivation to change would be positively related to neural alcohol cue reactivity in circuitry associated with introspection and self-reflection and negatively related to neural alcohol cue reactivity in regions implicated in reward and incentive salience. We further

hypothesized that these relationships would be stronger in the intervention condition compared to the control condition.

MATERIALS AND METHODS

Participants and Screening Procedures

The study protocol and all procedures were approved by the Institutional Review Board of the University of California, Los Angeles. Detailed methodology of the general screening and experimental procedures has been published elsewhere (20) and are summarized here. Interested participants completed an initial telephone interview and eligible participants were invited to participate in an in-person screening visit. Upon arrival, all participants read and signed an informed consent form in accordance with the Declaration of Helsinki. During the in-person screening visit, participants completed a psychiatric diagnostic interview and a battery of individual difference measures, including demographics and alcohol and drug use assessments. All participants were required to have a breath alcohol concentration of 0.000 g/dl and to test negative on a urine drug test (except for marijuana, which was allowed to be positive).

Participants were non–treatment-seeking heavy drinkers, indicated by consuming five or more drinks per occasion for men or four or more drinks per occasion for women at least four times in the month preceding study enrollment, and who scored at least an 8 on the Alcohol Use Disorder Identification Test (AUDIT) (21). A total of 120 participants were screened in the laboratory for eligibility; 38 did not meet inclusion criteria, and 12 elected not to participate, leaving 60 participants who were enrolled and randomized. Of the 60 participants randomized, 46 participants completed the entire study. Participants who completed all study visits were compensated US $160.

Study Design

Participants were assessed at three time-points: at baseline, at randomization, and 1-month follow-up. During the randomization visit, participants were randomly assigned to receive a one-session brief drinking intervention or to an attention-matched control condition. Immediately following the intervention or control session, participants completed an fMRI scan to assess brain activity during exposure to alcohol and water taste cues. Participants returned for a follow-up visit approximately 4 weeks after the intervention or control session to assess alcohol use.

The brief intervention consisted of a 30- to 45-min individual face-to-face session based on the principles of motivational interviewing (22, 23) and adhered to the FRAMES model, which includes personal feedback (F), emphasizing personal responsibility (R), providing brief advice (A), offering a menu (M) of change options, conveying empathy (E), and encouraging self-efficacy (S). The aim of the intervention was to help participants understand their level of risk and to help initiate changes in their alcohol use. Participants randomized to the attention-matched control condition viewed a 30-min video about astronomy. In the control condition, there was no mention of alcohol or drug use beyond completion of research assessments.

Individual Difference Measures

The following individual questionnaires and interviews were administered during the study: 1) the 30-day timeline follow-back (TLFB) was administered in interview format to capture daily alcohol use over the 30 days prior to the visit (24), 2) the self-report AUDIT was administered to assess for drinking severity (21), and 3) the Penn Alcohol Craving Scale (PACS) was administered to assess alcohol craving (25). Participants also completed the Fagerstrom Test for Nicotine Dependence (26). The Structured Clinical Interview for DSM-5 (SCID) (27) was administered by a clinician to assess for lifetime and current AUD. Lastly, participants completed a demographics questionnaire reporting, among other variables, age, sex, and level of education.

Motivation to Change Assessment

At each visit, participants also completed three decision rulers designed to measure their motivation to change their drinking behavior [based on Refs. (5, 28)]. Participants were asked to rate on a scale from 1 to 10: "As of now how important is it for you to make a change in your drinking?" (importance ruler), "If you decided to make a change in your drinking how confident are you that you could do it?" (confidence ruler), and "As of now how ready are you to make a change in your drinking?" (readiness ruler).

Neuroimaging Procedures

At the start of the scanning visit, participants were required to have a BrAC of 0.00 g/dl and a urine toxicology screen negative for all drugs (excluding tetrahydrocannabinol). Additionally, female participants were required to have a negative pregnancy test.

Neuroimaging data were acquired on a 3.0T Siemens Prisma scanner at the UCLA Staglin Center for Cognitive Neuroscience. Detailed neuroimaging parameters can be found in Grodin et al. (20). Briefly, the protocol consisted of a high-resolution, matched-bandwidth (MBW) scan and a structural magnetization-prepared rapid-acquisition gradient echo (MPRAGE) scan. This was followed by two runs of a modified version of the Alcohol Cues Task, which involves the delivery of oral alcohol or control (water) tastes to elicit physiological reward responses (29, 30). During the task, participants were presented with a visual cue indicating the trial type (Alcohol Taste or Water Taste), which was followed by a fixation cue and the delivery of the alcohol or water taste (1 ml).

Preprocessing of the neuroimaging data followed conventional procedures implemented in FMRIB's Software Library (FSL 5.0) (www.fmrib.ox.ac.uk/fsl). This included motion correction [Motion Correction Linear Image Registration Tool (McFLIRT, Version 5.0)], high-pass temporal filtering (100-s cutoff) using FSL's FMRI Expert Analysis Tool (FEAT, Version 6.00), and smoothing with a 5-mm full-width at half-maximum Gaussian kernel. FSL's Brain Extract Tool (BET) was used to remove skull and non-brain tissue from both the structural and functional scans. Data were denoised using ICA-AROMA (31) to reduce motion artifacts associated with swallowing.

Data Analysis

General linear models with OLS regression were used to test the main effect of study condition on each of the three motivation-for-change decision rulers (importance, confidence, and readiness). Analyses were adjusted for baseline AUDIT score, age, sex, smoking status, and the baseline ratings from the corresponding decision ruler.

The analysis of the Alcohol Cues Task was conducted using FSL's FEAT as described in Ref. (20). Briefly, alcohol and water taste cues were convolved with a double-gamma hemodynamic response function (HRF). Six motion regressors representing translational and rotational head movement were included as regressors of no interest. Data for each subject were registered to the MBW, followed by the MPRAGE using affine linear transformations, and then were normalized to the Montreal Neurological Institute (MNI avg152) template. Registration was refined using FSL's non-linear registration tool. The primary contrast of interest, the Alcohol Taste Cue > Control Taste Cue contrast, was defined in the first-level models. The second-level model combined the contrast images across the two task runs, within subjects. The third-level model combined the contrast images between subjects. To evaluate if the intervention moderated the association between motivational readiness ratings and brain activation to alcohol taste cues, three interaction models were run with baseline-corrected ratings of importance, confidence, and readiness mean-centered across all subjects. Age, sex, cigarette smoking status, positive urine for tetrahydrocannabinol (THC), and AUD severity were entered as covariates. Z-statistic images were thresholded using a cluster threshold of $Z > 2.3$ and a (corrected) cluster significance threshold of $P < 0.05$ (32). Given the exploratory nature of this study and the dearth of studies on behavioral interventions, neural reactivity to alcohol cues, and mechanisms of motivation to change, we also implemented a more restrictive approach presented in the **Supplementary Materials**. Specifically, we conducted a separate set of analyses using the regions significantly activated in the Alcohol Taste Cue > Water Taste Cue contrast as a mask to investigate if the intervention moderated the association between motivation to change ratings and task-specific brain activation. As the neuroimaging literature has not reached a standard whereby such masks are systematically used to test treatment effects, we provide both approaches in this manuscript (33).

RESULTS

Effect of Brief Intervention on Motivation to Change Ratings

The groups significantly differed on their post-session ratings of importance ($F_{1,40} = 8.77$, $p = 0.005$), after controlling for age, gender, smoking status, and baseline ratings of importance. Specifically, the intervention group had higher post-session ratings of importance than the control group (intervention group, 6.27 ± 0.39; control group, 4.67 ± 0.37; predicted values). However, there was no significant effect of group on ratings of confidence ($F_{1,40} = 1.35$, $p = 0.25$; intervention group: 7.13 ± 0.44; control group: 6.25 ± 0.42; predicted values) or readiness ($F_{1,40} = 0.04$; $p = 0.85$; intervention group, 4.73 ± 0.48; control group, 4.62 ± 0.43; predicted values) following the intervention or control sessions (see **Table 1**).

Relationship of Motivation to Change and Neural Alcohol Taste Cue Reactivity

Importance Ruler

Averaging across intervention and control groups, there was no significant association between importance ratings and brain activation to alcohol taste cues. However, consistent with our hypothesis, there was a significant interaction between group and importance ratings on brain activation to alcohol vs. water taste. Specifically, there was a positive association between importance ratings and brain activation in frontal, limbic, and visual regions in the active intervention group ($p < 0.05$ corrected), whereas there was no significant association in the control group (see **Figure 1**, **Table 2**).

For the analyses restricted to the mask representing significant clusters for Alcohol Taste Cue > Control Taste Cue, averaging across intervention, and control groups, there was no significant association between importance ratings and brain activation masked within the alcohol taste cue > water taste cue contrast. There was a significant interaction between group and importance ratings on brain activation to alcohol vs. water taste. Specifically, there was a positive association between importance ratings and brain activation in frontal regions, including the middle and superior frontal gyri and paracingulate, in the active intervention

TABLE 1 | Participant characteristics.

Characteristics	Intervention group (n = 22)	Control group (n = 24)	Statistic	p
Age	36.41 ± 13.56	32.29 ± 9.89	t = 1.18	0.24
Sex (M/F)	13/9	15/9	$\chi^2 = 0.06$	0.81
Cigarette smokers (n)	11	12	$\chi^2 = 0.00$	1
THC positive (n)	6	6	$\chi^2 = 0.04$	0.86
Education (years)	15.45 ± 2.13	15.04 ± 1.78	t = 0.72	0.48
AUDIT total score	17.68 ± 6.49	17.17 ± 7.61	t = 0.25	0.81
PACS score	19.32 ± 6.94	18.79 ± 7.15	t = 0.25	0.80
AUD severity (no diagnosis/ mild/moderate/severe)	1/9/5/7	5/8/5/6	$\chi^2 = 0.95$	0.34
Baseline Visit Motivation Ruler Ratings (T1)				
Importance ruler	4.27 ± 2.53	5.25 ± 2.80	t = 1.21	0.23
Confidence ruler	5.68 ± 2.67	6.08 ± 2.43	t = 0.52	0.60
Readiness ruler	3.23 ± 1.88	3.88 ± 2.01	t = 1.10	0.28

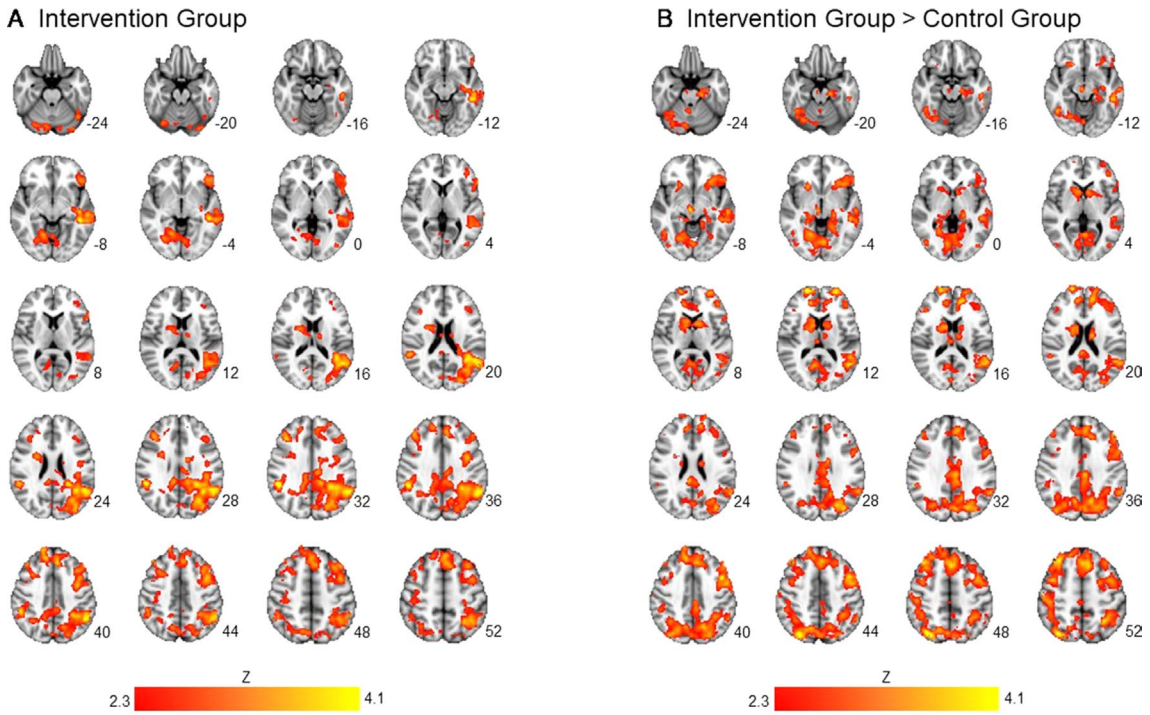

FIGURE 1 | Association between importance ratings and brain activation to alcohol taste cues. The association between ratings of importance of behavioral change and brain activation to alcohol taste cues. **(A)** The intervention group showed a significant positive association between ratings of importance and brain activation in the precuneus, posterior cingulate, and caudate. **(B)** Between groups, the intervention group showed a significant association between importance ratings and brain activation in the posterior cingulate, insula, precuneus, caudate, and anterior cingulate. These associations were not present in the control group. See **Table 2** for a full list of significant regions. Z-statistic maps are whole-brain cluster corrected, $Z > 2.3$, $p < 0.05$. Coordinates are in Montreal Neurological Institute (MNI) space. Brain is displayed in radiological convention (L = R).

group ($p < 0.05$ corrected), whereas there was no significant association in the control group (see **Figure S1**, **Table S1**).

Confidence Ruler

There were no significant associations between ratings of confidence and brain activation to alcohol taste cues across or between groups. There was also no significant interaction between group and confidence ratings on neural alcohol taste cue reactivity.

For the masked analyses, there were no significant associations between ratings of confidence and masked brain activation to alcohol taste cues across or between groups. There was also no significant interaction between group and confidence ratings on masked neural alcohol taste cue reactivity.

Readiness Ruler

Across groups, there was no significant association between readiness ratings and brain activation to alcohol taste cues. There was a significant interaction between group and readiness ratings on neural activation to alcohol taste cues in the temporal lobe. Specifically, the control group showed a negative association between ratings of readiness to change and brain activation in the middle and superior temporal gyrus ($p < 0.05$ corrected). There was no significant association, positive or negative, between ratings of readiness to change and brain activation to alcohol cues in the intervention group (see **Figure 2**, **Table 3**).

For the masked analyses, there were no significant associations between ratings of readiness and masked brain activation to alcohol taste cues across or between groups. There was also no significant interaction between group and confidence ratings on masked neural alcohol taste cue reactivity.

DISCUSSION

This study examined the effect of a brief intervention on motivation to change, as indicated by ratings of importance, confidence, and readiness, in a sample of non–treatment-seeking heavy drinkers. This study also explored the relationship between indices of motivation to change and the neural substrates of alcohol taste cue-reactivity after a brief drinking intervention. We found that the brief intervention was successful in significantly increasing ratings of importance of changing behavior related to alcohol use. However, there was no effect of the intervention on ratings of confidence or readiness to change. Correspondingly, we found that the brief intervention moderated the association between ratings of importance of behavioral change and neural alcohol taste cue reactivity. Specifically, there was a significant positive association between ratings of importance and neural alcohol taste cue reactivity in regions associated with introspection and self-awareness in the intervention group, but not in the control group.

TABLE 2 | association between importance ratings and brain activation to alcohol vs. water taste cues in intervention and control groups.

Brain region	Cluster voxels	Max. Z	x	y	z
Intervention group positive					
L Middle temporal gyrus	10,401	4.34	–46	–36	–10
L Angular gyrus		4.13	–52	–52	36
L Posterior cingulate gyrus		3.55	–14	–40	32
R Posterior cingulate gyrus		3.42	10	–40	28
R Precuneus		3.08	16	–70	50
L Middle frontal gyrus	4,187	3.90	–42	6	46
L Superior frontal gyrus		3.80	–4	24	48
L Cerebellar pyramis	2,374	4.49	–22	–80	–36
R Caudate	1,142	4.31	22	2	20
R Middle frontal gyrus		3.47	42	34	36
Control group positive					
N/A					
Intervention group negative					
N/A					
Control group negative					
N/A					
Intervention group > control group					
R Precuneus	11,068	4.69	32	–72	48
R/L posterior cingulate		3.64	–6	–24	34
L Precuneus		3.76	–14	–64	36
L Caudate		3.23	–10	8	10
R Lateral occipital cortex		3.11	26	–722	34
L middle frontal gyrus	7,647	4.11	–44	10	40
L frontal pole		3.83	–24	62	12
L superior frontal gyrus		3.57	–10	20	56
R/L anterior cingulate		3.46	16	42	10
L insula		3.17	–28	24	–4
R caudate	865	4.43	20	2	20
Control group > intervention group					
N/A					

One goal of this study was to explicitly test if the brief intervention was effective at impacting motivation to change indices, which may serve as mechanism of behavior change (MOBC) (17). As we hypothesized, the brief drinking intervention increased ratings of importance of behavioral change. The intervention did not, however, impact ratings of confidence or readiness. Notably, as reported elsewhere, there was no significant main effect of the intervention on alcohol outcomes in the 4 weeks following the brief intervention (20). Therefore, it may not be surprising that the intervention was also not successful at increasing ratings of confidence or readiness to change. Importance, confidence, and readiness measure different elements of the change process, with each element being necessary, but not sufficient to induce a behavioral change (10, 22, 28). These results are similar to those of a motivational interview study among young adults admitted to an emergency room who reported risky drinking *via* the AUDIT or exhibited elevated blood alcohol content (34). In this study, a motivational interview, relative to personalized feedback alone, increased readiness to change ratings only at a trend level, and readiness to change did not mediate treatment effects on drinking outcomes. By contrast, adult emergency department heavy drinkers randomized to receive brief intervention relative to those receiving standard care reported higher readiness scores at 3 months post-treatment (35), and readiness mediated intervention effects only among those with high baseline motivation to change. Changes in readiness to change have also been shown to mediate brief intervention effects among underage heavy drinkers (36). Overall, these findings corroborate potential mechanisms of action of brief intervention, and may also explain the relatively small effect sizes reported in meta-analyses (2). Further, these results extend the literature by suggesting that neuroimaging tools, and cue reactivity in particular, were sensitive to changes in importance ratings, despite the fact that such changes did not lead to detectable treatment effects on alcohol use.

Notably, there is significant heterogeneity in measures utilized in the literature to capture readiness to change, with varying number of factors included in an instrument [e.g., Contemplation Ladder (37)], without widespread consensus on associations among measures. In light of these differences, studies utilizing the three ladders in this study suggest that baseline importance and confidence rather than readiness predict favorable drinking outcomes at 6 months post-brief intervention (38, 39). However, another study monitoring measures of readiness to change using these ladders found significant effects of confidence and readiness ratings on 12-month alcohol outcomes, with weaker effects of importance of change (40). Other brief intervention studies,

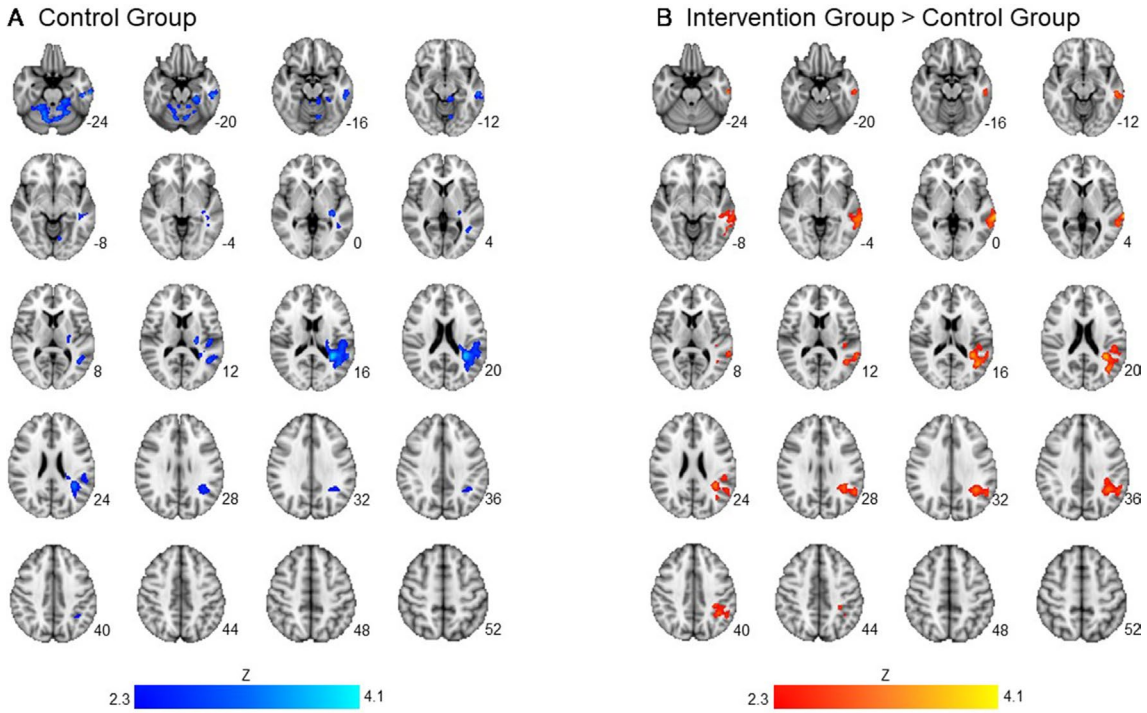

FIGURE 2 | Association between readiness ratings and brain activation to alcohol taste cues. The association between ratings of readiness to change and brain activation to alcohol taste cues. **(A)** The control group showed a significant negative association between ratings of readiness and brain activation in the temporal lobe. **(B)** Between groups, the intervention group showed a significantly greater activation in the temporal lobe due to the negative relationship found in the control group. See **Table 3** for a full list of significant regions. Z-statistic maps are whole-brain cluster corrected, $Z > 2.3$, $p < 0.05$. Coordinates are in MNI space. Brain is displayed in radiological convention (L = R).

TABLE 3 | Association between readiness ratings and brain activation to alcohol vs. water taste cues in intervention and control groups.

Brain region	Cluster voxels	Max. Z	x	y	z
Intervention group positive					
N/A					
Control group positive					
N/A					
Intervention group negative					
N/A					
Control group negative					
R cerebellar tonsil	2,385	3.50	24	−66	−36
L superior temporal gyrus	2,232	3.96	−32	−44	18
L middle temporal gyrus		2.82	−60	−24	−18
Intervention group > control group					
L middle temporal gyrus	2,660	3.78	−66	−36	0
Control group > intervention group					
N/A					

however, have identified that baseline perception of alcohol-related problems is predictive of *greater* drinking 3 months later, whereas "Taking Action" ratings and having a personalized plan for change were significant predictors of reduced drinking 3 and 12 months later, respectively (41, 42). In light of this mixed literature, the findings for the present study may provide evidence for a modest effect of brief interventions on at least one dimension of readiness to change among non–treatment-seeking adult heavy drinkers. Additional research is needed to examine the clinical utility of the importance measure, as well as its overlap with other readiness to change assessments. Within this mixed literature, however, what remains more consistently corroborated is that alterations in importance ratings alone are insufficient to produce behavioral change. Within an MOBC context, the brief intervention within this study was successful at increasing the recognition of the importance of changing drinking behavior, when compared with the attention-matched control. Similarly, as the intervention was not successful in increasing ratings of confidence or readiness or in reducing drinking reported at follow-up, the brief behavioral intervention may need to be better modified to target these motivation to change ladders in efforts to induce reductions in drinking. Furthermore, there is evidence to suggest that during brief interventions, patients who set clear objectives for alcohol use reduction have better alcohol use outcomes over 12 months (43). These individuals also engaged in more change talk during the intervention and had higher ratings of importance and readiness to change (43). These results suggest that targeting patient goals for alcohol reduction may improve outcomes, potentially through motivation to change mechanisms.

The present findings did not support an overall association between motivation to change and neural alcohol taste cue

reactivity; however, they did identify a moderating effect of the brief intervention on the relationship between motivation to change and neural alcohol taste cue reactivity. More specifically, we found that in the intervention group, but not in the control group, there was a significant positive association between ratings of importance of behavioral change and neural alcohol taste cue reactivity in regions implicated in introspection and self-reflection, e.g., precuneus, posterior cingulate, insula. Several studies have identified a role for the precuneus and the insula in self-related cognitive processes (44–46). Our findings are in line with other studies which have found increases in the recruitment of interoceptive and self-referential processing regions in response to motivational interventions (14, 47–50). Addictive disorders have been theorized to be associated with a deficit in insight and self-awareness (51) and metacognitive processing (52, 53). Therefore, the brief intervention's emphasis on personalized level of risk and focus on change may have allowed individuals to increase their awareness of their drinking problems, thereby activating brain regions associated with interoceptive awareness when exposed to alcohol taste cues. In contrast, the control group, who did not receive personalized feedback, did not show an association between importance of behavioral change and activation in interoceptive circuitry.

This pattern of findings suggests a potentially important role of self-reflection in brief intervention and the neurobiology of alcohol cue reactivity. To wit, self-reflection during the intervention may have yielded higher problem awareness (i.e., importance for change). This self-reflection generalized to the scanning environment, wherein problem awareness prompted by the intervention was associated with greater introspection in response to alcohol cues. In contrast, participants in the control group did not engage in a self-reflective process about their drinking before the scanning session, and for them, the rating of importance was not associated with greater introspection in response to alcohol cues. These findings imply that it matters how people arrive at varying states of motivational readiness and that people who engage in self-reflection and also rate high on importance for change are the ones most likely to respond to subsequent alcohol cues with introspection. Future analyses should examine how these processes relate to alcohol use.

There was also a significant moderating effect of the brief intervention on the association between importance ratings and neural alcohol taste cue reactivity in regions implicated in incentive reward processing. The intervention group, when contrasted with the control group, showed a significant positive association between importance ratings and neural alcohol taste cue reactivity in the caudate, anterior cingulate, and insula, key regions of the incentive reward network (54). Intriguingly, the anterior cingulate is also implicated in monitoring conflict (55, 56). The activation of the anterior cingulate may represent the conflict between personal realizations of the importance of changing drinking behavior and the alcohol cue-elicited craving responses in incentive reward regions. Notably, the neuroimaging results using the mask-based approach did not fully conform with the pattern of findings from whole brain analyses discussed herein, and more broadly, did not address the study hypotheses given that the task contrast mask did not include brain regions subserving interoception.

Although the effects on the importance ratings were consistent with our prediction, this study also yielded a counterintuitive finding with regard to the association between neural activation to alcohol taste cues and the readiness to change ratings. Specifically, we found a significant interaction between group and post-session readiness ratings on neural activation to alcohol taste cues in the temporal lobe, such that the control group showed a negative association between ratings of readiness to change and brain activation in the middle and superior temporal gyrus. In the intervention group, however, there was no significant association, positive or negative, between ratings of readiness to change and brain activation to alcohol cues. In interpreting these findings, we considered two possibilities. The first is that this may be a spurious finding or type II error. The second possibility is that in fact these results reflect underlying effects such that in the control group, readiness to change was associated with decreased neural activation in the superior temporal gyrus during alcohol taste cues, compared to neural cues. We choose to refrain from reverse inference (57) in this case and note that additional studies and/or advanced data modeling may be required (58) to fully unpack this counterintuitive finding. Nonetheless, this result allows us to ponder on the very nature of this thematic issue, which is the degree to which clinical phenomenon will lend itself to cognitive neuroscience examination. Specifically, by breaking down clinical phenomena too finely we may lose its clinical significance, whereas having "large chunks" of clinical data explained by neuroimaging may lead to inconclusive or unreliable findings (59).

This study represents an initial step toward understanding the neurobiological mechanisms through which a brief intervention may improve motivation to change. Although this study has several strengths, it should be considered in light of its limitations. First, this study has a modest sample size; future studies should recruit larger sample sizes, particularly as the effect sizes of brief interventions are modest (60). Relatedly, this study recruited and enrolled non–treatment-seeking individuals from the community, and therefore, may not have shown the same changes in motivation to change following a psychosocial intervention as a treatment-seeking sample, which in turn may have reduced our power to identify associations between measures of readiness to change and neural alcohol cue reactivity. Additionally, the scanning portion of the study did not employ a pre-/post-treatment design, which may have been more sensitive to the effects of the intervention.

In conclusion, this study sought to identify the neurobiological mechanisms underlying changes in motivation induced by a brief intervention in non–treatment-seeking heavy drinkers. The current study found that a brief intervention increased ratings of importance of behavioral change, but was unsuccessful in impacting ratings of confidence or readiness to change compared to an attention-matched control. The brief intervention also moderated the association between neural alcohol taste cue reactivity and ratings of importance, such that in the intervention condition, there was a significant, positive relationship between ratings of importance and activation in regions associated with interoceptive awareness and self-reflection. This association may provide initial support for the role of interoceptive circuitry subserving increases in understanding of importance of behavioral change.

ETHICS STATEMENT

The study protocol and all procedures were approved by the Institutional Review Board of the University of California, Los Angeles. Detailed methodology of the general screening and experimental procedures has been published elsewhere (20) and are summarized here. Interested participants completed an initial telephone interview and eligible participants were invited to participate in an in-person screening visit. Upon arrival, all participants read and signed an informed consent form in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

MK, LR, and JM were responsible for the study concept and design. AL and LR conducted the study. EG analyzed the data. EG and AL wrote the manuscript. MK, LR, and JM provided critical feedback on the manuscript. All authors critically reviewed content and approved the final version for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00408/full#supplementary-material

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REVIEW
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Neurocognitive Precursors of Substance Misuse Corresponding to Risk, Resistance, and Resilience Pathways: Implications for Prevention Science

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Studies of substance misuse prevention generally focus on characteristics that typify risk, with the assumption that the prevalence of the problem will be optimally reduced by identifying, targeting, and reducing or eliminating risk factors. However, this risk-centered approach neglects variations in individual-level and environmental characteristics that portend differential pathways that are distinguishable by timing of substance use initiation (e.g., early versus delayed), the likelihood of use escalation versus eventual desistance, and enduring abstinence, despite exposure to significant risk factors. Considering the various underpinnings of these distinct substance use trajectories is critical to a more nuanced understanding of the effects, potency, and malleability of factors that are known to increase risk *or* confer protection. Here, we discuss three pathways relative to substance use patterns and predictors in the context of adversity, a well-known, highly significant influence on propensity for substance misuse. The first pathway is designated as "high risk" based on early onset of substance use, rapid escalation, and proneness to substance use disorders. Individuals who defy all odds and eventually exhibit adaptive developmental outcomes despite an initial maladaptive reaction to adversity, are referred to as "resilient." However, another categorization that has not been adequately characterized is "resistant." Resistant individuals include those who do not exhibit problematic substance use behaviors (e.g., early onset and escalation) and do not develop substance use disorders or other forms of psychopathology, despite significant exposure to factors that normally increase the propensity for such outcomes (e.g. trauma and/or adversity). In this paper, we apply this conceptualization of risk, resistance, and resilience for substance misuse to a more fine-grained analysis of substance use pathways and their corresponding patterns (e.g., non-use, initiation, escalation, desistance). The significance of the progression of neurocognitive functioning over the course of development is discussed as well as how this knowledge may be translated to make a science-based determination of intervention targets. This more encompassing theoretical model has direct implications

for primary prevention and clinical approaches to disrupt risk pathways and to optimize long-term outcomes.

Keywords: neurocognitive, neuroimaging, substance misuse/abuse, risk, resilience, resistance, prevention science

INTRODUCTION

Adolescents who initiate substance use and later develop substance use disorders (SUDs) transition through multiple sequential stages, including experimental or social use, escalation of use, maintenance, abuse, and eventual dependence (1, 2). However, a linear progression along this pathway is not often realized, with individuals showing considerable variability in the likelihood of early, experimental use and significant fluctuations in patterns of usage, escalation, and desistance (3, 4). For example, there are subgroups of users who may never escalate, maintaining nondependent use for decades. While some exhibit intermittent periods of cessation or abstain permanently, others rapidly escalate and go on to develop SUDs. Discriminating between these different user types and delineating which individuals are more likely to follow different pathways is key to identifying critical windows of opportunity for preventing substance misuse.

A potent risk factor influencing the transition from social/experimental use to problematic use and eventual dependence is the experience of traumatic and other chronic or severely stressful events in childhood (5, 6). Indeed, exposure to adversities such as child maltreatment, poverty, and witnessing or experiencing violence have been repeatedly implicated in trajectories leading to SUDs (7–9). The literature is replete with studies documenting the impact of early adversity on neurocognitive development throughout childhood and adolescence and, in turn, how adversity-related deficits or delays in neurocognitive function in youth can increase vulnerability to a myriad of risk behaviors, such as substance misuse (10–12). Integrity of neurocognitive development translates to the ability to self-regulate behavior and emotion via "top-down" cognitive control over affective responses to life's challenges. The development of these processes may be particularly influential in adaptations to adversity. Thus, variations in neurocognitive trajectories are likely more pronounced in populations where adversity prevails, which, in turn, may correspond to a wide range of behavioral pathways and outcomes, from low to high risk (13–15). In other words, adversity can result in diverse outcomes (*multifinality*) depending largely upon the ways in which the nervous system is affected in exposed individuals.

Substance use outcomes in response to adversity, including its impacts on the brain, may manifest in the following general developmental pathways: *risk* (initial and sustained reactions to adversity, resulting in maladaptive outcomes), *delayed risk* (apparent early resistance to adversity but eventual decline toward maladaptive outcomes), *resilience* (initial reaction followed by gradual degradation of response to adversity with eventual restoration of adaptive developmental outcomes), and *resistance* (absence of change in developmental trajectory despite exposure to adversity). Developmental periods that correspond with these patterns may include an initial departure in direction (e.g., risk vs. resistance), the time point at which trajectories may diverge (e.g., resistance vs. delayed risk *or* risk vs. resilience), and the time beyond which specific risk outcomes emerge (e.g., substance abuse). Developing more precision-based interventions will require a clearer delineation of critical time points when influential factors in substance misuse act on emergent neurocognitive systems in a manner that increases the likelihood of following one of these pathways versus another.

As described herein, our *Accumulative Risk Model* (see **Figure 1**) depicts the interactive influence of genetic risk markers and environmental contexts (both detrimental and protective) on intermediate phenotypes, including distinct or interwoven cognitive, affective, and behavioral trajectories and associated neural factors (i.e., variability in brain structure and function) that underpin pathways for outcomes ranging from adaptive to maladaptive. In our model, the dynamic interplay of factors in the developmental context exerts differential impacts on these intermediate phenotypes and their neurobiological substrates in a manner that is contingent upon developmental stage. As such, missing time-dependent opportunities to intervene and redirect development translates to a higher probability of individuals exceeding a liability threshold for high risk behaviors, including substance misuse. In this paper, we review the evidence in support of this integrative framework and its relevance to the ability of evidence-based prevention programming to strengthen these neurodevelopmental processes, thereby attenuating negative effects of risk factors and reinforcing resilience and/or resistance. Such a science-based strategy has potential to redirect developmental pathways away from risky behaviors such as substance abuse.

The content presented in this review was selected via a nonsystematic/narrative review process, whereby we searched standard sources (e.g., PubMed; www.ncbi.nlm.nih.gov) for relevant but broad terms. This included various combinations of the following terms: substance abuse/misuse; SUD(s); development; risk; resilience; genetics; environment; and prevention/intervention. In addition to the articles that resulted from these searches, we engaged in an iterative process by which relevant publications that were cited in specific articles were also included in our review.

The Accumulative Risk Model

Defining Risk: The Accumulative Developmental Context

Risk is commonly thought of as binary and deterministic, as reflected in the tendency to designate individuals as either "at risk" or not, and the assumption that those who are "at risk" are more likely to assume a maladaptive pathway, characterized by

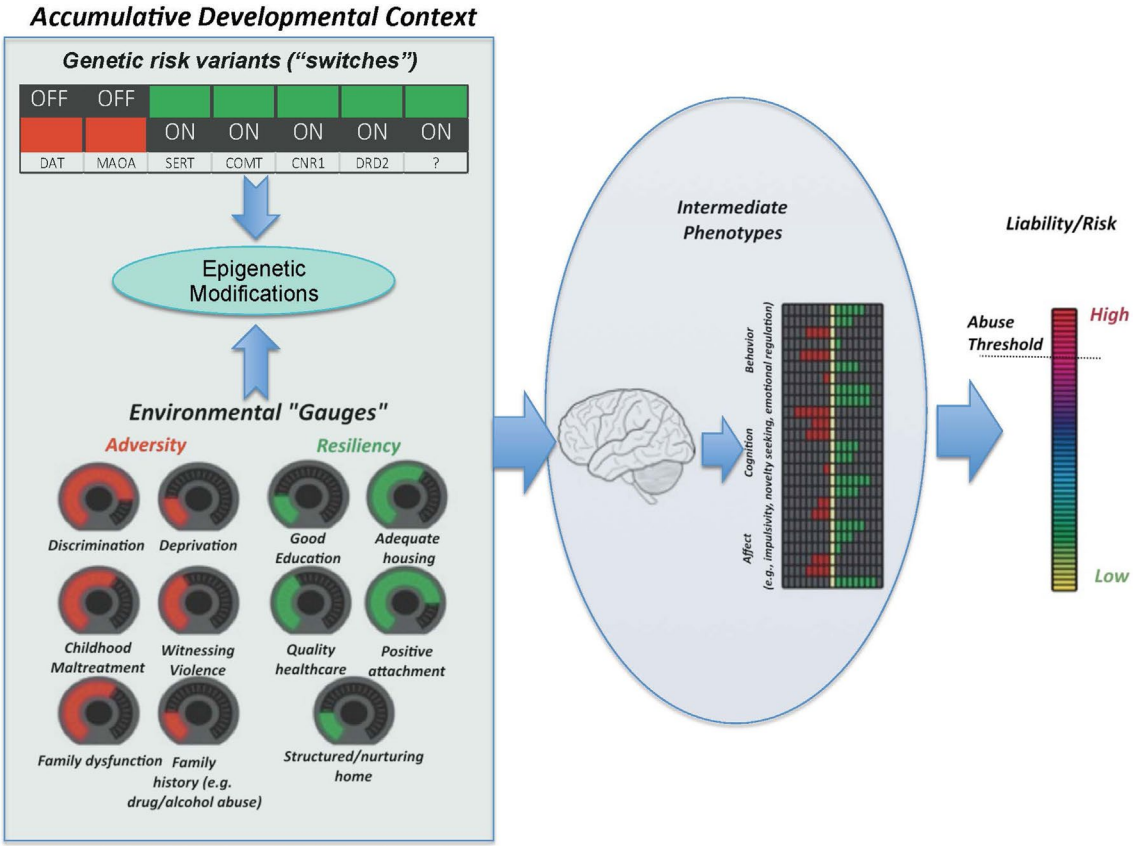

FIGURE 1 | The Accumulative Risk Model. Shown here are the two main categories of factors that constitute the accumulative developmental context, i.e., genetic and environmental factors. The combined effect of the number, type, and severity of these factors confers risk for substance abuse. Genetic variants are considered as switches, which are either "on" or "off." This conceptualization reflects the common binary consideration of genetic risk (i.e., individuals are often considered at risk or not depending on the particular variant of a given gene that they happen to carry). To reflect their more continuous nature, environmental factors are presented as dials, turned up or down depending on the magnitude of the experience. The unique combination of genetic switches and environmental dials drives neurodevelopmental trajectories that underlie particular cognitive, behavioral, and affective intermediate phenotypes, which, in turn, can result in an increased liability threshold, beyond which an individual is considered to be at greater likelihood of developing problematic substance use behaviors and eventual SUD. Importantly, the functional relationship between factors is not linear, and some environmental factors may exacerbate or attenuate the effects of the particular genes via epigenetic modifications.

high-risk behaviors such as substance abuse. However, risk is better conceptualized as a continuous trait—*liability*—with values ranging from low to high. An individual's positioning along the liability continuum is determined by a number of pertinent intermediate phenotypes—such as patterns of behavior, cognition, and affect—modulated by an individual's unique brain structure and function. This neurobiological variability is, itself, a function of a highly complex and individualized range of factors, including those that are potentially malleable, such as environmental and contextual conditions, and those that are not so amenable to change or manipulation, such as genetic factors.

The constellation of factors that confer adaptive or maladaptive neurodevelopmental trajectories can be conceptualized as the "accumulative developmental context." Within this context are factors that either increase (i.e., risk factors) or decrease (i.e., protective factors) liability (**Figure 1**). Importantly, the number and type of risk and protective factors are presumed to be unique between individuals and the interplay between factors determines an individual's level of liability more so than any one factor alone. The influence of each factor, whether risk or protective, is not necessarily linear and some factors may act as moderators of other relevant factors, either amplifying or decreasing their risk or protective potential. Understanding these relationships and how the accumulative developmental context increases liability for SUD or, alternatively, offers protection and fosters resilience or resistance, promises to provide critical information on which to base the development of approaches to prevent SUDs.

Putatively Distinct Developmental Trajectories

Liability for high-risk behaviors or other suboptimal outcomes is commonly considered from the perspective of being either at risk or resilient, with the corresponding assumption being that either trajectory is strongly associated with the prevalence (or

sheer number) of risk or protective influences, respectively (16–19). While there is a wealth of experimental evidence to support this characterization, possible developmental pathways arising from any given context includes a range of potential positive and negative trajectories (20, 21) (see **Figure 2a**). Pathways that lead to maladaptive outcomes include the typically considered "risk" pathway; i.e., adverse external conditions and the development of suboptimal intermediate phenotypes, together that increase an individual's likelihood of crossing the liability threshold for high-risk outcomes, such as SUD and other psychopathologies. Typically, risk is described as occurring in close temporal proximity to the factors that promote its expression (e.g., changes in cognitive or behavioral functioning that more or less immediately follow some stressful life event). A related, but not commonly considered, negative trajectory is "delayed risk," which occurs when there is a temporal delay or disconnect between the factors that promote a high-risk trajectory and the observable changes the portend a maladaptive outcome. Though not often distinguished in the literature, determining those aspects of the developmental context that confer risk vs. delayed risk may be helpful in the design of preventive interventions. In particular, such information may lead to programs aimed at individuals who may not immediately appear to be at risk but for whom early evidence-based intervention may be particularly advantageous (i.e., potentially stemming the proliferation of maladaptive phenotypes).

At the positive end of the spectrum are resilience and the related, but theoretically distinct, concept of "resistance." Resilience can be defined as the later expression of adaptive/optimal outcomes despite initially exhibiting negative responses to challenging or threatening circumstances (e.g., adversities and traumas, such as poverty, maltreatment, violence). Resilience-related factors are those that enable an individual to rebound from adversity- or trauma-related dysfunctions or deficits and to achieve their original state or otherwise adaptive outcome(s). In contrast, *resistance* is characterized by the maintenance of the original state despite exposure to stressful events or contexts; i.e., developmental pathways remain unaltered despite significant stress/trauma. A third possible positive trajectory—"recovery"—involves the resumption of function following the development of a maladaptive outcome, such as SUD, and subsequent intervention/treatment (**Figure 2a**). Although possibly driven by the same or similar factors as resistance and resilience (e.g., more optimal levels of neurocognitive functioning or emotional regulation), it is probable that recovery is at least partially distinct in terms of the pathway itself, the factors that promote it, and the timing (i.e., only following intervention). As such, recovery may constitute a third distinct class of positive adaptation. In support of this notion, and in the context of SUD specifically, recovery is highly likely to be distinguishable from resistance and resilience since SUD-related neuroadaptations may not be reversible (23); thus, individuals who recover from SUD do so without regaining a substantial degree of original functioning. Instead, other compensatory mechanisms may facilitate overall functioning in a way that is adaptive and allows individuals with SUD to achieve recovery and avoid relapse (24–26).

PUTATIVE UNDERPINNINGS OF DISTINCT DEVELOPMENTAL TRAJECTORIES

Determining which experimental or social substance users will progress to abuse (i.e., a maladaptive pattern of substance use manifested by recurrent and significant adverse consequences) and dependence (i.e., a chronic relapsing brain disease characterized by compulsive drug seeking despite harmful consequences) is a longstanding question that has compelled researchers and practitioners to better understand, predict, and effectively intervene in maladaptive patterns of substance use. As depicted in the Accumulative Risk Model, the interplay between an individual's genetics and their environmental and contextual experiences during critical periods of development give rise to patterns of neurobiological functioning, stress physiology, personality/temperament, and emerging coping strategies that determine the individual's response to the prevailing social and environmental conditions. The nature of this response contributes to eventual substance use outcomes, including whether an individual will or will not engage in substance use and whether use will progress to abuse and dependence. A critical step in delineating the distinct etiological pathways under consideration here is understanding how relevant person-level characteristics predict or moderate outcomes and interact with environmental influences in unique and complex ways to either promote or preclude substance misuse.

Neurocognitive Pathways to Substance Misuse

As noted above, there are commonalities in the key factors (risk and protective) that give rise to particular types of substance use pathways (i.e., adaptive or maladaptive); distinguishing between those that are more tightly coupled to one specific pathway (i.e., risk, delayed risk, resilience, or resistance) is not possible based on current knowledge and given limitations of the extant research. For example, most studies consider outcomes as either positive/adaptive or negative/maladaptive (e.g., having an SUD or not) at a single time point and lack the longitudinal perspective and temporal specificity needed to distinguish the putative pathways under consideration here. Nonetheless, defining the differential constellations of influences that lead to distinctive pathways toward or away from substance abuse is a paramount task; one holds considerable potential to lead to more personalized interventions with potential for population level impacts. Working backwards within the Accumulative Risk Model, from cognitive and behavioral phenotypes to their more basic substrates, risk and protective factors that cross trajectories are described briefly below. The following subsections consider evidence that implicates neurocognitive factors in the four divergent pathways under consideration here (i.e., risk, delayed risk, resistance, and resilience).

Risk for Substance Misuse

Genetic Vulnerabilities

There have been many genetic risk studies for SUDs that have delineated gene variants that appear to be associated with specific types of abuse (e.g., alcohol/alcohol dehydrogenase genes;

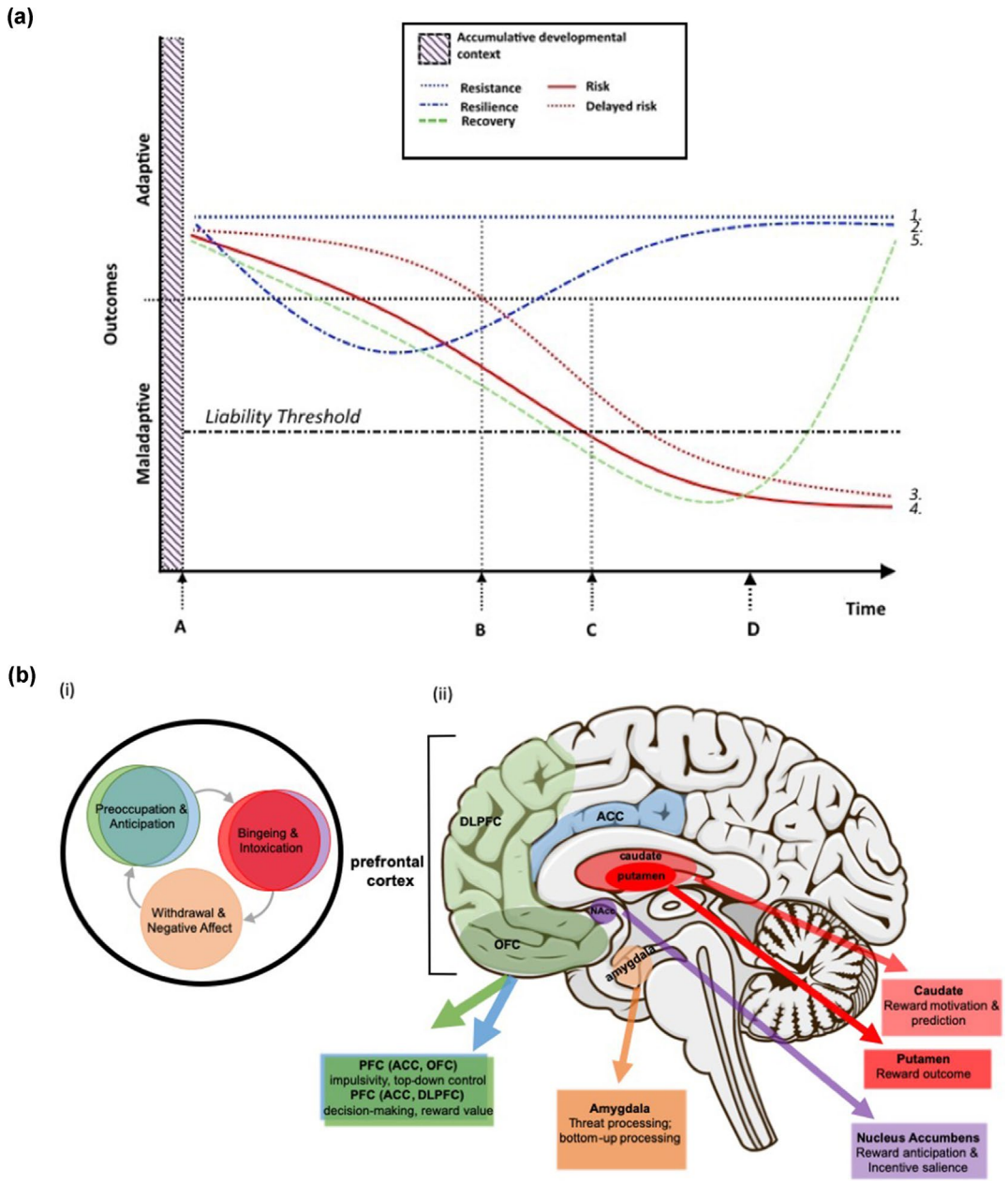

FIGURE 2 | (a) Theoretical neurodevelopmental trajectories corresponding to adaptive and maladaptive outcomes. **(1)** *Resistance*: absence of change in the developmental trajectory despite exposure to adversity; **(2)** *Resilience*: initial reaction followed by gradual degradation of the response to adversity and eventual restoration of an adaptive developmental trajectory; **(3)** *Delayed risk*: apparent early resistance to adversity but eventual decline toward maladaptive outcomes/risk; **(4)** *Risk*: initial and continued reaction to adversity, resulting in maladaptive outcomes, and **(5)** *Recovery*: a shift in neurodevelopmental trajectory back toward adaptive outcomes, following disease onset/crossing the liability threshold for a disorder, and corresponding to intervention (i.e., treatment) onset. Critical time points in delineating those factors that contribute to risk or resistance and resilience include **(A)** the initial departure in neurodevelopmental trajectories, perhaps corresponding to adversity or other stressors, **(B)** the time point at which trajectories may deviate from initial direction (i.e. resilience and delayed risk), **(C)** the time beyond which specific risk outcomes (e.g., substance abuse) are highly probable and beyond which individuals with high levels of risk are likely to have crossed the liability threshold, and **(D)** intervention/treatment onset. Note: "outcomes" includes all relevant intermediate phenotypes consisting of or related to neurodevelopment (e.g., brain structure and function, cognition, behavior, affect, etc.). The "accumulative developmental context" refers to the combined genetic and environmental context that drives brain development (as depicted in **Figure 1**), and although this context is critical to neurodevelopment it precedes observable distinctions between neurodevelopmental trajectories; this includes those factors that may be considered to be detrimental or protective. **(b) (i)** Key stages in the cycle of addiction (after 22) and **(ii)** brain regions that these key stages map to and putative functions of each region that are relevant to the development of SUD. Included here are critical regions in which functional and structural deficits have been shown to be associated with at least one of the stages in the cycle of addiction. Functional variability in these regions in response to the characteristics of the accumulative developmental context (i.e., key genetic, environmental, and psychosocial influences on neurodevelopment) likely underlie the likelihood of which trajectory (i.e., from 2a.) an individual follows. If so, these same regions and the cognitive, behavioral, and affective functions they support have considerable potential to serve as targets for preventive interventions.

nicotine/cholinergic receptor genes; opiates/opioid receptor mu genes). However, individual gene variants do not necessarily increase risk of using or abusing *specific* substances and, indeed, there is evidence that certain genes impact neurobiological systems and phenotypic traits in a manner that may directly influence pathways toward or away from substance use more *generally* (27). This includes genes that are involved in stimulus–reward processing pathways in dopaminergic (e.g., *DRD2, MAOA, COMT*), serotonergic (e.g., *HTR3A, HTR1B, HTR3B*), GABAergic (e.g., *GABRA1, GABRA2, GAD1, KCNJ9/GIRK3*), and glutamatergic neurotransmission systems [e.g., *GRIN2C*; see Ref. (28) for a review]. The phenotypic traits that are associated with these types of "risk" genotypes (e.g., high reward sensitivity, high impulsivity, low risk aversion, a tendency toward compulsive drug seeking) fundamentally interact with stress exposures that, when repeated and/or severe, have potential to compromise the development of neural systems that underlie social, behavioral, cognitive, and emotional functioning in profound and enduring ways (29, 30).

Genetic vulnerabilities in combination with the developmental stage(s) of exposure are critical to the differential effects that the exposure to stress can have on social, psychological, and neural functioning and, in turn, risk for substance abuse (31, 32). Genetic variations contribute an individual's response to existing social influences; thus, genetic influences on propensity to substance abuse and dependence are thought to mediate or moderate the impact of environmental factors on individual characteristics that are associated with risk, with stress exposures being particularly impactful (33). At the core of the gene-by-environment interaction are epigenetic modifications that occur at the level of gene functionality in response to changes in the environment. Adverse experiences, especially in early life, have potential to modify gene expression or suppression with important implications for phenotypic impact on stress hormones and behavior (34, 35). Ongoing environmental change can further modify epigenetic processes, for better or for worse, helping to explain individual differences in response to stress as well as the potential for positive environmental change (e.g., intervention) to reverse earlier negative modifications. Thus, as indicated in our conceptual model (**Figure 1**), not all who are exposed to stress and/or trauma will exhibit maladaptive physiological and psychological stress responses that affect substance abuse liability; differential susceptibility to this outcome is a function of the complex interrelationships among genetic, environmental, and epigenetic factors that individuals dynamically experience.

Environmental Influences

As noted in **Figure 1**, there are a variety of environmental factors that can influence developmental trajectories in a manner that increases the risk for substance misuse. Of particular relevance here are those factors that we know promote adaptations of relevant neurodevelopmental pathways such that an individual's liability for substance abuse and/or dependence are substantially increased. Contextual factors known to interact with biological factors to increase SUD liability include social and cultural systems, stress, and trauma (36).

Childhood maltreatment (CM) is a particularly potent risk factor for substance abuse and dependence (6). Those who experience CM initiate illicit substance use twice as often as nonmaltreated peers and are more likely to abuse substances earlier in adolescence (5, 37). Moreover, an estimated 40–50% of individuals who experience this type of trauma will develop a substance abuse problem in their lifetime (5). Neurobiological changes at the level of brain structure and function have been shown to underlie both CM and SUD and are often found in overlapping brain regions and networks (38–42). Disentangling the specific contributions of CM *per se*, versus those changes that arise in response to early and sustained abuse of substances, presents an interesting and important challenge. Although more research is needed in this domain to understand the independent, interactive, and potentially synergistic, contributions of CM and SUD to neurodevelopmental trajectories in young people, a recent review of the neurocognitive evidence of neurobiological pathways underlying SUD risk provides support for CM-related alterations in three interconnected systems that may heighten SUD vulnerability (**Figure 2b**), (1) *reward processing*—ventral striatum, anterior cingulate cortex (ACC), mPFC (including OFC) and amygdala; (2) *executive cognitive function (ECF)*—prefrontal cortex (PFC), including dlPFC and mPFC; and (3) *threat processing*—medial temporal lobe, in particular the amygdala (43).

Poverty is another common and particularly potent environmental influence to consider when delineating the neural pathways underlying SUD risk. There is consistent evidence to suggest that a child's socioeconomic status (SES) is predictive of neurocognitive trajectories across development and longer-term outcomes, such as academic achievement (44), with lower SES children experiencing suboptimal or maladaptive developmental trajectories, including neurodevelopmental pathways (32, 45–48). The most consistent *structural* impacts of poverty/low SES are seen in brain areas and processes that are sensitive to the effects of stress, including those that are relevant for SUD risk (e.g., hippocampus/memory; amygdala and medial temporal lobe/emotional regulation and threat processing; ACC/reward and decision-making) (44). Moreover, children in lower SES groups also show a range of *functional* deficits, including in brain regions that support ECF, such as prefrontally-mediated attentional focus (49–51), and in prefrontal and parietal regions supporting working memory (52, 53). Lower SES is also associated with greater amygdala responsivity to threatening and fearful stimuli (e.g., faces) in adolescence (54). Interestingly, the functional networks between these cortical and subcortical regions appear to be disrupted by the experience of poverty, with low SES children showing reduced functional connectivity between cortical and subcortical regions during both task-oriented (i.e., emotional processing) and resting-state imaging paradigms (55–57). A recent analysis of the structural connectome in healthy children (6–11 years) found that lower income-to-needs ratios were predictive of greater network inefficiency, particularly for girls, in a range of SUD-relevant regions (e.g., cingulate, insula, amygdala), further supporting the notion that childhood poverty leads to widespread disruption of brain networks (58) and suggesting at least one potential environmental factor that

may differentially contribute to risk between males and females. Collectively, these studies, while not explicitly considering substance use or misuse as an outcome, all point to a disruption of structural and functional neurodevelopmental trajectories for those who are economically disadvantaged in regions that are considered relevant for neurocognitive functions related to the extent of SUD liability. Importantly, the impacts of poverty are inextricably linked to the influences of stress and trauma on neurodevelopmental pathways that underlie the risk for substance abuse, since these experiences often occur in concert with one another. However, from a prevention perspective, it may be particularly advantageous to consider poverty as a key factor underlying a maladaptive risk pathway, since economic disadvantage can be more clearly—albeit not more simply—targeted via widely scaling appropriate, evidence-based interventions and policies.

As noted above, it is likely that a key factor underlying the impact of these types of environmental factors (i.e., CM, poverty) on SUD risk are epigenetic modifications that mediate gene-by-environment interactions, specifically those epigenetic factors involved in altering gene regulation of neurobiological systems that are relevant for maladaptive pathways that lead to SUD (59). Of note in the relationship between stress/trauma, neurodevelopment, and substance abuse liability is the role of micro RNAs (MiRNAs) (60). MiRNAs are short noncoding RNAs that epigenetically modulate gene expression. They also regulate central nervous system physiology and have the potential to contribute to alterations in complex systems, including dopaminergic and glutamatergic systems, which are both implicated in SUD (60). A particularly intriguing observation from preclinical studies of SUD-related behaviors is the phenomena of transgenerational epigenetic effects. For example, in rat models, adult drug taking that precedes conception appears to influence reward-related behavior and drug self-administration in first-generation offspring (61, 62). While these types of transgenerational impacts of SUD are potentially highly relevant for those families and communities that are at highest risk for SUD and for which effective prevention is most urgently needed, further study is required to demonstrate similar transgenerational mechanisms in humans. If such effects are found, this information may offer a particularly novel opportunity for cross-generational preventive interventions for SUD.

Neurological Development

The role of deviations or delays in neurodevelopmental pathways underlying problem (especially high risk) behaviors that often precede substance use has been increasingly recognized in studies of SUD risk. As in our Accumulative Risk Model, perturbations in brain structure and function are commonly viewed as critical mediators between the developmental context (i.e., relevant genetics and environmental factors) and the cognitive, behavioral, and affective phenotypes that precede problematic substance use. Understanding the neurobiological contribution to the etiology of substance use involves characterization of brain maturational processes that underlie neurocognitive development during critical periods of development, such as adolescence, that are associated with substance use (e.g., reduced inhibitory control and increased reward sensitivity).

While substance abuse is the result of maladaptive developmental trajectories with their roots in the prenatal period and lasting until the mid to late 20s, substance use initiation is most typical in early to mid-adolescence and, for the subgroup that escalates, substance abuse peaks during the transition into emerging adulthood (63). Critically, new social challenges facing adolescents (e.g., increased autonomous decision-making) coincide with complex changes in brain function and connectivity taking place throughout this time, which have implications for adaptive decision-making and the ability to self-regulate behavior and emotion (64, 65). In effect, some degree of impulsivity, risk-taking, and sensation seeking is normative during adolescence, as indicated above; however, a heightened level of risk-taking may extend from a combination of social circumstances and nonnormative neurodevelopmental immaturity or dysfunction.

Neurobiological development during adolescence occurs transitionally rather than as a single snapshot in time (66). The PFC, which is responsible for ECFs, such as decision-making, impulse control, and working memory, undergoes prolonged development and is still largely under construction during adolescence. A central role of ECFs is to promote behaviors that shield long-term goals from the temptations afforded by short-term benefits that often lead to negative consequences (67). Prefrontal "top-down" neurocognitive regulation over subcortical regions that support affective processes (e.g., emotion regulation, affective decision-making) is somewhat functionally disconnected throughout adolescence (68), translating into a natural bias in adolescents toward acting on emotional stimuli with relatively little cognitive control over those actions. Through both the natural course of development and environmental experience, connections between these regions are strengthened, providing a mechanism for increasing top-down regulation of emotional brain systems and improved behavioral outcomes (69, 70).

In addition, brain circuits involved in reward processing (e.g., the mesocorticolimbic pathway that involves typical reward-related regions, such as the ventral striatum) show rapid maturation during the adolescent years (71–73), which can have the effect of heightening sensitivity to rewarding experiences (i.e., making adolescents typically more reward sensitive and less risk averse). Paralleling this increase in reward sensitivity during this developmental period is a greater tendency toward sensation/novelty seeking (74). The developmental trajectory of reward circuitry likely plays a critical role in substance use initiation rates in early to mid-adolescence and may be especially pronounced in the subgroup that escalates use. Moreover, subsequent use of substances has the potential to exacerbate an already heightened reward sensitivity in some adolescents, resulting in a strengthening of the drug's reinforcing properties (75).

Compounding these neurological liabilities (i.e., reduced ECF and heightened reward sensitivity) are early puberty and erratic hormone levels, as well as the potential to experience detrimental environmental conditions, such as stress, adversity, maltreatment, and other negative experiences that compromise

neurodevelopment and can cause measurable dysfunction in these systems. Thus, regardless of the source of delayed or deficient neurodevelopment, the imbalance between increasing social demands and emergent neurobiological systems during adolescence may lead to heightened vulnerability to substance use and escalation (76). This evidence has direct implications for attempts to parse the developmental trajectories that give rise to SUD and the design of intervention components that effectively target this period of development.

Stress Exposures and Physiological Reactivity

"Stress" refers to processes involving perception, appraisal, and response to harmful, threatening, or challenging external events or conditions, known as "stressors," such as poverty, prenatal exposures, child maltreatment, divorce, and bereavement (77). It is a major common denominator across the neurobiological and psychological domains discussed above and is a ubiquitous factor in susceptibility to substance use, escalation, relapse, and treatment resistance (78, 79). There is substantial evidence to support the role of stress in substance use trajectories [e.g., Refs. (6, 80)]; early life adversity is markedly associated with increased risk for substance use, abuse, and dependence (5, 81, 82).

Chronic and/or severe stress early in life alter emergent stress signaling pathways that, in effect, impair the ability of the PFC to exert cognitive control over more reflexive responses. For example, studies have shown neurodevelopmental deficits or delays in mesocorticolimbic circuits in adults who were maltreated as children, suggesting that functional aberrations may be due, in part, to dysregulation in this network of prefrontal and limbic regions (83, 84). Stress exposures also disrupt both hormonal and physiological systems that regulate these functions at the level of brain and peripheral nervous system, thereby impairing learning, memory, decision-making, and other functions that normally support self-regulation of behavior (85–87). Alterations in hormonal systems (e.g., cortisol) that modulate these functions (85) occur with chronically elevated levels of stress hormones which can reduce hippocampal volume, impair memory, and decision-making (2, 87). Psychophysiological studies also show effects of stress on autonomic responses such as heart rate that, when perturbed, are associated with psychopathology (88–90). In general, greater levels of stress alter brain circuitry, largely impacting the ability of the PFC to maintain behavioral and cognitive control over affective responses (91). These biological stress responses activate the same neural systems found altered in many mental health disorders and that underlie the rewarding effects of drugs (e.g., dopaminergic mesocorticolimbic circuitry), potentially reinforcing drug-taking behaviors (92, 93). As a result, when an individual experiences a great deal of stress or adversity, these stress responses affect brain function, leading to poor decision-making and other executive cognitive skills; thus, drug taking may occur as a maladaptive response to stressful experiences.

Adversity and stress have been inextricably linked to risk for substance abuse throughout adolescence (5, 6) possibly via effects on neurocognitive development in a way that predisposes individuals to impulsivity and externalizing behaviors (94, 95). In fact, numerous studies have demonstrated associations between increasing levels of emotional and physiological stress and decreases in behavioral control, heightened impulsivity, and greater incidence of maladaptive behaviors [e.g., Refs. (96–98)]. Moreover, a growing body of evidence suggests that impulsivity and externalizing behaviors may, in particular, mediate the association between adversity and risk for later substance abuse (99). These behaviors have also been consistently associated with deficits in ECFs (15, 100–102) and reportedly develop in response to exposure to early adversity [for review, see Ref. (43)]. As such, there is a plausible confluence of factors at play, corresponding to the Accumulative Risk Model, which may shed light on the delayed development of adverse outcomes; specifically, pathways from early adversity that interact with risk genotypes to impact emergent neural circuits and, in turn, externalizing and impulsive behaviors, thereby increasing propensity to substance misuse.

These findings suggest that very early development sets the stage for a heightened response to substances through primary biological, psychological, and social systems. Andersen and Teicher (103) provide evidence that early life stress predisposes individuals to abuse substances later via alterations in immature neurophysiological systems that have yet to come on board. In adolescence, when these emergent systems become increasingly functional, the damage is expressed in heightened risk for psychopathology. If the behavioral effects of early childhood stress are not observable until neural connections begin to onboard during adolescence (103, 104), implications for prevention are intriguing. For example, a few studies are now suggesting that training to reduce impulsivity, improve ECF, and integrate components that focus on "top-down" cognitive control has potential to reduce substance use initiation *and* escalation (105). Recognizing the increased risk for substance use in people who have experienced early life stressors is critical to guide prevention efforts designed to both prevent the exposure and counteract the potential subsequent negative consequences.

Cognitive and Behavioral Phenotypes

Externalizing disorders are consistently implicated in the use and abuse of a range of substances (106). The neurocognitive characteristics of children and adolescents with externalizing behaviors include heightened reward sensitivity, poor inhibitory control, aggression, and novelty seeking (107, 108). Variation in these dimensions, particularly impulsivity and reward seeking, contributes to the likelihood of substance use initiation as well as the transitions from initial to intermittent to regular substance use, the transition from abuse to addiction, and the propensity for repeated relapse after achieving abstinence (109). Individuals who measure highly on these traits tend to seek highly stimulating and risky situations and show less anxiety in anticipation of the consequences of their behavior (109, 110). Importantly, these cognitive and behavioral predispositions have differential impacts on substance use patterns at different developmental stages (111, 112). Normative development during adolescence is typified by heightened levels of impulsivity and novelty seeking, in part due to dramatic fluctuations in hormone levels that affect brain development and other systems modulating neurocognition (113). However, the subgroup of

adolescents that exhibit heightened impulsivity and sensation seeking are at elevated risk to abuse substances (4, 114). These characteristics may, in effect, contribute to individual differences in the reinforcing effects of substances (115).

Psychopathology in many forms [e.g., posttraumatic stress disorder (PTSD), depression, anxiety, conduct disorder (CD), attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), antisocial personality disorder (ASPD)] is strongly and consistently related to the risk of substance abuse [for review, see Ref. (116)]. Individuals with these disorders are more likely to use/abuse substances and at an earlier age than those without such disorders (117, 118). They are also more likely to be resistant to substance abuse treatment (119). In general, individuals afflicted with mental health problems are often compromised in their ability to effectively meet social task challenges, as doing so requires intact neurocognitive functions, which are often compromised in psychiatric disorders (120, 121). Further compounding the risk, the development of mental health disorders increases use in an effort to manage symptoms and this association is likely to vary as a function of the type of mental health disorder. Mood and anxiety disorders, for example, double the risk for SUDs (122). Relatedly, alexithymia (i.e., an emotional processing deficit, whereby one experiences difficulty identifying or describing one's emotions), has been identified as a pertinent risk factor for SUD (e.g., up to 2/3 of patients with SUD exhibit alexithymia) (123) and may increase the risk of negative outcomes such as suicide and self-harm in those who develop SUD (124–126). Since alexithymia predicts poor emotional regulation (127), which in turn predicts poor response to intervention [e.g., Ref. (128)], along with other forms of psychopathology that predict SU liability, it may be an important phenotypic characteristic to consider in the context of the differential trajectories highlighted here.

Gender is also an important factor in the association between SUD and other types of psychopathology. For example, males more often exhibit antisocial personality and conduct disorders (129), while females often have higher rates of mood and anxiety disorders (130); as a result of these gender-specific differences in prevalence of certain psychopathologies and their differential associations with substance misuse, these disorders confer differential gender-related risks for substance abuse (131).

Delayed Risk for Substance Misuse

The second maladaptive pathway toward substance misuse that is theorized here and conceptualized in our model is characterized as *delayed risk*: i.e., individuals who either initiate in adolescence but do not escalate until early/emerging adulthood, or who initiate and develop substance-related problems in late adolescence or early adulthood [e.g., Ref. (132)]. While understudied, delayed risk is also seen in those who do not develop SUD until middle or late adulthood [e.g., Ref. (133)], although the critical factors (especially environmental influences) that underlie such trajectories later in life may be distinct from those that drive misuse and escalation in earlier developmental periods.

Longitudinal studies have distinguished delayed risk in late adolescence/emerging adulthood by histories of externalizing behaviors, child maltreatment, and being bullied by peers, whereas other patterns of use (e.g., limited use) have been characterized by family instability and anxiety disorders (134). However, a nonlongitudinal study of men with substance abuse reported nearly identical childhood and adolescent risk factors (135), while another longitudinal study (136) found similar factors to be predictive of adolescent and adult illicit drug use, with the addition of early cannabis use as a significant catalyst for both groups, thus complicating our ability to disentangle which factors may be more closely coupled with delayed vs. early risk.

It may also be the case that the social transitions into emerging adulthood represents a significant risk factor for substance abuse in those who have difficulty with the novel demands of this developmental period. Though social role transitions (e.g., stable employment, marriage/cohabitation, parenthood) are typically associated with decreases in substance use (137), timing of, preparedness for, and adjustment to these transitions may be critical in predicting delayed risk for substance abuse. For example, in a longitudinal study of 18–33 year olds, an earlier transition into parenthood (i.e., late teens, early 20s) was associated with an increased rate of tobacco misuse (138). Likewise, high school seniors making the transition into early adulthood who have no plans for college are more likely to misuse prescription opioids compared to their peers who did have such plans (139). It is possible that the stress of newfound social demands and responsibilities for which some individuals are not developmentally prepared provides a generative context for substance abuse (138). In other words, there may be a developmental mismatch between expectations in adolescence for mature, autonomous behavior and their neurological, psychological, and social capacity for taking on a significantly greater level of responsibility during this transitional period. This mismatch may be an important predictor of delayed substance abuse, both during emerging adulthood and in later adulthood (140). Interestingly, the discordance between demands and abilities as adolescents approach adulthood may actually predict substance misuse later in adulthood. For instance, Green and colleagues (133) reported that individuals who were unmarried, unemployed, and had lower social integration during young adulthood were more likely to have delayed onset SUDs during middle adulthood. Taken together, these results suggest that individuals who experience difficulty adapting to developmentally normative social transitions, particularly during emerging adulthood, when there is less parental support, greater opportunities to engage in risky behaviors, and more access to substances, may be at increased risk for developing SUDs.

Resilience and Resistance to Substance Misuse

Trajectories of *resilience* (i.e., rebounding from adversity after an initially altered trajectory or decline in functioning) and *resistance* (i.e., maintenance of adaptive functioning, despite adversity) are less well characterized than risk in the existing literature, for several reasons. First, since adversity and its negative consequences are major public health concerns, there has historically been a strong emphasis on deleterious sequelae of developmental adversity

and stress, to the relative neglect of positive outcomes. Second, resilience and resistance are often not delineated as separate processes in the literature; that is, some proportion of those who are operationally defined as resilient may more aptly be defined as resistant. While studies typically characterize "resilience" as the absence of behavioral health or psychiatric disorders in adulthood, the majority do not track fluctuations in pathways over time and, thus, are unable to distinguish subgroups that sustain mental and behavioral health from childhood into adulthood relative to subgroups that respond to adversity with a decline in function but eventually improve; both classes will appear similar when outcomes are measured in adulthood. Thus, conceptualizing resilience as a single-end point (e.g., lack of psychopathology) may be misleading and prohibits the differentiation of subgroups that have followed pathways that may have diverged at various points in development. Finally, resistance is not often considered explicitly in the SUD literature. This is likely because characterizing subgroups *not* engaging in high-risk behaviors has been less of a priority and possibly also because this subgroup—which does not misuse substances or exhibit other forms of psychopathology—is not readily discernable, particularly in nonlongitudinal, cross-sectional studies. Consequently, the concept of resistance has largely not been in the SUD research lexicon, and has thus been almost entirely overlooked. A notable exception is a study by Hobfoll and colleagues (141) where they contrasted between resistance and resilience, both behaviorally and biologically, in individuals who experienced significant trauma and, yet, ultimately followed different pathways. These trajectories were identified and characterized in individuals who experienced ongoing terrorism. The authors suggested that resistance and resilience differ in terms of impact (resist vs. absorb), function (continue vs. gradually degrade), resumption of function (immediate vs. delayed), as well as overall response to adversity (defeat vs. limit).

While the conceptual model presented in this paper is focused on differentially characterizing trajectories on the basis of neurocognitive evidence, the paucity of literature clearly distinguishing resilience from resistance precludes such a review specifically for outcomes that are overall adaptive. Therefore, to explore the distinction between resilience and resistance further, we instead describe the few existing studies that delineate some of the relevant factors that likely contribute to and distinguish these two positive developmental pathways. Given associations between these influential factors, neurocognitive development, and functioning across the lifespan, we rely on these findings to formulate hypotheses regarding how these positive pathways may operate.

Neurocognitive Factors Relating to Adaptive Pathways

Despite overwhelming evidence of early stress and trauma's adverse influences on adult outcomes, many individuals exposed to trauma exhibit healthy adult functioning [e.g., Refs. (142–144)]. Some studies have begun to highlight the potential of strengthening cognitive and emotion regulatory skills to act in a protective capacity in those who have experienced trauma. For example, in a study of highly traumatized urban adults compared those who did or did not exhibit psychopathology, those who did not develop psychopathology had better nonverbal memory than those who did, despite similar levels of CM and trauma (145). Other work has suggested that emotion regulation, which is related to impulsivity and subsequent substance use patterns (146), is predictive of extent of adaptive coping in maltreated children (147). Moreover, in children exposed to political violence, higher levels of cognitive flexibility has been shown to moderate the relationship between violence exposure and psychological well-being (148). Though these studies did not explicitly measure substance use, it is possible that having well-developed neurocognitive skills (e.g., memory, cognitive flexibility, emotion regulation) enables individuals who have experienced trauma to adaptively navigate their environments and avoid substance misuse and eventual dependence, despite a history of adverse experiences. Indeed, deficits in these neurocognitive skills are related to substance abuse (149–151), providing further support for the inverse relationship, with more robust neurocognitive skills predicting a decreased likelihood of developing SUDs.

Interestingly, a few studies suggest that early adversity may drive neurocognitive adaptation in some individuals in ways that enables them to outperform healthy controls or those who have had fewer adverse experiences. For example, Nolin and Ethier (152) reported that children who had a history of neglect evinced better planning and problem-solving skills than children without histories of abuse. There are also similar findings from research with older adults (i.e., 50 years and older) who have experienced CM, providing additional evidence of preserved cognitive functioning in spite of adverse experiences (e.g., visual memory, verbal memory, executive functioning, attention, processing speed) (153, 154). For example, Feeney and colleagues reported that older adults who had experienced childhood sexual abuse had better executive functioning, attention, and processing speed than those without maltreatment history (153). Similarly, another study demonstrated that, compared to those with moderate levels of CM, individuals with severe levels of maltreatment had lower risk of cognitive impairment (i.e., visual memory, executive functioning, and verbal memory) later in life (154).

Taken together, this work supports the concept of a subset of individuals who may have protective assets, particularly in neurocognitive domains of functioning, that enable them to thrive despite experiences of adversity, trauma, and stress. The extent to which their adaptation corresponds to resilience vs. resistance pathways in patterns of substance use remains to be explored. However, we posit that, based on indices of neurocognitive functioning, classes of individuals may be more aptly characterized by longitudinal investigations that aid in the delineation of critical time points corresponding to these divergent developmental pathways. In particular, a clearer understanding of adaptations to adversity will emerge with further investigation into resilient and resistant trajectories that correspond to the behavioral and mental health endpoints of interest. Longitudinal observations will allow us to more fully characterize adaptations, which are important predictors of ultimate outcomes (adaptive vs. maladaptive) and that may fluctuate or be sustained at particular developmental time points. As such, future work characterizing these different developmental pathways is critical for understanding the precursors of these trajectories and how they unfold *and* to identify and bolster neurocognitive factors that confer resilience or resistance.

Neuroimaging Correlates of Adaptive Pathways

A few recent neuroimaging studies have begun to pinpoint brain regions that differentiate trauma exposed individuals who do or do not exhibit adaptive outcomes (e.g., based on psychopathology or adaptive functioning status). For example, compared to those who experienced maladaptive outcomes, trauma-exposed youths who exhibit adaptive functioning have been found to have lower resting-state functional connectivity (rsFC) within default mode, salience, and executive control networks (155). Interestingly, all of these networks have been shown to be disrupted in substance-abusing samples (156, 157). Other rsFC studies have highlighted the dorsal ACC (dACC) as a region showing distinguishable patterns of connectivity in adaptive vs. maladaptive outcomes for those who have experienced early life stress and/or trauma (158, 159). For example, Philip and colleagues found increased rsFC between the thalamus and dACC in adults who experienced early adversity *without* psychiatric disorders compared to those with psychiatric disorders (158). These findings are intriguing with respect to potential neural correlates of resilient and resistant pathways pertaining to substance use, given that previous work has reported diminished activation and connectivity patterns in the dACC in substance-dependent individuals, particularly when processing rewards (160, 161).

Findings from several other neuroimaging studies suggest that the structure and function of the frontal lobe (e.g., volume, activation, connectivity) is implicated in adaptive functioning following adversity (162–164). Specifically, one study found that adaptive adolescents who had experienced early adversity had increased middle frontal and superior frontal gyri volumes compared to maladaptive adolescents who had experienced early adversity as well as those who had not experienced adversity (163). Moreover, the same study reported that middle frontal gyrus volume negatively correlated with problematic drinking in adolescents who were deemed adaptive but experienced early adversity (163). Another study found that compared to individuals with PTSD, those who were also trauma exposed but did not have any psychiatric disorders showed enhanced ability to recruit frontal regions associated with top-down attentional control during an emotional Stroop Task (165). Similarly, patterns of increased frontolimbic connectivity seem to distinguish maltreated individuals from healthy controls who were comparable in adaptive functioning, including a lack of substance abuse (164). Although these studies did not all measure substance use or neurocognitive functioning, they do provide initial support for increased volume and functional recruitment of frontal regions as being a neuroprotective factor in individuals who have experienced early adversity. Such findings are promising in their ability to distinguish neural profiles of adaptive and maladaptive traumatized populations; however, they also evoke many questions about how frontal lobe development progresses in individuals who follow resilient or resistant pathways in response to adversity. For instance, future studies could probe how specific neuroprotective factors (e.g., increased or decreased frontal lobe activation and connectivity) interact with other factors (e.g., genetic or environmental liabilities) to confer a likelihood of following a resilient or resistant pathway subsequent to early adversity.

Delineating Resilience and Resistance: Future Work

By and large, the literature points to several neurocognitive factors that likely contribute to resilience or resistance pathways subsequent to adversity. However, as noted, prior research has not made concerted attempts to disentangle these pathways, their precursors, and their trajectories. Therefore, many open questions remain as to how subgroups who attain successful outcomes following trauma, maltreatment, or other environmental adversities rebound from or, in contrast, resist engaging in substance misuse. Since not all survivors of adversity develop SUDs or other forms of psychopathology, it is critical for future work to pinpoint and characterize these subgroups. Moreover, the preliminary evidence cited above suggests that individual differences in neurocognitive skills or patterns of connectivity in regions of interest for SUDs may differ across development but may still ultimately predict similar adaptive outcomes. For instance, it is plausible that individuals who are less adept at regulating emotions and engaging executive functions (i.e., regulating top-down processes) may experience initial developmental disruptions that lead to substance use that they rebound from (i.e., resilience trajectory). In contrast, those who are more adept at these neurocognitive skills may resist substance use altogether (i.e., resistance trajectory). As others have suggested in the literature, resilience to adversity is a dynamic, state-like process, not simply a trait, and individuals who appear adaptive later in life may or may not have experienced initial maladaptive pathways from which they have rebounded. Recent studies have also proposed novel models [e.g., the *Resilience Portfolio Model* (165) or the *Diversity Portfolio Model* (166)] that conceptualize "resilience" as an arsenal of protective factors associated with healthier outcomes following trauma. Accordingly, the density and/or diversity of available protective resources and assets may shape their long-term capacity to adapt and thrive despite adverse experiences. As such, future studies that thoroughly characterize neurocognitive profiles, across the developmental timeline, and which delineate how such profiles interact with other factors known to bolster adaptive functioning, may be able to meaningfully distinguish those who are resilient and rebound from those who are resistant. This distinction in pathways is crucial, as those who are resilient may be categorized by particular vulnerabilities during specific windows of time that may serve as critical opportunities to successfully intervene with prevention programs. In summary, delineating the neurocognitive profiles of individuals who exhibit resistant vs. resilient pathways may be critical for identifying novel ways to bolster functioning in those who experience maladaptive pathways/outcomes.

METHODOLOGICAL APPROACHES TO DISTINGUISH TRAJECTORIES

While there is convincing evidence for distinctions between risk, resistance, and resilience trajectories based on phenotypic presentations, studies have yet to effectively delineate the possible neurocognitive correlates or underpinnings that support their distinctions. This information may have important implications

for more precision-based, developmentally sensitive intervention targeting. It is reasonable to surmise that environmental risk and protective factors may impact neurocognitive development in unique ways across individuals and/or subgroups, leading to different phenotypic outcomes. With respect to positive outcomes such as resilience, resistance, and recovery, this assumption is supported by the equifinality of the result—i.e., a similarly adaptive outcome profile across these different trajectories—and thus may be logistically difficult to differentiate. Cross-sectional research designs are inadequate in this endeavor; they may be able to confirm that various outcomes are predicted by the level of neurocognitive functioning at a single time point but they are unable to chart the dynamic interplay of risk and protective factors that impact the course of neurodevelopment and its relationship to final outcomes. In contrast, by establishing temporal ordering within subjects, longitudinal research designs are uniquely positioned to pinpoint developmental phenomena and their divergent pathways. Thus, a longitudinal approach is able to model the experiential and contextual impact on neurobiological factors across development to understand the nature of the various pathways that lead to eventual maladaptive versus adaptive outcomes. Pinpointing neural markers that distinguish individuals who move along these distinct pathways will help us to identify novel targets for intervention. By fully characterizing and differentiating these trajectories, longitudinal studies have the potential to aid in the delineation of the precise nature of influential factors at optimal time points along their development (e.g., adversity onset, treatment onset, redirection) and, in doing so, to identify malleable targets that exist along these trajectories, which will serve to maximize the translational potential of this research.

Latent class modeling has the potential to substantially aid in the determination and delineation of unique pathways that underlie SUD liability, including risk, resilience, and resistance. Latent class modeling refers to a group of statistical methods aimed at identifying unobservable (*latent*) subgroups within a particular population. It includes latent class analysis (LCA), which considers outcomes at a particular time point (e.g., adolescence), and a related methodology, latent transition analysis (LTA), which facilitates estimation of transition between subgroups over time. An application of LCA that includes consideration of the types of risk- and resilience/resistance-relevant factors outlined in the Accumulative Risk Model (**Figure 1**) and, especially, pertinent neurodevelopmental factors (e.g., neurocognitive processes, variation in brain structure, function, and connectivity) will facilitate the determination of which specific constellations of factors give rise to which intermediate phenotypes and associated pathways. Moreover, an LTA approach will allow us to determine which factors are particularly relevant at the time points where we see real or apparent shifts in developmental trajectories, either toward or away from increased liability and adverse outcomes.

These latent class approaches hold considerable potential for determining opportunities and methods to optimize preventive interventions. However, to-date, there is a relative paucity of research using latent class modeling in the context of risk for substance abuse and dependence that has focused on neuro-related factors and/or on the types of longitudinal approaches to SUD liability that we are suggesting here. Nonetheless, application of latent class models to substance abuse risk and treatment have revealed some interesting outcomes regarding how patterns of use may impact substance use behaviors or brain activity [e.g., Refs. (167–169)] and support the appropriateness of these methods in the context of SUD liability pathways.

THE POTENTIAL FOR PREVENTION

Based on a burgeoning body of evidence, brain development and function are, for better or for worse, clearly experience dependent. For worse, adversity in its many forms has the potential to impact neurodevelopmental trajectories in ways that undermine emergent self-regulatory mechanisms, increasing risk for psychopathology, including eventual SUD. However, for the better, the brain's substantial plasticity translates to the potential for well-conceived prevention strategies to improve behavioral and mental health outcomes by positively impacting the same neurodevelopmental pathways. Although most prevention science studies do not attempt to elucidate the neural mediators of intervention responses, a considerable number of prevention programs have been shown to reliably reduce risk for substance abuse. Research to enhance our understanding of the neurodevelopmental effects of prevention programming has potential to further differentiate the pathways involved in the relationship between risk factors and behavioral outcomes and, in doing so, will identify mediating mechanisms that explain outcome heterogeneity. This argument is particularly compelling given that, at present, the evidence-based programs that have emerged from various disciplinary perspectives produce only small to modest effects on the phenotypes predictive of SUD risk and resilience/resistance pathways, as well as SUD itself. More comprehensive and in depth information is needed to advance predictive analytics and increase the precision with which we target programmatic components.

It is likely that evidence-based programs work at the level of the brain, driving adaptive changes in brain structure, function, and connectivity. Programs that focus on socioemotional and cognitive functioning are strong candidates in this regard. Development of these skills, both behaviorally and neurobiologically, are particularly vulnerable to adverse psychosocial and environmental influences. Programs that redirect and possibly normalize these specific dimensions of a child's developmental pathway may exert a potent impact on corresponding behavioral, emotional, mental, and physical (e.g., brain function and fitness) domains. The effects of appropriately targeted interventions may be particularly remarkable for children who are disadvantaged by poverty and other social ills. Research that integrates multiple disciplines to better understand influences and outcomes related to substance abuse have directed us toward solutions for these problems that target underlying mechanisms and not solely the distal outcome of substance abuse, *per se*. In other words, it is vital that we address the factors that eventually lead to drug abuse prior to its development, the key principle behind prevention science.

The integrity of the way in which the brain develops in children is a prerequisite for adaptive responses to socioenvironmental

challenges and thus, to favorable responses to intervention [e.g., Ref. (170)]. Thanks to the vast brain plasticity throughout childhood and adolescence, there is a great deal of variability in the way children develop in response to environmental inputs, including the divergent pathways under discussion here. This plasticity throughout early childhood and adolescence offers several optimal windows of opportunity for intervention. When neurodevelopment is on course or shows a trend toward improvement, overall intervention outcomes are likely to be favorable. In contrast, existing or emergent neurodevelopmental deficits or delays may compromise intervention effects, potentially explaining differential outcomes in response to even the most highly regarded and efficacious programs. A comprehensive evidence-based set of solutions (programs and policies) to prevent psychopathology and eventual drug abuse that operates to enhance developmental indicators of brain function in multiple domains are needed. This approach will, in turn, improve the ability to self-regulate behavior and reduce the risk for developing SUDs.

Applying this integrative and developmental perspective will lead to significant advancements in our ability to prevent substance use and the eventuality of SUD for some. Indeed, SUD intervention researchers have begun to incorporate cognitive training, mindfulness approaches, behavioral and environmental modifications, and other innovative strategies that target malleable neurodevelopmental processes that contribute to substance abuse (171, 172). Determining which early influences are particularly relevant will be critical to designing interventions that target the underlying generators of SUDs, before behavioral problems and substance use patterns become entrenched. And while there are many outstanding questions in this line of research, we do know enough about prevailing conditions that influence risk for SUDs to exert a positive impact now.

CONCLUSIONS

Studies on the successes and failures in the treatment of SUDs are benefitting from the inclusion of neuroimaging, leading to the identification of biomarkers of SUDs and increasing our understanding of variability in treatment outcomes. Proximal biomarkers in prevention studies are similarly needed to provide targets for intervention, detect differentially receptive subgroups, predict intervention response, and broadly improve outcomes. This technique could be particularly promising for "proven" prevention strategies with protective longitudinal results from early childhood through adolescence and adulthood, but were created before the explosion of biomarker research. Important advances in studies including neuroimaging and other biomarkers have revealed activity within relevant neural circuits in association with behavioral change reflective of protection from substance abuse. The application of early neuroimaging to well-established prevention strategies has potential to elucidate the neural correlates of dimensions of functioning commonly implicated in substance use and related disorders, such as impulsivity, reward sensitivity, and cognitive control, among others. While these dimensions of functioning have been related to substance misuse, SUD treatment outcomes, and relapse, a better understanding of these dimensions and their neural correlates and how they correspond to the distinct adaptive and maladaptive developmental trajectories considered here (i.e., *risk, delayed risk, resilience,* and *resistance*) could identify malleable brain–behavior biomarkers for improving preventive intervention effects. Extending models from treatment research to prevention is sorely needed by identifying functional, malleable mediators, and moderators of well-established prevention programs. Indeed, this line of research—to identify biomarkers and conditions within which they interact that distinguish between developmental pathways—has potential to identify novel targets for intervention. Such information will provide curriculum developers with data critical to optimizing programs and compelling public, mental health, and educational policies to further scale effective prevention strategies. In effect, improving our ability to disrupt pathways to SUD would constitute a significant public health advancement with potential for population level effects.

AUTHOR CONTRIBUTIONS

DF initiated the concept for the paper. DF and ER conceived of the framework and ER elaborated on a proposed new model for understanding distinctive pathways to substance misuse and addiction, including pathways that eventually diverge and lead to positive outcomes despite prevailing risks. By and large, DF and ER framed and wrote the majority of the paper. ER and GP constructed the figures. GP contributed to the writing, referencing, and reviewing/editing of the paper.

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BRIEF RESEARCH REPORT
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Dysfunctional Personality Beliefs Linked to Emotion Recognition Deficits in Individuals With Cocaine Addiction and Personality Disorders

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Background: Facial emotion recognition is impaired in addiction and personality disorders. Dysfunctional personality beliefs reflect negative interpersonal schemas that may underpin emotion recognition deficits. We aimed to examine the association between personality beliefs and emotion recognition among participants with cocaine use disorder including those with comorbid personality disorders.

Methods: We recruited 70 participants with cocaine use disorder aged between 19 and 52 who had used 14 g of cocaine over 4.8 years on average. Thirty-eight participants had an additional personality disorder (11 Borderline, 7 Histrionic, 5 Antisocial, 10 Avoidant, and 5 Obsessive–Compulsive). Dysfunctional beliefs were indicated with the Personality Belief Questionnaire, and facial emotion recognition was indicated with the Ekman's Test. We applied correlations/multiple regressions to test the relationship between beliefs and emotion recognition.

Results: Personality beliefs reflecting paranoid, borderline, and antisocial schemas were negatively associated with emotion recognition. Antisocial beliefs were associated with poorer recognition of fear, and paranoid beliefs with poorer recognition of disgust. Antisocial beliefs were significantly associated with emotion recognition after adjusting for cocaine use.

Conclusion: Dysfunctional personality beliefs are associated with poorer emotion recognition in cocaine addiction. Personality-related negative schemas about the self and others can impact social cognition and interaction during cocaine treatment.

Keywords: emotion recognition, personality disorders, cocaine use disorder, personality beliefs, antisocial beliefs

INTRODUCTION

Facial emotion recognition reflects the ability to identify basic emotions in others and is essential for adaptive social interaction (1, 2). Deficits in facial emotion recognition are a hallmark of substance use disorders (SUD) (3). However, although SUD often co-occur with personality disorders (4),

little is known on the relationship between comorbid personality dysfunction and facial emotion recognition. This is important because personality disorders are characterized by difficulties with social interaction and disturbed representations of others (5–7). Individuals with personality disorders have lower facial emotion recognition accuracy than healthy controls (8–10). However, we do not know if the comorbidity between SUD and personality disorders is associated with additive or specific impacts on facial emotion recognition. Unraveling the link between personality dysfunction and facial emotion recognition can contribute to understand social interaction problems and persistence of SUD among individuals with comorbid personality disorders.

In the context of SUD without comorbidities, previous studies have found that individuals with cocaine-SUD have poorer recognition of specific emotions such as anger and fear (11). In the only study comparing individuals with cocaine-SUD with and without personality disorders, Morgan and Marshall (12) found no significant effects of comorbidity on fear recognition. Using psychophysiological measures of fear and arousal reactivity, Baschnagel et al. (13) also failed to find a significant effect of the comorbidity on psychophysiological measures of emotion processing. However, these studies have adopted a categorical approach, by comparing comorbid versus non-comorbid participants (13) or covarying the effect of the comorbid personality diagnosis (12). However, current evidence supports the view that dimensional measures of personality dysfunction are better suited than categorical approaches to gain insight on emotion recognition deficits (14). Dimensional measures of antisociality and anxiety are negatively associated with emotion recognition accuracy, and specifically with poorer recognition of anger and fear among healthy individuals (15).

Personality beliefs are key dimensional features of personality disorders that have been neglected in previous studies of emotion recognition (16, 17). Dysfunctional beliefs reflect deep-rooted negative schemas that can consistently bias cognitive and affective judgments about oneself and others (17). Since these negative schemas are linked to specific personality disorders, the degree of disturbance can be estimated by measuring endorsement of specific sets of beliefs (e.g., antisocial—"I should do whatever I can get away with"; obsessive–compulsive—"Any flaw or defect may lead to a catastrophe") (18). The Personality Belief Questionnaire (PBQ) was originally designed to measure these personality beliefs and has received recent attention and excellent kudos as a dimensional measure of personality dysfunction that is well aligned with contemporary views, as well as reliable and predictive of severity of personality dysfunction (17, 19). Previous studies have shown that individuals with cocaine-SUD have elevated PBQ scores compared to healthy controls (20, 21). Moreover, those with cocaine-SUD and personality disorders exhibit higher scores than controls in antisocial, borderline, histrionic, and narcissistic scales (20). PBQ scores are also elevated among people with other psychiatric disorders (i.e., depression and eating disorders) who have comorbid personality disorders compared to those with single diagnoses (17, 19).

In this study, we aimed to examine the relationship between dimensional estimates of dysfunctional personality beliefs, measured with the PBQ, and emotion recognition, indicated by the gold-standard Ekman facial emotion recognition test, among people with cocaine-SUD including those with comorbid personality disorders. In fitting with previous evidence on dimensional personality correlates of emotion recognition, we hypothesized that dysfunctional beliefs associated with antisocial and anxious-like personality disorders would be linked to lower emotion recognition accuracy and specifically poorer recognition of fear and anger.

METHODS

Participants

The sample comprised 70 participants (11 females) with cocaine use disorder, of whom 38 (54%; consistent with previously reported comorbidity rates) (22) had comorbid personality disorders (11 Borderline, 7 Histrionic, 5 Antisocial, 10 Avoidant, and 5 Obsessive–Compulsive). Participants with and without comorbid personality disorders did not significantly differ on sociodemographic characteristics or cocaine use patterns (**Table 1**).

TABLE 1 | Sociodemographic characteristics, drug use patterns, and personality beliefs and emotion recognition scores in participants with and without personality disorders.

	Whole sample (*n* = 70)	SUD (*n* = 32)	SUD + PD (*n* = 38)	*t*	*p*
Age	33.53 (6.84)	32.60 (6.38)	34.32 (7.19)	–1.050	0.297
Education (yrs.)	10.20 (1.77)	10.00 (1.61)	10.37 (1.91)	–0.864	0.391
Cocaine grams/mo.	14.00 (19.92)	14.45 (20.15)	13.63 (20.01)	0.169	0.866
Cocaine duration (mo.)	57.37 (51.32)	55.02 (53.10)	59.29 (50.45)	–0.342	0.734
PBQ Paranoid	19.91 (13.63)	16.56 (12.68)	22.73 (13.92)	–1.925	0.058
PBQ Schizoid	23.04 (10.96)	21.22 (10.45)	24.58 (11.29)	–1.283	0.204
PBQ Antisocial	17.21 (8.51)	15.84 (8.13)	18.37 (8.75)	–1.242	0.219
PBQ Borderline	16.41 (10.29)	12.28 (9.48)	19.89 (9.75)	–3.296	0.002*
PBQ Histrionic	16.66 (8.58)	15.09 (7.18)	17.97 (9.51)	–1.408	0.164
PBQ Narcissistic	12.04 (7.65)	11.75 (8.80)	12.29 (6.62)	–0.294	0.769
PBQ Avoidant	17.44 (9.06)	14.44 (8.89)	19.97 (8.51)	–2.657	0.010
PBQ Dependent	20.26 (10.52)	17.41 (8.94)	22.73 (11.25)	–2.152	0.035
PBQ O–C	25.16 (10.78)	23.41 (11.57)	26.63 (9.98)	–1.252	0.215
Total Emotion Recognition	48.74 (4.94)	49.40 (4.41)	48.18 (5.34)	1.032	0.306

*SUD, substance use disorder (cocaine); PD, personality disorder; yrs., years; mo., months; PBQ, Personality Beliefs Questionnaire; O–C, Obsessive–compulsive. *p < 0.005.*

All participants were recruited from a city-wide public outpatient addiction treatment center in Granada (Spain). Treatment consisted of cognitive behavioral therapy and psychosocial support. The inclusion criteria were as follows: i) meeting Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (23) criteria for cocaine dependence indicated with the Structured Clinical Interview for DSM-IV Disorders–Clinical Version (SCID-CV) (24), ii) being abstinent for at least 2 weeks indicated by self-report and regular urine analyses, and iii) IQ levels ≥80 (to ensure facial emotion recognition was not impacted by general cognitive dysfunction) indicated with the Kaufman Brief Intelligence Test (25). Personality disorders included in the DSM-IV-TR were diagnosed by an accredited clinical psychologist (JM-G) using the International Personality Disorders Examination (26). Participants received personality disorders diagnosis at the same time as cocaine dependence diagnosis. The exclusion criteria were as follows: i) other Axis I comorbid disorders, with the exceptions of alcohol abuse and nicotine dependence, indicated with the SCID-CV; ii) history of head injury and/or neurological, infectious, systemic, or any other diseases affecting the central nervous system, indicated by self-report and clinical records.

Measures

Interview for Research on Addictive Behavior (27): This semi-structured interview collects information about substance use patterns (i.e., dosage, frequency, and duration) and yields two main measures: monthly use of each substance (quantity per month) and total duration of use of each substance (duration in months).

Personality Belief Questionnaire (PBQ) (18): The PBQ was administered to dimensionally measure dysfunctional beliefs or negative schemas associated with personality disorders. It is a 126-item self-report questionnaire that measures the degree of endorsement of dysfunctional beliefs associated with personality disorders, i.e., paranoid, schizoid, antisocial, borderline, histrionic, narcissistic, avoidant, dependent, and obsessive–compulsive beliefs. The Spanish version of the scale that we used in this study has demonstrated sound psychometric characteristics (28).

Ekman Faces Test (EFT): This is a computer task that assesses recognition of facial emotional expressions. The task uses stimuli from the Facial Expressions of Emotion: Stimuli and Tests (FEEST) (29). We presented 60 faces depicting expressions of anger, disgust, fear, happiness, sadness, and surprise (6 emotions, 10 faces each). Each face was presented on a computer monitor for a maximum of 5 s, after which individuals were asked to select the emotion that best described it. The performance measure was the sum score of total correct identifications (total recognition: range, 0–60).

Procedures

The Human Research Ethics Committee of the University of Granada approved the study. All participants provided written informed consent. Participants underwent two assessment sessions: one to diagnose substance use and personality disorders, and a second one to complete personality beliefs and emotion recognition measures, along with other cognitive measures that have been published elsewhere.

Analyses

First, we contrasted emotion recognition scores between participants with and without personality disorders using *t*-tests. Next, we examined the relationship between personality beliefs and total emotion recognition scores using *Spearman* correlation coefficients. When there was a significant association between specific dysfunctional beliefs and total emotion recognition, we run additional correlations between such beliefs and discrete emotions recognition scores (e.g., anger and fear). Finally, we tested if the relationship between dysfunctional beliefs and total emotion recognition scores stood after adjusting for sociodemographic characteristics and lifetime substance use using multiple regression. Results from group contrasts and correlational analyses, involving multiple tests, were considered significant if p values were below 0.005 to protect against Type I error. Results from targeted regression analyses were considered significant at the standard $p < 0.05$ value. Data is available at https://monash.figshare.com/s/f35e993c96fbb2899ecb.

RESULTS

Emotion Recognition in Participants With Versus Without Personality Disorders

We found no significant differences between participants with and without personality disorders in total emotion recognition scores (**Table 1**). As expected, participants with personality disorders had generally higher PBQ scores (reflecting greater endorsement of dysfunctional personality beliefs), but the group differences were only significant for borderline beliefs (**Table 1**).

Relationship Between Emotion Recognition and Dysfunctional Personality Beliefs

We found significant negative associations between the total emotion recognition score and antisocial, borderline, and paranoid beliefs (**Table 2**). Subsequent analyses showed that

TABLE 2 | Correlations between dysfunctional personality beliefs and emotion recognition.

	Emotion recognition total score	
	rho	*p*
PBQ Paranoid	–0.359	0.002*
PBQ Schizoid	–0.186	0.122
PBQ Antisocial	–0.399	0.001*
PBQ Borderline	–0.355	0.003*
PBQ Histrionic	–0.133	0.272
PBQ Narcissistic	–0.212	0.080
PBQ Avoidant	–0.247	0.039
PBQ Dependent	–0.321	0.007
PBQ Obsessive–Compulsive	–0.329	0.005

*PBQ, Personality Beliefs Questionnaire. *p < 0.005.*

TABLE 3 | Multiple regression model entering sociodemographic characteristics, drug use patterns, and dysfunctional beliefs as predictors of emotion recognition.

	Age		Education		Cocaine (gr)		Cocaine (mo)		Paranoid		Antisocial		Borderline	
	β	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*
Emotion recognition total score	−0.031	0.813	0.139	0.253	−0.021	0.860	−0.070	0.586	0.144	0.482	−0.342	0.019*	−0.322	0.109

*gr, grams; mo, months; O-C. *p < 0.05.*

antisocial beliefs were negatively associated with recognition of fear, $r = -0.376$, $p = 0.001$, whereas paranoid beliefs were negatively associated with recognition of disgust, $r = -0.372$, $p = 0.002$ (**Supplementary Table S1**).

Regression Analyses Adjusted by Sociodemographic and Drug Use Characteristics

After adjusting for age, education, and lifetime drug use, antisocial beliefs were significantly associated with total emotion recognition scores ($F_{\text{full model}} = 3.647$, $Adj\ R^2_{\text{full model}} = 0.214$, $p_{\text{full model}} = 0.002$, $Beta_{\text{antisocial}} = -0.342$, $p_{\text{antisocial}} = 0.019$) (**Table 3**). No other individual predictors were significantly associated with emotion recognition.

DISCUSSION

Our findings show that, although participants *with* and *without* personality disorders did not differ in emotion recognition, the degree of endorsement of dysfunctional personality beliefs was negatively associated with facial emotion recognition accuracy. These results suggest that individuals with more negative schemas associated with personality dysfunction can have greater problems to identify and interpret emotions in others, and ultimately more social interaction problems.

The link between dysfunctional personality beliefs and poorer emotion recognition provides support to the notion that maladaptive personality schemas are associated with social interaction deficits in people with SUD (30, 31). This relationship is acknowledged in modern definitions of personality disorders and stimulant addiction, which refer to disturbances in interpersonal functioning (32, 33). The directionality of the association is unclear. It is possible that emotion recognition deficits predate personality dysfunction and thus contributes to the formation of dysfunctional beliefs *via* early negative social interaction experiences (34). It is also plausible that dysfunctional beliefs cause stable biases in affective judgment that ultimately impact emotion recognition (e.g., "Others will try to use me or manipulate me if I don't watch out") (16). Since participants were in the "craving phase" of their SUD (35), it is also possible that state-related symptoms such as anhedonia modulate the link between personality and emotion recognition (36). Furthermore, the link between emotion recognition and dysfunctional personality beliefs, which are dimensional measures of personality dysfunction, supports the view that dimensional (versus categorical) indices of personality dysfunction can be more tightly aligned with social cognition and interaction phenotypes (37). Although emotion recognition is a well-recognized index of social cognition skills (1, 2), our findings can also stimulate further research on other aspects of social cognition and interaction in the context of addiction and personality disorders.

The link between specific personality beliefs and difficulties to recognize emotions in others has also important clinical value. In fact, we found specific associations between antisocial beliefs and poorer recognition of fear, which is consistent with previous findings among individuals with antisocial personality disorder (38) and align with the "low fear" theory of antisocial personality and psychopathy (39). Since fear recognition is essential to avoid risk (e.g., by recognizing others' appraisal about potentially risky situations such as those conducive to relapse) and harm to others (e.g., by recognizing their fear in response to one's actions), individuals with greater endorsement of antisocial beliefs and poorer emotion recognition might be at particularly high risk of poor clinical outcomes (40). We also found negative associations between paranoid beliefs and poorer recognition of disgust, but this relationship did not survive adjustment for sociodemographic and clinical characteristics. Therefore, these relationships might be conflated with other indicators of severity (e.g., higher levels of drug use) and should be reassessed in future studies. Establishing these links is important, since little is known about the social cognition correlates of personality dysfunctions associated with paranoid schemas compared to antisocial or borderline schemas (38).

Our findings need to be appraised in the context of relevant limitations. First, results are cross-sectional and correlational, meaning that we cannot draw causal conclusions. Second, we focused on two very specific indices of personality dysfunction (beliefs) and social cognition (emotion recognition), and hence, more comprehensive assessments are needed to confirm if the relationship between these constructs stands in the context of other indices of personality dysfunction (e.g., dimensional diagnostic tools) and social cognition (e.g., empathy). Third, according to the cognitive theory of personality disorders (41), participants with personality disorders should have generally elevated dysfunctional beliefs; the fact that we only found differences in borderline beliefs may be due to the small number of cases. Fourth, although we interpret findings mostly in the context of personality dysfunction, other etiological and clinical aspects of cocaine addiction (e.g., genetic vulnerability and cocaine dosage) may also contribute to emotion recognition deficits.

ETHICS STATEMENT

The Human Research Ethics Committee of the University of Granada (Spain) approved this study.

AUTHOR CONTRIBUTIONS

AV-G, JM-G and OL-R designed the study. NA-U and JM-G conducted assessments. OL-R and AV-G conducted statistical analyses. NA-U and AV-G wrote a first draft of the manuscript, which was reviewed by all authors.

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The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00431/full#supplementary-material

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ORIGINAL RESEARCH
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A Novel Hierarchical LATER Process Model: Evaluating Latent Sources of Variation in Reaction Times of Adult Daily Smokers

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Reaction time data from cognitive tasks continue to be a key way to assess decision-making in various contexts to better understand addiction. The goal of this paper is twofold: to introduce a nuanced modeling approach for reaction time data and to demonstrate the novel insights it can provide into the decision processes of nicotine-dependent individuals in different contexts. We focus on the Linear Approach to Threshold with Ergodic Rate (LATER) model, which is a cognitive process model that describes reaction time data in terms of two distinct aspects of cognitive functioning: speed of information accumulation ("accretion") and threshold amount of information needed prior to execution ("caution"). We introduce a novel hierarchical extension to the LATER model to simultaneously account for differences across persons and experimental conditions, both in the accretion and caution parameters. This approach allows for the inclusion of person-specific predictor variables to explain between-person variation in terms of accretion and caution together with condition-specific predictors to model experimental condition manipulations. To highlight the usefulness of this model, we analyze reaction time data from a study on adult daily cigarette smokers. Participants performed a monetary incentivized Go/No-Go task during two testing sessions, once while following their typical smoking patterns and again following 12 h of verified smoking abstinence. Our main results suggest that regardless of trial type, smokers in a period of abstinence have faster accretion rates, and lower caution thresholds relative to smoking as usual.

Keywords: smoking, cognition, cognitive model, abstinence, Go/NoGo task

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INTRODUCTION

A fundamental goal of psychiatry and neuroscience research is to understand how and why humans make decisions and behave as they do across various contexts. In particular, work aimed at understanding how exposure to addictive substances like nicotine impacts and alters decision-making is of considerable interest. The examination of reaction time data acquired from cognitive tasks continues to be a major way to assess decision-making, yet traditional analysis of such data (e.g., evaluation of group-level means and variances) limits the extent to which we can assess or estimate latent (psychological) processes that may be underlying the decision/behavior. To address these limitations, *cognitive process models* were developed, which use theoretically derived model

parameters that represent latent psychological constructs to better account for individual differences in the complex processes underlying human decisions and behavior; see, for example, Stout et al. (1), Yechiam et al. (2), Cohen et al. (3), and Hauser et al. (4) for a variety of models and applications.

In this paper, we focus on one particular process model, the Linear Approach to Threshold with Ergodic Rate (LATER) model, which was developed to capture individual differences in the underlying mechanisms of decision-making using data from reaction time tasks (5, 6). We extend the basic LATER model hierarchically in order to assess sources of both individual and experimental condition specific differences in reaction times. Moreover, we cast the hierarchical LATER model in the Bayesian framework, which provides a convenient approach for simultaneous estimation of person-specific LATER process parameters and regression coefficients related to person-specific (e.g., age) and condition-specific (e.g., experimental manipulation of reward, smoking status) effects. Additionally, casting the model in the Bayesian framework allows for inference in terms of statements about posterior probabilities. We assert that coalescing advanced process models with experimental manipulations (e.g., abstinence vs. smoking to satiety in smokers) can help us better understand how drug exposure (e.g., nicotine) affects the underlying mental processes guiding decision-making and behavior, and may provide insights for a better understanding of addiction, particularly at the individual level.

In the sections that follow, we first describe the use of process models and specify the LATER model we hierarchically extended and employed. We then apply this novel model to reaction time data obtained from a sample of adult daily smokers to demonstrate its potential utility in addiction research.

Modeling Reaction Times With the LATER Model

The time interval between stimulus presentation and initiation of a behavioral response is defined as the reaction time, or latency, and includes multiple underlying physiological processes occurring on varying time scales. For example, relatively rapid processes, on the order of tens of milliseconds, include transduction of the external stimulus energy to a neural response, signal propagation time from the periphery to the central nervous system and back, and muscle activation, among others. More temporally extended processes comprising reaction time include brain network-level computations (on the order of hundreds of milliseconds) related to making a decision, that is, forming and maintaining internal representations of the stimuli, then planning and executing a goal-directed motor plan. It is believed that these central, network-level computations comprise a majority of the reaction time (7, 8). As fast sensory and motor times are relatively fixed, reaction time variability is therefore a useful approximation of *decision time* (9). In other words, reaction time largely reflects the time needed to decide.

Researchers utilize tailored tasks that attempt to delineate the cognitive processes underlying reaction times in order to gain insight into decision processes and factors that influence them. However, reaction times are typically evaluated in terms of average performance across groups and/or study conditions. This approach disregards the potential variability in the processes underlying latency values, i.e., intraindividual variability across trials in a task. Indeed, in experimental paradigms, reaction time can vary significantly between one trial to the next, even if the same experimental conditions are maintained (9).

Capturing variability in reaction times with process models can provide additional information about the underlying mechanisms of decisions. One major theoretical framework for understanding decision-making holds that the brain accumulates relevant information until the resultant probability reaches a threshold that warrants action (10). The length of time in which it takes to reach this threshold depends on the dynamics of the rise-to-threshold (10). The LATER model describes the latency distributions of observed reaction times by characterizing the decision-making process in terms of two cognitive variables. The first is *caution*, or the amount of information needed to exceed a threshold to respond. The caution parameter represents the attitude toward partial prior information in a similar manner as a loss function represents the attitude toward risk (11). The second variable is *accretion,* or the rate (speed) of information accumulation. Bickel and colleagues (11) argue that caution can be seen as assigning an operational definition to the degree of conservatism toward ambiguity, and accretion rate as the assimilating capacity.

Utilizing the LATER model to describe reaction time data based on accretion rates and caution thresholds better reflects the actual shape of reaction time data relative to traditional averaging approaches. One of the most salient properties of the stochastic distribution of reaction times is that they are generally positive skewed; the distributions rise rapidly and then fall off slowly with a long, right-tailed skew. This is a near universal finding, regardless of stimulus type (e.g., visual, auditory), response (e.g., manual, oculomotor), or species [see Ref. (12)]. Interestingly, when plotted, this skewed distribution does not fit any of the traditional mathematical distributions like Gaussian or Poisson particularly well [e.g., Refs. (9, 12, 13)]. However, if one wants to examine the underlying mechanisms for the variability, rather than its effect (14, 15), then the *reciprocal* of the reaction time should be examined. If reciprocal latencies are plotted cumulatively (a reciprobit plot), a straight line will be obtained. This represents the *rate* at which the decision reaches completion, and follows a normal, Gaussian distribution (see below). Accordingly, the LATER model explains this general feature of reaction time distribution by appropriately modeling the rate of rise for each trial, varying in a Gaussian fashion, which explains the observed shape of latency distributions [see Ref. (12) for review].

This results in describing reaction time distributions by utilizing a model with a decision signal starting point, which then rises at a constant rate until it reaches a threshold value, at which point a response is initiated. Accordingly, the LATER model is a sequential-sampling model, which assumes that during the course of a trial, information is accumulated sequentially until a threshold amount of information is reached and a response

is executed. Indeed, the LATER model explains the observed features of reaction time distributions by assuming that a stimulus triggers a neuronal decision signal to rise linearly until it reaches a threshold value in which a response is then executed. This rate of rise for each trial varies in a Gaussian fashion, explaining the observed shape of latency distributions. Modeling reaction time with the LATER model has provided novel insight into the cognitive components (accretion, caution) underlying reaction times in healthy individuals [see Ref. (12) for review and additional details on the original LATER model].

We argue that the LATER model can benefit from being cast in a hierarchical/multilevel framework (16, 17). Oravecz et al. (18) described a hierarchical extension to the LATER model that allowed for a person-specific accretion rate. We extend this approach by allowing for individual differences in both accretion *and* caution parameters. The multilevel extension enables us to model the individual-level repeated measures of reaction times with the LATER process and pool information across the resulting latent, person-specific accretion and caution parameters *via* joint population (group-level) distributions. The multilevel framework also provides us with a statistically principled way to add person-level predictors on these two latent parameters (e.g., to test if the number of cigarettes smoked per day is related to slower information accumulation). In our proposed model, all latent person-specific parameters and corresponding regression coefficients are estimated simultaneously, as opposed to first obtaining point estimates of caution and accretion for each person and then regressing those on predictors, which can lead to bias in the regression coefficient estimates [see Ref. (19)]. Importantly, we will also introduce condition-specific predictors to capture how accretion and caution differ as a function of experimental manipulation (e.g., smoking as usual vs. abstinence). The estimation of condition and person-specific effects is again simultaneous. The ability to have different groups and experimental manipulations within the same model also allows for direct statistical comparisons between the conditions/groups.

Specification of the Hierarchical LATER Model

Next we introduce the model specification for the hierarchical LATER model. We start with describing the LATER model as originally outlined [see Ref. (5); for reviews see Refs. (9, 12)], but with multilevel extensions to both caution and accretion parameters. Then we describe how the single-step regression is formulated on the person-specific caution (threshold) and accretion rate (information accumulation), and we finish with showing how condition-specific effects can be incorporated in the same model.

Data will be denoted as $y_{p,i}$ for person p and trial i. We allow each subject p to have their own accretion (v_p) and caution (θ_p) parameters. On a trial i, a trial and person-specific realization of the accretion rate, $z_{p,i}$ is modeled through a normal (Gaussian) distribution with the following specification:

$$Z_{p,i} \sim N(v_p, 1) \tag{1}$$

We can get the predicted response time (or latency) at trial i for person p ($y_{p,i}$) by dividing the person-specific caution by the person-specific accretion rate on trial i:

$$y_{p,i} = \frac{\theta_p}{Z_{p,i}},$$

which can be rearranged to yield:

$$\frac{z_{p,i}}{\theta_p} = \frac{1}{y_{p,i}}$$

To get the distribution of $\frac{z_{p,i}}{\theta_p}$, we divide the distribution of $z_{p,i}$ specified in Equation 1 by θ_p:

$$\frac{z_{p,i}}{\theta_p} = \frac{1}{y_{p,i}} \sim N\left(\frac{v_p}{\theta_p}, \frac{1}{\theta_p^2}\right)$$

To summarize, the LATER model assumes sequential sampling; it assumes that over the course of a trial, information is accumulated sequentially until a threshold amount of information is reached, at which time a response is executed. This resulting accretion process (i.e., information accumulation) is assumed to be linear and eventually reaches a fixed threshold, with a rate that is random from trial to trial, as shown in **Figure 1**. Importantly, this trial-to-trial random rate is one of the key motivations to model reaction time with the LATER model approach.

To model similarities across individuals in terms of accretion and caution, we will assume that all person-specific LATER process parameters come from joint group-level (or level-2 or population) distributions. These group-level distributions also provide for a straightforward manner to regress these parameters on relevant person predictors (e.g., cigarettes smoked per day) to further improve the model. Therefore, in our application, the means of the population distributions of caution and accretion are made into the function of person predictors. Assume that K person covariates are measured and $x_{p,k}$ denotes the score of person p on covariate k (k = 1, …, K). For example, in our application we considered that age, gender, cigarettes smoked per day, and nicotine dependence level (as assessed by the Fagerström Test for Nicotine Dependence; FTND) could be possible sources of individual differences among persons; therefore, we included them as person predictors. All person-specific covariate scores are collected into a vector, with the length K+1, denoted as $\mathbf{x}_p = (1, x_{p1,} x_{p2}, \ldots, x_{pK})^T$, where the first element is an intercept. The group-level distribution of the person-specific accretion parameters v_p is then formulated as

$$v_p = \mathbf{x}_p \beta v + \varepsilon_{p,v}$$

where vector $\boldsymbol{\beta}_v$, of dimension $1 \times (K+1)$, contains the regression weights for the person predictors (e.g., association between FTND and accretion) and $\varepsilon_{p,v}$ is normally distributed with

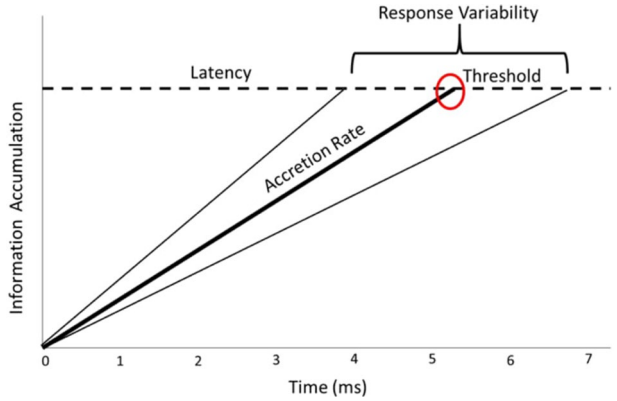

FIGURE 1 | Visual representation of the cognitive processes (accretion rate and caution threshold) examined in the Linear Approach to Threshold with Ergodic Rate (LATER) model.

mean 0 and variance σ_v^2, quantifying residual unexplained inter-individual differences (random effects). Following similar logic, the group-level distribution of the person-specific caution parameters was modeled similarly: $\theta_p = \mathbf{x}_p\ \beta_\theta + \varepsilon_{p,\theta.}$ Besides person-specific differences, covariates capturing experimental conditions can also be included in the model. In our application (described below), smokers completed the task under two conditions, smoking as usual vs. abstinent. Abstinence was operationalized as abstaining from smoking for a minimum of 12 h. Baseline measures of exhaled CO were taken during a screening procedure, allowing for verification of an abstinence state. The task was composed of two trial types, reward vs. neutral. The design was completely crossed; all participants completed both conditions and trial types (smoking as usual-reward trials, smoking as usual-neutral trials, abstinent-reward trials, abstinent-neutral trials). We selected smoking as usual and neutral as the baseline, and dummy coded the neutral–abstinent, reward–abstinent, and reward–smoking as usual conditions. The regression coefficients corresponding to these dummy-coded condition-specific variables represent the deviations of a condition from the baseline (i.e., smoking as usual-neutral reward).

We denote these covariates for every data point as $g_{n,c}$ where $n = (1, 2, \ldots, N)$, with N representing the total number of reaction times in the experiment and $c = (1, 2, \ldots, C)$, and C representing the number of dummy-coded conditions minus 1 (baseline). Corresponding regression coefficients are denoted as $\delta_{v,c}$ for accretion and $\delta_{\theta,c}$ for the caution threshold. **Table 1** shows the conditions (reward vs. neutral and smoking as usual vs. abstinent) with corresponding regression terms for further clarification of the design. To formulate the LATER model with these experimental condition effects, we introduce a more general notation than that of Equation 1 for data $y_{p,i}$: we stack all trials for the persons p under each other, resulting in a long vector of reaction time scores, where n stands for a single trial (up to N), and then we rewrite the model as:

TABLE 1 | Describes the design matrix of the current study; the two conditions (Smoke as Usual, Abstinent) and two trial types (reward, neutral) with corresponding regression terms are shown here for the person-specific pater parameters.

	Smoke as Usual	Abstinent
Neutral	$\delta_{v,1}$,$\delta_{\theta,1}$	Baselines
Reward	$\delta_{v,3}$,$\delta_{\theta,3}$	$\delta_{v,2}$,$\delta_{\theta,2}$

$$y_n \sim N\left(\frac{\nu_n}{\theta_n}, \frac{1}{\theta_n^2}\right)$$

For example, with the three conditions we introduced, the accretion is then modeled as:

$$\nu_n = \nu_p + g_{n,1}\delta_{v,1} + g_{n,2}\delta_{v,2} + g_{n,3}\delta_{v,3}$$

which can be written in a more general form:

$$\nu_n = \nu_p + \boldsymbol{g}\delta_v$$

Similar formulation applies to the caution parameter:

$$\theta_n = \theta_{p+}\boldsymbol{g}\delta_\theta$$

This formulation allows us to model the effect of the experimental manipulation in terms of meaningful process model parameters while also capturing individual differences in these parameters.

Modeling in the Hierarchical Bayesian Framework

The hierarchically extended LATER model was cast in the Bayesian framework. In this framework, both data and model parameters are defined as random variables and the Bayesian model specifies their joint probability distribution (20). With this approach, statistical inference is focused on the posterior probability distribution of the parameters, which is derived by combining the likelihood and prior distribution on the model parameters based on Bayes' rule. The prior distributions are integral parts of the model; the mean of the prior suggests the likely parameter value, and the variance of the prior distribution reflects the level of uncertainty about the possible values of the parameter of interest. This analysis is the mathematically normative way to reallocate credibility across parameter values as new data arrive (21).

In the Bayesian framework, inferences about parameters are based on the posterior probability distributions of the parameters. The posterior distribution is stochastically approximated by taking a large number of samples from it, and then calculating posterior point estimates, posterior standard deviations (similar to that of the standard error), and posterior credible intervals for each parameter. One of the key strengths in fitting a hierarchical

model with a Bayesian statistical approach is that these algorithms are able to fit increasingly complex models to the data (22). This is especially useful for our model as we can estimate all person-specific parameters, group-level variances, and regression coefficients corresponding to person and condition effects simultaneously. Parameter estimation was implemented in Stan (23); software code for the model is provided in **Appendix A**. The utilized data and accompanying R script are also provided as an **Online Supplement** on the project's Open Science Framework (OSF) page: https://osf.io/5h8m4/?view_only=f6c1e50dcfa04244bba428d6cf259d36

Model Application—Smokers

We fit the hierarchical LATER model to data from "go" trials from a Go/No-Go task performed by a group of adult daily smokers to gain further insight into cognitive changes associated with smoking abstinence. While the Go/No-Go task is a paradigm typically used to investigate inhibitory control (no-go trials), it can also be a highly informative task in terms of assessing what cognitive mechanisms support "go" decisions (12, 24). Notably, go trials in this task far outnumber the number of no-go trials, increasing power and adding an additional dimension of rich data to analyze from this classic task. Prior studies have utilized the Go/No-Go behavioral paradigm to study the effect of nicotine use on cognitive systems using reaction times [e.g., Refs. (25–27)]; these studies manipulate the task environment in various ways, such as smoking status (e.g., daily smoker vs. non-smoker) and session type (e.g., smoking to satiety vs. abstinent). However, findings from these studies thus far have only demonstrated differences in reaction times (and error rates) between these various manipulations. While these studies have been informative in highlighting the fact that nicotine impacts task performance under particular task manipulations, they fail to explain how. That is, what are the underlying mechanisms of reaction times (i.e., components of decision-making) that nicotine affects?

Given widespread effects of nicotine on cognitive brain systems [e.g., Refs. (25, 26, 28–35)], we hypothesize that nicotine will affect psychological (cognitive) processes important for decision-making, including caution threshold and accretion rates. Furthermore, given that nicotine is known to alter (decrease) responsiveness to non-drug (e.g., money), particularly during periods of smoking abstinence [e.g., Refs. (33, 36–38)], we hypothesize that the availability of rewards may differentially impact caution and accretion depending on smoking status, as these likely interact with reward processes during incentivized decision-making [e.g., Ref. (29)]. We suggest that these effects may be masked or confounded when analyzing latencies via traditional average mean scores. In addition, traditional analysis is often based on averaging task performance across individuals per experimental condition, disregarding possible intraindividual differences that may be present. Failure to account for such differences may contribute to inconsistent results found in previous work [see Ref. (39)]. By utilizing the LATER process modeling approach instead of relying on statistical summaries of raw reaction times, substantively meaningful latent model parameters (accretion and threshold) are calculated and updated in a trial-by-trial manner, better capturing intraindividual processes. Moreover, by allowing individual differences in the latent process model parameters, this ensures that condition-specific differences are not biased by an averaging artifact. To this end, our proposed modeling approach was employed in an attempt to elucidate the effects of nicotine exposure (smoke as usual vs. abstinence) on cognitive functioning and potential moderating effects of rewards on Go/No-Go task performance.

The current dataset has previously been explored via the traditional frequentist approach to examine the effects of reward and smoking conditions on the latency and accuracy of task performance (see Ref. 40). However, it is not well understood which cognitive parameters nicotine affects. As a result, it remains unknown if non-drug rewards affect particular components of cognitive functioning in smokers. One goal in extending the LATER model was to explore intraindividual differences among daily cigarette smokers in their information accumulation and caution cognitive processes. In addition, we also wanted to study the difference in these two processes across experimental conditions (i.e., reward/neutral condition; smoke as usual/abstinence).

METHODS

Participants

After Institutional Review Board approval, 23 smokers were recruited *via* community advertisements. Inclusion criteria were the following: a) ≥18 years old, b) smoked at least four cigarettes/day for the past 12 months, c) inhale while smoking, and d) no intention to quit smoking in the next 1 month. Exclusion criteria were the following: a) women who were pregnant or lactating, or who planned to become pregnant or breastfeed during the study, and b) other tobacco use within the past 12 months. Participants who dropped out before completing the study (n = 5) were excluded, leaving a final sample of 17 (5 females). While this is a relatively low sample size, each person has a high number of trials (750), which facilitate the estimation of the person-specific process parameters. Fewer trials would certainly result in more uncertainty (higher posterior standard deviation) in the parameter estimates; however, via hierarchical modeling, we pool information across participants to improve parameter estimation. Moreover, a large number of trials in fact are not uncommon in the Go/NoGo literature, as it helps build a prepotent response. In addition, as we take a multilevel modeling approach, we pool information across persons, which helps handle outlier effects and reduces the risk of model over-fitting. The mean age of these participants was 31.06 (SD = 13.82). Participants identified as Caucasian, (66.7%), Asian (27.8%), and mixed race (5.6%). Participants reported smoking an average of 11.08 cigarettes per day. The sample exhibited low nicotine dependence on the Fagerström Test of Nicotine Dependence (FTND), with a mean score of 2.61 (SD = 2.35).

Procedure

Participants attended a baseline session. A coVita|Bedfont Micro Smokerlyzer® was used to monitor CO levels. The Beck Depression Inventory–II (41) and the Center for Epidemiologic Studies Depression Scale–Revised (42) were used to screen for current depression. A screening for dependence on drugs other than nicotine was also administered. Participants then completed the FTND (43). Participants then attended two counterbalanced sessions—smoke as usual and abstinent. For the abstinent session, participants were instructed not to smoke for at least 12 h before the session. For the smoke as usual session, participants were instructed to continue their regular smoking habits.

Participants began the experimental sessions by providing a CO sample to ensure abstinence or smoke as usual conditions. Abstinence was determined by a CO level of at least one half of the participant's CO level at their baseline session. Individuals then completed a recent nicotine, alcohol, and substance use measure, and the Questionnaire of Smoking Urges–Brief (QSU) (44). Participants reporting the use of alcohol or other substances within 24 h before experimental sessions were asked to return at a later date when they had refrained from substance use. Investigators then administered a measure of nicotine withdrawal, followed by an antisaccade (inhibitory control) and a working memory task (not reported here), as well as a monetary incentivized Go/No-Go task. Each session lasted approximately 2 h. Results of questionnaires utilized in the current analyses and additional demographics can be found in **Table 2**.

Go/No-Go Task

An incentivized version of the Go/No-Go task was administered *via* a computer with a 17-in. monitor presented in E-Prime (Psychology Software Tools, Inc., Pittsburgh, PA). The task consisted of three trial types: frequent-Go (FGO; 75%), infrequent-Go (IFGO; 12.5%), and NoGo trials (12.5%) (45). Only data from the FGO trials are analyzed in this study as a main aim of the current modeling approach was to examine inter-individual variability in reaction times. Including IFGO trials would introduce additional sources of variability, confounding the findings. The participants were required to press the space bar on a computer keyboard using the index finger of their dominant hand. Each trial consisted of the presentation of a colored square for 400 ms followed by the presentation of a fixation cross for 400 ms. Responses were collected during this 800-ms period. Participants were instructed to respond as quickly and as accurately as possible. Trials with reactions times <150 ms were excluded from analyses to avoid the inclusion of potentially premature responses. This was a threshold that we set in order to ensure that the response was in fact a reaction to the stimulus. If reaction times are too fast, they are not a reaction to the stimulus; rather they reflect general responding. Utilizing a threshold is well documented in the reaction time literature [see, e.g., Ref. (40)] (46). The trial types were presented pseudo-randomly. Participants completed 10 runs, and each run was composed of 100 trials. Five runs were preceded by a ring of dollar signs ($), indicating the availability of monetary reward depending on run performance. Five runs were preceded by a ring of pound signs (#), indicating that no monetary reward was available. The order of runs was randomized. Participants were instructed that they could earn up to $5.00 in addition to their participation earnings, and that faster and more accurate performance on rewarded blocks would result in a greater reward amount. Participants were instructed that they would receive the earned rewards once they had completed the study and the investigators analyzed their data. At the end of the trials, the participants were told that they were getting the full reward amount.

TABLE 2 | Participant characteristics.

	Mean	SD
Age	34.15	18.31
Age of first use	19.63	5.34
FTND	2.63	11.32
Avg. cigarettes per day	2.29	11.00

FTND, Fagerström test for nicotine dependence.

Bayesian Data Analysis

In the present application of the model, we used weakly informative prior distributions, specified in **Appendix A**. As we had no prior knowledge, we chose weakly informative priors so that the prior distributions would have very little impact on the results. Parameters were estimated by running six chains with 2,000 iterations each, discarding the first 1,000 samples as burn-in. Convergence of the six chains was tested by the $\hat{R}$ statistic (the Gelman–Rubin convergence statistic, used to test the degree of convergence of a random Markov Chain; see Ref. 47). $\hat{R}$ is calculated by taking the ratio of variance within and between chains. $\hat{R}$ was lower than 1.01 for all parameters (conventional criterion being $\hat{R}$ <1.1), indicating no problems with convergence. The full R script and accompanying data that allow for replicating the analysis can be found on the Open Science Framework website of the project[1].

RESULTS

Individual Differences in the Decisions on Go Trials

We estimated an accretion and a caution threshold parameter for each person. Results show individual differences in accretion rate and caution threshold (**Figure 2**). Caution parameter estimates ranged between 2 and 6, while accretion rate was between 0.7 and 1.6. To relate these two scales, a person, for example, with caution parameter 4 and accretion rate 1 would need ¼ s (250 ms) to give a response. Alternatively, the same reaction time can arise from a faster accretion rate (e.g., 1.5) but also higher caution (e.g., 6). As can be seen in **Figure 2**, various combinations of accretion rates and caution parameters can result in very similar reaction times.

[1] https://osf.io/5h8m4/?view_only=f6c1e50dcfa04244bba428d6cf259d36

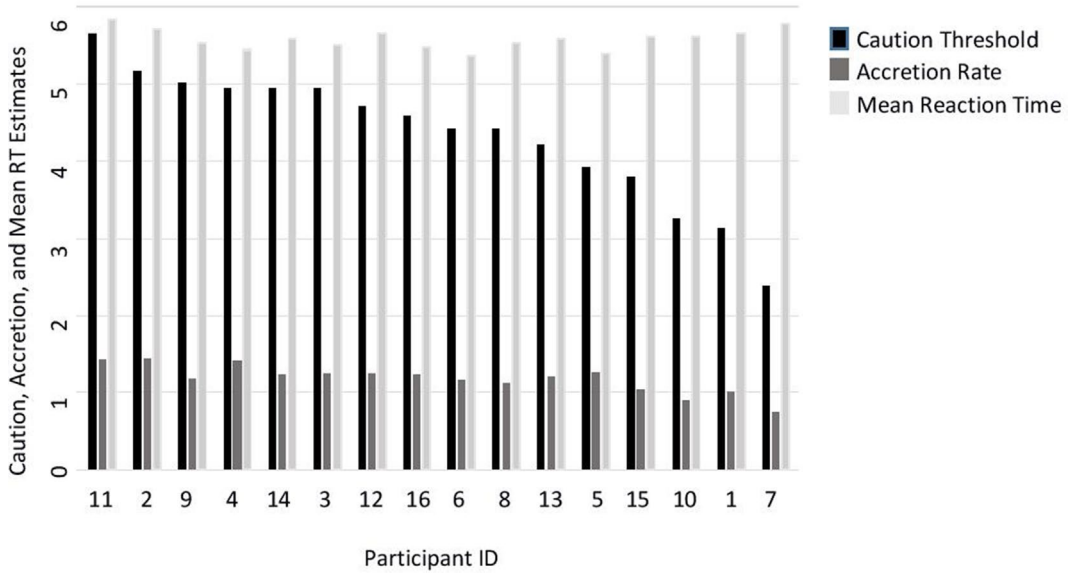

FIGURE 2 | Individual differences in participants' accretion, caution, and mean reaction time (RT) estimates. *Note.* Mean RT is log transformed. Mean reaction times were included in the figure to demonstrate the different combinations of caution and accretion, which could result in similar RTs.

We included person-level predictors (chronological age, age of smoking initiation, FTND score, average number of cigarettes smoked per day) to predict individual differences in accretion or caution, but no predictors explained differences in either parameter. Regression coefficients estimates and corresponding 95% credible intervals are reported in **Appendix B**.

Condition-Specific Differences in the Decisions on the Go Trials

We were interested in capturing differences in the decisions on the Go trials in periods when smokers abstained from smoking (vs. smoking as usual) and when a reward was offered depending on their performance (vs. neutral condition with no reward). These conditions were crossed for each person for a two-by-two design. We chose the neutral trials in the smoke as usual session as our baseline, and modeled the differences in the neutral and abstained from smoking, and the abstinent and smoking as usual reward conditions in terms of accretion and caution. Results are reported in **Table 3**. All accretion parameters had posterior distributions that had posterior mass largely concentrated away from zero, indicating support for a difference in these conditions on accretion, compared to the baseline (neutral trial, smoke as usual) condition. The $\delta_{v,1}$ and $\delta_{v,3}$ accretion parameters reveal that regardless of trial condition (neutral vs. reward), abstaining from smoking was associated with faster information accumulation compared to smoking as usual. The $\delta_{v,2}$ accretion estimate indicated that when smoking as usual, smokers had slower accretion rates relative to reward trials.

Compared to the baseline condition, regardless of trial condition, smokers had a lower caution threshold when in a period of abstinence, relative to the baseline condition ($\delta_{\theta,1}$,$\delta_{\theta,3}$)

TABLE 3 | Summary of the regression weights where response speed was modeled with the LATER model.

Condition	Posterior mean	Posterior SD	95% CrI
Neutral, abstinent	–0.3638	0.0552	(–0.4763, –0.2613)
Reward, smoke as usual	0.1231	0.0565	(0.0153 , 0.2360)
Reward, abstinent	–0.2494	0.0556	(–0.3573, –0.1384)
Neutral, abstinent	–0.0655	0.0145	(–0.0938, –0.0376)
Reward, smoke as usual	0.0835	0.0150	(0.0537, 0.1120)
Reward, abstinent	–0.0068	0.0147	(–0.0352 , 0.0222)

Negative Posterior Means indicate faster accretion rates and lower caution thresholds; positive values indicate slower accretion rates and higher caution thresholds. Mean and SD are posterior mean and standard deviation. "Neutral" refers to a neutral trial; "Reward" refers to a reward trial. CrI, credibility interval; SD, standard deviation.

The $\delta_{\theta,3}$ parameter had a 95% confidence interval containing 0, indicating less confidence for a meaningful difference between this parameter (abstinent, reward) to the baseline (smoke as usual, reward). The $\delta_{\theta,2}$ parameter indicates a larger caution threshold in the reward trials relative to the neutral trials in the smoke as usual session, suggesting that participants are integrating reward information into their cognitive appraisals of whether or not to execute a "go" response.

Model Fit

In addition to overall model convergence, we tested how well the LATER model fit the actual observed data through posterior predictive checks (PPCs). For this, we generated 100 new data sets from the posterior distributions of the LATER model parameters. **Figure 3** shows smoothed blue curves of these generated datasets overlaying the experimental data

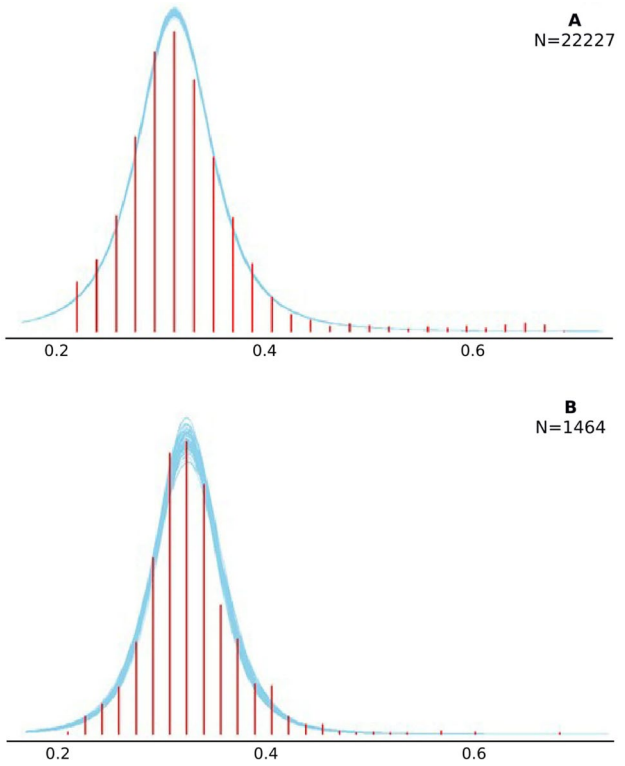

FIGURE 3 | Visual summary of the posterior predictive checks. Checks were completed with 100 generated data sets. Smoothed histograms of these generated datasets are depicted by the blue curves. The distribution of the experimental data is shown with the red bars. Plot **(A)** shows these checks on the level of the full data set, while Plot **(B)** shows it for a randomly selected participant.

(red histogram). Plot A depicts the full data PPC results, and Plot B displays a randomly selected participant's data. Overall, the LATER model adequately fit the experimental data well, demonstrated by generated data sets, which nicely overlay the real experimental data (i.e., the blue curves follow the same pattern of the red histogram). The results were analyzed in the Bayesian framework, which does not utilize traditional indices to show goodness of fit (e.g., CFI) but relies on PPCs. This entails "simulating replicated data under the fitted model and then comparing these to the observed data" (48, p. 158). Systematic discrepancies within these graphical checks are indicative of poor model fit. Here, our graphical PPCs shown in **Figure 3** do not reveal any systematic misfit.

DISCUSSION

In this paper, we articulated model implementation of a novel hierarchically extended LATER model, which parses reaction time into two distinct aspects of cognitive functioning: accretion rate and caution threshold. This model extension enables researchers to account for and compare differences in sources of variation related to experimental conditions and person-specific differences in accretion and threshold. We demonstrated the applicability and benefits of this model by applying it to reaction time data from a group of adult daily smokers, identifying condition and trial level effects. We aimed to place emphasis on both modeling and the nuanced substantive findings that this modeling makes possible. That is, we presented a novel hierarchical extension to the LATER model in order to account for differences across persons and experimental conditions simultaneously. We showcase the strength of this approach by demonstrating what researchers can learn about smoking status and the influence of rewards utilizing this modeling approach.

In the original analyses of the data, Lydon et al., (40) reported that task performance was more accurate (in regards to error processing) on rewarded trials relative to the neutral trials, but only in the smoke as usual session. There were no differences between reward and neutral trials during the abstinent session. And importantly, there were no significant differences in mean reaction times between the abstinent and smoke as usual sessions, regardless of the trial type. Here, our findings demonstrate differences in both cognitive parameters underlying reaction times.

In the current analyses, in the accretion parameter, the baseline (or comparative) condition was smoke as usual, neutral trials. Our results demonstrated the following: Relative to our baseline condition, when smokers were in an abstinent state, they had faster accretion rates in both reward and neutral trials. When smokers were smoking as usual, they had slower accretion rates when a reward was at stake relative to neutral trials. In regards to the caution threshold, again the baseline was smoke as usual, neutral trials. Relative to this baseline condition, when a participant was in a period of abstinence, regardless of the trial type (reward, neutral), s/he utilized a lower caution threshold. Compared to the baseline smoke as usual neutral condition, when a reward was at stake (still smoking as usual condition), smokers utilized a larger caution threshold.

Our study is the first to combine advanced process models with experimental manipulations to examine the effects of smoking on behavior. Understanding how rewards affect decisions is critical as contingency management treatment programs encourage continued abstinence by increasing the value associated with continued abstinence (49). Our findings demonstrate differences in both accretion and caution parameters when smokers were abstinent relative to smoking as usual: faster accretion rates and lower caution thresholds when participants were in a period of abstinence, regardless of trial type. This overall main finding falls in line with other studies demonstrating abstinence-related reward-insensitivities (28, 33, 36), with important implications for contingency management programs. If incentives used in smoking interventions are not overcoming cognitive deficits produced by acute nicotine withdrawal, incentives may fail to change the value associated with continued smoking abstinence, undermining the allocations of cognitive resources needed in attempts to remain abstinent. Future work should focus on examining the generalizability of reward/reward insensitivity, particularly in an abstinence state, to other types of motivating incentives (e.g., food, social praise) in order to investigate if alternative incentives can impact cognitive performance in

deprived smokers in order to inform the development of effective interventions.

Interestingly, when smokers were smoking as usual, rewarded trials produced slower accretion rates and increased caution thresholds. This finding suggests that when participants were smoking as usual, they seemed to be more careful in their decision time, perhaps a speed-accuracy tradeoff. Indeed, Lydon et al. (40) reported fewer errors when examining the no/go trials of this task in rewarded vs. neutral trials when participants were smoking as usual. Additionally, additional processing demands/time could have been needed in order to integrate information about the reward into the decision process.

To our knowledge, a LATER process model has never been applied to cigarette smokers to examine the underlying mechanisms of reaction or decision times. However, our findings fall in line with other research groups attempting to examine differences in underlying mechanisms of decision-making based on smoking state. Zack et al. (50) found that adolescent heavy smokers made more errors on a rapid information processing task relative to when they were smoking as usual, in line with the current results. These results support the notion that that accretion rate, the speed of information accumulation, is affected by abstinence. In a resting state magnetic resonance imaging study, Lerman and colleagues (30) reported that weaker inter-network connectivity (salience and default) predicted less suppression of default mode activity during performance of a working memory task. They argue that alterations in the coupling of these networks, and the inability to disengage from the default mode network, may be critical in cognitive alterations that underlie dependence. In our study, the trial type (reward vs. neutral) did not make a difference when smokers were in a period of abstinence. This could be due to alterations in the coupling of these networks as found in the study by Lerman and colleagues.

There are notable limitations in the current study. We implemented our model in the Bayesian statistical framework, which allowed us to fit a complex model to reaction time data in a single step. However, there are limitations to utilizing a Bayesian framework, namely in the computation power needed to implement such approaches. The current analysis was carried out using parallel computations [six cores running six Markov chain Monte Carlo (MCMC) chains] and took about 25 min. However, due to recent advances in statistical software, computational difficulty is becoming less of an issue. In addition, we had a limited sample size and unbalanced gender. However, as described in our Methods section, our implementation of a process model that utilizes a sequential sampling method and hierarchical modeling handles small sample sizes better than traditional approaches. We have made our scripts and data available to facilitate researchers utilizing this approach, hopefully with larger samples and more balanced samples to overcome this limitation in future work.

Taken together, our hierarchical extension of the LATER process model is able to separate the reaction time of the go trials into two cognitive processes, accretion and caution, while simultaneously accounting for differences in groups/session (smoke as usual vs. abstinent) and experimental condition (reward vs. neutral trials). Combing these approaches provides additional nuanced insight into nicotine's effects on behavior.

Our model examines differences across individuals together with condition specific differences. This is an important extension of the model as it is critical for researchers to have the ability to test both between- and within-person differences in experimental conditions. Continual use of marrying cognitive process models with experimental condition manipulations will help elucidate factors that may impact decision-making in smokers, and can be extended to additional types of addiction. This modeling approach can and should be used in future research; by combining this approach with other tasks, group conditions, etc., researchers can better understand the cognitive processes underlying decision-making within particular groups. These cognitive factors have the potential to inform the development and improvement of intervention programs by understanding which cognitive mechanisms need to be targeted by interventions. Although we did not find an association between individual level predictors and accretion/caution parameters, our novel extension to the LATER model puts us in a position to assess this in the future with larger sample sizes, more diverse samples (e.g., varying levels of nicotine dependence), and other types of addiction.

ETHICS STATEMENT

The study protocol was reviewed and approved by the Penn State Institution Review Board. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

NR contributed to data acquisition, analysis, interpretation, drafting the manuscript, and study conception and design. BS contributed to data analysis and drafting the manuscript. ZO and CG contributed to study conception and design, data analysis, interpretation, and drafting the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00474/full#supplementary-material

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Oxytocin-Induced Changes in Intrinsic Network Connectivity in Cocaine Use Disorder: Modulation by Gender, Childhood Trauma, and Years of Use

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Cocaine use disorder (CUD) is a major public health concern with devastating social, economic, and mental health implications. A better understanding of the underlying neurobiology and phenotypic variations in individuals with CUD is necessary for the development of effective and targeted treatments. In this study, 39 women and 54 men with CUD completed a 6-min resting-state functional magnetic resonance imaging scan after intranasal oxytocin (OXY) or placebo administration. Graph-theory network analysis was used to quantify functional connectivity changes caused by OXY in striatum, anterior cingulate cortex (ACC), insula, and amygdala nodes of interest. OXY increased connectivity in the right ACC and left amygdala in males, whereas OXY increased connectivity in the right ACC and right accumbens in females. Machine learning was then used to associate treatment response (placebo minus OXY) in nodes of interest with years of cocaine use and severity of childhood trauma separately for males and females. Childhood trauma and years of cocaine use were associated with OXY-induced changes in ACC connectivity for both men and women, but connectivity changes in the amygdala were associated with years of cocaine use in men and connectivity changes in the right insula were associated with years of cocaine use in women. These findings suggest that salience network nodes (ACC and insula) are potential OXY treatment targets in CUD, with the amygdala as a treatment target for men and the accumbens as a treatment target for women.

Keywords: connectome, graph-theory, resting state, gender differences, functional connectivity

INTRODUCTION

Gender differences in addictive and affective disorders are well established (1, 2). Both gonadal and stress hormones can modulate brain function, leading to different levels of susceptibility to neuropsychiatric disorders and treatment response. Biomedical research focused on understanding hormonal modulation and gender differences in brain function may be advanced by including

neuroimaging markers of functional brain organization. One such marker is resting-state functional brain connectivity (RSFC), which uses functional magnetic resonance imaging (fMRI) to image the brain while an individual is alert and awake but not engaged in any particular cognitive task; that is, when the brain is at "rest." This continuous resting-state fMRI (rsfMRI) paradigm can reveal brain regions that are temporally synchronized with other brain regions to characterize brain regions that seem to activate (or deactivate) in unison, revealing additional phenotypes that are not captured with current behavioral assessments or neurobiological markers. Therefore, the addition of rsfMRI as a tool in understanding psychiatric illness and gender-specific susceptibility to different disorders may ultimately lead to better treatments and outcomes.

rsfMRI has been widely used in addictions research, including studies in cocaine use disorder (CUD) (3, 4). Differences in RSFC between CUD and control subjects have been reported in numerous circuits, but there is no clear consensus that any particular circuit or resting-state network can be considered a reliable phenotype for CUD. Nevertheless, RSFC has been associated with important clinical variables, such as measures of cocaine use (5–7), impulsivity, inattention, or cognitive control (5, 6, 8–10) and risk for relapse (10–16). For example, years of cocaine use (which will be the primary cocaine use variable in the present study) have been associated with reduced RSFC in the ventromedial prefrontal, hypothalamic, insula, and anterior cingulate cortex (ACC) regions (7, 14). Although not all studies have shown an association between compromised RSFC and years of use (5), the collective findings point to RSFC as a promising imaging biomarker for relapse risk or other behaviors implicated in the addiction process (17).

However, two important variables that are known to modulate addiction neurocircuitry—gender and trauma exposure—have been less studied in rsfMRI studies of CUD. Sex differences were examined in only one RSFC study (7) and revealed greater connectivity between the medial hypothalamus and a critical node of the default mode network, the precuneus, in female cocaine users compared to males. A recent study has also examined modulation of RSFC by history of childhood trauma in CUD (18). The CUD group reported that some childhood trauma showed greater amygdala RSFC with several striatal regions, the insula, medial temporal regions, and the brain stem. These studies are an important step toward understanding individual differences in RSFC, but more studies are needed to characterize RSFC phenotypes that may lead to the development of individualized treatment approaches.

One potential treatment being explored for substance use disorders (SUD) is the neuropeptide oxytocin (OXY). Childhood trauma (19, 20) and chronic substance use (21) can both lead to neuroadaptations in the OXY system. In addition, some studies have shown that exogenous OXY may reverse drug-induced neuroadaptations [see Ref. (21), for review] or can alter neural response in stress-related circuitry (22–24). However, the effect of exogenous OXY may not be the same in men and women because of gender differences in neuropsychiatric sequelae of childhood trauma and the neurobiology of OXY (25, 26).

Few studies, however, have examined gender differences in RSFC changes caused by acute OXY administration, and no studies have examined these changes in individuals with CUD. Seeley and colleagues (27) reviewed 11 studies that examined changes in RSFC caused by acute intranasal OXY administration in healthy controls and individuals with anxiety disorders (posttraumatic stress disorder, generalized social anxiety disorder) or autism spectrum disorder. Most of these studies focused on connectivity of the amygdala with medial prefrontal or cingulate regions. Although findings are mixed as to whether OXY increases or decreases amygdala connectivity, individual differences like gender and psychopathology modulate this connectivity. Whole-brain analyses of RSFC have indicated that acute administration of OXY also increases connectivity in brain regions other than the amygdala, including the striatum, insula, and cingulated (28, 29). In addition, enhanced connectivity under OXY may depend on gender and trauma history, as well as the specific amygdala (24) or striatal nuclei (30) targeted in a given study.

Prior research has demonstrated that females with SUD associate relapse with interpersonal stress and negative affect (31, 32), whereas males with CUD show a more robust reward circuitry response to cocaine cues than females (33, 34). Potenza et al. (35) reported that corticostriatal-limbic hyperactivity was associated primarily with drug cues in men and stress cues in women. These findings suggest that stress circuitry may play a more important role in intrinsic functional brain organization in women with CUD, whereas reward circuitry may play a more prominent role in men with CUD.

To gain a better understanding of gender differences in neural response to OXY in CUD, the present study used RSFC to examine changes in stress- and addiction-related neurocircuitry in response to an acute dose of intranasal OXY in men and women with CUD. More specifically, the goal of this study was to understand the association between graph-theory-based network properties that reflect OXY treatment response and two individual subject variables of interest for SUD: childhood trauma and years of cocaine use. Predictive modeling was used to establish network profiles of OXY response associated with childhood trauma and years of cocaine use in men and women with CUD. The focus was on network connectivity of regions implicated in both substance use and childhood trauma, that is, the striatum, amygdala, insula, and ACC.

Given prior findings, the predictions of this study were that a) childhood trauma was expected to be more strongly associated with OXY connectivity changes in the amygdala because of its involvement in stress reactivity and trauma history (36, 37) and modulation of amygdala RSFC in posttraumatic stress disorder (PTSD) (24) and recent trauma exposure (38); b) years of cocaine use was expected to be more strongly associated with OXY connectivity changes in the striatum because of neuroadaptations of striatal circuitry in addiction (39); c) the major nodes of the salience network (insula, cingulate) were expected to be associated with both childhood trauma and years of cocaine use because of the role of this network in SUD (17) and psychiatric disorders more broadly (40); d) OXY response in network regions associated with childhood trauma and years of

cocaine use was expected to be different in men and women. Prior findings suggest that stress circuitry (e.g., amygdala) will exert a stronger network influence in females and reward circuitry (e.g., striatum) will exert a stronger network influence in males.

MATERIALS AND METHODS

Participants

Participants took part in a large study investigating the effect of OXY on subjective and neuroendocrine responses to stressors. The current crossover analysis included only data from the rsfMRI component of the study. A total of 93 non-treatment-seeking CUD individuals who responded to local media advertisements over a 54-month period completed the fMRI scanning procedures. Written informed consent was obtained before study assessments were administered. All procedures were conducted in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki and received institutional review board (IRB) approval. General exclusion criteria included 1) pregnancy, nursing, or plan to become pregnant during the course of the study; 2) women who had a complete hysterectomy, were postmenopausal, or receiving hormone replacement or hormonal contraceptive therapy; 3) history of or current significant hematological, endocrine, cardiovascular, pulmonary, renal, gastrointestinal, or neurological diseases; 4) history of or current psychotic, panic, eating, or bipolar affective disorders; 5) current major depressive disorder and PTSD; 6) history of or current medical conditions that might affect hypothalamic pituitary axis (HPA)axis activity; 7) synthetic glucocorticoid or exogenous steroid therapy within 1 month of testing; 8) psychotropic medications (with the exception of selective serotonin reuptake inhibitors), opiates or opiate antagonists, benzodiazepines, antipsychotics, beta-blockers, and other medications that might interfere with HPA axis activity or physiologic measurements; 9) acute illness or fever; 10) *Diagnostic and Statistical Manual of Mental Disorders-IV* (DSM-IV) criteria for substance dependence except alcohol, nicotine, or marijuana within the past 60 days; 11) unwillingness or inability to maintain abstinence from cocaine and other drugs of abuse (except nicotine) for 3 days prior to the cue–reactivity sessions; or 12) MRI contraindications.

Assessment

Participants meeting prescreening criteria were evaluated for study eligibility with the Mini-International Neuropsychiatric Interview (MINI) (41). The substance use module of the Structured Clinical Interview for DSM-IV (SCID-IV) was used to assess current and lifetime SUD (42). Substance use in the 90 days before the study was assessed using the Time-Line Follow-Back (43). The Childhood Trauma Questionnaire (CTQ) (44) was used to assess the extent to which individuals experienced five domains of childhood abuse and neglect (sexual abuse, physical abuse, emotional abuse, emotional neglect, and physical neglect). Participants answered each of 25 questions using a 5-point Likert scale ranging from 1 (never true) to 5 (very often true). A medical history and physical examination were completed to assess for medical exclusions. Participants meeting inclusion criteria and no exclusion criteria were scheduled to complete the study procedures and instructed to not use cocaine or other drugs of abuse for a minimum of 3 days before the test sessions.

Study Procedures

Participants completed one 6-min resting-state fMRI session on each of two consecutive days (a cocaine cue reactivity task was also completed on each day, but those results are not reported here). On day 1 of testing, participants arrived at the Medical University of South Carolina's (MUSC) Addiction Sciences Division research clinic at 10:00 a.m. Upon arrival, urine pregnancy tests were administered. Smokers were provided with a nicotine patch. Self-reports, urine drug screens (Roche Diagnostics, Indianapolis, Indiana), and breathalyzer tests (AlcoSensor III, Intoximeters, Inc., St. Louis, Missouri) were used to assess abstinence. If the pregnancy and drug tests were negative [with the exception of Tetrahydrocannabinol (THC)], study procedures continued. At 11:30 a.m., subjective ratings were obtained. A modified version of the Within Session Rating Scale was used to assess subjective ratings of craving, anxiety, and stress (45). This 1–10 visual analogue scale is anchored with the adjectival modifiers ("not at all," "mildly," "moderately," and "extremely"). The Cocaine Craving Questionnaire (CCQ)-Brief was used to assess cocaine craving. The State-Trait Anxiety Inventory (STAI) was used to assess anxiety symptoms (46). Participants were then provided a standardized lunch.

At 1:20 p.m., participants were administered 40 IU of OXY nasal spray or matching placebo (PBO). This dose was selected based on previous studies using similar doses of OXY (47–49) as well as our own previous work (50, 51). Timing of administration was also based on previous studies showing central activity of OXY 40 min after intranasal administration (50, 52). Intranasal OXY and matching PBO were compounded by the MUSC Investigational Drug Service. To achieve balance in sample size with respect to treatment order across genders, a block randomized design with randomly varying block sizes was used. Half of the participants were randomized to OXY on day 1 and half to PBO.

Subjective measures were repeated at 1:55 p.m. Scanning procedures commenced at 2:00 p.m. The 6-min rsfMRI session instructed participants to fixate a centrally presented crosshair but otherwise had no specific instructions other than to remain awake and alert and minimize head movement.

fMRI data images were acquired on a Siemens Trio 3.0 Tesla scanner with a 12-channel head coil (Siemens Medical, Erlangen, Germany) at MUSC for the majority of subjects (36 females, 53 males). Data from four of the subjects (one male) were collected on a Siemens PRISMA FIT 3.0 Tesla scanner with a 32-channel head coil, also at MUSC. During initial scanner tuning, localizing, and structural scanning, participants were shown relaxation images (i.e., 20 scenic pictures, each displayed for 30 s, and repeated if necessary). A high-resolution T1-weighted MPRAGE anatomical scan (TR = 2.25 s, TE = 4.2 ms, flip angle = 9°, 176 sagittal slices, field of view = 256 mm, 256 × 256 matrix, thickness = 1.0 mm) covering the entire brain and positioned

using a sagittal scout image was acquired for coregistration and normalization of functional images. T2*-weighted gradient echo EPI images were acquired with the following parameters (parameters were identical for the TRIO and PRISMA): TR = 2,000 ms, TE = 27 ms, flip angle = 76°, 36 axial slices (field of view = 237 mm × 237 mm, thickness = 3.7 mm voxels, in interleaved order). A gradient field map image was collected to match the spatial parameters of the EPI images.

After completion of the first scan, participants returned the next day and completed identical procedures with the opposite treatment condition. At the end of the second scan day, participants were debriefed and compensated.

Data Analysis

Demographics and Subject Characteristics

Baseline demographic and subject characteristics as well as prescan subjective ratings were compared across genders using independent-samples *t*-tests for continuous variables and chi-square tests across categorical characteristics. Data are reported as means and standard deviations for continuous variables and proportions for categorical variables.

An independent-samples *t*-test (unequal variances assumed because of unbalanced sample sizes) compared PBO minus OXY difference score for TRIO versus PRISMA scanner data in each of the 20 nodes of interest for clustering coefficient (CC) or eigenvector centrality (EC). Significance was determined using the false discovery rate (FDR) controlled at a 5% level (53, 54). Similarly, an independent-samples *t*-test (assuming unequal variances) examined whether PBO minus OXY difference score was different for smokers versus nonsmokers in each of the 20 nodes of interest for CC or EC.

Although several measures were taken to minimize the contributions of head motion to the fMRI time series, there are more stringent approaches to control for the influence of head motion on fMRI time series (55) than used here. To address whether any residual head motion was correlated with graph-theory measures of connectivity, we examined Spearman-rank correlations between head motion and any of the 20 nodes × 2 graph-theory measures (EC and CC) × 2 genders × 2 treatment conditions (OXY or PBO) using FDR correction.

Finally, an exploratory analysis examined whether any of the five subjective rating measures collected before scanning on each visit (craving, anxiety, stress, STAI, CCQ) was correlated with graph theory measures. Spearman rank correlations were conducted for each of the five subjective measures × 20 nodes × 2 graph-theory measures (CC and EC) × 2 genders × 2 treatment conditions (OXY or PBO) using FDR correction.

fMRI Preprocessing

FMRIB's FSL package[1] was used unless otherwise noted. Images in each participant's time series on each day were corrected for geometric distortion and head motion. Slice timing correction and spatial filtering (FWHM = 7.5 mm) were applied to each time series, which was then submitted to multiple regression using FSL to remove effects of global signal and head motion. Regressors included global signal [extracted from gray matter, white matter and cerebrospinal fluid (CSF) masks, which were created using FSL's FAST tissue segmentation tool], and six head motion parameters. The residual image from this regression step was then band-pass filtered (0.009 to 0.08 Hz) using AFNI (56). The spatially normalized image was then parcellated using a 294 region atlas—the 264 regions from Power et al. (57) with 30 additional subcortical regions (amygdala, hippocampus, striatum). Each region of interest (ROI) was represented by a 10-mm-diameter sphere. The BOLD signal time series was extracted in each of the 294 ROIs using FSL's "feat query" function.

Connectome Measures

Before computing the 294 × 294 functional connectivity matrix, corrupt time points were identified with fractional displacement values using the "fsl_motion_outliers" command. For each corrupt time point, the preceding time point and two successive time points were removed from the time series for each subject and visit (57) using the RSFC Net toolbox[2] implemented using the R software package (58). The mean percent scrubbed time points averaged over both visits was not significantly different between males (M = 0.13, SD = 0.06) and females (M = 0.12, SD = 0.06) according to an independent-samples *t*-test, $t(91) = 0.56$, $p = 0.58$.

The connectivity matrix was a weighted, signed adjacency matrix representing a fully connected undirected graph. Each matrix element reflected the partial correlation between two discreters fMRI time series while controlling for all other time series. We applied a shrinkage factor as to create a well-conditioned covariance matrix (59–61)[3]. The mixing parameter is largely an optimal weight as a function of N to combine the observed covariance and a target matrix, such as a diagonal (i.e., no covariance/correlation between regions).

The RSFC Net toolbox was used to compute two graph-theory measures: EC and CC. EC is a spectral, self-referential measure of centrality (62, 63). A node with a high EC is connected to other nodes with a high eigenvector score. EC considers connections to influential nodes to be more important than connections to marginal nodes. Hence, EC reflects the *global influence* of a node on the network.

$$C_{Eig[i]} = \left| \frac{1}{\lambda'} \sum_{j=1}^{N} M_{i,j} x_j \right|$$

The eigenvector centrality of the i^{th} node, $C_{Eig[i]}$, is defined as the absolute value of the i^{th} number in the eigenvector belonging to the principal eigenvalue of the matrix M, which is denoted λ'.

CC is a local measure of segregation representing the fraction of a node's neighbors that are also neighbors of each other; these patterns effectively form triangles around the node (64–66).

[1] www.fmrib.ox.ac.uk/fsl

[2] https://doi.org/10.5281/zenodo.1403924

[3] http://strimmerlab.org/software/corpcor

We used the CC formula for weighted and signed connectivity matrices provided by (66):

$$CC_i = \frac{\sum_{i,j} w_{s(j,i)} w_{(i,q)} w_{s(j,q)}}{\sum_{i \neq j} \left| w_{s(j,i)} w_{s(i,q)} \right|}$$

CC reflects the degree of *local influence* in a network. In this formula, the triangle is denoted by the direct connection of the i^{th} and j^{th} nodes and an indirect connection through a q^{th} node; $s(i,j,q)$. The numerator is the sum of the products of the signed edge weights between the pairs $s(i,j)$, $s(i,q)$, and $s(j,q)$ divided by the sum of the absolute value of the product of the edge weights for pairs $s(j,i)$ and $s(i,q)$. The denominator represents the maximum magnitude of the value the numerator can obtain.

EC and CC measures were chosen because they reflect different aspects of network organization. Network measures were always calculated using all 294 nodes. Visualization of nodes used BrainNet Viewer (67).

Twenty nodes were used as ROIs in subsequent analyses (**Table 1**): five insula regions, five ACC regions, six amygdala regions, and four striatal regions. ROIs were selected based on being strongly implicated in addiction (3, 17) and trauma (68–71). Of the eight ACC regions available in the Power atlas, two that fell on the midline were eliminated and five of the remaining six that sampled different aspects of the rostral to dorsal gradient were chosen. Of the seven insula regions available in the Power atlas (only two in the left hemisphere), five were chosen that sampled anterior, mid, and posterior aspects of the insula, primarily in the right hemisphere as there were more of those in the Power atlas. All six amygdala, two accumbens, and two caudate regions were selected. Importantly, the network measures reflected the connectivity of a given node with all other nodes in the whole brain network, not just the connectivity among the 20 nodes of interest.

TABLE 1 | Twenty regions of interest used as predictors.

Region name	MNI coordinate		
	x	y	z
Right dorsal ACC	10	–2	45
Right posterior insula	36	–9	14
Right mid insula	37	1	–4
Left ACC	–5	18	34
Left rostral ACC	–11	45	8
Right rostral ACC	12	36	20
Left anterior insula	–35	20	0
Right anterior insula	36	22	3
Right anterior ventral insula	34	16	–8
Right ACC	10	22	27
Left dorsal amygdala	–22	–4	–12
Right dorsal amygdala	22	–4	–12
Left medial amygdala	–14	–4	–20
Right medial amygdala	14	–4	–20
Left ventrolateral amygdala	–28	–4	–22
Right ventrolateral amygdala	28	–4	–22
Left caudate	–13	7	10
Right caudate	14	8	11
Left nucleus accumbens	–10	12	–7
Right nucleus accumbens	10	10	–8

ACC, anterior cingulate cortex; MNI, Montreal Neurological Institute.

Generalized Linear Model Analysis (Analysis 1)

The purpose of this analysis was to isolate regions that showed effects of OXY treatment and establish that changes in connectivity caused by OXY were modified by gender, childhood trauma (CTQ), and years of cocaine use (YRSUSE).

Generalized linear mixed effects models were developed to assess Analysis 1 (IBM SPSS tatistics; Version 24.0; IBM Corp., Armonk, NY). Models were developed to specifically assess the effects of treatment (OXY, PBO) and node (20 ROIs described above) as repeated effects, with gender, head motion, CTQ, and YRSUSE as additional variables. All models further adjust for study-specific design variables, specifically study visit and treatment order. To assess the hypothesis that gender, CTQ, and YRSUSE may modify the relationship between OXY and node response, model interactions were included in subsequent analysis. Both main effects and interactions were considered significant if $p \leq 0.05$. Separate generalized linear models were conducted with CC and EC as outcome variables. This step was conducted before model selection (Analysis 2) to investigate and establish important interactions among variables of interest. Analysis 2 will then examine such interactions in more depth using model selection.

Automatic Linear Modeling (Analysis 2)

The purpose of this analysis was to conduct model selection to select the best set of brain regions and network properties associated with differing levels of childhood trauma and years of cocaine use. Eight different models were examined based on the combination of two different outcome variables (CTQ, YRSUSE), two genders (male, female), and two different network measures (CC, EC). For each of the eight models, model selection was conducted over 10 replications.

Model selection used Automatic Linear Modeling (ALM; IBM SPSS Statistics). ALM is a linear modeling approach in which a set of variables (i.e., network properties in each of the 20 ROIs) predicts an outcome (i.e., CTQ or YRSUSE). The treatment effect was expressed as a difference score in either CC or EC in the PBO condition minus the OXY condition in each of the 20 ROIs. A positive difference score reflected a *reduction* in connectivity because of treatment with OXY, whereas a negative difference score reflected *increased* connectivity because of OXY. ALM automatically trims outliers and transforms variables, if needed. ALM divides the full sample of subjects into a training set (70% of the data) and a test set (30% of the data; called the overfit prevention set in IBM SPSS Statistics). The modeling process used 10 replicated data sets, and training and test sets are randomly selected from each. Replicates were a random sample with replacement.

In ALM, if the number of predictor variables is 20 or fewer, a large subset of possible models is examined using "best subsets" (72). This approach determines the best subset of predictor

variables using the average squared error (ASE) of the test set. The model with the lowest ASE is chosen by ALM as the best model. ALM yields a measure of model accuracy, which is 100 times the adjusted R^2 of the final model, Akaike's Information Criterion (AIC), as well as the importance and weight (coefficient) of each predictor.

Predictor importance is a relative measure of how important each variable was in the prediction. IBM SPSS Statistics uses the leave-one-out method to compute importance based on the residual sum of squares by removing one predictor at a time from the final full model. The importance values all sum to 1.

To determine whether EC or CC yielded a better model for predicting CTQ or YRSUSE for males and females separately, the average accuracy across the 10 replications were compared qualitatively, and the number of significant models ($p \leq 0.05$) across the 10 replications was considered. The network measure that yielded the highest average accuracy and more significant replications for a given gender and outcome variable combination was considered the better model. To determine the final set of predictors, the cumulative importance of predictors across the 10 replications was calculated. Predictors with cumulative importance >1 were considered for interpretation. Finally, to address potential collinearity among the predictors in the final models, the predictors with cumulative importance >1 were entered into a simultaneous linear regression, and variance inflation factors (VIFs) were determined for each model covariate; if a VIF exists greater than 4.0 (73), multicollinearity will be mitigated by choosing the collinear variable that produces the greatest model fit when included.

TABLE 2 | Demographics and subject characteristics.

Characteristic	Sex		*p* value
	Female	Male	
	(*n* = 39)	(*n* = 54)	
Demographics			
Age in years (SD)	40.0 (8.5)	44.5 (9.8)	0.024
Cigarette Smoker % (*n*)	84.6 (33)	75.9 (41)	0.305[a]
Cigarettes per day (SD)	11.5 (6.9)	10.8 (6.9)	0.715
Caucasian % (*n*)	30.1 (12)	22.2 (12)	0.352[a]
Cocaine use characteristics			
Age at first use (SD)	22.1 (5.8)	21.1 (6.3)	0.427
Total years use (SD)	14.1 (7.7)	18.3 (8.2)	0.014
Age at dependence onset[b] (SD)	29.2 (8.1)	29.5 (8.7)	0.849
Using days per month (SD)	17.5 (8.1)	17.0 (7.4)	0.753
Baseline trauma			
CTQ total score[c] (SD)	51.2 (21.4)	43.8 (14.3)	0.079
Prescan subjective ratings—Visit 1			
Craving (SD)	2.3 (2.7)	2.7 (2.5)	0.563
Anxiety (SD)	2.4 (2.4)	2.3 (2.2)	0.857
Stress (SD)	1.5 (2.3)	2.2 (2.4)	0.167
STAI (SD)	32.2 (9.7)	35.2 (12.1)	0.210
CCQ (SD)	5.5 (1.3)	5.5 (1.1)	0.981
Prescan subjective ratings—Visit 2			
Craving (SD)	2.2 (2.5)	2.5 (2.5)	0.534
Anxiety (SD)	2.0 (2.4)	2.1 (2.5)	0.726
Stress (SD)	1.5 (2.4)	1.7 (2.2)	0.747
STAI (SD)	32.4 (12.0)	34.4 (12.0)	0.430
CCQ (SD)	5.7 (1.3)	5.6 (1.2)	0.677

SD, standard deviation; STAI, State-Trait Anxiety Inventory; CCQ, Cocaine Craving Questionnaire.

[a]*p value calculated using chi-square test.*

[b]*Based on responses from 37 females and 53 males.*

[c]*Based on responses from 36 females and 49 males.*

RESULTS

Demographics and Subject Characteristics

Males were older than females and reported more years of cocaine use (**Table 2**). However, males and females were not different on any of the other demographic, cocaine use characteristics, or subjective measures. There were no significant differences between TRIO and PRISMA scanner data in any of the 20 nodes of interest for either CC or EC. There were also no significant differences between smokers and nonsmokers in any of the 20 nodes of interest for either CC or EC. Therefore, scanner type and smoking status were not included as variables in subsequent analyses.

Head motion was not correlated with CC or EC in any of the 20 nodes or treatment conditions. Although none met the threshold for significance, head motion was included in the two primary analyses below as a precaution given that only six head motion parameters were used as nuisance variables in preprocessing.

Finally, the exploratory correlation analysis between subjective ratings and graph theory measures yielded one significant correlation: males in the PBO condition who reported higher stress before scanning also showed higher EC in the left dorsal amygdala, *rho* = 0.53, $p = 0.000046$.

Analysis 1: Establish whether graph-theory measures reflecting treatment response are associated with childhood trauma and years of cocaine use and whether gender moderates these associations.

The generalized linear model with CC as the outcome variable and node, treatment, gender, head motion, CTQ, and YRSUSE as predictors yielded several significant effects and interactions (**Supplement 1**). CC varied by node ($p = 0.0001$), CTQ ($p = 0.009$), and head motion ($p = 0.0001$). The node effect was further modified by treatment (Node × Treatment interaction, $p < 0.0001$), and significant three-way interactions indicated that the treatment effect in different nodes was further modified by gender (Node × Treatment × Gender, $p = 0.0001$), CTQ (Node × Treatment × CTQ, $p = 0.0001$), and YRSUSE (Node × Treatment × YRSUSE, $p = 0.0001$). **Figure 1A** illustrates the Node × Treatment × Gender interaction for CC. OXY increased CC for males in the right ACC and left dorsal amygdala, whereas OXY increased CC for females in the right accumbens.

The generalized linear model with EC as the outcome variable and node, treatment, gender, head motion, CTQ, and YRSUSE as predictors yielded a main effect of node ($p = 0.0001$) and higher-order interactions with node (**Supplement 1**). The node effect was further modified by treatment and gender (Node × Treatment × Gender, $p = 0.0001$), treatment and CTQ (Node × Treatment × CTQ, $p = 0.0001$), and treatment and YRSUSE (Node × Treatment × YRSUSE, $p = 0.0001$). **Figure 1B**

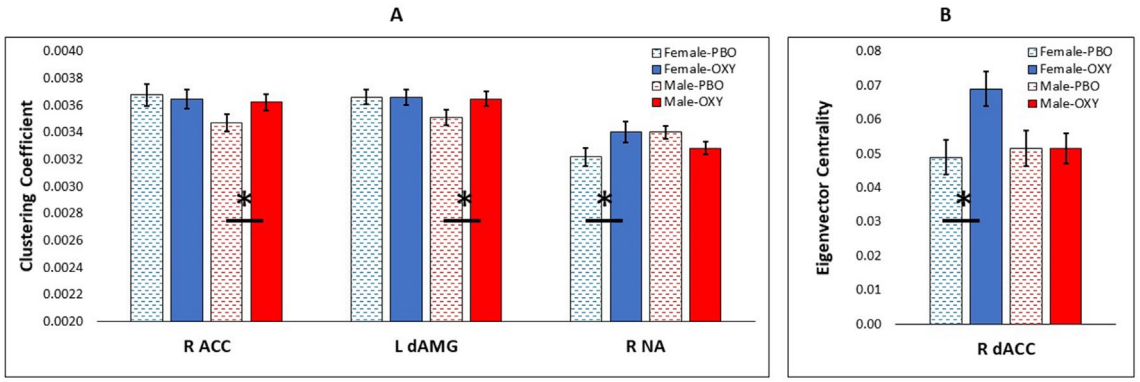

FIGURE 1 | Significant effect of oxytocin (OXY) treatment (solid bars) versus placebo (PBO) (shaded bars) in CUD females (blue) and males (red). **(A)** Effect of OXY on clustering coefficient in three nodes of interest: right anterior cingulate cortex (R ACC), left dorsal amygdala (L dAMG), and right nucleus accumbens (R NA). **(B)** Effect of OXY on eigenvector centrality in one node: right dorsal ACC (R dACC). Error bars are standard error of the mean. Horizontal bars with asterisk indicate a significant difference of OXY versus PBO at $p < 0.05$.

illustrates the Node × Treatment × Gender interaction for EC. OXY increased EC for females in the right dorsal ACC.

These analyses modeled the spatial correlation among the 20 nodes and isolated treatment effects in some of the nodes. For both EC and CC, these treatment effects were modified by gender, CTQ, and YRSUSE. The goal of the next analysis was to use model selection and machine learning to establish the network profiles associated with OXY-related changes in connectivity measures and CTQ or YRSUSE. Because gender modified these effects in Analysis 1, these analyses are conducted separately in males and females.

Analysis 2: Conduct model selection to select the best set of brain regions and network properties associated with childhood trauma and years of cocaine use.

Table 3 summarizes the performance of the 10 replications for each of the 8 models.

Network Profile for CTQ in Males

In males, neither the CC nor the EC model was associated with CTQ reliably across replications. Only one replication was significant for CC, and no replications were significant for EC.

TABLE 3 | Model accuracy (adjusted R^2, top row) and p value (bottom row) for each replication for each model of interest.

			Replication										
Outcome Variable	**Gender**	**Graph-theory Measure**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Mean**
CTQ	Male	CC	12%	7%	14%	1%	9%	7%	2%	19%	11%	13%	9%*
			0.11	0.26	0.09	0.40	0.10	0.22	0.36	0.03	0.09	0.07	
	Male	EC	0%	0%	1%	0%	0%	0%	3%	2%	3%	0%	1%
			0.68	0.60	0.42	0.58	0.42	0.79	0.29	0.38	0.31	0.60	
	Female	CC	15%	13%	15%	15%	9%	0%	11%	6%	6%	3%	9%
			0.06	0.17	0.11	0.11	0.17	0.52	0.20	0.23	0.34	0.36	
	Female	EC	28%	29%	39%	37%	23%	35%	31%	24%	21%	7%	27%*
			0.04	0.02	0.01	0.01	0.03	0.01	0.01	0.03	0.03	0.29	
YRSUSE	Male	CC	17%	5%	6%	2%	7%	15%	2%	0%	21%	4%	8%
			0.05	0.18	0.26	0.36	0.17	0.11	0.34	0.64	0.03	0.29	
	Male	EC	18%	23%	19%	10%	15%	17%	27%	3%	1%	22%	16%*
			0.03	0.01	0.01	0.07	0.06	0.03	0.01	0.34	0.30	0.02	
	Female	CC	6%	24%	11%	30%	24%	25%	14%	28%	21%	21%	20%*
			0.23	0.01	0.16	0.01	0.02	0.02	0.10	0.01	0.03	0.05	
	Female	EC	13%	21%	16%	37%	40%	34%	4%	6%	14%	11%	19%
			0.16	0.06	0.06	0.01	0.01	0.02	0.34	0.27	0.09	0.18	

**Indicates best model based on average accuracy and number of significant replications when comparing EC and CC.*
CTQ, Childhood Trauma Questionnaire total score; YRSUSE, years of cocaine se; CC, clustering coefficient; EC, eigenvector centrality.

These results indicate that OXY-related changes in graph-theory measures in the 20 nodes of interest are not associated with individual variations in CTQ scores in males.

Network Profile for CTQ in Females

In females, the best model for CTQ was based on EC. Across 10 replications, this model had an average adjusted R^2 of 0.27. Nine of the 10 replications yielded significant models. The model using CC as the graph-theory metric for CTQ had an average adjusted R^2 of 0.09, and none of the replications was significant.

In the EC model, three predictors had cumulative importance >1 (**Figure 2**). The scatter plots (**Supplement 2**) illustrate that for the right ACC, a higher CTQ was associated with a greater global influence on PBO than OXY, but for the right dorsal ACC and left rostral ACC, a higher CTQ was associated with a greater global influence on OXY than PBO.

Network Profile for YRSUSE in Males

In males, the best model for YRSUSE was based on EC. Across 10 replications, this model had an average adjusted R^2 of 0.16. Six of the 10 replications yielded significant models. In contrast, the model using CC as the graph-theory metric for YRSUSE had an average adjusted R^2 of 0.09 and only two replications were significant.

In the EC model, three predictors had cumulative importance >1 (**Figure 3**). The scatter plots (**Supplement 2**) illustrate that for the right dorsal ACC, higher CTQ was associated with greater global influence on PBO than OXY, but for the left medial amygdala, higher CTQ was associated with a greater global influence on OXY than PBO. Greater head motion was associated with fewer years of cocaine use.

Network Profile for YRSUSE in Females

In females, the best model for YRSUSE was based on CC. Across 10 replications, this model had an average adjusted R^2 of 0.20. Seven of the 10 replications yielded significant models. Although the model using EC as the graph-theory metric for CTQ had an average adjusted R^2 of 0.19, only three of the replications were significant. Although the two models had comparable accuracy, the models using CC as a predictor had more replications that were significant, so it was considered a better model than the EC model.

In the CC model, four predictors had cumulative importance >1 (**Figure 4**). The scatter plots (**Supplement 2**) illustrate that for the right rostral ACC, a higher CTQ was associated with a greater local influence on PBO than OXY, but for the left rostral ACC and right anterior-ventral insula, a higher CTQ was associated with a greater local influence on OXY than PBO. Greater head motion was associated with more years of cocaine use.

For all of the final models, VIFs were less than 2 for all predictors, indicating no collinearity issues, so all variables were retained.

DISCUSSION

The overall goal of this study was to discover how OXY changes functional network organization in men and women with CUD and to isolate network profiles that are associated with severity

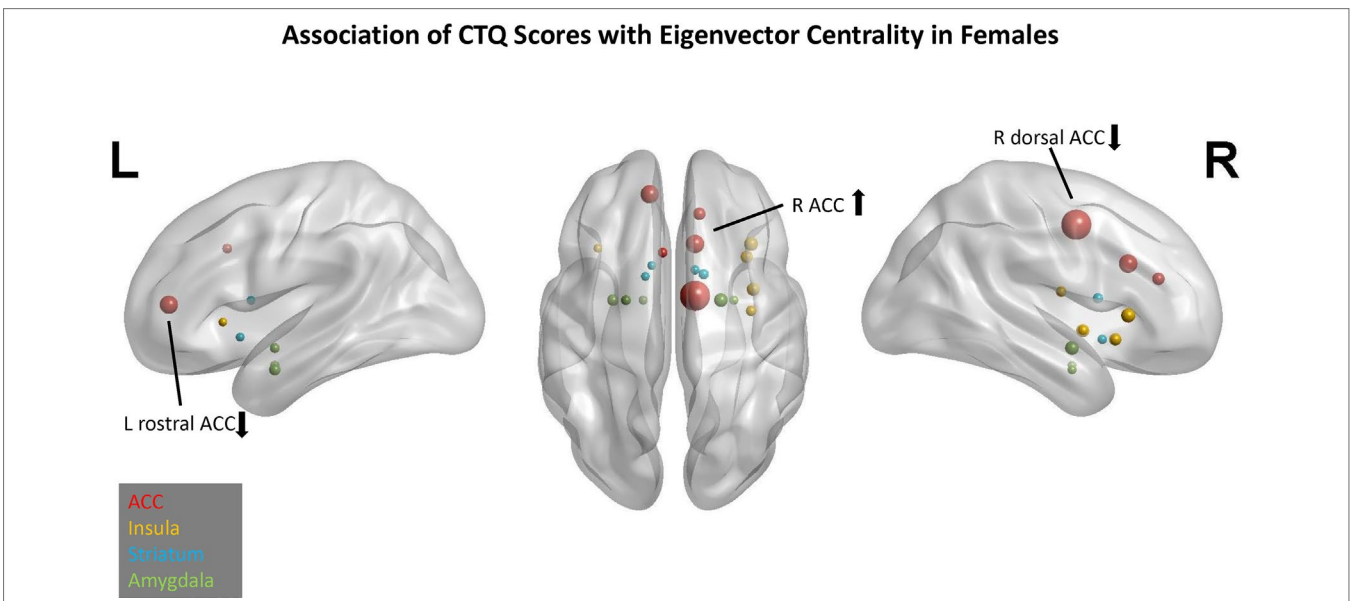

FIGURE 2 | Association of Childhood Trauma Questionnaire (CTQ) scores with eigenvector centrality in females. Network nodes of interest are shown on a template brain in Montreal Neurological Institute (MNI) space, with left lateral (left panel), right lateral (right panel), and axial views (center). Anterior cingulate (ACC) nodes appear in red, insula nodes in yellow, striatum nodes in blue, and amygdala nodes in green. The size of each node reflects its cumulative importance across 10 replications of predictive modeling. Nodes with cumulative importance >1 are labeled anatomically. The arrow next to each label indicates the sign of the regression coefficient for that node. Nodes that failed to appear in any of the 10 replications do not appear in this figure.

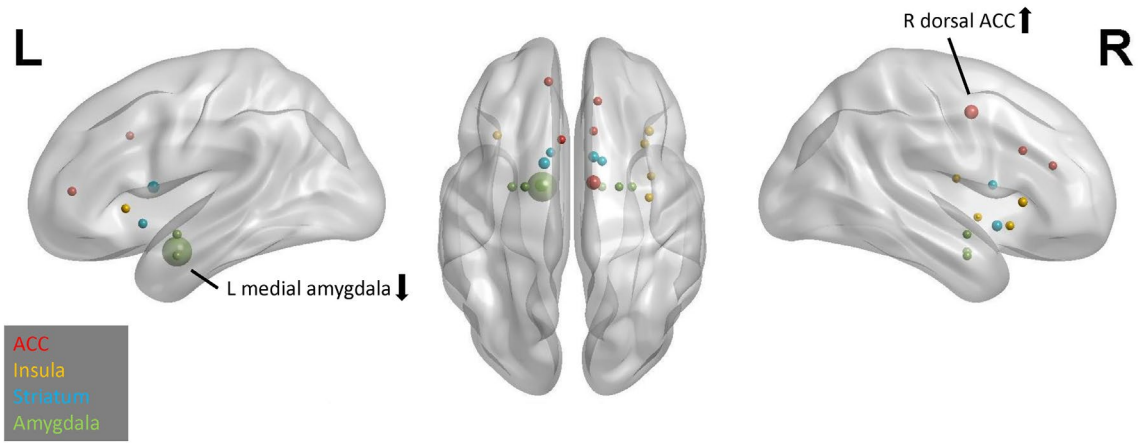

FIGURE 3 | Association of years of cocaine use with eigenvector centrality in males. Network nodes of interest are shown on a template brain in MNI space, with left lateral (left panel), right lateral (right panel), and axial views (center). ACC nodes appear in red, insula nodes in yellow, striatum nodes in blue, and amygdala nodes in green. The size of each node reflects its cumulative importance across 10 replications of predictive modeling. Nodes with cumulative importance >1 are labeled anatomically. The arrow next to each label indicates the sign of the regression coefficient for that node. Nodes that failed to appear in any of the 10 replications do not appear in this figure.

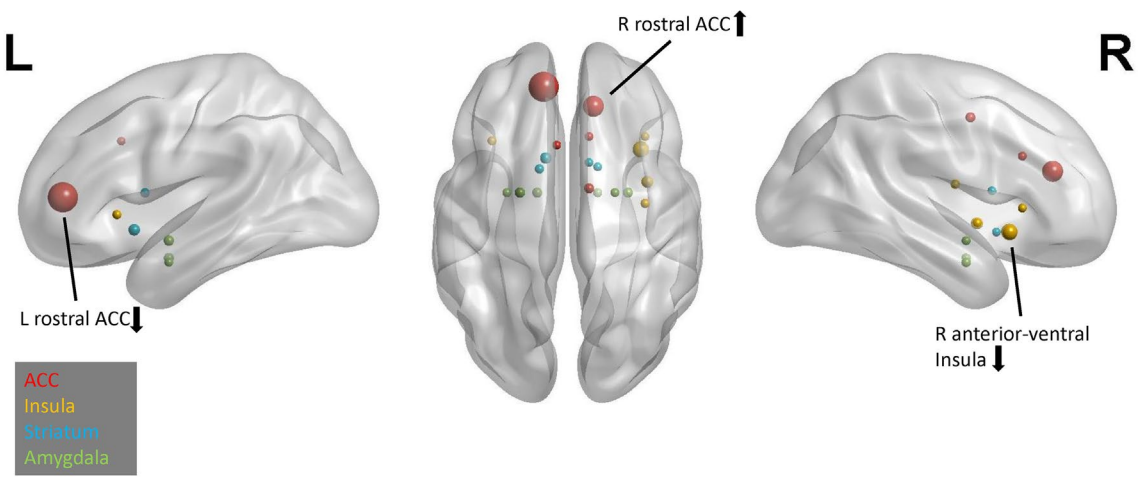

FIGURE 4 | Association of years of cocaine use with clustering coefficient in females. Network nodes of interest are shown on a template brain in MNI space, with left lateral (left panel), right lateral (right panel), and axial views (center). ACC nodes appear in red, insula nodes in yellow, striatum nodes in blue, and amygdala nodes in green. The size of each node reflects its cumulative importance across 10 replications of predictive modeling. Nodes with cumulative importance >1 are labeled anatomically. The arrow next to each label indicates the sign of the regression coefficient for that node. Nodes that failed to appear in any of the 10 replications do not appear in this figure.

of cocaine use and childhood trauma. OXY induced increases in connectivity differently in men and women with CUD. In women, OXY increased local influence of the right accumbens and increased global influence of the right dorsal ACC. In men, OXY increased local influence of the left dorsal amygdala and right ACC.

The first hypothesis that childhood trauma would be associated with OXY-related connectivity changes in the amygdala was not strongly supported. Network profiles associated with individual variations in childhood trauma for females did not include amygdala nodes, and modeling of network profiles in males did not reliably yield significant models. Although the amygdala was not implicated in individual variations in childhood trauma, OXY increased local influence (CC) of the left dorsal amygdala in men. In addition, a higher global influence of this same amygdala region was associated with higher stress ratings in men on PBO. Although the functions of different amygdala

nuclei in higher-level human behaviors is still debated, the dorsal (i.e., superficial) amygdala is involved in emotion processing, whereas the other amygdala nuclei play a role in fear, anxiety, and fear conditioning (27). Consequently, the association between dorsal amygdala global influence and stress ratings on PBO (in males) may reflect current emotional state rather than trauma history. In the PBO condition, a higher reported stress in males was associated with stronger global influence and more widespread connectivity of the left dorsal amygdala in males. In other words, the amygdala is exerting a stronger influence on other brain circuitry in the PBO condition, especially for males reporting more stress. Notably, OXY increased *local* influence of the left dorsal amygdala in males, suggesting that OXY shifts the influence of the left dorsal amygdala from global to more local and segregated from other brain circuitry. This shift on OXY may reflect an adaptive process, whereby stress-related amygdala activity is reduced.

The second hypothesis that years of cocaine use would be more strongly associated with OXY connectivity changes in the striatum was also not strongly supported given that none of the striatum nodes in males or females had cumulative importance that exceeded 1. However, OXY increased local influence of the right nucleus accumbens in females, indicating that it was influenced by OXY in females. Bethlehem and colleagues (28) similarly showed that OXY increased connectivity of the striatum with a broad network of brain regions in non-SUD women.

The third hypothesis that the major nodes of the salience network (insula, ACC) were expected to be associated with both childhood trauma and years of cocaine use was largely confirmed. ACC nodes predicted CTQ scores in females, and ACC and insula nodes predicted years of cocaine use in both males and females. The ACC was an important predictor in all models while the insula was an important predictor in one model (prediction of years of use in females). Local influence of the right ACC also increased on OXY in men, and global influence of the right dorsal ACC increased on OXY in women.

The fourth hypothesis was that network profiles associated with childhood trauma and years of cocaine use would be different between men and women. Stress circuitry (e.g., amygdala nodes) was expected to be more influential on network organization in females, whereas reward circuitry (e.g., striatum nodes) was expected to be more influential on network organization in males. Whereas the network profiles were indeed different between males and females, the amygdala was an important predictor of cocaine use in males rather than females (and was modulated by OXY in males), and the striatum was not an important predictor for either males or females, but the right accumbens was modulated by OXY in females.

The finding that amygdala connectivity was modulated by OXY, was associated with stress ratings under PBO, and was a significant component in the network profile for years of cocaine use in males but not females was not predicted. However, preclinical studies have reported that male rodents show greater OXY receptor binding in the amygdala than females, which is also modulated by breeding status in males (74). In addition, maltreated female adolescent rodents show significantly decreased OXY receptor binding in the amygdala compared to female controls (75). Although caution should be taken when translating preclinical findings to human study results, it is possible that the more prominent role for amygdala connectivity in CUD males in the present study is driven by higher OXY receptor binding in males and lower OXY receptor binding in females, particularly in those reporting more severe childhood trauma. This speculation, however, would need to be tested more directly in humans in future studies.

The predominant finding of the present study was that the salience network emerged as a critical component for OXY-induced changes in network profiles for childhood trauma and cocaine use in both males and females. Moreover, the ACC (rather than the insula) was the most prominent component in all models. The ACC is a critical node in the salience network that is functionally coupled to the insula. The ACC serves to influence external behaviors and motoric responses based on input from the insula (76), which processes interoceptive information and internal autonomic states (77). Given that the present study examined intrinsic connectivity (i.e., resting state) in the absence of external environmental input, the most salient information to be processed by subjects likely originated from internal bodily states. This may explain why the salience network was the primary influence on network organization. Had this study used external stimuli that could trigger reward responses, craving, or stress reactivity, the amygdala and striatum may have exerted a stronger influence on network organization.

Another potential explanation for the predominance of ACC nodes in influencing network organization is that the ACC is rich in OXY receptors (25). Because the present analysis focused on change in network connectivity related to OXY administration, those nodes that fall within brain regions with OXY receptors may have dominated network organization compared to regions that have fewer OXY receptors in humans, such as the striatum (25). It should be noted that the amygdala is also rich in OXY receptors, and this brain region emerged as an influential node in network profiles for individual variations in years of cocaine use in males. In addition, the exploratory analysis of subjective stress before scanning showed that higher reported stress was associated with greater global influence (EC) of the left dorsal amygdala in males in the PBO condition. These findings indicate that the amygdala may be an important locus for attenuating stress response in CUD males.

Wilcox and colleagues (17) have suggested that RSFC may be an important biomarker for treatment targets in SUDs. In their review of RSFC studies in SUD, they concluded that reduced connectivity between the salience network and executive control network and reduced connectivity within the executive control network are the most promising treatment targets for SUD. The present study has shown that OXY-related connectivity changes in components of the salience network, ACC, and insula are important for understanding individual variations in childhood trauma severity and cocaine use severity. Consequently, the present findings are consistent with the suggestion that the salience network is a potential treatment target.

It should be noted that associations between OXY-induced connectivity changes and childhood trauma or cocaine use severity were not universally in a single direction. In other words, higher cocaine use and greater childhood trauma were associated

with both increases and decreases in connectivity because of OXY relative to PBO. Because this analysis considered a node's relation to all other nodes in the network, it is reasonable that connectivity in one region could increase on OXY, whereas connectivity in another region could decrease. This is particularly true for graph-theory measures like CC and eigenvector centrality, which consider not only the direct connections to a node but also the connections of the connected nodes.

The two graph-theory properties examined here represent different aspects of network organization—local influence (CC) versus global influence (EC) of a node on the whole-brain network. CC has been investigated in prior rsfMRI studies of SUD (78–83), and only one study has examined EC in smokers (83). In the present study, both properties showed utility in characterizing network profiles for CTQ and years of cocaine use in CUD, but EC explained more variance across models and replications. The present findings demonstrate that EC is a potentially more useful graph-theory measure to consider when characterizing network profiles associated with individual differences in CUD. However, CC was more sensitive to changes in RSFC because of OXY.

Limitations

One potential limitation of the present study is that we did not examine executive control network connectivity directly but focused instead on the influence of salience network, amygdala, and striatum nodes on intrinsic network organization. This could be viewed as a missed opportunity given a recent review suggesting that executive control network connectivity is a promising treatment target for SUD (17). However, the reason to limit the number of network nodes in the analysis was to avoid overfitting with automatic linear modeling. Nevertheless, the graph-theory measures used in this study reflect the connectivity of a given node with the entire brain, including frontal regions, thereby allowing for more specific hypotheses involving frontal cortex connectivity to be tested in future investigations.

The present analysis took several approaches to minimize contributions of head motion to graph-theory measures of connectivity (i.e., elimination of data sets with excessive head motion, temporal censoring, inclusion of six rigid-body head motion parameters as nuisance variables), and none of the graph-theory measures in individual nodes of interest was correlated with head motion. Therefore, the effects of head motion did not contaminate the measures of connectivity. Nevertheless, there are many other approaches to head-motion nuisance regression that are more stringent than the approach used in the present study [e.g., Ref. (55)], which could be considered a limitation. In addition, head motion emerged as a significant predictor of years of cocaine use in the final models that resulted from ALM. These findings indicate that head motion was associated with the outcome variable years of cocaine use. However, this association was different in males and females. For males, more years of cocaine use was associated with reduced head motion, but for females, more years of cocaine use was associated with increased head motion. The reason for this gender-specific divergence is not immediately apparent, but the present findings suggest that the extent of head motion is linked to individual variations in cocaine use and should probably be included in analyses even when head motion effects on connectivity are minimized.

Another potential limitation is that several substance use characteristics were not considered in the analyses but could be additional influences on changes in connectivity because of OXY. For example, positive THC tests and length of abstinence period before scanning could all affect resting-state connectivity and change in connectivity because of OXY. Future studies with larger samples should examine the influence of these substance use variables on OXY treatment response in CUD.

CONCLUSION

In conclusion, this study adds to the evidence suggesting that RSFC may be an important biomarker in identifying treatment targets in SUDs. Salience network regions, especially the ACC, emerged as primary loci for OXY-induced changes in connectivity in both men and women with CUD, whereas the amygdala was an additional important locus for OXY response in males with CUD. These brain regions may serve as potential target areas for future OXY-based treatments. In addition, the present findings suggest that treatment strategies for CUD need to consider gender differences in OXY response.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Good Clinical Practice Guidelines and the Declaration of Helsinki with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Medical University of South Carolina Institutional Review Board.

AUTHOR CONTRIBUTIONS

NB, KB, JJ, AM-C, and MM-S contributed to the design and conduct of the study. NB and JJ supervised and conducted the data analysis with contributions from KB, CC, AM-C, and BV. NB, KB, JJ, AM-C, and BS were involved in the interpretation of the data. JJ wrote the first draft of the manuscript. NB, KB, AM-C, BS, and BV helped write sections of and edited the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00502/full#supplementary-material

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REVIEW
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Brain and Cognition for Addiction Medicine: From Prevention to Recovery Neural Substrates for Treatment of Psychostimulant-Induced Cognitive Deficits

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Addiction to psychostimulants like cocaine, methamphetamine, and nicotine poses a continuing medical and social challenge both in the United States and all over the world. Despite a desire to quit drug use, return to drug use after a period of abstinence is a common problem among individuals dependent on psychostimulants. Recovery for psychostimulant drug-dependent individuals is particularly challenging because psychostimulant drugs induce significant changes in brain regions associated with cognitive functions leading to cognitive deficits. These cognitive deficits include impairments in learning/memory, poor decision making, and impaired control of behavioral output. Importantly, these drug-induced cognitive deficits often impact adherence to addiction treatment programs and predispose abstinent addicts to drug use relapse. Additionally, these cognitive deficits impact effective social and professional rehabilitation of abstinent addicts. The goal of this paper is to review neural substrates based on animal studies that could be pharmacologically targeted to reverse psychostimulant-induced cognitive deficits such as impulsivity and impairment in learning and memory. Further, the review will discuss neural substrates that could be used to facilitate extinction learning and thus reduce emotional and behavioral responses to drug-associated cues. Moreover, the review will discuss some non-pharmacological approaches that could be used either alone or in combination with pharmacological compounds to treat the above-mentioned cognitive deficits. Psychostimulant addiction treatment, which includes treatment for cognitive deficits, will help promote abstinence and allow for better rehabilitation and integration of abstinent individuals into society.

Keywords: cocaine, nicotine, methamphetamine, memory, extinction, nucleus accumbens, prefrontal cortex

INTRODUCTION

Addiction to psychostimulant drugs such as cocaine, methamphetamine, and nicotine adds a significant burden on healthcare budgets in the form of premature morbidity and mortality. Alarmingly, the use and abuse of illicit psychostimulant drugs like cocaine and methamphetamine is showing a trend of steady increase than in the last decade (1). In addition to illicit stimulant

use, use and abuse of licit weak stimulant like nicotine continues to increase especially in the form of e-cigarettes and vaping (2). In addition, abuse of prescription stimulants like amphetamine, which are used to treat patients with attention deficit hyperactivity (ADHD), also adds to the problem of psychostimulant addiction. While not all people who experiment with psychostimulants will get addicted, an increasing trend of initiation does not augur well for psychostimulant addiction rates. Importantly, factors that promote transition from use/abuse to addiction are not fully understood (3, 4).

Considerable progress has been made over the last few decades in understanding the brain circuitry and pathological changes that facilitate and promote abuse of drugs (5). Despite this progress, significant challenges remain in the treatment of psychostimulant drug addiction (6). For example, currently, among the different psychostimulants described above, the Food and Drug Administration (FDA) has approved treatments for only nicotine (7, 8). Current treatment protocol for psychostimulant addiction depends largely on managing withdrawal symptoms of dependent individuals, providing behavioral/psychotherapy and utilizing self-help support groups (6). The inadequacy of current psychostimulant drug addiction is supported by high rates of relapse among abstinent addicts.

The goal of behavioral/psychotherapy is to help prevent relapse among abstinent addicts by helping them develop coping strategies to deal with cravings and emotional disturbances occurring as a result of withdrawal from psychostimulant drugs (9). This requires engagement of various cognitive domains such as attention, learning, and memory. Ironically, research over the last two decades and more has demonstrated that abuse of psychostimulants results in several cognitive deficits such as impulsivity (i.e., inability to inhibit disadvantageous rapid behavioral responses), risky and/or poor decision making, impaired cognitive flexibility (i.e., impaired ability to alter behavioral responses based on changing environmental contingencies), deficits in learning and memory, and/or hyperattentiveness to drug-associated cues compared with non-drug associated cues (10–13). Interestingly, individuals with pre-existing deficits in cognition and/or suffering from psychiatric disease states that are associated with impaired cognitive function (e.g., schizophrenia and depression) are more vulnerable to abusing illicit and licit stimulants (14, 15). Importantly, recovering addicts with significant cognitive deficits are more vulnerable to relapse (12, 16). Thus, cognitive deficits in recovering drug addicts irrespective of whether they were pre-existing or drug induced need to be adequately treated to promote abstinence among drug addicts (**Figure 1**).

Among the different psychostimulant-induced cognitive deficits, this review will focus on psychostimulant-induced cognitive deficits such as impulsivity and impairments in learning and memory. The review will primarily identify neural substrates that could be pharmacologically targeted to alleviate psychostimulant-induced cognitive deficits. Finally, the review will discuss evidence from animal studies that support use of non-pharmacological approaches to alleviate the above-mentioned cognitive deficits.

DRUG-INDUCED COGNITIVE DEFICITS

Impulsivity

Impulsivity in the human literature is often conceptualized as a personality trait (17). However, in the cognitive neuroscience field and for the purpose of this article, we will refer to impulsivity as behavior resulting from impaired inhibition in specific brain regions that play a role in regulating behavioral output (18). Based on the specific cognitive domains that are disrupted, impulsivity can be divided broadly into behavioral and decisional impulsivity (19). Behavioral impulsivity as the name suggests usually involves a quick behavioral response without consideration to consequences of the behavioral response (19). In contrast, decisional impulsivity

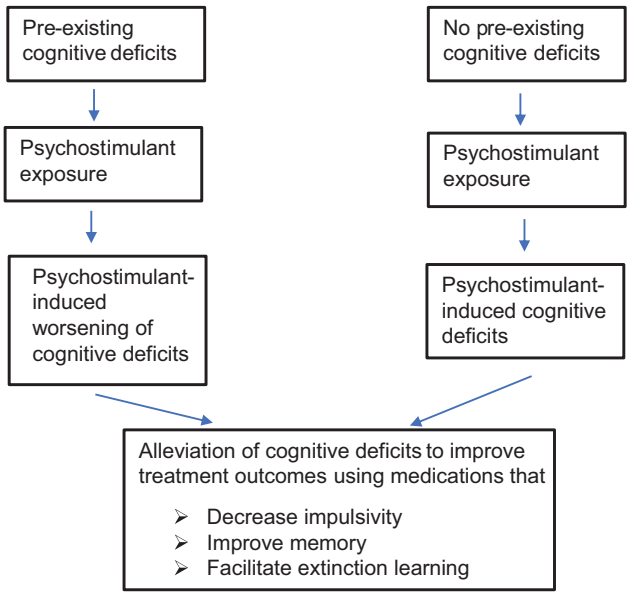

FIGURE 1 | Figure shows overall hypothesis of the review and possible treatment strategies to improve outcomes of psychostimulant addiction treatment. Psychostimulant-induced cognitive deficits include impulsivity, learning/memory impairments, attentional impairment, and impairment in decision making. In this review, we mainly restrict ourselves to targets that could potentially alleviate impulsivity and/or learning/memory impairments and facilitate extinction learning. Patients with pre-existing cognitive deficits prior to drug abuse may need more aggressive treatment to break the vicious cycle of drug addiction.

Abbreviations: ACPC, 1-aminocyclopropanecarboxylic acid; AMPA, amino-3-hydroxy-5-methyl-4-isoxazolepropionate/kainate; AP-5, (2*R*)-amino-5-phosphonovaleric acid; AQP-4, aquaporin-4; CDPPB, 3-cyano-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide; CPP, conditioned place preference; 5-CSRTT, 5-choice serial reaction time task; DBS, deep brain stimulation; DDT, delay discounting task; 5HT, serotonin; GABA, γ-aminobutyric acid; GLT, glutamate transporter; MDMA, 3,4-methylenedioxymethamphetamine; MK-801, (5*R*,10*S*)-(−)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cylcohepten-5,10-imine; mPFC, medial prefrontal cortex; mGlu, metabotropic glutamate; MPEP, 2-methyl-6-(phenylethynyl)pyridine; MTEP, 3-(2-methyl-1,3-thiazol-4-yl)ethynyl)pyridine; mRNA, microRNA; MOR, mu opioid receptor; NAcc, nucleus accumbens; NMDA, *N*-methyl-D-aspartate; OFC, orbitofrontal cortex; PAMs, positive allosteric modulators; Trk B, tropomyosin-related kinase B; VTA, ventral tegmental area; xCT, cystine–glutamate exchanger.

involves actions and decisions taken by the individual that are less advantageous to the individual.

Psychostimulant addicts show high levels of both behavioral and decisional impulsivity than do healthy controls (20–27). It is hypothesized that this impulsive behavior is responsible for high rates of relapse among these addicts during abstinence. Consistent with these data, a recent human study reported that smokers and polysubstance abusers who abused nicotine, cocaine, and alcohol were more impulsive than controls (28).

Impulsivity observed in drug-dependent individuals can exist prior to drug abuse and worsens with repeated drug use (**Figure 1**). In support of this hypothesis, several studies have shown that individuals who are impulsive have greater sensitivity to drugs of abuse, are more likely to experiment with drugs of abuse, and are more vulnerable to develop drug dependence (29–36). This hypothesis is also supported by animal studies. For example, animals showing poor inhibitory control prior to exposure to drugs of abuse (i.e., showed more impulsive behavior) acquired cocaine self-administration behavior much more rapidly than did animals that showed good inhibitory control (37). Additionally, animals that showed more risk-taking behavior as assessed using the rodent model of Iowa gambling task (rIGT) self-administered greater amount of cocaine than did animals that did not display high risk behavior in the same task (38). However, it is not known if repeated use of drugs of abuse induces impulsivity in humans. In animals, repeated administration of cocaine, methamphetamine, and nicotine increased impulsive behavior in animals (39–43). This increase in impulsivity was observed both when animals were challenged with the drug of abuse and during withdrawal from the drug (i.e., when animals were not under the influence of the drug). Thus, these studies support the hypothesis that exposure to drugs of abuse may *de novo* induce impulsivity.

Keeping with focus of this review, we will only discuss assessment of behavioral and decisional impulsivity in animals. Behavioral impulsivity in animals can be assessed by measuring either premature responding or the ability of an animal to stop already initiated action. In animals, premature responding is measured using the five-choice serial reaction time task (5-CSRTT), while ability of an animal to stop already initiated action is measured using the stop-signal reaction time (SSRT) (44, 45) (**Box 1**). Several brain regions such as the nucleus accumbens (NAcc), dorsal striatum, infralimbic prefrontal cortex

BOX 1 | Tasks used to measure psychostimulant-induced impulsivity.

Task	Parameter measured	Description
5-Choice serial reaction time task (5-CSRTT)	Behavioral impulsivity	The apparatus for the 5-CSRTT consists of five apertures. During a trial, a signal is presented in one of the apertures. Upon presentation of a signal, the animals must respond in the form of a nose poke into the aperture where the signal is presented. Nose poke in the aperture not presenting the signal is considered as an incorrect response. Similarly, response of the animal prior to presentation of a signal is considered as a premature response. Increase in premature responding is a measure of behavioral impulsivity. Lack of response by the animal is considered an omission and is indicative of impaired motor activity. Increase in incorrect responses is considered a manifestation of lack of attention. Every correct response of the animal is rewarded with a food pellet, which is collected by the animal from an aperture located on the opposite wall from the five apertures.
Go/No-Go task	Behavioral impulsivity	Each chamber is equipped with two retractable levers and tri-colored stimulus lights centered above each lever. The Go/No-Go trials consist of four alternating Go and No-Go components. Each component is usually 15 min long with a 5-s timeout between components for a 2-h session. During the Go component, the light on the active lever is illuminated, and a response on the active lever produces a food reward pellet on a variable interval of 30 s, and a press on the inactive lever has no consequence. Alternatively, the No-Go trial is indicated by a continuous flashing light on the active lever, and the animal must withhold a response on the active lever for a specific duration (e.g., 30 s). Responding on the active lever during the No-Go trial resets the time the animal must withhold their response (i.e., 30-s timer). The number of times the timer is reset is used as an index of behavioral impulsivity.
Delay discounting task (DDT)	Decisional impulsivity	The apparatus usually consists of three levers or apertures on one wall of the apparatus. Each lever or aperture usually has a light above it. The center aperture/lever and associated light are used to initiate trials. The two levers/apertures on either side of the center aperture are associated with rewards. Response on one of the apertures/levers is associated with immediate access to an assured small reward. In contrast, response on the other lever/aperture is associated with an assured larger reward. However, this larger reward is available after a delay. Preference of an animal for an immediate small reward compared with the delayed larger reward is suggestive of decisional impulsivity.
Rodent version of Iowa gambling task (rIGT)	Decisional impulsivity	The apparatus for the rIGT consists of five apertures like the 5-CSRTT. However, unlike the 5-CSRTT, during a trial, a signal light is presented in four apertures at the same time. Each aperture is associated with a different size of reward, and the probability of the reward is also different for each aperture. For example, responding on one of the apertures may earn the rat one pellet 90% of the time. In contrast, responding on an adjoining aperture may earn the rat four pellets, but only 40% of the time. The other two apertures may be associated with two pellets 80% or three pellets 50% of the time. Thus, the rat can choose the aperture for the amount of reward and hedge its luck. Because not all trials are rewarded, the unrewarded trials are considered punishment and are indicated by flashing light. Response of the animal prior to presentation of a signal is considered a premature response. Lack of response by the animal is considered an omission and could be indicative of impaired motor activity. Selection of aperture that is associated with larger reward but with lower probability is suggestive of risky choice and termed as "decisional impulsivity."

(infralimbic PFC), insula, and hippocampus have been shown to mediate behavioral impulsivity (19, 46–49). In contrast, decisional impulsivity in animals is usually assessed by measuring either temporal discounting or probability discounting. Temporal discounting is assessed using the delay discounting task (DDT), which involves assessing the ability of animal to wait for a larger reward compared with opting for an immediate smaller reward (50) (**Box 1**). Several studies have identified the role of the basolateral amygdala, orbitofrontal cortex (OFC), and hippocampus in mediating the DDT (51–53). In contrast, probability discounting is assessed using a task known as rIGT or probability discounting task and involves choosing a smaller sure reward (i.e., 100% chance to obtain the reward) compared with a larger reward, which is not always assured (i.e., approximately 50% chance or risky choice) (54, 55) (**Box 1**). Research has shown that the OFC, amygdala, habenula, and prelimbic PFC play a role in mediating probability discounting (56–58). Despite identifying the role of specific brain regions in specific types of impulsive behavior, more work is required to identify specific signaling mechanisms between the different brain regions.

Learning and Memory Deficits

Both learning and working memory deficits have been reported in abstinent psychostimulant addicts (21, 59–63). These learning/memory deficits are hypothesized to result in poor treatment outcomes among abstinent addicts. It is also hypothesized that working memory deficits prior to drug exposure increase vulnerability to drug addiction. Consistent with this hypothesis, individuals suffering from psychiatric disorders with significant learning and memory deficits such as depression and schizophrenia have high rates of stimulant addiction (14, 15, 64, 65). Also, a recent study reported that adolescents with weak working memory were more vulnerable to get addicted to drugs of abuse (66). In fact, acute administration of drugs like nicotine and cocaine enhances hippocampal function (67–69). Thus, individuals may compensate for memory deficits by abusing psychostimulants. Together, these findings suggest that use of psychostimulants induces memory deficits and that memory deficits present prior to drug use promote experimentation with stimulants leading to drug addiction.

Several models such as the Morris water maze, novel object recognition, and delayed match-to-sample task are used to assess learning/memory deficits in animals (**Box 2**) (70, 71). Similar to humans, chronic exposure and/or withdrawal from psychostimulants induced working memory deficits in animals. For example, animals with chronic extended-access cocaine self-administration experience showed working memory and learning deficits (72, 73). Further, animals undergoing withdrawal after chronic extended access to cocaine showed decreased functional activity of brain circuits mediating learning and memory such as the PFC, hippocampus, and striatum as measured by determining glucose utilization by these brain regions (74). Further memory deficits have been reported after withdrawal from nicotine, methamphetamine, and 3,4-methylenedioxymethamphetamine (MDMA) (75–79). Moreover, consistent with human studies, animals with memory deficits show significantly greater drug-seeking behavior than do controls. For example, neonatal ventral hippocampal lesions in rats, which lead to working memory deficits, resulted in increased reinstatement of nicotine seeking (80).

In abstinent addicts, exposure to stress, drug of abuse itself, and/or drug-associated environmental cues induces cravings, which promotes drug seeking often resulting in relapse (81–84). In humans, several behavioral and cognitive therapies, such as behavioral therapy, cue exposure therapy, motivational enhancement therapy, and contingency management, are used to

BOX 2 | Tasks used to measure psychostimulant-induced memory impairment and described in this review.

Task	Parameter measured	Description
Delayed match-to-sample (DMTS)	Working memory	In this task, as the name suggests, animals are initially presented with a particular stimulus on a computer touchscreen. For example, the stimulus could be a triangle of a particular color, e.g., red. Once the animal touches the triangle, the triangle disappears from the screen. There is then predefined delay. At the end of the delay, the animal is presented with two stimuli. One of the stimuli is the previously presented red triangle. The other stimulus is new triangle of a different color, e.g., blue. Selection of the "red triangle" is considered as the correct response, while selection of the "blue triangle" is considered as the incorrect response. A high percentage of correct response is indicative of intact working memory. In contrast, a high percentage of incorrect responses is indicative of impaired working memory.
Novel object recognition	Episodic memory	In this task, the animal is exposed to two identical objects for a defined period of the time. The animal can explore these objects, and they are termed as familiar objects. After a period of time, which can range for 24 to 72 h, animals are again exposed to two objects. One of them is the previously exposed "familiar object," and the other object is termed as the "novel object." Retention of memory in the animal is determined by calculating the discrimination index, which is defined as the time spent on the novel object divided by the sum of the time spent on the novel and familiar objects. A higher discrimination index indicates intact memory. In contrast, a low discrimination index suggests impairment of memory.
Morris water maze	Spatial memory	The apparatus consists of black painted circular pool containing water and divided into four quadrants with four starting points. The pool contains a platform that is submerged (hidden) in the water in a particular quadrant. During training, animals are trained to locate the hidden submerged platform irrespective of the start position. During the test trials, the submerged platform is removed, and animals are placed in a quadrant opposite to the quadrant where the platform was previously hidden (quadrant of interest). The time taken for the animal to reach the quadrant of interest, the path taken to reach the quadrant of interest, and time spent in the quadrant of interest are suggestive of spatial memory. In case of impairment of spatial memory, the animal will either take longer time to reach the quadrant of interest or spend less time in the quadrant of interest or take circuitous path to reach the quadrant of interest.

help abstinent addicts overcome craving (6, 85). The main goal of all these therapies is to decrease emotional and physiological responses to drug-associated cues among abstinent addicts. In animals, extinction learning is used to suppress learned responses to drug-associated cues (86–88). Extinction learning is a form of learning that involves exposure to drug-associated cues/contexts in the absence of the drug, which ultimately leads to decreased responses to drug-associated cues/contexts. In fact, reinstatement of drug seeking in response to drug-associated cues/environments after extinction training is a putative model of relapse in humans (89, 90). Several brain regions such as the infralimbic PFC, basolateral amygdala and NAcc shell, hypothalamus, and thalamus play a role in extinction learning (88). In fact, extinction learning resulted in decrease in activity of neurons in the prelimbic PFC and increase in activity of neurons in the infralimbic PFC (91–93). It has been hypothesized that facilitation of extinction learning could help in attenuating responses to drug-associated cues and prevent relapse (94, 95). Interestingly, there is significant overlap in pathways that mediate extinction of fear-associated memories and extinction of drug-associated memories (93). In fact, currently, behavioral therapies are being used to concurrently treat both substance abuse and post-traumatic stress disorder (96). Thus, in this review where direct evidence is lacking, we suggest neural substrates that play a role in extinction of fear-associated memories as possible targets for promoting extinction of drug-associated memories. It goes without saying that any such proposed targets will need to be assessed in models assessing extinction of drug-associated memories (**Box 3**). In summary, treatment of psychostimulant-dependent subjects must include procognitive agents that could alleviate working memory deficits and enhance learning/memory. Importantly, facilitation of extinction learning will help improve efficacy of cognitive behavioral therapies in humans especially cue exposure therapy.

PHARMACOLOGICAL TARGETS TO TREAT PSYCHOSTIMULANT-INDUCED COGNITIVE IMPAIRMENTS

Dopamine Receptors and Uptake Transporters

Changes in dopamine neurotransmission and dopamine receptors after exposure to psychostimulants like nicotine, cocaine, and methamphetamine have been previously described (97–100). Dopamine neurotransmission is primarily mediated *via* D1-like (D1 and D5) and D2-like (D2, D3, and D4) dopamine receptors. Most of the action of synaptic dopamine is terminated *via* uptake of dopamine by the dopamine uptake transporter (DAT). The dopamine uptake transporter is one of the primary targets for medications that are used to treat ADHD (101, 102). Thus, dopamine neurotransmission plays a role in both impulsivity and psychostimulant addiction. In this section, the role of D1- and D2-like dopamine receptors as possible targets for treatment of psychostimulant-induced cognitive deficits is discussed.

D1-Like Dopamine Receptors

Several studies have evaluated the role of D1-like dopamine receptors in impulsivity [see Jupp and Dalley (103) for review].

BOX 3 | Tasks used to assess facilitation of extinction learning.

Task	Parameter measured	Description
Extinction of drug-induced CPP	Extinction of drug-associated memories	In this model, a conditioned place preference (CPP) apparatus consisting of two main chambers is used. The two chambers are distinct in terms of their walls and/or floors. First, preference of the animal to the two main chambers is assessed. Next, animals are conditioned to the effects of the drug and saline/vehicle. During conditioning, animals are administered the drug and restricted to one of the chambers. Subsequently, animals are administered the vehicle/saline and restricted to the other distinct chamber. The conditioning trials are conducted either on the same day separated by at least 4–6 h or on alternate days. Once the animals are conditioned, drug-induced CPP is determined by allowing animals to assess both chambers freely. Animals will spend more time in the drug-associated chamber, suggesting rewarding effects of the drug. Subsequently, animals undergo extinction trials when they are repeatedly exposed to both chambers without drug treatment. Over a period of a few days, the time spent by the animals in the drug-associated chamber decreases, suggesting extinction of drug-induced CPP. A treatment, compared with controls, is said to facilitate extinction if the time spent by the animal in the drug-associated chamber diminishes faster.
Extinction of drug seeking	Extinction of drug-associated memories	In this model, animals are first trained to intravenously self-administer the concerned drug in self-administration chambers. A typical chamber has two levers—one is called the active lever and the other is called the inactive lever. Responses on the active lever are associated with drug administration. Drug administration is also associated with visual cues such as illumination of a light located above the lever. Once the animals establish stable intravenous self-administration, they undergo extinction training. During extinction training, animals can respond on either the active or inactive levers. Responses on the active lever are accompanied by neither presentation of visual cues nor drug administration. With time, responses of the animal on the active lever decrease to a point where no further decrease occurs (asymptote). A treatment is said to facilitate extinction if the animal takes fewer days to reach the lowest asymptote levels and/or if the responses on the active lever are lower compared with those of controls. In this model, reinstatement of drug seeking can be assessed by presenting the animal with drug-associated cues and by measuring responses on the active/drug-associated lever. Reinstatement of drug seeking is a putative model of relapse in humans.

Blockade of D1 receptors alone after systemic administration of a D1 receptor antagonist had no influence on decisional impulsivity (104). However, blockade of D1 receptors after systemic administration of a D1 receptor antagonist in mice lacking DAT attenuated behavioral impulsivity as assessed using the 5-CSRTT (105). Interestingly, D1 receptors in specific brain regions such as the NAcc and PFC play a differential role in impulsivity. For example, blockade of D1 receptors in the NAcc core and shell decreased behavioral impulsivity (106). Consistent with these data, blockade of D1-like receptors in the NAcc shell attenuated reinstatement of cocaine seeking in rats (107). In contrast, blockade of D1-like receptors in the medial PFC (mPFC) induced decisional impulsivity (108). Together, these data suggest that D1-like receptors in specific brain regions and circuits may play a differential role in impulsivity. A recent study reported that mice lacking D1 receptors compared with control did not show premature responding after morphine exposure (109). However, the effects of D1 receptor activation and blockade in psychostimulant-induced impulsivity have not been investigated.

D1-mediated dopamine neurotransmission in the PFC has been shown to play a role in extinction of drug-associated memories. For example, genetically induced overexpression of D1 dopamine receptors on glutamate neurons in the PFC facilitated extinction of cocaine-induced CPP in juvenile male rats compared with controls (110) (**Table 1** ; **Figure 2**). Activation of dopamine D1-like receptors results in increase in activity of the cAMP/protein kinase A/cyclic AMP-dependent response binding element (CREB) pathway. Rolipram, a phosphodiesterase 4 (PDE-4) inhibitor, increases cAMP levels and PKA activation that resulted in facilitation of fear extinction (116). Moreover, rolipram *via* an increase in CREB levels alleviated working memory deficits associated with alcohol withdrawal (117). Withdrawal from psychostimulants is also associated with decreased activity in PKA/CREB pathway especially in brain regions mediating learning/memory such the hippocampus and PFC (118, 119). Therefore, it is possible that rolipram may help facilitate extinction learning and/or working memory deficits associated with psychostimulant withdrawal. In summary, targeting D1 receptors in specific brain regions and circuits may have utility in the treatment of psychostimulant-induced cognitive deficits especially learning and memory deficits.

D2-Like Dopamine Receptors

Acute cocaine dose dependently decreased decisional impulsivity in rats as assessed using the DDT (120). The same study showed that systemic administration of D2 receptor antagonist, eticlopride, reversed acute cocaine-induced inhibition of decisional impulsivity, suggesting that the effects of cocaine on decisional impulsivity are mediated by D2 receptor activation. Further, the study showed that D2 receptors in the amygdala possibly mediate the inhibitory effect of acute cocaine on decisional impulsivity. Chronic cocaine exposure decreased striatal D2 receptor mRNA in both high and low impulsive rats and selectively decreased immediate early gene zif268 mRNA in the OFC and infralimbic cortices of high impulsive animals (121). Thus, impulsive behavior observed after chronic cocaine exposure was possibly due to decreased D2-mediated dopamine signaling in the above-described brain regions.

D2 dopamine receptors located in the NAcc, ventral tegmental area (VTA), and PFC also play a role in impulsive behavior. Specifically, D2/3 receptor availability was significantly decreased in the NAcc of high impulsive rats compared with low impulsive rats (122, 123). Further chronic methylphenidate treatment decreased impulsivity in high impulsive rats by increasing expression of D2 receptor availability in the dorsal striatum and NAcc (123). Similarly, decreased D2-mediated dopamine transmission in the PFC and VTA induced decisional impulsivity (124, 125). Interestingly, systemic administration of D2 agonist ropinirole induced decisional impulsivity as assessed using the rIGT (126). However, ex vivo analyses of brain slices revealed that chronic ropinirole treatment led to upregulation of the β-arrestin-AKT-GSK3β intracellular cascade, which usually suggests D2-mediated signaling under hyperdopaminergic conditions.

Interestingly, activation of D3 receptors induced decisional impulsivity as assessed using the rIGT (109, 127–129). In contrast, blockade of D3 receptors decreased decisional impulsivity. In addition, blockade of D3 receptors attenuated cocaine and methamphetamine seeking (130, 131). Together, the data suggest that blockade of D3 receptors may help to attenuate decisional impulsivity and drug seeking. Further studies are required to assess the effects of D3 antagonists on psychostimulant-induced impulsivity.

In summary, the above-described evidence suggests that D2-mediated dopamine neurotransmission in specific brain regions such as striatum and mPFC receptors may help to alleviate decisional impulsivity associated with psychostimulant addiction (**Box 4**). In contrast to D2 receptors, blockade of D3 dopamine receptors may help alleviate psychostimulant-induced decisional impulsivity. Overall, D2-like dopamine receptors are useful targets in the treatment of psychostimulant addiction.

Adrenergic Receptors and Noradrenergic Reuptake Transporters

The role of noradrenaline in impulsivity is evident by use of medications that increase noradrenergic transmission in the treatment of ADHD (101, 102). Noradrenergic transmission is mediated by α (α1 and α2) and β (β1 and β2) adrenergic receptors, and the action of synaptic noradrenaline is terminated by the noradrenaline uptake transporter (NET). Several drugs approved by the FDA for ADHD treatment include α2 adrenergic receptor agonists (e.g., guanfacine and clonidine), NET and DAT inhibitors (e.g., amphetamine and methylphenidate), and selective NET inhibitor (e.g., atomoxetine). Importantly, exposure to psychostimulants like cocaine, nicotine, and methamphetamine alters noradrenergic neurotransmission in the brain (132–135). In this section the role of α2, β2, and NET in psychostimulant-induced cognitive deficits is discussed.

α2 Adrenergic Receptors and NET

Like in humans, drugs that increase noradrenergic transmission decreased impulsivity in animal models (136–138). Guanfacine, a selective α2A adrenergic receptor agonist, attenuated cocaine-induced behavioral impulsivity and memory impairment in monkeys (139) (**Tables 2** and **3**). More recently, it was reported

TABLE 1 | Brain region-specific manipulation on psychostimulant-induced cognitive deficits.

Brain region	Manipulation	Species	Task	Reward	Findings	Reference
PFC (prelimbic)	D1 receptor overexpression	Rats	Extinction of cocaine-induced CPP	Cocaine	Facilitated extinction of cocaine-induced CPP	Brenhouse et al. (110)
PFC (infralimbic)	Blockade of β receptors	Mice	Extinction of cocaine-induced CPP	Cocaine	Inhibited extinction of cocaine-induced CPP	Huang et al. (111)
PFC (infralimbic)	β-Arrestin 2 knockdown	Mice	Extinction of cocaine-induced CPP	Cocaine	Inhibited extinction of cocaine-induced CPP	Huang et al. (111)
PFC (infralimbic)	β-Arrestin 2 overexpression	Mice	Extinction of cocaine-induced CPP	Cocaine	Facilitated extinction of cocaine-induced CPP	Huang et al. (111)
PFC (infralimbic)	BDNF	Rats	Extinction of cocaine-induced CPP	Cocaine	Facilitated extinction of cocaine-induced CPP	Otis et al. (112)
PFC (infralimbic)	TrkB receptor antagonist (ANA-12)	Rats	Extinction of cocaine-induced CPP	Cocaine	Inhibited extinction of cocaine-induced CPP	Otis et al. (112)
PFC (infralimbic)	GluN2B receptor antagonist ifenprodil	Rats	Extinction of cocaine-induced CPP	Cocaine	Inhibited extinction of cocaine-induced CPP	Otis et al. (112)
PFC (infralimbic)	HDAC3 deacetylase inhibitor	Rats	Extinction of cocaine-induced CPP	Cocaine	No effect on extinction of cocaine-induced CPP	Alaghband et al. (113)
PFC	CB1 antagonist (rimonabant)	Mice	Extinction of cocaine-induced CPP	Cocaine	Facilitated extinction of cocaine-induced CPP	Hu et al. (114)
NAcc shell	$GABA_A$ agonist (muscimol)	Rats	Morris water maze	Methamphetamine	Improved methamphetamine withdrawal induced spatial memory deficit	Heysieattalab et al. (115)
NAcc shell	$GABA_A$ antagonist (bicuculline)	Rats	Morris water maze	Methamphetamine	Worsened methamphetamine withdrawal induced spatial memory deficit	Heysieattalab et al. (115)
NAcc shell	NMDA antagonist (AP-5)	Rats	Morris water maze	Methamphetamine	Improved methamphetamine withdrawal induced spatial memory deficit	Heysieattalab et al. (115)
Dorsal hippocampus	HDAC3 deacetylase inhibitor	Rats	Extinction of cocaine-induced CPP	Cocaine	Facilitated extinction of cocaine-induced CPP	Alaghband et al. (113)

BDNF, brain-derived neurotrophic factor; Trk B, tropomyosin-related kinase B.

BOX 4 | Potential targets/approaches for alleviation of psychostimulant-induced impulsivity, memory impairment, and/or facilitation extinction of drug-associated memories. BDNF, brain-derived neurotrophic factor; CRF, corticotrophin-related factor; Trk B, tropomyosin-related kinase B; nACh, nicotinic acetylcholine; IGF, insulin growth factor; PAM, positive allosteric modulator; PPARγ, peroxisome proliferator agonist receptor gamma.

Decreasing impulsivity	Reversing memory impairment	Facilitating extinction learning
α2 agonists	NMDA receptor antagonists	mGlu5 receptor PAM
NET blockers	mGlu5 receptor PAM	AMPA receptor agonist
Orexin receptor antagonists	*N*-Acetylcysteine, riluzole	Glycine receptor coagonist
CB1 receptor antagonists	α7 nACh receptor agonist/PAM	$GABA_B$ agonist
D3 receptor antagonists	CB1 antagonists	Phosphodiesterase inhibitors
α4β2 nACh receptor antagonists	Activation of PKCε	Orexin receptor antagonists
mGlu4 PAM	Insulin	Increase BDNF levels
mGlu2/3 agonists	PPARγ agonists	TrK B receptor activation
5-HT3, 5-HT2A, and 5-HT2c antagonists	IGF-2 agonists	Increase in oxytocin levels
5-HT1A agonist	Exercise	Increase in ghrelin levels
Progesterone	Brain stimulation	CRF receptor antagonists
Exercise	Neurogenesis	IGF-2 agonists
		17β-estradiol
		Exercise
		Brain stimulation

that guanfacine improved inhibitory control in abstinent cocaine-dependent subjects (153). Also, α1 and α2 adrenergic receptor agonists decreased reinstatement of cocaine seeking (154). In contrast, α2 adrenergic receptor antagonist yohimbine is commonly used to pharmacologically induce reinstatement of psychostimulant drug seeking (155).

In addition, direct injection of atomoxetine in the NAcc shell, but not NAcc core or the PFC, reduced behavioral impulsivity as assessed using the 5-CSRTT (156). However, decisional impulsivity as measured using DDT was not altered by atomoxetine injections into either the mPFC or OFC (125). Importantly, relevant to this review, atomoxetine reduced decisional impulsivity for cocaine rewards using the DDT in male rats [(144) (**Table 2**), but see Ref. (157)]. In contrast, atomoxetine alone did not attenuate decisional impulsivity associated with cocaine rewards in female rats. However, decisional impulsivity for cocaine rewards in females was attenuated after treatment with either progesterone alone or progesterone in combination

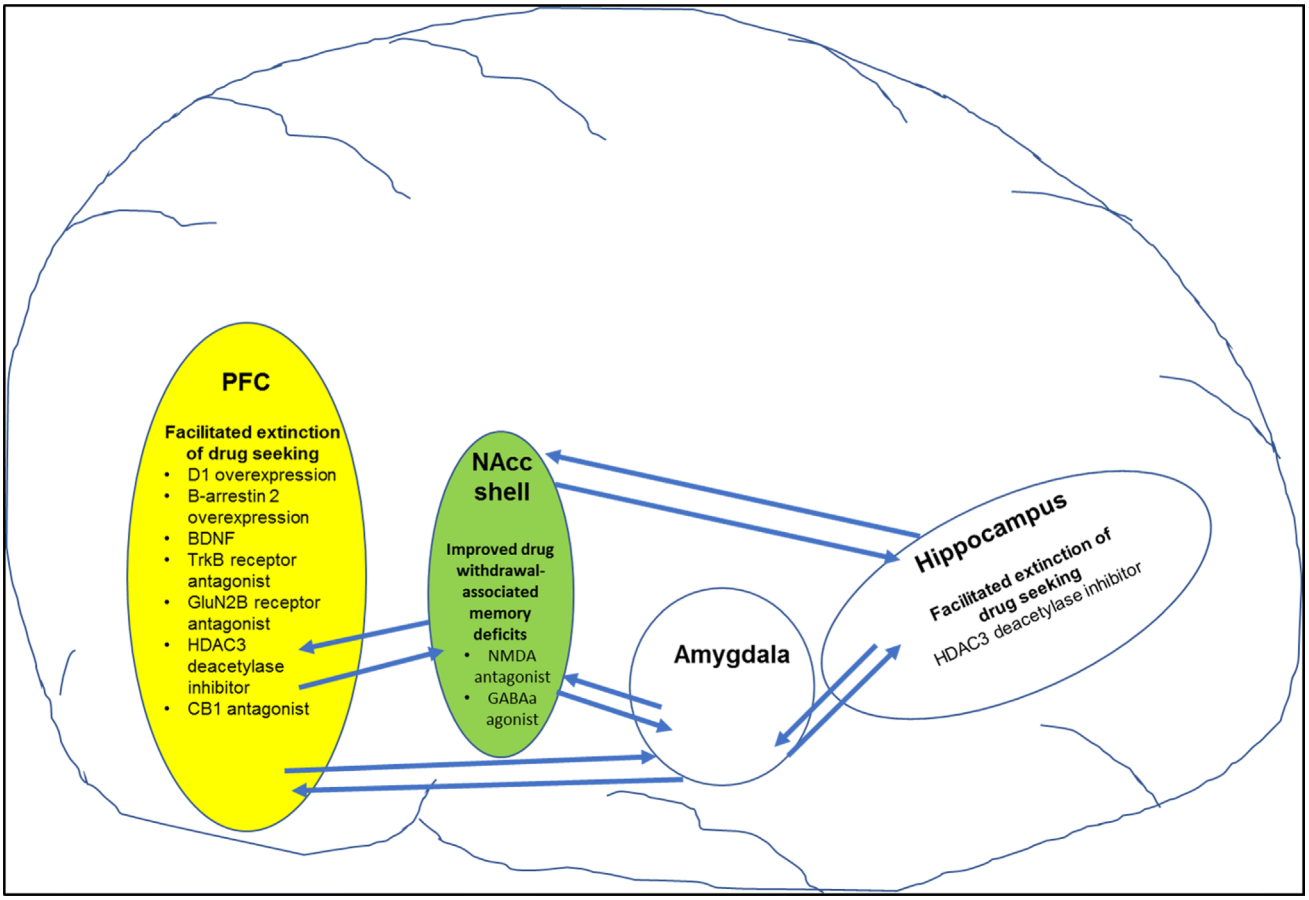

FIGURE 2 | Figure shows specific targets in brain regions that play a role in improving drug-induced cognitive deficits (also see **Table 3** for more details). For example, pharmacological manipulation of targets in the prefrontal cortex (PFC) and hippocampus facilitated extinction of drug-seeking behavior. In addition, pharmacological manipulation of targets in the nucleus accumbens shell (NAcc shell) improved drug-withdrawal associated memory.

TABLE 2 | Pharmacological alleviation of psychostimulant-induced impulsivity in animals.

Target	Task	Species	Drug	Findings	Reference
α2A adrenergic receptor agonists (guanfacine)	5-CSRTT	Rats	Acute cocaine	Dose-dependent decrease in behavioral impulsivity	Terry et al. (139)
Orexin receptor antagonist (suvorexant)	5-CSRTT	Rats	Acute cocaine	Decreased behavioral impulsivity but had no effect on decisional impulsivity	Gentile et al. (140)
Progesterone	Go/No-Go task	Rats	Acute cocaine	Decreased behavioral impulsivity in female but not male rats	Swalve et al. (141)
NET uptake blocker (atomoxetine)	DDT	Rats	Acute cocaine	Decreased decisional impulsivity in male rats compared with controls; no effect of atomoxetine alone in females	Smethelss et al. (142)
CB1 antagonists (rimonabant)	DDT	Rats	Repeated cocaine exposure	Both prevented and reversed cocaine-induced decisional impulsivity	Hernandez et al. (39)

5-CSRTT, 5-choice serial reaction time task; DDT, delay discounting task.

with atomoxetine. Together, the data suggest atomoxetine may not be as effective in female compared with male cocaine abusers, suggesting a role for gender in psychostimulant-induced impulsivity treatment (discussed later). Systemic administration of atomoxetine also attenuated reinstatement of cocaine seeking (157–159). Overall, the data support the role of α2 adrenergic receptor agonists and/or selective NET inhibitors in the treatment of psychostimulant-induced impulsivity (**Box 4**).

β Adrenergic Receptors

The role of noradrenergic neurotransmission *via* β adrenergic receptors has been explored in both consolidation of drug-associated memory and extinction learning. Specifically, administration of β receptor antagonist propranolol immediately after nicotine administration attenuated reinstatement of nicotine seeking in animals (160). Consistent with these findings, administration of propranolol attenuated craving among abstinent

TABLE 3 | Pharmacological alleviation of psychostimulant-induced memory impairment and/or facilitation of extinction learning.

Compounds	Task	Species	Drug treatment	Findings	Reference
α2A adrenergic receptor agonists (guanfacine)	Delayed match-to-sample (DMTS)	Monkeys	Acute cocaine	Alleviated cocaine-induced impairment in accuracy in the DMTS task suggesting improvement in working memory	Terry et al. (140)
NMDA antagonist (memantine)	Novel object recognition	Rats	Amphetamine withdrawal	Attenuated amphetamine withdrawal-induced impairment in memory	Marszalek-Grabska et al. (145)
CB1 antagonist (rimonabant)	Novel object recognition	Mice	Nicotine withdrawal	Attenuated nicotine withdrawal-induced impairment in memory	Saravia et al. (146)
Glycine site partial agonist (D-cycloserine)	Extinction of cocaine-induced CPP	Rats	Cocaine	Facilitated extinction of cocaine-induced CPP	Botreau et al. (147)
mGlu5 PAM (CDPPB)	Extinction of cocaine-induced CPP	Rats	Cocaine	Facilitated extinction of cocaine-induced CPP	Gas and Olive (148)
	Extinction of cocaine seeking	Rats	Cocaine	Facilitated extinction of cocaine seeking	Cleva et al. (149)
PD4 inhibitor (rolipram)	Extinction of cocaine-induced CPP	Mice	Cocaine	Facilitated extinction of cocaine-induced CPP	Liddie et al. (150)
PD9 inhibitor (BAY-73-6691)	Extinction of cocaine-induced CPP	Mice	Cocaine	Facilitated extinction of cocaine-induced CPP	Liddie et al. (150)
TrK B agonist	Extinction of cocaine-induced CPP	Rats	Cocaine	Facilitated extinction of cocaine-induced CPP	Otis at al. (112, 113)
17β estradiol	Extinction of cocaine-induced CPP	Rats	Cocaine	Facilitated extinction of cocaine-induced CPP	Twining et al. (151)
Vagal nerve stimulation	Extinction of cocaine seeking	Rats	Cocaine	Facilitated extinction of cocaine seeking	Childs et al. (152)
$GABA_B$ agonist (baclofen)	Extinction of methamphetamine-induced CPP	Rats	Methamphetamine	Facilitated extinction of methamphetamine-induced CPP	Voigt et al. (153)

DMTS, delayed matching to sample task; CPP, conditioned place preference.

smokers for a novel conditioned stimulus associated with nicotine. Inhibition of hippocampal β receptors attenuated expression of cocaine-associated memory as assessed using the cocaine-induced CPP model (113). Importantly, propranolol facilitated extinction of fear in rabbits (162). However, a recent study has reported that direct injections of propranolol in the infralimbic PFC attenuated extinction learning of cocaine-induced CPP *via* inhibition of ERK-signaling pathway (111) (**Table 1**; **Figure 2**). In fact, the study also reported that overexpression of β-arrestin 2 in the infralimbic PFC promoted extinction of cocaine-induced CPP. Further, knockout of β-arrestin 2 in the infralimbic PFC impaired extinction of cocaine-induced CPP. Taken together, the data suggest a role for β-adrenergic receptors in facilitating extinction of drug-associated memories. Further, development of β-adrenergic ligands that selectively promote signaling *via* β-arrestin 2 pathway will help in better understanding the role of β-adrenergic receptors in extinction learning. In summary, α2 and β adrenergic receptors and NET are very viable targets for treatment of cognitive impairments associated with psychostimulant addiction. Future work must focus on determining specific circuits that are targeted by α2 and β adrenergic receptor agonists and/or selective NET inhibitors to decrease impulsivity and facilitate working memory and/or extinction of drug-associated cues.

Serotoninergic Receptors

Alteration in serotoninergic neurotransmission after chronic exposure to cocaine and other psychostimulants has been previously described (163). Serotoninergic tone in the brain plays an important role in inhibitory control (164). Several lines of evidence suggest that a decrease in brain serotonin (5-HT) increases impulsivity, while elevation of brain 5-HT levels decreased impulsivity (165–167). Interestingly, increased 5-HT release in the PFC was found to be associated with higher levels of behavioral impulsivity as assessed using the 5-CSRTT (168, 169). Overall, a majority of the data suggest that elevation of serotoninergic transmission improves impulsive behavior.

In addition to 5-HT, several studies support a role of both 5-HT2A and 5-HT2C receptors in impulsive behavior. For example, 5-HT2A receptor expression in the mPFC was higher in high compared with low impulsive animals (170). Further, activation of 5-HT2A receptors induced behavioral impulsivity, while blockade of 5-HT2A receptors inhibited behavioral impulsivity (170, 171). Moreover, 5-HT2A receptor activation in the OFC induced decisional impulsivity (172). Future work needs to assess the effects of 5-HT2A receptor antagonists in psychostimulant-induced impulsivity. Similar to 5-HT2A, 5-HT2C receptor expression was significantly greater in the OFC in high compared with low impulsive animals (122). In contrast, no difference in 5-HT2C receptor expression was reported in the striatum between high and low impulsive animals. Blockade of 5-HT2C receptors selectively improved decisional impulsivity in the rIGT (173). Chronic cocaine self-administration decreased 5-HT2C receptor expression in the NAcc shell in the high impulsive animals but decreased 5-HT2C receptor expression in the infralimbic PFC in the low impulsive animals (122). Together, the data suggest that cocaine differentially influences 5-HT2C receptor expression in different brain regions depending on the impulsivity in the

animals prior to cocaine exposure. Based on the above data, it is hypothesized that 5-HT2C receptor antagonists will attenuate psychostimulant-induced impulsivity.

5-HT3 antagonists, granisetron and ondansetron, decreased decisional impulsivity in the DDT (173) (**Box 4**). This decrease in decisional impulsivity was not observed after administration of the 5-HT reuptake blocker (paroxetine) or the 5-HT1A receptor agonist (8-OH-DPAT). Interestingly, infusion of 5-HT1A receptor agonist 8-OH-DPAT into the OFC decreased decisional impulsivity (124). Together, 5-HT3 receptor antagonists and 5-HT1A receptor agonists could be potentially useful in treating psychostimulant-induced impulsivity. In summary, establishing serotoninergic tone in psychostimulant-dependent subjects may help ameliorate cognitive deficits induced by abuse of psychostimulants. Further, 5-HT1A, 5-HT2A, 5-HT2C, and 5-HT3 receptors are possible targets that need to be further explored for the treatment of psychostimulant-induced impulsivity.

GABA Receptors

Exposure to psychostimulants like cocaine, nicotine, and methamphetamine alters GABAergic neurotransmission (174–176). GABA also plays a role in both impulsivity and learning/memory (177–179). Activation of $GABA_A$ receptors in the mPFC induced behavioral impulsivity, while blockade of $GABA_A$ receptors in the same region reduced behavioral impulsivity (180–182). Moreover, activation of $GABA_A$ receptors in the lateral habenula increased cue-induced cocaine seeking, suggesting lack of inhibitory control in response to drug-associated cues (183). Importantly, activation of $GABA_A$ receptors in the NAcc shell improved methamphetamine-induced working memory deficit as measured using the Morris water maze (115). Together, the data suggest that $GABA_A$-mediated neurotransmission in different brain regions plays a differential role in psychostimulant-induced impulsivity and memory deficits (**Box 4**).

In addition to $GABA_A$ receptors, $GABA_B$ receptors play a role in drug seeking. For example, $GABA_B$ agonists and positive allosteric modulators (PAMs) attenuated reinstatement of nicotine and cocaine seeking (174, 184, 185). Importantly, activation of $GABA_B$ receptors facilitated extinction of methamphetamine-induced CPP (152) (**Table 3**). In summary, both $GABA_A$ and $GABA_B$ receptors mediate psychostimulant-induced cognitive deficits. However, further work is required to fully exploit the potential of $GABA_A$ and $GABA_B$ receptors in the treatment of psychostimulant-induced cognitive deficits.

Glutamate Neurotransmission

Dysregulation in glutamate transmission has been reported after exposure to psychostimulants (174, 186–188). Further, research has shown that both ionotropic and metabotropic glutamate (mGlu) receptors play a role in impulsivity, memory deficits, and extinction of drug-associated memories (189, 190) (**Box 4**).

NMDA Receptors

Systemically administered GluN2B antagonists Ro 63-1908 and traxoprodil increased premature responses in the 5-CSRTT, suggesting behavioral impulsivity (191). Similarly, systemic administration of NMDA antagonists induced decisional impulsivity as assessed using the DDT [(192, 193); but also see Higgins et al. (191)]. Together, the data suggest that blockade of NMDA-mediated glutamate transmission after systemic administration of NMDA antagonists induced behavioral and decisional impulsivity. However, blockade of NMDA receptors in specific brain regions had a differential effect on behavioral and decisional impulsivity. For example, blockade of NMDA receptors in the infralimbic PFC induced behavioral impulsivity (181). In contrast, blockade of GluN2B-containing NMDA receptors in the NAcc core induced decisional impulsivity in rats (194). Together, these data suggest that NMDA-mediated glutamate transmission in the infralimbic PFC and NAcc core plays a role in behavioral and decisional impulsivity, respectively. The effects of NMDA-antagonists and specifically GluN2B antagonists in psychostimulant-induced impulsivity still need to be assessed.

The role of NMDA-mediated glutamate transmission in learning and memory including extinction learning is well documented (189, 195, 196). Relevant to this review, systemic administration of NMDA antagonist memantine improved amphetamine withdrawal-induced memory deficit as assessed using the novel object recognition test (143) (**Table 3**). Similarly, blockade of NMDA receptors in the NAcc using NMDA antagonist AP-5 improved methamphetamine-induced working memory deficit as measured using the Morris water maze (115) (**Table 1**; **Figure 2**). Interestingly, increasing activity of NMDA-mediated glutamate transmission *via* manipulation of the glycine site facilitated extinction of fear- and cocaine-associated memories (145, 197, 198) (**Table 3**). In addition, increased NMDA-mediated transmission especially *via* GluN2B-containing NMDA receptors facilitated extinction of fear memories (199). Consistent with these findings, increasing glutamate transmission *via* GluN2B-containing NMDA receptors in the infralimbic cortex facilitated extinction of cocaine-associated memory (112) (**Table 1**; **Figure 2**). More recently, it was reported that aquaporin-4 (AQP-4) deletion increased GluN2B-mediated glutamate transmission in the CA3–CA1 hippocampal pathway (200). AQP-4 is the predominant water channel primarily expressed in astrocytes and plays a role in regulating synaptic plasticity. Importantly, deficiency of AQP-4 facilitated fear memory extinction (200). Future work must investigate if AQP-4 may be a potential target for facilitating extinction of psychostimulant drug-associated memories. In summary, NMDA receptors could serve as targets for alleviation of psychostimulant-induced impulsivity and memory deficits. Furthermore, NMDA receptors could be targeted to facilitate extinction of drug-associated memories.

AMPA Receptors

The AMPA receptors are also involved in extinction learning. For example, AMPA receptor activation facilitated extinction of fear-associated memories (199, 201). Activation of AMPA receptors in the infralimbic PFC facilitated extinction of heroin-associated memories (202). However, the effects of AMPA receptor activation on extinction of psychostimulant-associated memories have not been evaluated. Surface expression of AMPA receptors can be

regulated by a process called ubiquitination. Ubiquitination of AMPA receptors results in internalization of AMPA receptors, which indirectly decreases AMPA-mediated glutamate transmission. More recent work has shown that ubiquitination of AMPA receptors is partially regulated by epidermal growth factor receptor substrate 15 (Eps15). Decreased expression of Eps15 resulted in decreased internalization of GluA1-containing AMPA receptors possibly by decreased ubiquitination of GluA1 subunits of the AMPA receptors (204). However, further work is required to determine if knockdown of Eps15 facilitates extinction learning *via* decreased internalization of AMPA receptors. In summary, Eps15 *via* AMPA-mediated glutamate transmission could be a potential target to facilitate extinction learning of psychostimulant-associated memories.

Metabotropic Glutamate (mGlu) Receptors

Several experimental studies support the role of mGlu receptors in cognitive deficits. For example, blockade of mGlu1 receptors resulted in decisional impulsivity (195). These data suggest that PAMs of the mGlu1 receptors may help to reduce decisional impulsivity, although this hypothesis needs to be experimentally tested in psychostimulant-induced impulsivity. In addition to mGlu1 receptors, mGlu2/3 receptors also mediate behavioral and decisional impulsivity. Pretreatment with the mGlu2/3 agonist LY379268 attenuated 5-HT2A agonist-induced behavioral impulsivity (205). Furthermore, direct injections of mGlu2/3 agonist in the OFC and mPFC attenuated intra-OFC and intra-PFC 5-HT2A agonist-induced decisional and behavioral impulsivity, respectively (172). Moreover, systemic administration of mGlu4 PAM, 4-((*F*)-styryl)-pyrimidin-2-ylamine (Cpd11), induced behavioral impulsivity but decreased decisional impulsivity (206). In contrast to mGlu4 receptors, blockade of mGlu5 receptors, using a mGlu5 negative allosteric modulator (NAM), attenuated behavioral impulsivity (207). In addition, activation of mGlu5 receptors, using a mGlu5 receptor PAM, attenuated NMDA antagonist MK-801-induced behavioral impulsivity. Interestingly, no effects of mGlu5 receptor modulation on decisional impulsivity were observed (207). Importantly, systemic administration of mGlu5 PAM, CDPPB, facilitated extinction of fear- and cocaine-associated memories (148, 149, 208) (**Table 3**). Consistent with these findings, decreased glutamate transmission *via* mGlu1 and mGlu5 receptors in the mPFC facilitated resistance to extinction of cocaine-associated memories in animals with chronic cocaine self-administration experience (209). Taken together, the data suggest that mGlu5 receptors have a role in behavioral impulsivity and can also be targeted to facilitate extinction of psychostimulant-associated memories. Based on the above-described data, mGlu1, mGlu2/3, mGlu4, and mGlu5 receptors can serve as potential targets in psychostimulant-induced impulsivity.

Drugs That Restore Glutamatergic Tone

As described above, dysregulation in glutamate transmission has been reported after exposure to psychostimulants. Thus, agents that restore glutamatergic tone may help to treat psychostimulant addiction. Administration of riluzole, a pharmacological compound that reestablishes glutamatergic tone, decreased activity of the prelimbic PFC and increased activity of the infralimbic PFC (210). Also, direct injections of riluzole in the amygdala facilitated extinction of fear-associated memories, possibly due to the increase infralimbic PFC activity (211). Importantly, riluzole attenuated reinstatement of cocaine seeking (210). Like riluzole, *N*-acetylcysteine, a cystine–glutamate antiporter that helps restore glutamatergic tone, attenuated reinstatement of cocaine and nicotine seeking (212, 213). *N*-Acetylcysteine also reduced reinstatement of nicotine seeking observed in animals with neonatal ventral hippocampal lesions (80, 214). As described above, animals with neonatal ventral hippocampal lesions show memory deficits and higher nicotine seeking than do controls. It is hypothesized that memory deficits associated with ventral hippocampal lesions are partially responsible for this increased nicotine seeking. Together, the data suggest that *N*-acetylcysteine helps animals overcome memory deficits and thus possibly helps reduce drug seeking. Overall, the above data with riluzole and *N*-acetylcysteine suggest that correcting the dysregulation in glutamate transmission can improve memory deficits and/or facilitate extinction learning. Future work needs to determine if these drugs can facilitate extinction of drug-associated memories. In summary, both ionotropic and metabotropic glutamate receptors are viable targets for treatment of psychostimulant-induced cognitive deficits. However, more work is required to understand glutamate dysregulation in specific brain circuits after psychostimulant exposure to fully exploit the various glutamate targets for treatment of psychostimulant-induced cognitive deficits.

Nicotinic Acetylcholine Receptors (nAChRs)

The role of nAChRs in impulsive behavior has been discussed previously (215). In humans, polymorphism in the α4 subunits of the nAChRs (CHRNA4) was associated with pathological gambling in Korean gamblers (216). Also, systemic administration of varenicline, a partial agonist of α4β2 nAChRs, induced behavioral impulsivity in animals (217). Importantly, blockade of α4β2 nAChRs in the infralimbic PFC attenuated varenicline-induced behavioral impulsivity, suggesting that the effects of varenicline are mediated by α4β2 nAChRs in the infralimbic PFC (218). Also, intra-cerebroventricular injection of α4β2 nAChR antagonist decreased behavioral impulsivity in animals (219). Together, the data highlight that the role of α4β2 nAChRs in behavioral impulsivity and α4β2 nAChR antagonists may help to alleviate behavioral impulsivity. More recently, compounds that decrease signaling *via* α4β2 nAChRs attenuated cocaine and methamphetamine seeking (220). In addition, systemic administration of partial agonists of the α7-containing nAChRs decreased behavioral impulsivity and improved attention as assessed using the five choice-continuous performance task (5-CCPT) (221). The decrease was specifically observed in female rats that had been classified as animals with low attention at baseline. α7 nAChR agonists have also been shown to improve memory (222, 223). Together, the data suggest a possible role for α4- and α7-containing nAChRs in cognitive deficits such as impulsivity and impairment of memory. However, the role of the different nAChR subunits in psychostimulant-induced cognitive deficits is yet to be evaluated.

Opioid Receptors

Several lines of evidence support the role of endogenous opioids in impulsive behavior. For example, human imaging studies suggest upregulation of μ opioid receptor (MORs) in the mPFC and OFC in individuals with traits suggestive of impulsivity (223). Further, pathological gamblers, who are known to be impulsive and impaired in making rational decisions, show decreased endogenous opioid release in the brain than do healthy volunteers (224). Consistent with these findings, administration of MOR antagonist decreased pathological gambling (225, 226). MORs and opioid peptides are extensively found in PFC and regulate PFC neuronal activity (227). Activation of MORs in the PFC induced behavioral impulsivity (228). In addition, mice lacking MORs showed markedly decreased behavioral impulsivity (229). In contrast, the same study showed that mice lacking delta opioid receptors (DORs) showed increased behavioral impulsivity. More recently, it was reported that α2 agonist yohimbine-induced increase in behavioral impulsivity was attenuated by blockade of kappa opioid receptors (KORs) (230). Interestingly, KOR activation on its own decreased behavioral impulsivity possibly due to impairment of motor activity. Together, the data from these pharmacological and genetic studies suggest a differential role for MORs, DORs, and KORs in behavioral impulsivity. Further, the data suggest that MOR and KOR antagonists may help to reduce impulsivity.

Chronic cocaine administration is associated with upregulation of MORs and KORs in the PFC (231). Furthermore, upregulation of MORs in the anterior cingulate cortex predicts both severity of craving and relapse in cocaine users (232, 233). Similarly, dysregulation of endogenous opioid neurotransmission occurs after exposure to nicotine (234). However, much work needs to be done in determining the role of MORs, MOR antagonists, and other opioid receptors in psychostimulant-induced cognitive deficits especially impulsivity (**Box 4**). Moreover, most of the research on the role of opioid receptors in impulsivity has focused on the PFC. However, further work must be carried out in other brain regions to determine the role of endogenous opioids in psychostimulant-induced impulsivity.

Cannabinoid Receptors

The endogenous cannabinoid system is altered after exposure to psychostimulant drugs. For example, exposure to cocaine administration during adolescence increased expression of CB1 receptors and decreased expression of CB2 receptors in the PFC and hippocampus (235). In contrast in adult rats, chronic cocaine self-administration resulted in decreased CB1 and CB2 receptor expression in the PFC, dorsal striatum, and amygdala (236). Further, blockade of CB1 receptors attenuated both cocaine intake and reinstatement of cocaine seeking (237). Importantly, blockade of CB1 receptors prevented cocaine-induced impairment in decisional impulsivity as assessed using the DDT (39) (**Table 2**). In addition, acute administration of CB1 antagonists prior to DDT in cocaine-treated rats reversed cocaine-induced decisional impulsivity. Together, these data support a role for endogenous cannabinoids in both preventing and reversing cocaine-induced impulsivity. Consistent with the findings of this study, activation of CB1 receptors using cannabidiol (CBD) did not improve impulsivity during tobacco abstinence in human smokers (238).

In addition, CB1 receptors located in the amygdala and hippocampus play a role in learning and memory. For example, blockade of CB1 receptors attenuated nicotine withdrawal-induced memory deficits (144) (**Table 3**). Interestingly, the same study also showed that selective deletion of CB1 receptors in the GABA neurons also mitigated nicotine withdrawal-induced memory deficits. Overall, these data suggest that CB1 receptor antagonists may have therapeutic utility in promoting smoking cessation by decreasing memory deficits associated with nicotine withdrawal. Importantly, systemic or intra-mPFC administration of CB1 receptor antagonist rimonabant enhanced extinction of cocaine-associated memories (114) (**Table 1**; **Figure 2**). Together, these data suggest that CB1 receptor antagonists could be potentially used to treat psychostimulant-induced impulsivity and memory impairment (**Box 4**). However, further research is required to fully exploit the potential of the endocannabinoid system as a potential treatment for psychostimulant-induced cognitive deficits.

Phosphodiesterase Inhibitors

The role of cAMP/protein kinase A/cyclic-AMP response element binding (CREB) protein pathway plays an important role in both memory and reinforcing effects of psychostimulant drugs (239–241). The enzyme phosphodiesterase (PDE) plays a role in breakdown of cAMP and thus indirectly decreases CREB formation. Phosphodiesterase inhibitors, which increase CREB formation, facilitate learning and memory (242). For example, subchronic administration of rolipram, a PDE4 inhibitor, using osmotic pumps facilitated learning of conditioned fear (243). Importantly, more recently it has been reported that rolipram facilitated extinction of fear-associated memory in mice (116). Interestingly, PDE4 inhibitors did not facilitate extinction of cocaine-induced CPP (148) (**Table 3**). However, the same study showed that PDE9 inhibitor BAY-73-6691 facilitated extinction of cocaine-induced CPP (**Table 3**). This effect of PDE9 inhibitor was possibly mediated by an increase in cGMP levels in the hippocampus and amygdala. Further work is required to assess the effects of PDE9 inhibitors and other PDE inhibitors in facilitation of extinction of drug-associated memories. In summary, the various isoforms of the PDE enzyme continue to be viable targets for treatment of psychostimulant addiction.

Orexin

Orexin neurons (also referred to as hypocretin) are found in the hypothalamus and release the neuropeptides orexin A and orexin B (also referred to as hypocretins 1 and 2) throughout the CNS (244). With its widespread targets, the orexin system is involved in a number of functions including stress, reward, wakefulness, and food seeking (245). The hypocretin/orexin system plays an important role in the reinforcing effects of cocaine. For example, suvorexant, a dual orexin receptor antagonist, attenuated both the rewarding and motivational effects of cocaine (141). Also, knockdown of hypocretin/orexin neurons in the dorsal hypothalamus attenuated cocaine self-administration (246). Further knockdown of orexin 1 receptor in the VTA both altered dopamine signaling in the NAcc and attenuated cocaine-induced increase in NAcc DA (248). The hypocretin/orexin system also plays a role in opioid- and alcohol-dependent behaviors (249, 250).

Increased activation of medial hypothalamic orexin neurons, but not lateral hypothalamic neurons, was reported during a Go/No-Go task involving food reward, suggesting a role for medial hypothalamic orexin neurons in behavioral impulsivity (251). More recently, systemic or intra-VTA administration of suvorexant, a dual orexin receptor antagonist, attenuated cocaine-induced behavioral impulsivity (140) (**Table 2**). Interestingly, neither suvorexant nor orexin 1 (SB334867) nor orexin 2 (TCS-OX2-29) receptor-selective compounds altered decisional impulsivity. Taken together, the data suggest that orexin receptor antagonists may be useful in reducing psychostimulant-induced behavioral impulsivity.

The hypocretin/orexin receptors are also found in brain regions that play a role in memory especially the hippocampus. Administration of orexin peptides increased firing of hippocampal neurons and facilitated learning and memory (252–256). The orexin-induced facilitation of learning is mediated by increasing neurogenesis in the hippocampus (257). The hypocretin/orexin system also plays a role in extinction learning. For example, blockade of orexin 1 receptor facilitated extinction of fear-associated memories possibly by increasing amygdalar input to the infralimbic PFC during extinction learning (258). However, the role of the orexin system in facilitation of extinction of drug-associated memories has not been explored. In summary, blocking orexin-mediated signaling decreased behavioral impulsivity and facilitated extinction learning (**Box 4**). The hypocretin/orexin system is a very promising target, but further work is required to fully exploit the orexin system for the treatment of psychostimulant-induced cognitive deficits.

Brain-Derived Neurotrophic Factor (BDNF)

BDNF, a neurotrophin, is extensively distributed in the brain (259). BDNF plays a role in psychostimulant-induced behavioral effects. Inhibition of BDNF signaling and/or decreased expression of BDNF attenuated the rewarding effects of cocaine and cocaine-seeking behaviors (260–262). Methamphetamine withdrawal was associated with elevated BDNF levels in the dorsal striatum (263). In addition, genetically induced depletion of BDNF expression resulted in social cognitive deficits after chronic methamphetamine treatment compared with controls (264). Impaired BDNF signaling in the frontal and striatal regions during nicotine withdrawal was also associated with cognitive deficits (265). Together, the data suggest that decreased BDNF signaling possibly mediates psychostimulant-induced cognitive deficits.

Importantly, increase in BDNF signaling plays a role in consolidation of both recognition and spatial memory (266). Intracerebroventicular injection of antibodies to BDNF attenuated spatial learning in rats (267). Increase in BDNF signaling was also associated with extinction of fear-associated memories (268, 269). Interestingly, infusing BDNF into the ventral hippocampus increased the firing rate of neurons in the infralimbic PFC, which plays an important role in extinction learning (270). Importantly, increased BDNF signaling *via* stimulating tropomyosin-related kinase B (Trk B) receptors in the infralimbic PFC facilitated extinction of cocaine-induced CPP (112) (**Table 1**; **Figure 2**). Also, the study showed that systemic administration of Trk B receptor agonist facilitated extinction of cocaine-associated memories (**Table 3**). Overall, receptors mediating BDNF signaling are promising targets for facilitation of extinction of drug-associated memories and could be used for advancing treatment of psychostimulant addiction (**Box 4**). However, further work is required to understand BDNF signaling in specific circuits to maximally exploit its receptors as a therapeutic target.

Corticotrophin Releasing Factor (CRF) Receptors

The role of CRF receptors in the behavioral and rewarding effects of psychostimulants has been previously reviewed (271–273). Blockade of CRF1 and CRF2 receptors in the VTA attenuated the reinforcing effects of cocaine (274). Interestingly, the rewarding effects of cocaine were enhanced in mice lacking CRF1 receptors compared with wild-type controls (275). Importantly, chronic cocaine administration induced memory deficits in wild-type mice but not in CRF1 deficient mice (276). In addition, cocaine withdrawal-induced memory deficits were observed in CRF2-deficient mice compared with wild-type controls (277). These data suggest that CRF receptors mediate cocaine withdrawal-induced impairment of memory and other cocaine-dependent effects.

CRF receptors are extensively distributed in brain regions that play a role in learning and memory (278). Blockade of CRF receptors, using CRF antagonist D-Phe-CRF, improved cognitive performance (279). Further, the study also showed that blockade of CRF1 receptors using CRF1 selective antagonist NBI 35965 improved memory in PFC-dependent tasks. Taken together, the data suggest that CRF receptors can be targeted to alleviate psychostimulant-induced memory deficits.

Importantly, CRF receptors in the VTA play a role in reinstatement of cocaine seeking (280). In addition, the same study showed that after cocaine self-administration and extinction training, stimulation of CRF2 receptors in brain slices resulted in increased glutamate release and decreased GABA release as compared in cocaine-naïve animals. These data suggest that extinction training and cocaine exposure altered CRF2-mediated transmission. Importantly, infusions of the CRF receptor antagonist α-helical CRF(9-41) into the basolateral amygdala enhanced extinction of fear-associated memories (281). However, further work needs to be carried out to determine if CRF receptors play a role in extinction of psychostimulant drug-associated memories. In summary, CRF receptors could serve as a potential target to alleviate psychostimulant-induced memory deficits and/or promote extinction of drug-associated memories.

NON-PHARMACOLOGICAL APPROACHES FOR TREATMENT OF PSYCHOSTIMULANT-INDUCED COGNITIVE DEFICITS

Brain Stimulation

Brain stimulation can be achieved using a variety of different approaches such as transcranial magnetic stimulation, deep brain stimulation (DBS) using intracranial electrodes, transcranial direct current stimulation, and vagus nerve stimulation (282). Evidence from both human and animal studies supports use of brain stimulation to ameliorate cognitive deficits and improve

learning and memory. For example, in humans, increase in verbal working memory accuracy was observed following transcranial magnetic stimulation (283). Similarly, DBS of the ventromedial PFC resulted in improvement in novel object recognition memory compared with that in controls in animals (284). Intracranial DBS also improved spatial memory in rats as assessed using the Morris water maze task (285). Also, DBS facilitated extinction of fear-associated memories (286, 287).

More importantly, DBS using intracranial electrodes attenuated reinstatement of cocaine seeking (288). Also, low-frequency DBS, but not high-frequency DBS, of the ventral striatum strengthened extinction of morphine-associated memories in rats (289). In addition, low-frequency stimulation of the ventral striatum was accompanied by an increase in immediate early gene c-fos synthesis in brain regions associated with extinction such as the infralimbic PFC and amygdala, suggesting increased activity of these regions. Importantly, vagal nerve stimulation during extinction training improved rates of extinction and reduced reinstatement of cocaine seeking in rats (151) (**Table 3**). Interestingly, DBS of subthalamic nucleus and vagal nerve stimulation also helped in decreasing decisional impulsivity in "risk preferring" rats compared with controls (290, 291).

Together, these data suggest that brain stimulation can help in both decreasing impulsivity and facilitating extinction of psychostimulant-associated memories. Thus, brain stimulation has the potential to alleviate multiple cognitive deficits. Future work must focus on identifying precise neural substrates and brain stimulation parameters to fully exploit the benefits of brain stimulation in psychostimulant addiction treatment. Furthermore, identification of pharmacological compounds that will help in improving efficacy of brain stimulation in addiction treatment will also be very useful.

Exercise

Exercise in animals influences psychostimulant-dependent behavioral effects. For example, exercise attenuated reinstatement of cocaine seeking after a period of abstinence (292, 293). In addition, reinstatement of cocaine seeking in high impulsive rats was attenuated when animals were treated with a combination of atomoxetine and exercise during withdrawal from cocaine compared with either treatment alone (294). Importantly, post-extinction exercise training was more effective than extinction alone in attenuating reinstatement of cocaine seeking (295).

Exercise in the form of wheel running and swimming has been shown to improve learning and memory (296). Consistent with these findings, exercise using a treadmill attenuated morphine withdrawal-induced memory deficit in rats (297). Also, exercise facilitated extinction of fear-associated memories (298, 299). However, it is not known if exercise facilitates extinction of psychostimulant-associated drug memories. Further, effects of exercise on amelioration of psychostimulant withdrawal-associated memory deficits have not been explored. Several questions such as intensity and duration of exercise, neural changes as a consequence of exercise, and optimal combination of exercise with pharmacological medications need to be determined to use exercise most efficaciously as a tool for psychostimulant addiction treatment.

Promoting Neurogenesis

Psychostimulant exposure impairs neurogenesis in the hippocampus in adult animals. For example, chronic exposure to nicotine, methamphetamine, and cocaine altered/blunted neurogenesis in the hippocampus (300–303). In addition, cocaine withdrawal-induced memory deficits were associated with blunted neurogenesis in the hippocampus (304). Hippocampal neurogenesis has been shown to play a role in consolidation of memory (305). Also, disruption of adult hippocampal neurogenesis impaired short- and long-term memory formation (306).

Relevant to this review, enhancing neurogenesis facilitated extinction of fear-associated memories (307, 308). Furthermore, pharmacological facilitation of neurogenesis facilitated extinction of morphine-associated memory (309). Importantly, increasing hippocampal neurogenesis in adult animals using chronic intracerebroventricular infusions of lysophosphatidic acid (LPA; an endogenous lysophospholipid with pro-neurogenesis effects) facilitated extinction of cocaine-associated memories (310). In contrast, suppression of neurogenesis using cranial irradiation resulted in resistance to extinction of cocaine seeking (311). Together, the above data suggest that pharmacological manipulation of adult hippocampal neurogenesis could facilitate extinction of drug-associated memories (**Box 4**). In summary, promoting neurogenesis can serve as an important strategy to treat psychostimulant addiction. However, future research must focus on understanding cellular mechanisms that underlie psychostimulant-induced impairment of hippocampal neurogenesis and identify pathways that can promote neurogenesis. Together, both of the above-described approaches will help to effectively treat psychostimulant-induced cognitive deficits.

FUTURE DIRECTIONS

Ghrelin

Ghrelin is an orexigenic peptide hormone acting on receptors in both the brain and periphery (312). Modulation of ghrelin altered effects of psychostimulants. For example, administration of ghrelin enhanced the rewarding effects of cocaine (313). Consistent with these findings, blockade of ghrelin-mediated transmission attenuated behavioral effects of cocaine, amphetamine, and nicotine (314, 315). In cocaine-experienced animals, during early withdrawal, ghrelin levels were elevated possibly in anticipation of cocaine (316). Similarly, in abstinent smokers, elevated ghrelin levels were associated with increased craving and relapse (317).

More importantly, ghrelin is neuroprotective, promotes hippocampal neurogenesis, and enhances learning and memory (318–320). Elevation of ghrelin levels as a consequence of food deprivation facilitated extinction of fear-associated memories, possibly by inhibition of long-term depression in the lateral amygdala (321). Consistent with these findings, a human clinical study reported facilitated extinction of fear-associated memories in subjects that had increased ghrelin levels as a result of overnight fasting (322). Based on these data, it is hypothesized here that increasing ghrelin-mediated signaling during extinction training may facilitate extinction of drug-associated memories. However,

experimental data supporting this hypothesis are currently lacking. Besides, the precise mechanism of how ghrelin facilitates learning still needs to be explored. Nevertheless, there exists strong rationale for assessing the effects of ghrelin in extinction of drug-associated memories. Finally, based on the above data, it appears that elevated ghrelin levels are associated with craving in abstinent drug-dependent individuals, facilitation of extinction learning, and neuroprotection/neurogenesis. It is possible that ghrelin in different brain regions may have a differential role. Future work may need to understand the role of ghrelin in specific brain circuitries to fully exploit the therapeutic potential of ghrelin.

Oxytocin

Oxytocin is synthesized by hypothalamic nuclei such as the supraoptic, parvocellular, and accessory nuclei. Oxytocin-containing neurons from these nuclei primarily project to posterior pituitary, but they also innervate brain regions mediating reward and emotion such as the PFC and amygdala (323). Systemic administration of oxytocin attenuated reinstatement of cocaine and methamphetamine seeking (324, 325). Consistent with this study, direct injection of oxytocin in the NAcc attenuated methamphetamine-induced CPP (326). Together, these data suggest that activation of oxytocin receptors attenuated drug-associated memories. Additionally, cocaine withdrawal was associated with increased oxytocin receptor binding in the piriform cortex, lateral septum, and amygdala (327).

Oxytocin receptors are extensively found in the PFC (328). Interestingly, activation of oxytocin receptors in the infralimbic PFC facilitated extinction of fear-associated memories (329, 330). Further social cues, such as presence of an animal, during extinction learning increased PFC oxytocin transmission (330). Overall, the data suggest that oxytocin receptor activation in the PFC facilitated extinction learning. However, the effects of increased oxytocin transmission on extinction of drug-associated memories have not been investigated. Together, these findings suggest that changes in oxytocin transmission may mediate some of the emotional and cognitive deficits associated with cocaine use. Based on the above-described findings, oxytocin receptors may serve as useful targets for the treatment of psychostimulant addiction, especially in promoting extinction of drug-associated memories (**Box 4**).

Vasopressin

Vasopressin and its receptors play a role in psychostimulant-dependent behavioral effects. For example, elevated levels of vasopressin mRNA in the amygdala were observed in animals during withdrawal from cocaine (331). Additionally, blockade of vasopressin 1a receptors in the NAcc during conditioning attenuated expression of cocaine-induced CPP. Blockade of vasopressin 1b receptor also attenuated reinstatement of methamphetamine-induced CPP (332). Finally, blockade of vasopressin 1a receptors reversed oxytocin-induced attenuation of reinstatement of methamphetamine seeking (325). Together, the above evidence suggests a role for vasopressin in cocaine- and methamphetamine-dependent behavioral effects.

Vasopressin neurons and receptors are extensively found in brain regions involved in learning and memory such as the hippocampus, PFC, and amygdala (333–335). Knockout of vasopressin 1b receptor impaired hippocampal-dependent memory tasks (336). Vasopressin also plays an important role in social memory (337). Furthermore, blockade of vasopressin 1b receptor attenuated stress-induced impairment of memory (338). Elevated levels of vasopressin mRNA in the amygdala were also reported in animals showing high predisposition to stress-induced reinstatement of heroin seeking (339). A recent study has suggested that vasopressin may be involved in risky behaviors in humans, which suggest that it may have a role in impulsivity (340). In summary, the above data suggest that vasopressin-mediated neurotransmission is involved in memory and drug-dependent effects. Although still early, vasopressin receptors may serve as targets for treatment of psychostimulant-induced cognitive deficits.

Protein Kinase Cε

PKCε is extensively found in the brain and is a downstream mediator of G-protein receptor signaling (341). Recent studies suggest that PKCε possibly mediates the reinforcing effects of psychostimulants like nicotine and cocaine. For example, mice lacking PKCε showed reduced mRNA levels of α6 and β3 nAChR subunits in brain regions associated with drug reward such as the VTA and striatum (342). Consistent with these findings, knockout of PKCε reduced nicotine-induced CPP and attenuated nicotine self-administration compared with wild-type controls. Relevant to this review, the infralimbic PFC showed elevated levels of PKCε after with withdrawal from extended cocaine self-administration experience (343). More importantly, inhibition of PKCε in the infralimbic PFC attenuated reinstatement of cocaine seeking. However, the effects of PKCε expression in the infralimbic PFC on extinction learning have not been assessed.

Activation of PKCε facilitates learning and memory (344, 345). In fact, inhibition of PKCε using peptides that directly bind to PKCε attenuated recognition memory as assessed using novel object recognition task (345). It is postulated that the memory-enhancing effects of PKCε activation are mediated *via* increased activity of ERK1/2 in the hippocampus. Together, the above data suggest that activation of PKCε could be useful in facilitating extinction of drug-associated memories. Based on the role of PKCε in memory and cocaine-dependent behaviors, it is hypothesized that PKCε may be an attractive target for treating psychostimulant addiction by promoting extinction learning.

Peroxisome Proliferator-Activated Receptor γ (PPARγ) Receptors and Insulin

Insulin and PPARγ agonists influence the behavioral and psychological effects of drugs of abuse. For example, a recent double-blind randomized study reported that patients receiving PPARγ agonist pioglitazone compared with placebo reduced cocaine craving and improved brain white matter integrity in cocaine-dependent patients (346). In animals with cocaine self-administration experience, insulin levels were reduced by approximately 40–70% during cocaine self-administration (316). In addition, intra-VTA injections of insulin attenuated cocaine-induced increase in NAcc dopamine and decreased cocaine-induced increase in locomotor activity (347).

Additionally, insulin and PPARγ agonists play a role in alleviating memory deficits. For example, systemic administration of insulin and insulin-growth factor 2 (IGF-2) facilitated learning and memory (348, 349). Additionally, intranasal insulin administration improved memory in patients with either mild cognitive impairment or early Alzheimer's disease (350). Further, PPARγ agonists improved memory in some humans with early Alzheimer's disease (351). These memory-enhancing effects of PPARγ agonists are possibly mediated by actions of PPARγ agonists on hippocampal dentate neurons (352, 353). In summary, both insulin and PPARγ play a role in cognition and memory and could influence the behavioral effects of psychostimulants.

Importantly, PPARγ agonist pioglitazone attenuated alcohol-induced spatial memory deficit as assessed using the Morris water maze (354). Additionally, pioglitazone attenuated drug-induced heroin seeking (355). Finally, increased IGF-2-mediated transmission in the hippocampus facilitated extinction of fear-associated memories (356). It is hypothesized that this IGF-2-mediated facilitation of extinction occurs *via* stimulation of neurogenesis (357). However, it is not known if insulin and PPARγ agonists could facilitate extinction of drug-associated memories? Could insulin and PPARγ agonists be used to ameliorate psychostimulant withdrawal-induced memory impairment? Future work will need to address these and other questions.

Enzymes Involved in Epigenetic Changes

Epigenetic changes occur as a consequence of behavioral activity, learning, and/or drug exposure (358). In fact, enzymes involved in epigenetic DNA changes are involved in psychostimulant and non-psychostimulant drug-associated memories. For example, DNA methylation *via* chronic L-methionine (MET) attenuated reinstatement of cocaine seeking (359). Also, knockdown of histone methyltransferase PR containing domain 2 (PRDM2) in the dorsomedial PFC using viral vectors enhanced stress-induced reinstatement of alcohol seeking (360). Genetically induced loss of histone acetyltransferase CREB-binding protein (CBP) in the NAcc attenuated cocaine-induced CPP.

Activity-dependent epigenetic changes play an important role in learning and memory consolidation (361). Importantly, the enzymes that mediate these epigenetic changes could be targeted to facilitate learning and memory. For example, blocking of histone deacetylase (HDAC3) enzyme activity in the dorsal hippocampus enhanced long-term memory for object location (114). Additionally, manipulation of enzymes involved in epigenetic changes facilitated extinction learning. For example, inhibition of histone acetyltransferase (HAT) p300 enzyme, which is highly expressed in pyramidal neurons of the infralimbic PFC, facilitated extinction of fear-associated memories (362). Importantly, blocking of HDAC3 deacetylase activity in the dorsal hippocampus, but not the infralimbic PFC, facilitated extinction of cocaine-associated memories (114) (**Table 1**; **Figure 2**). Overall, these data suggest that enzymes involved in epigenetic changes could play a role in facilitation of extinction of psychostimulant-associated memories. More generally, they could also play a role in the treatment of cognitive deficits associated with psychostimulants such as impulsivity and memory impairments. However, much work remains to not only identify specific enzymes but also to identify specific brain regions where these enzymes are actively involved in psychostimulant-induced cognitive deficits.

MicroRNAs (miRs)

The role of non-coding microRNAs (miRs) has been implicated in psychostimulant-dependent behaviors. For example, methyl CpG binding protein 2 (MeCP2) and miR-212 in the dorsal striatum play a role in regulating escalation of cocaine intake in rats with extended access to cocaine (363). Further, upregulation of miR-212 and miR-132 in the dorsal striatum persisted for approximately 10 days after withdrawal of cocaine (364). Similarly, miR-496-3p, miR-194-5p, miR-200b-3p, and miR-181a-5p were upregulated significantly following methamphetamine exposure (365). Together, the data suggest that exposure to psychostimulants alters expression of microRNAs.

The role of non-coding miRs has been implicated in cognitive processes such as impulsivity, learning, and memory. For example, several miRs in the amygdala such as miR-190b, miR-28a, miR-340, miR-219a, and miR-491 have been reported to correlate with inhibitory control (366). Thus, theoretically decreased expression of these miRs could result in impulsive behaviors, although direct experimental evidence for this hypothesis is currently lacking. Similarly, miR-641, which binds to SNAP-25 gene, has been implicated in impulsive behaviors (367). In addition, miR-183-96-182 has been associated with comorbid ADHD and drug addiction (368). Together, these data suggest that miRs play a role in regulating impulsive behavioral traits.

miRs also play a role in memory (369). For example, inhibition of miR-9-3p resulted in deficits in hippocampal-dependent tasks (370). Overexpression of miR-144-3p in the basolateral amygdala facilitated extinction of fear-associated memories in C57BL/6 mice (371). In addition, the same study showed that overexpression of miR-144-3p in the basolateral amygdala rescued extinction of fear memories in S1 mice, which show resistance to extinction of fear memories. Similarly, extinction training after fear conditioning trials resulted in increase in expression of miR-128b in the infralimbic PFC, and overexpression of miR-128b in the infralimbic PFC facilitated extinction of fear-associated memories (372). Importantly, significant increases in the expression of miR-101b, miR-137, miR-212, and miR-132 in NAcc shell and miR-137 in the dorsal striatum were observed after extinction training and reinstatement of cocaine seeking in rats (373). Future studies must focus on brain regions associated with extinction learning such as the basolateral amygdala and infralimbic PFC to identify miRs that are involved in extinction of drug-associated memories. Although currently data are lacking, based on the above data, non-coding miRs could be targeted to facilitate extinction of drug-associated memories and to reduce psychostimulant-associated impulsivity.

Gender and Sex Gonadal Hormones

Both gender and sex gonadal hormones influence cognition. For example, behavioral impulsivity was greater in males

compared with females (374). In contrast, females compared with males showed more decisional impulsivity, preferring small immediate rewards compared with larger delayed rewards. Treatment with progesterone attenuated decisional impulsivity for food reward in both males and females (375). Interestingly, progesterone alone attenuated both behavioral and decisional impulsivity for cocaine rewards in female but not male rats (141, 142) (**Table 2**). These data suggest that sex gonadal hormones influence impulsive behaviors. Also, amphetamine worsened impulsive behavior in females compared with males (376). Together, the above data suggest that gender and sex gonadal hormones influence psychostimulant-induced impulsive behaviors.

With respect to extinction of fear-associated memories, differential electrophysiological responses in the infralimbic and prelimbic PFC have been reported between males and females. For example, female rats compared with male rats showed persistent activity in the prelimbic PFC during extinction training, and there was lack of activity in the infralimbic PFC during extinction recall (377). Additionally, the role of estrogen and progesterone in extinction of fear-associated memories has been evaluated. In ovariectomized female rats, estrogen alone or in combination with progesterone facilitated extinction of fear-associated memories (378). Several other studies support the role of estrogen in extinction of fear-associated memories (379, 380). Together, the data suggest that gender and sex gonadal hormones may influence extinction learning.

Gender and sex gonadal hormones also influence psychostimulant drug-associated memories. Extinction of cocaine-induced CPP took longer in male compared with female adolescent rats (110). More recent work has shown that after similar extinction training, context-induced reinstatement of methamphetamine seeking was more pronounced in male compared with female rats (381). Further, the study showed that this difference in methamphetamine seeking between male and female rats was possibly mediated by differential plasticity in the dentate gyrus in the hippocampus. Together, the data suggest differential gender-dependent responses to extinction of psychostimulant drug-associated memories. Treatment with 17β estradiol compared with controls facilitated extinction of cocaine-induced CPP in female rats (150) (**Table 3**). Allopregnanolone, a steroid synthesized from progesterone, attenuated reinstatement of drug-induced cocaine seeking in female but not male rats (382). Allopregnanolone also attenuated reinstatement of cocaine seeking in low impulsive female rats but not in high impulsive female rats, classified as such on baseline performance prior to cocaine exposure (383). However, further studies are required to fully exploit the role of estrogen and progesterone in facilitation of extinction of psychostimulant drug-associated memories. In summary, the above data suggest that gender and sex-gonadal hormones could play an important role in cognitive deficits associated with psychostimulant drugs. However, further work is required to develop more efficacious gender-based treatments for cognitive deficits in human drug-dependent subjects.

CONCLUSION

Addiction to psychostimulant drugs continues to be a challenge, and current treatment options available for psychostimulant addiction are not adequate. Targeting cognitive deficits in patients dependent on psychostimulants provides an excellent opportunity to improve retention and clinical outcomes of addiction treatment programs. Cognitive deficits should especially be targeted in psychostimulant-dependent patients with a history of prenatal drug exposure and patients with comorbid psychiatric disorders known to be associated with cognitive deficits. In this review, several neural substrates mediating psychostimulant-induced cognitive deficits and identified using preclinical animal models have been discussed. It remains to be seen if these could be translated into viable pharmacological targets for medications to be used in humans to improve clinical outcomes of patients dependent on drugs of abuse. However, the main question is which of the described targets would be most ideal to carry forward into the clinic. Among the various targets described, it will be important to focus on targets that could help alleviate multiple psychostimulant-induced cognitive deficits such as impulsivity and memory impairment (e.g., orexin and cannabinoid receptors). Further, drugs that facilitate/strengthen extinction of drug-associated memories should be an essential strategy of addiction treatment programs.

Future studies must focus on identifying specific circuits mediating psychostimulant-induced cognitive deficits. Better understanding of the role of non-coding miRs, neurogenesis, and enzymes involved in epigenetic changes will greatly help in developing highly selective treatments. Finally, combining non-pharmacological strategies such as brain stimulation and exercise with pharmacological compounds will enhance alleviation of psychostimulant-induced cognitive deficits. In this review, the focus has been on targeting specific psychostimulant-induced cognitive deficits such as impulsivity and impairment of learning/memory. However, psychostimulant-induced cognitive deficits include other deficits such as impairment in attention, lack of cognitive flexibility, and impaired decision making, which have not been discussed in this review but need to be therapeutically addressed. In conclusion, a multipronged strategy targeting behavioral, emotional, and cognitive deficits in recovering abstinent addicts will greatly improve outcomes of psychostimulant addiction treatment.

AUTHOR CONTRIBUTIONS

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Heterogeneity in Disordered Gambling: Decision-Making and Impulsivity in Gamblers Grouped by Preferred Form

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Background: Previous research has indicated that disordered gamblers display deficits in impulsivity and risky decision-making, compared to healthy control groups. However, disordered gamblers are not a homogenous group, and differences in performance on neurocognitive tasks may be related to the form of gambling in which an individual chooses to engage. The present study used neurocognitive tasks and questionnaire measures to ascertain group differences in gamblers grouped by preferred form of gambling.

Method: Treatment-seeking pathological gamblers from the National Problem Gambling Clinic, London (n = 101), completed a neurocognitive assessment comprising the Cambridge gamble task (CGT), the stop-signal task (SST), a probabilistic reversal learning task (PRL), and the Kirby Monetary Choice Questionnaire, as well as questionnaire measures of gambling severity, impulsivity, depression, and anxiety. Analyses compared gamblers who favored fixed-odds betting terminals (FOBTs) (the modal form) to gamblers who preferred other forms of gambling (non-FOBT).

Results: The FOBT group showed impaired decision-making under risk on the CGT compared to the non-FOBT group, choosing the likely option less on more uncertain decisions. The FOBT group made fewer perseverative errors on the PRL task, had lower depression and anxiety scores, and were less likely to have a family history of problem gambling than the non-FOBT group.

Discussion: Decision-making and cognitive flexibility differences between gamblers grouped by gambling type supports preferred form as an important source of heterogeneity in gambling disorder. Decision-making strategies and risk attitudes should be considered when approaching cognition-focused treatment strategies, allowing interventions to be targeted at specific cognitive deficits.

Keywords: gambling, impulsivity, decision-making, disordered gambling, heterogeneity

INTRODUCTION

Pathological gambling was re-classified from an impulse control disorder to an addictive disorder in the most recent versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (1) and the International Classification of Diseases and Related Health Problems (11th edition) (ICD-11) (2) in acknowledgement of the parallels between behavioral and substance addictions (3). The term "disordered gambling" is used hereafter as an umbrella term for people experiencing gambling-related harm.

Disruption of executive functions has been identified as being important in the development and maintenance of addictive behaviors (4). More specifically, risky decision-making and low self-control (i.e., impulsivity) are markers that cut across different forms of addiction, through the interaction of impulsive and reflective systems for assessing reward options (5, 6). As in substance addictions, groups of pathological gamblers display statistically significant impairments in decision-making using the Iowa gambling task (IGT), selecting more cards from the disadvantageous decks (7). Pathological gamblers also show deficits in risky decision-making using the Cambridge gamble task (CGT) (8, 9), the Information Sampling Test (IST) (8), and the game of dice task (10). Brevers et al. (11) found that problem gamblers perform worse than controls on tasks assessing decision-making under both explicit risk (where the odds are known) and decisions under ambiguity (where the probabilities are unknown).

Similarly, impulsivity has been seen to be elevated in both substance addictions (12) and disordered gambling (13). Impulsivity can be measured with delay discounting tasks (i.e., impulsive choice) (14–16) as well as tests of response inhibition (i.e., impulsive action) on tasks including the stop-signal task (17), the Go–No Go task (18), and the Stroop test (19). Additionally, disordered gamblers display increased response perseveration and compulsivity on reversal learning tasks (20), although Boog et al. (21) suggest these deficits may arise as a function of reward motivation rather than cognitive inflexibility *per se*. Nevertheless, the multi-dimensional nature of impulsivity has not been fully parsed in disordered gambling. Using a thorough assessment with both neurocognitive tasks and questionnaire measures, Billieux et al. found that disordered gamblers exhibited higher urgency, lower premeditation, impairment in prepotent inhibition, and lower tolerance of delayed rewards than a control group. However, they also observed considerable heterogeneity in the impulsivity profiles of the gamblers: although disordered gamblers reported elevated impulsivity at an overall level, individual gamblers displayed atypical scores on different UPPS subscales, and the disordered gamblers were not reliably impaired across all inhibition tasks, indicating that impulsivity is not universally present in disordered gamblers (22).

In comparing problem gamblers to healthy controls, an alcohol dependent group and a Tourette syndrome group on four impulsivity-related dimensions (self-reported impulsivity, prepotent response impulsivity, choice impulsivity, and motor impulsivity), Kräplin et al., (23) found that gamblers were more impulsive than the healthy control group across all dimensions, and the problem gamblers were the only group that differed on choice impulsivity, indicating some dimensions of impulsivity although a key feature in gambling disorders, are not disorder specific (23).

Traditional models of sub-typing problem gamblers primarily rely on personality traits and clinical characteristics (24–26). Three dominant subtypes of gambler are proposed, termed "behaviorally conditioned," "emotionally vulnerable," and "antisocial impulsivist," with impulsivity emphasized as a dispositional factor in the third pathway. However, approaches to subtyping gamblers to date have rarely consider the form(s) of gambling the individual engages in. The level of skill, or strategy involved in different forms of gambling, can vary: lotteries are chance games, where no single outcome is more likely than any other, whereas gambling forms such as poker offer far greater potential for experienced players to develop successful strategies (27). Studies that utilize preferred form as a source of heterogeneity commonly use a dichotomy of strategic (e.g., sports, cards) *versus* non-strategic (e.g., slots, lotteries) games, describing differences in demographic variables (28–30), personality traits (31), and gambling severity (32).

Preferred form of gambling has also been investigated preliminarily in relation to neurocognitive performance. After characterizing group deficits in pathological gamblers on the IGT and a reversal learning task, Goudriaan et al. (33) separated gamblers based on their preferred forms (slot machine gamblers and casino gamblers); the slot machine gamblers displayed greater impairments in decision-making than the casino gamblers. Using a computational model to decompose performance on the IGT, Lorains et al. (34) found that strategic gamblers were significantly influenced by both gains and losses but demonstrated an inconsistent choice style, where non-strategic gamblers were less sensitive to losses and exhibited poor learning during decision-making. Navas et al. identified non-strategic gamblers displayed higher delay discounting whereas strategic gamblers reported higher cognitive distortions and self-reported reward sensitivity (35). However, in a study by Grant et al. (36), both strategic and non-strategic gamblers were impaired compared to healthy controls on tests of cognitive flexibility or motor impulsivity, but the subgroups did not differ from each other.

In the UK, fixed-odds betting terminals (FOBTs) are a form of electronic gaming machine (EGM) located in high-street betting shops and casinos. These terminals offer multiple games with "fixed odds," including electronic roulette as a popular form. FOBTs appear to be a particularly problematic form of gambling. Disordered gamblers are estimated to account for over 22% of money and over 25% of time spent on FOBTs in the UK (37). In a small sample of treatment-seeking pathological gamblers from the London National Problem Gambling Clinic, FOBTs were the preferred form of gambling in 60% of the sample (16). Subsequent analyses found that FOBT preference is associated with increased gambling severity (38), and that use of "gaming machines" was a significant predictor of pre-treatment dropout (39). Furthermore, in data collected from gamblers seeking residential treatment in the UK, FOBTs were the most common and fastest increasing form of gambling identified by those clients as problematic (40).

Recent meta-analyses have confirmed robust differences on neurocognitive tasks in groups with disordered gambling compared to healthy comparison groups (7, 13, 20, 41). The present study focuses specifically on disordered gamblers, by exploring heterogeneity on neurocognitive and questionnaire measures of impulsivity and risky choice. A moderately large sample of treatment-seeking pathological gamblers were grouped as a function of preferred form of gambling, distinguishing FOBTs as the modal form against a non-FOBT group comprising all other preferred forms. Considering the heterogeneity in previous studies explained by strategic *vs*. non-strategic form preferences, we predicted that FOBT preferences would also predict neurocognitive performance.

METHODS

Participants

Treatment-seeking pathological gamblers were recruited from the National Problem Gambling Clinic, London (NPGC). Inclusion criteria were a current diagnosis of pathological gambling using the Massachusetts Gambling Screen (MAGS) (42), a 12-item gambling screen based on the DSM-IV pathological gambling criteria. This was corroborated by scores indicating problem gambling on the Problem Gambling Severity Index (PGSI > 7) (43). Exclusion criteria were the presence of neurological disorders, previous serious head injury or history of psychotic disorder, leading to exclusion of nine participants. This resulted in a final sample of 101 pathological gamblers (92 male; age M = 37.6, SD = 11.3).

The study protocol was approved by Cambridge South Research Ethics Council, Ref: 09/H0305/77. Participants gave written informed consent in accordance with the Declaration of Helsinki and were reimbursed for time and travel expenses. Participants completed a general screening questionnaire to collate demographic data including age, gender, nationality, ethnicity, education level, employment status, relationship status, and handedness. This questionnaire recorded participants' preferred form of gambling, and family history of disordered gambling.

Participants were grouped based on their stated preferred form of gambling. The modal preferred form was FOBTs in 43 participants (age M = 36.9, SD = 11.7, 41 male). Other forms (n = 58; age M = 38.1, SD = 11; 51 male) comprised sports betting (n = 14), fruit machines (n = 13), betting on horses (n = 10), poker (n = 6), casinos (n = 6), blackjack (n = 4), online casinos (n = 2), stocks and shares (n = 2), and betting shops (n = 1). Smoking status was measured by the Fagerstrom Test for Nicotine Dependence (FTND) (44). IQ estimates were obtained from two measures, the National Adult Reading Test (NART) (45) and the composite of the Matrix Reasoning and Vocabulary tests on the Wechsler Abbreviated Scale of Intelligence (46). All participants were recruited following initial assessment at the NPGC and were either awaiting treatment (FOBT n = 27; non-FOBT n = 38), receiving psychological treatment (FOBT n = 11; non-FOBT n = 14), or had completed a course of CBT (FOBT n = 5; Non-FOBT n = 6). Groups did not differ on treatment stage distributions (χ^2 (2) = .33, p = .85).

Neurocognitive Assessment

Kirby Monetary Choice Questionnaire (Kirby MCQ) (44)

Delay discounting was measured using the Kirby MCQ (47), a temporal discounting task involving 27 binary choices between an immediate smaller reward *versus* a larger reward available following a delay. All rewards were hypothetical monetary rewards. Larger rewards varied across three levels of magnitude (low, medium, and high). The indifference points at each magnitude are used to derive a hyperbolic k value, where higher k values indicate steeper discounting of delayed rewards and thus higher impulsivity. k Values are log transformed to reduce skew and averaged over the three magnitudes to calculate the overall discounting rate.

Cambridge Gamble Task (CGT) (45)

Risky decision-making was examined using the Cambridge gamble task (48). On each trial, 10 boxes are presented that are colored red or blue. The ratio of colors varies from trial to trial (9:1, 8:2, 7:3, and 6:4). The participant is instructed that a token has been hidden under one box. Each trial involves two responses. First, the participant makes a decision regarding which box color the token is hidden, and second, they place a bet of some points on their color choice. Across two conditions (in counterbalanced order), bets are offered in either an ascending or descending sequence, in fixed proportions of the current tally (5, 25, 50, 75, and 95%). Participants complete four blocks of nine trials in each of two conditions; at the start of each block the participant is endowed with 100 points. Key measures were proportion of choice of most likely outcome, deliberation time, and proportion of points bet.

Stop-Signal Task (SST) (46)

Response inhibition was measured using the stop-signal task (49). This is a two-choice response task, where participants are presented with a "Go" stimulus that requires a rapid response (left response key for an arrow pointing left, and right response key for an arrow pointing right). Participants were instructed to inhibit the Go response if an auditory stop signal was presented (a 300-Hz tone). These stop signals occurred on 25% of trials, a short delay after the Go stimulus. This delay was adjusted over successive stop trials using a staircase procedure, to identify a point at which the participant successfully inhibited on 50% of stop trials. The task contained five blocks of 64 trials, resulting in 80 stop trials over the task. Key measures were the median Go reaction time and the stop-signal reaction time.

Probabilistic Reversal Learning Task (PRL) (47)

Perseverative responding was measured with a probabilistic reversal learning task (50). This is a two-choice visual discrimination, with a red and a green stimulus randomly displayed in two of four screen locations. Selection of one stimulus is positively reinforced on 80% of trials (by the word "CORRECT" appearing on the screen); the other stimulus is incorrect ("WRONG") on 80% of trials. After 40 trials

for learning the initial discrimination, the contingencies reverse for 40 trials, such that the previously incorrect stimulus is now correct on 80% of selections. Key measures are the number of errors made in the two stages, the number of consecutive errors following the reversal (i.e., perseveration), and the number of response switches following the misleading (probabilistic) feedback.

Self-Report Measures

Anxiety was measured using the Beck Anxiety Inventory (BAI) (51), a 21-item questionnaire measuring anxiety symptoms in the past month on a scale from 0 (not at all) to 3 (severely). Scores of less than 21 indicated low anxiety, scores of 21–35 indicate moderate anxiety, and scores of ≥36 indicated severe anxiety. Depression was measured using the Beck Depression Inventory II (BDI-II, 52), a 21-item scale with scores ranging from 0 to 3. A total BDI-II score of 0–13 indicated minimal depression, scores of 14–19 indicate mild depression, 20–28 indicate moderate depression, and scores of 29–63 indicate severe depression. Impulsivity was measured using the UPPS-S (53), a 59-item self-report scale designed to measure five subscales of impulsivity. Items are answered on a Likert scale, anchored at 1 (agree strongly) to 4 (disagree strongly). The five subscales are negative urgency, positive urgency, (lack of) planning, (lack of) perseveration, and sensation seeking. Gambling cognitions were measured using the Gambling-Related Cognitions Scale (GRCS) (54), a 23-item scale where items are presented as statements, and participants are required to respond on a Likert scale anchored at 1 (strongly disagree) and 7 (strongly agree). The GRCS can be divided in to subscales of inability to stop (five items), interpretative bias (four items), illusion of control (four items), gambling expectancies (four items), and predictive control (six items).

Data Analysis

The neurocognitive tests that involved repeated-measures factors (Kirby MCQ: reward magnitude; CGT: color ratio and ascend/descend condition; PRL: stage) were analyzed with a mixed-factorial ANOVA with group as the between-subject factor. *Post hoc* analysis utilized *t* tests where appropriate. All data were checked for homogeneity of variance, and Greenhouse–Geisser was corrected where $p > .05$. Group differences on the scores on the questionnaire measures between the FOBT and non-FOBT gambling groups were analyzed using independent samples *t* tests. Chi-squared analyses were used for categorical data. Error bars represent the standard error of the mean. Data from the Kirby MCQ was log transformed prior to analysis.

RESULTS

The two subgroups did not differ significantly on age, gambling severity [(MAGS, (42); PGSI, (43))], IQ estimates, or nicotine dependence (**Table 1**). Although the non-FOBT group showed a trend toward having a greater proportion of females, the groups did not differ significantly on gender distribution (χ^2 (1) = 3.15, p = .06). The non-FOBT group (38.6%) were more likely to have a family history of problem gambling than the FOBT group (23.8%; $\chi^2(1) = 5.21$, p = .02). The FOBT group scored significantly lower than the non-FOBT group on the BDI (*t* (99) = 2.16, p = .03) and BAI (*t* (97) = 2.87, p = .005). Groups did not differ on scores on any of the UPPS-P or GRCS subscales (**Table 2**).

Kirby MCQ: The ANOVA indicated a significant main effect of magnitude ($F(1.8,173) = 52.91$, $p < .001$), such that the k values were lower for delayed rewards of larger absolute magnitude, with significant differences between each of the three levels (lowest *t* = 5.43, all tests $p < .001$). The main effect of group ($F(1,94) = .043$, p = .84) and the magnitude x group interaction ($F(1.8,173) = .051$, p = .94) were not significant.

Cambridge Gamble Task: On quality of decision-making, the ANOVA for proportion of trials on which the participant chose the more likely option showed a significant ratio x group interaction ($F(1.6,121.4) = 4.78$, p = .016), as well as significant main effects of ratio ($F(1.6,121.4) = 43.84$, $p < .001$) and group ($F(1,76) = 9.1$, p = .003). The FOBT group were less likely to choose the favorable option, and especially so at the more uncertain box ratios (6:4 ratio: *t* (56.8) = 2.84, p = .006; 7:3 *t* (52.8) = 2.13, p = .05). The 8:2 and 9:1 ratios were non-significant (lowest *t* = 1.47, $p > .05$), **Figure 1**.

An equivalent model for deliberation times indicated a significant ratio x group interaction ($F(2.7,247.7) = 3.86$, p = .02). The non-FOBT group demonstrated the expected pattern of longer deliberation times when the box color ratio was more evenly distributed (e.g., 6:4), than when the odds were greater (e.g., 9:1). The FOBT group demonstrated the opposite pattern, but analysis of simple effects indicated that the two groups did not differ significantly at any individual ratio (lowest *t* = .29, all

TABLE 1 | Group differences.

Questionnaire/test		Group				Test statistics		
		FOBT (n = 43)		Non-FOBT (n = 58)		T	df	p
		Mean	*Sd*	Mean	*Sd*			
Age		36.86	*11.73*	38.1	*11*	0.55	99	0.59
FTND	44	.77	*1.86*	1.46	*2.46*	1.59	98	0.11
MAGS	42	7.19	*2.04*	7.21	*1.5*	0.06	73.4	0.96
PGSI	43	18.59	*4.5*	19.16	*4.4*	0.63	96	0.53
NART	45	115.7	*6.54*	116.13	*6.58*	0.30	92	0.76
WASI	46	103.7	*17.4*	106.3	*13.34*	0.81	72.1	0.42

TABLE 2 | Questionnaire measures.

Questionnaire/test	Group				Test statistics		
	FOBT (n = 43)		Non-FOBT (n = 58)		t	df	P
	Mean	Sd	Mean	Sd			
GRCS							
Gambling experiences	12.79	*6.17*	13.6	*7*	.61	99	.55
Illusion of control	9.6	*5.51*	7.84	*4.89*	1.69	99	.09
Predictive control	17.67	*8.53*	15.16	*7.39*	1.59	99	.12
Inability to stop	18.98	*7.69*	18.79	*8.11*	.12	99	.91
Interpretive bias	15.26	*6.21*	15.52	*6.79*	.2	99	.84
Beck Depression Inventory	17.51	*10.1*	21.86	*9.86*	2.16	98	0.03*
Beck Anxiety Inventory	11.19	*8.88*	17.37	*11.68*	2.87	97	0.005*
UPPS-P							
Positive urgency	33.74	*9.17*	34.4	*9.62*	0.35	98	0.73
Negative urgency	34.91	*5.74*	36.05	*6.23*	0.94	98	0.35
Lack of perseverance	22.88	*4.74*	23.67	*5.54*	0.74	98	0.46
Lack of premeditation	26	*5.31*	26.91	*5.5*	0.83	98	0.41
Sensation seeking	34.81	*8.08*	32.04	*7.5*	1.77	98	0.08
Kirby MCQ (ln k)							
Magnitude—small	–3.46	*1.31*	–3.48	*1.27*	0.1	94	0.92
Magnitude—medium	–3.9	*1.27*	–3.98	*1.26*	0.32	94	0.75
Magnitude—large	–4.4	*1.5*	–4.44	*1.32*	0.16	94	0.88

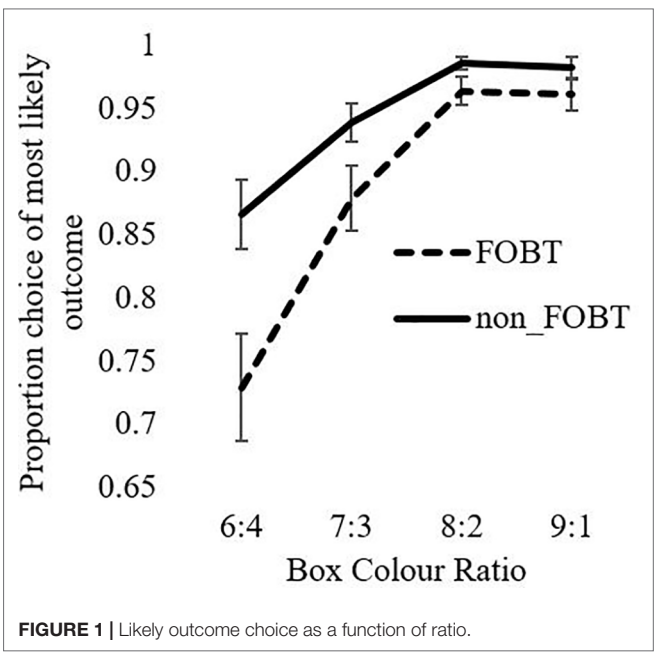

FIGURE 1 | Likely outcome choice as a function of ratio.

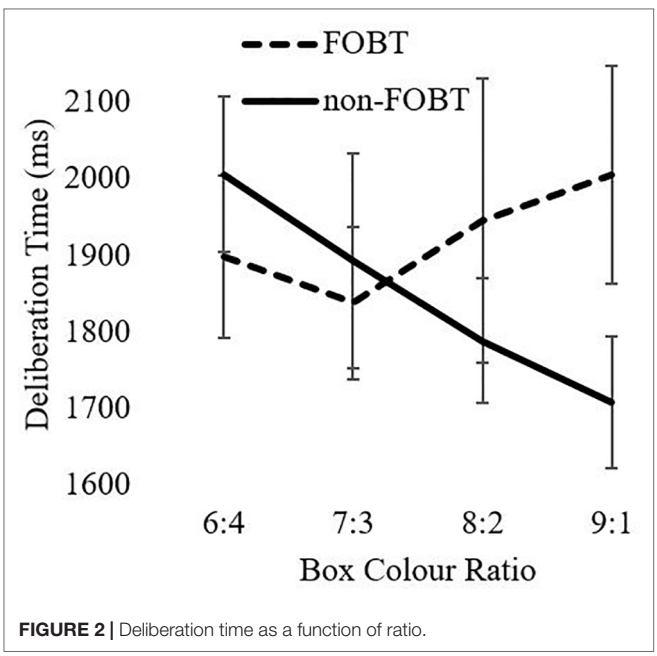

FIGURE 2 | Deliberation time as a function of ratio.

p > .05). Main factors of ratio (F(2.7,247.7) = .88, p = .44) and group (F(1,93) = .243, p = .62) were not significant (**Figure 2**).

For the analysis of betting behavior, the model shows significant main effects for ratio (F(1.6,150.3) = 256.6, p < .001) and condition (F(1,93) = 129.4, p < .001). The ratio x condition interaction was also significant (F(2.1,194) = 8.04, p < .001). Both groups bet more points in the descending condition than the ascending condition across all ratios. The main effect of group and the condition x group, ratio x group, and condition x group x ratio interactions were all non-significant (**Figure 3**). The number of "bankruptcies" (i.e., losing all points within a block, *t* (96) = .15, p = .88) and total points accrued across all trials (*t* (96) = .06, p = .95) did not differ between groups.

Stop-Signal Task: The groups did not differ on the stop-signal reaction time (FOBT M = 142.99ms, SD = 47.88; non-FOBT M = 131.86ms, SD = 41.21; *t* (80) = 1.13, p = .26). The median reaction time on "Go" trials did not differ between groups (FOBT: M = 469.93ms, SD = 113.91, non-FOBT M = 444.59ms, SD = 105.73; *t* (80) = .92, p = .36) indicating the groups did not differ in overall reaction time to go trials. In accordance with the SSD adjustment

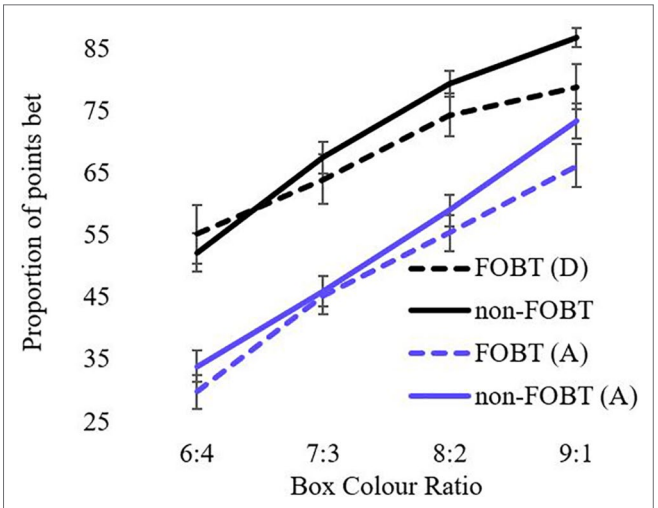

FIGURE 3 | Proportion of points bet as a function of ratio.

procedure, the proportion of successful stop inhibitions was close to 50% and not significantly different between groups (FOBT M = .51, SD = .06; non-FOBT M = .51, SD = .06; t (80) = .095, p = .92).

Probabilistic Reversal Learning: The ANOVA for errors by stage indicated a significant main effect of stage (F(1,87) = 36.63, p < .001), with both groups making more errors in stage 2 (**Figure 4**). The main effect of group (F(1,87) = 1.08, p = .30) and the stage x group interaction (F(1,87) = 1.57, p = .21) were non-significant. However, the groups differed significantly on perseverative errors specifically (t (85.9) = 2.27, p = .03); the non-FOBT group perseverated longer following the reversal switch (M = 5.43, SD = 4.8) than the FOBT group (M = 3.39, SD = 2.9) (**Figure 5**).

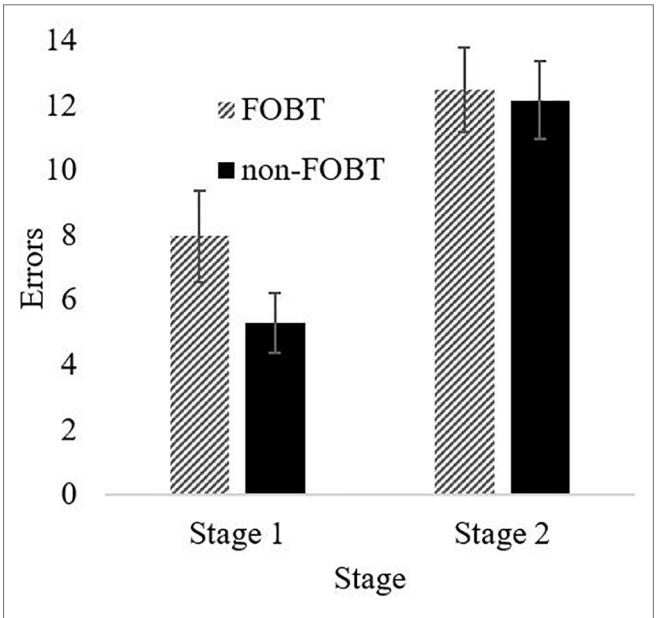

FIGURE 4 | PRL errors by task stage.

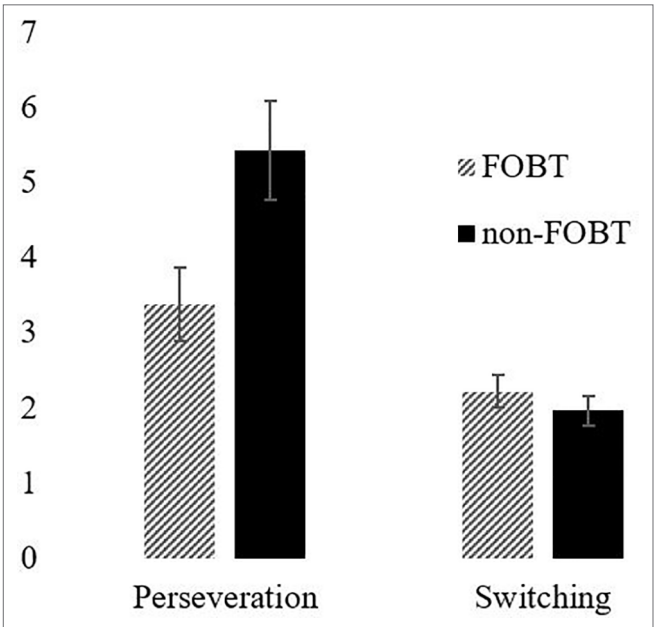

FIGURE 5 | Perseveration and switching by group.

The groups did not differ on the number of times they switched choice following misleading feedback (t (87) = .60, p = .55).

DISCUSSION

The key aim of this study was to explore the heterogeneity within a group of pathological gamblers using a psychological assessment focused on neurocognitive measures of decision-making, and questionnaire measures of impulsivity and common clinical comorbidities. Due the consistently high prevalence of FOBT gambling in UK treatment-seeking samples (including the present sample), our analyses compared FOBT gamblers against a mixed group of non-FOBT-preferring gamblers. The groups were comparable in terms of demographics and gambling severity. Analysis indicated both cognitive strengths and weaknesses in the FOBT gamblers. On the Cambridge gamble task, the FOBT group made fewer "rational" choices (i.e., of the majority color) on decisions with more uncertain odds. However, on the probabilistic reversal learning task, the FOBT group demonstrated lower levels of perseveration, potentially indicative of enhanced cognitive flexibility following the rule switch.

The CGT is a test of decision-making under risk (the odds are explicit) rather than under ambiguity. In prior research, individuals with pathological gambling differed from healthy comparison groups in terms of elevated betting and poorer quality of decision-making (8, 23). In the present study, the FOBT and non-FOBT groups did not differ in betting as a measure of impulsive and risky decision-making. However, differences were observed on decision quality, measured by the proportion of trials where the participant chooses the more likely outcome. Choice was also highly sensitive to the box ratio, with a stepwise increase

in advantageous decisions as the ratios became more certain. The FOBT group made a lower proportion of advantageous choices, and this difference was strongest at the 6:4 and 7:3 ratios, where the outcomes were most uncertain. This choice of the unlikely option could be linked to the "gambler's fallacy" (55), a classic cognitive distortion in which gamblers expect the opposite outcome to the recent sequence. On the CGT, if the token has appeared several times under the more likely color, a participant may feel that the unlikely option is "due" and opt against the rational choice. Indeed, this type of gambling distortion is prevalent in roulette, where tables often display history information regarding "hot" and "cold" numbers and colors to emphasize the recent history. FOBT players may therefore be more susceptible to gambler's fallacy-type risky decisions.

Deliberation times to the CGT color choices also differed by preferred form, as an interaction with box ratio. The non-FOBT group showed the expected pattern whereby deliberation times became faster as the decisions became more certain (i.e., toward the 9:1 ratio). The FOBT group demonstrated the opposite pattern, with a trend toward *longer* deliberation at the more certain (9:1) color ratios. Notably, the two groups did not differ significantly at any individual box ratio. This pattern could also be explained by the conflict invoked by cognitive distortions such as the gambler's fallacy at the most certain ratios. Anticipatory regret may be a further influence on these decisions. Regret is a powerful emotion associated with counterfactual thinking ("what might have been") (56), and regret may increase if people do not win in a situation where they can easily imagine themselves winning (57)—for example, when choosing the majority color on the CGT. The pattern of decision latencies in the FOBT group supports the notion that probability is not the sole factor driving their color choice. This may be further expounded by gamblers who exhibit deficient emotion regulation (58).

The probabilistic reversal learning task showed that both groups made more errors in the second stage of the task, indicating increased perseveration and cognitive inflexibility. However, the results demonstrate a difference in perseveration between the two groups following the rule switch; the non-FOBT group perseverated significantly more than the FOBT group, demonstrating lower cognitive flexibility. The higher cognitive flexibility demonstrated by the FOBT group could be reflective of the cognitions associated with the different forms of gambling; the non-FOBT group contained a large number of sports and fruit machine gamblers, forms of gambling that either have relatively long outcome resolution (sports), or do not require any variation in the gambling mechanism (fruit machines), therefore do not require a great deal of quick-fire "switching" between win opportunities. Roulette on an FOBT requires the gambler to process the outcome in a number of different ways (color, odd/even, row, etc.) and then assimilate this outcome in to the decision-making process for subsequent bets, which on an FOBT can occur within 20 s. The continual updating of information requires cognitive flexibility. However, it is unclear from the current study whether a gambler with increased cognitive flexibility is drawn to FOBT machines or develops this capacity through persistent play on the terminals.

Using the Kirby Delay Discounting, both groups discounted smaller rewards more steeply than larger rewards, replicating impulsive behavior as previously demonstrated by Petry (14), Dixon et al. (15), and Michalczuk et al. (16). However, the two groups did not demonstrate any significant difference on discounting rates. The stop-signal task also failed to identify any group differences.

Strengths and Limitations

The current study chose to focus on the heterogeneity within pathological gamblers by classifying gamblers based on their preferred form of gambling, similar to Petry (32) and Goudriaan et al. (33). Although electronic roulette and other games available on FOBTs are primarily non-strategic forms, gamblers often believe they have a strategy, or a winning formula, and will therefore often erroneously believe there are elements of skill in chance games (e.g., fruit machines) (59). This complicates the traditional strategic/non-strategic dichotomy used by Grant et al. (36) and others, as some gamblers will likely play non-strategic games in a strategic manner. In addition, the strategic/non-strategic dichotomy can be dominated by certain specific games, such as Navas et al. (35) whose "type II non-strategic gamblers" were almost exclusively slot machine gamblers. However, for the classification used in the present study, it should be noted that EGM gamblers are present in both subgroups, given that FOBTs and slot machines are both types of EGMs. These forms do differ by gambling environment: FOBTs are housed specifically in gambling facilities (bookmaker's shops) while slot machines are also available in non-gambling venues such as pubs. The influence of these environmental factors on the cognitive differences we have observed is unclear and warrants further investigation. Furthermore, our method for categorizing gamblers was based on their stated single preferred form, but it is acknowledged that many participants also engaged in other forms of gambling.

Although the two groups did not differ on gender distribution, the sample was heavily male dominated (nine females), which prevented analyses of gender within the gambling subgroups. Our sample was treatment seeking with some variability in relation to stage of treatment (waiting list, during treatment or post-treatment). Our results may not be generalizable to the larger numbers of "at risk" gamblers. Therefore, results should be interpreted with caution. Additionally, this study did not have a non-gambling control group; differences in neurocognitive performance between gamblers and non-gamblers are well documented; the aim of this study was to better understand heterogeneity within gamblers who identify different forms as problematic.

Results indicate cognitive differences between pathological gamblers grouped by preferred form, indicating that problem gamblers are a heterogeneous group. This result should be considered when comparing gamblers as a single group to control groups, as the preferred form distribution of the gamblers could influence results.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Cambridge South Research Ethics Council (Ref: 09/H0305/77) with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Cambridge South Research Ethics Committee.

AUTHOR CONTRIBUTIONS

SS was responsible for data collection, data analysis, and manuscript preparation. LC was responsible for study design, data analysis and manuscript preparation. AR was responsible for manuscript preparation. RM and RC were responsible for data collection. HB–J was responsible for study design and manuscript preparation.

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Rewiring the Addicted Brain Through a Psychobiological Model of Physical Exercise

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Drug addiction is a worldwide public health problem, resulting from multiple phenomena, including those both social and biological. Chronic use of psychoactive substances has been shown to induce structural and functional changes in the brain that impair cognitive control and favor compulsive seeking behavior. Physical exercise has been proven to improve brain function and cognition in both healthy and clinical populations. While some studies have demonstrated the potential benefits of physical exercise in treating and preventing addictive behaviors, few studies have investigated its cognitive and neurobiological contributions to drug-addicted brains. Here, we review studies in humans using cognitive behavioral responses and neuroimaging techniques, which reveal that exercise can be an effective auxiliary treatment for drug addictive disorders. Moreover, we describe the neurobiological mechanisms by which exercise-induced neuroplasticity in the prefrontal cortex improves executive functions and may decrease compulsive behaviors in individuals prone to substance use disorders. Finally, we propose an integrative cognitive-psychobiological model of exercise for use in future research in drug addiction and practical guidance in clinical settings.

Keywords: aerobic exercise, neuralplasticity, substance use disorder, addiction, alcohol abuse

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INTRODUCTION

Addiction to psychoactive substances (e.g., nicotine, cocaine, marijuana, alcohol, heroin, inhalants, LSD, and ecstasy) is a public health problem of the modern world (1). The Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (DSM-V 2013) classifies drug addiction as a substance use disorder (SUD) when an individual meets two or more of the following criteria regarding the use of psychoactive substances: tolerance, craving, repeated attempts to stop use, or social, personal, physical, or psychological problems related to drug use (2). In addition to the influences of biological, cultural, social, economic, and psychological factors on individuals with SUD (3), studies in animal models and humans have shown that psychoactive substance use induces epigenetic, molecular, structural, and functional changes to the brain (4). Thus, the neurobiological model of drug addiction has proposed a complex interaction between biological and environmental factors and created new integrative perspectives for prevention, treatment, and pharmacological targets (5).

SUD is traditionally related to abnormal dopamine release and sensitivity in the brain reward system. This neural network is composed of several interconnected brain areas, including the ventral tegmental area, nucleus accumbens, amygdala, striatum, hippocampus, and prefrontal

cortex (PFC) (6). The PFC is an integrated neural system in humans required for normal executive functioning, including decision-making and inhibitory control, and beneficial socio-emotional functioning (7). Studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have demonstrated that individuals with SUD present decreased activityin the PFC (8). This condition seems to be related to a reduced number of dopamine receptors and an abnormal firing rate of dopaminergic neurons (9). These changes in the dopamine system and PFC activity may favor compulsive substance intake and seeking behaviors, as well as loss of control over drug consumption (8). Similarly, incomplete prefrontal cortex development and the resulting decrease in ability to control impulsive decisions has been suggested as an explanation for adolescents' particular vulnerability to drug abuse (10), highlighting the importance of preventing the use of addictive psychoactive drugs during this period of brain development. Hence, contemporary rehabilitation programs have emphasized the importance of interdisciplinary treatment approaches that target the reestablishment of normal PFC functioning while combining the use of medication, social care, and behavioral therapy supported by psychiatrists, psychologists, social workers, and family (5).

Physical exercise has been proposed as a complementary therapy for individuals with SUD undergoing treatment at different stages of addiction rehabilitation (11–13). Preclinical animal research has shown evidence of neurobiological mechanisms induced by physical exercise that support its potential use as a therapeutic strategy to treat drug addiction. Examples are the following: normalizing dopaminergic and glutaminergic transmissions, promoting epigenetic interactions mediated by BDNF (brain-derived neurotrophic factor), and modifying dopaminergic signaling in the basal ganglia (11, 14). However, identifying similar molecular interactions between exercise and the human brain presents significant methodological challenges that need to be overcome in order totranslate these findings from animal models to humans.

The benefits of physical exercise for cognitive functioning and brain structure in humans are, on the other hand, well documented in literature (15). For instance, aerobic exercise is linked to improvements in executive functions and increased gray matter volume and activity in PFC regions (16, 17). Furthermore, children and adults with higher cardiorespiratory fitness (i.e., VO_2 max) show improved cognitive performance and neuronal activity in the PFC and anterior cingulate cortex (ACC) (18). The results of preclinical animal studies show that these brain adaptations seem to be related to the release of exercise-induced molecules, such as BDNF (19) and IGF-1 (insulin-like growth factor 1) (20). Both molecules act as neurotrophic factors and create new synapses, neurons, and neural networks (18). These adaptations are facilitated by an increase in cerebral blood flow during exercise (21) and a release of a vascular endothelial growth factor (VEGF) (22), which promotes mitotic activity in vascular endothelial cells, thereby promoting angiogenesis and enhancing the oxygen and nutrient supply to neurons (18). Additionally, exercise is also related to the integrity of the brain-blood barrier (23). However, despite the wide range of benefits of the exercising brain, its effects on individuals with SUD who have impaired PFCs and cognitive functions need to be further investigated.

In this mini review, we present the results of a review of the current literature on exercise and SUD. We limited our search to studies that investigated the effect of acute or chronic aerobic exercise on cognitive and/or neurobiological markers in humans with SUD. The search terms used to select the articles were "tobacco cigarettes," "nicotine," "alcohol," "methamphetamine," "crack," "cocaine and marijuana," "physical activity," "endurance exercise," "aerobic exercise," "addiction,":substance use disorder," "executive functions," "prefrontal cortex," "cognition," and "brain." Two authors selected the published and peer-reviewed articles identified on electronic databases (Pubmed Central, Medline, Scopus, and Web of Science) in February 2019, while a third author resolved differences in opinion. Only articles published in English were considered. Finally, we propose an integrative cognitive-psychobiological model of exercise to support future research on the subject and provide methodological guidance for its application in clinical settings as a therapeutic tool for the treatment of SUD.

The Effect of Aerobic Exercise on Brain and Cognitive Function in Individuals With SUD

Aerobic exercise is typically performed at submaximal intensity for a long duration with most of the energy consumption coming from mitochondrial oxygen-dependent production of ATP. Organic adaptations of the cardiorespiratory system as a result of aerobic training are mainly reflected by higher values of VO_2 max, which has been associated with improvements in several health parameters, as well as brain and cognitive functioning (18, 24). Examples of aerobic exercise include running, swimming, and cycling among summer sports and cross-country skiing or speed skating among winter sports (25). **Table 1** describes studies that investigated the effect of aerobic exercise on the brain and cognitive functions in individuals with SUD. Acute effects of aerobic exercise (i.e., immediately after exercise cessation) have been shown to include increases in PFC oxygenation associated with greater inhibitory control (26) and improved memory, attention, and speed processing in polysubstance users (27). Similarly, methamphetamine users who exercised on a stationary cycling ergometer exhibited improvements afterward, such as better drug-specific inhibitory control, reduced craving levels, and enhanced brain activity in the ACC, the area involved in conflict monitoring and inhibition (28). Wang et al. (29) and Wang, Zhou, and Chang (30) also studied methamphetamine users and showed that exercise performed at moderate intensity (i.e., 65–75% of maximum heart rate) elicits a decrease in craving levels, improves performance on a go/no-go task, and increases N2 amplitude during no-go conditions when the individuals have to inhibit the impulse to press the bottom of the computer screen after a visual cue. Notably, the N2 is an event-related potential, monitored using non-invasive electroencephalography (EEG), that originates from the fronto-parietal cortex and is directly associated with inhibitory control (31).

TABLE 1 | Studies investigating the effects of physical exercise on the brain and cognitive functions in individuals with substance use disorders.

Results from acute exercise studies

Reference	Study procedures	Drug type	Exercise (type; intensity; time)	Neurobiological marker and cognitive test	Outcomes
Janse Van Rensburg and Taylor, (2008) (32)	Smokers (N=23) underwent to conditions (Exercise and passive resting). They performed a cognitive test before and after the conditions.	Nicotine	Aerobic exercise on a treadmill; Light self-paced intensity; 2min warm-up and 15min exercise	Stroop test	Following the exercise session, smokers did not improve on the cognitive test performance compared to the control session.
Janse Van Rensburg et al., (2009) (33)	Smokers (N=10) underwent to conditions (Exercise and passive resting) followed by fMRI scanning while watching smoking and neutral images.	Nicotine	Aerobic exercise on cycleergometer; Moderate-intensity (RPE 11-13); 2min warm-up, 10min exercise.	fMRI	Smokers presented reduced brain activity in areas related to reward, motivation and visuo-spatial attention following exercise, compared to the control condition.
Rensburg et al., (2012) (34)	Smokers (N=20) underwent to conditions (Exercise and passive resting) followed by fMRI scanning while watching smoking and neutral images.	Nicotine	Aerobic exercise on cycleergometer; Moderate-intensity (RPE 11-13); 2min warm-up, 10min exercise)	fMRI	Smokers presented decreased activity in visual processing (i.e., occipital cortex) areas during smoking images after the exercise session
Wang, Zhou and Chang., 2015 (30)	Participants (N=24) performed two conditions: exercise and reading control sessions The cognitive tests and the brain electroactivity were measured following each condition.	Methamphetamine	Aerobic exercise on cycle-ergometer; 65-75% of estimated maximum HR, 30min (5min warm-up, 20min of exercise and 5min cool-down)	Electroencephalogram (EEG), GoNoGo	Both general and methamphetamine specific inhibitory control were improved after the exercise session compared to the control session. Greater N2 amplitude was observed during the cognitive tests on the Nogo conditions of both inhibitory control tests compared to the control session.
Wang et al., 2016 (29)	Participants (N=92) were randomly assigned to 4 groups: light exercise, moderate exercise, vigorous exercise and reading control group. Cognitive test and brain electroactivity were measure before and 20min after the exercise or reading session.	Methamphetamine	Aerobic exercise on a cycle-ergometer; each group had its own intensity based on estimated maximum HR (40-50%, 65-75% and 85-95%, corresponding to light, moderate and high intensities, respectively); 30min of exercise (5min warm-up, 20min of exercise and 5min cool-down)	Electroencephalogram (EEG) a while performing a general GoNogo task and a methamphetamine specific GoNogo task.	Moderate intensity group showed better reaction time and lower number of errors. The same group showed greater N2 amplitude during Nogo conditions of both general and meth-specific inhibitory control.
Da Costa et al., 2017 (35)	Individuals with substance use disorder (N=15) were compared with 15 healthy individuals during a maximum effort exercise session. During the session, all volunteers had their prefrontal cortex oxygenation measured while performing a cognitive test.	Multiple drug users (35.5% were addicted to one substance, 43% to two substances and 21.1% to three substances). 8 reported to be crack/cocaine user, 6 were alcohol users and 3 were marijuana users.	Aerobic exercise until voluntary exhaustion [20 on Borg Scale (6-20)]. The cycloergometer was kept in 60-70 rpm. The initial load was 25w and in every two minutes, 25w increment occurred.	Near infrared spectroscopy (NIRS) and Stroop test	Individuals with substance use disorder increased prefrontal cortex oxygenation during exercise associated to better reaction time on the Stroop test. Also, lower cravings was reported after the exercise session.

(*Continued*)

TABLE 1 | Continued

Results from chronic exercise studies

Reference	Study design	Drug type	Exercise (type; intensity; frequency; time)	Neurobiological marker and cognitive test	Outcomes
Da Costa et al., (2016) (36)	Individuals with substance abuse (N=9) performed 3 months of exercise intervention. They performed a cognitive test before and after the exercise protocol.	Crack and cocaine	Aerobic exercise (free running), self-selected intensity; 3 sessions/ week; 36-60min/session. The protocol lasted for 3 months.	Stroop test	It was found that the participants decreased the reaction time associated with improvements on cardiorespiratory fitness. The number of errors on the Stroop test kept the same comparing pre and post intervention.
Cabral et al., (2017) (37)(a)	Case report. The subject performed prefrontal cortex oxygenation during incremental exercise before, 45 days after and 90 days after the beginning of the running protocol.	Alcohol and nicotine	Aerobic exercise (free running); self-selected intensity; 3 sessions/ week; the running time was increased along the weeks (first week: 3-6min, last week: 40-50min). The protocol lasted for 12 weeks.	Near infrared spectroscopy (NIRS). Stroop test	After 90 days of running, the subject improved prefrontal cortex oxygenation in 921% at ventilatory threshold, 604.2% at respiratory compensation point and 76.1% at maximum effort. Moreover, the individual increased number of correct answers during inhibitory control test by 266.6% and reaction time by 23%.
Wang et al., (2017) (38)	Randomized controlled trial study. Participants were divided in two groups: exercise (N=25) and control group (N=25). Cognitive tests and electroencephalogram were measured in both groups before and after 12 weeks.	Methamphetamine	Aerobic exercise (cycling, jogging, jump rope); 65-75% of estimated maximum HR; 3 sessions/ week; 40min/session (5min warm-up, 30min of aerobic exercise and 5min cool-down). The protocol was conducted for 12 weeks.	Electroencephalogram (EEG), Go/NoGo	Both general and methamphetamine specific inhibitory control were improved after the exercise session compared to the control group. Greater N2 amplitude was observed during the cognitive tests on the Nogo conditions of both inhibitory tests compared to the control group.
Cabral et al., (2018) (39) (b)	Case report. The participant had its brain activity measured before and after the exercise protocol during rest, while doing a cognitive test. Moreover, prefrontal cortex oxygenation was measured during incremental treadmill exercise.	Crack/cocaine and alcohol	High intensity aerobic exercise; all out for 30s and resting for 4:30min 3 sessions a week. The protocol lasted for 4 weeks.	Electroencephalogram (EEG) and Near infrared spectroscopy (NIRS), Stroop test	Prefrontal cortex oxyhemoglobin increased 228.2% at the beginning of the treadmill test, 305.4% at the middle and 359.4% at the end of the test. Prefrontal cortex activity during the Stroop test was enhanced. The Stroop effect was decreased by 327%.

In nicotine users, a meta-analysis (40) and a systematic review (41) show little or no effect of exercise in smoking cessation. However, those reviews did not include studies using cognitive or neurobiological markers as outcomes. On the other hand, Rensburg et al. (32–34) conducted a series of important experiments that suggest potential benefits of aerobic exercise to the brain and cognitive functions of nicotine users. The first study showed that 15 min of light-intensity treadmill exercise reduced craving levels compared to a control condition (passive resting) but did not find improvements in inhibitory control. However, performance on the inhibitory control task was only measured by reaction time and not by the number of errors, which might limit our interpretation of the results (32). In the second experiment, 10 min of moderate-intensity cycling exercise elicited decreases in craving levels compared to a control condition (passive sitting for 10 min). After each condition, participants underwent fMRI scanning while viewing neutral pictures and pictures related to smoking. While viewing smoking images participants demonstrated reduced activation in brain areas related to reward (i.e., caudate nucleus), motivation (i.e., orbitofrontal cortex), and visuo-spatial attention (i.e., parietal lobe and parahippocampal gyrus) after exercise (33). Another study replicated the same experimental design with a larger sample of smokers. The results showed that 10 min of moderate-intensity exercise also reduced craving levels, and the fMRI analyses revealed decreased activity in visual processing (i.e., occipital cortex) areas during smoking images for the exercise condition but not for the control condition (passive sitting) (34). Thus, these results show the potential effects of aerobic exercise in modulating craving and correlated brain areas in nicotine users.

Therefore, despite the limited amount of studies available in the literature so far, it is apparent that acute sessions of aerobic exercise decrease craving levels and seem to benefit cognitive and brain functions in these individuals. However, it could also be important to understand if regularly performed exercise (i.e., chronic effects) may potentialize the acute benefits to the brain and cognition of individuals with SUD throughout weeks and months

of exercise training. To date, only two studies have investigated the chronic effects of aerobic exercise in individuals with SUD using neurobiological and cognitive markers (**Table 1**). In one study, methamphetamine users showed improved inhibitory control and greater activation of the ACC during an inhibition task after performing 3 months of moderate-intensity exercise for 30 min three times a week (38). Curiously, this pioneering work by Wang et al. (38) did not report changes in cardiorespiratory fitness, which limited the association between the cardiorespiratory adaptations induced by exercise and improvements in brain and cognitive functioning. However, the results of a different pilot longitudinal study with polysubstance users showed that 3 months of aerobic exercise improved inhibitory control and was correlated with cardiorespiratory fitness improvements (36).

Because of the lack of longitudinal studies in the literature, we have conducted two case reports, in which we tested two different exercise interventions. The first one was a 3-month running program (three times a week), based on self-selected moderate-intensity exercise. The study was conducted with a chronic alcohol user receiving treatment in a public psychiatric hospital. Measures of PFC oxygenation, inhibitory control, and the need for medical intervention were assessed before and after the exercise program. At the end of the 3-month period, the participant demonstrated improved PFC oxygenation, decreased reaction time in the inhibitory control task, and reduced need for medical intervention (37). The second case report involved a crack/cocaine and alcohol user receiving treatment. They engaged in 4 weeks of high-intensity exercise (three times a week), and we measured PFC oxygenation, brain activity through electroencephalography, and inhibitory control before and after the intervention. The participant showed increased PFC activity during the inhibitory control test and increased PFC oxygenation during exercise (39). Taken together, the relationship between cognitive abilities and brain function and regular exercise suggests a promising role of physical exercise in promoting greater executive control on the compulsive behavior of individuals with SUD.

PSYCHOBIOLOGY OF SELF-SELECTED EXERCISE INTENSITY: PRACTICAL TOOL FOR CLINICAL SETTINGS AND RESEARCH

From an evolutionary perspective, humans have adapted to withstanding prolonged aerobic exercise through the search for food and persistence hunting of prey (supposedly pursued until physical exhaustion) (42). Aerobic self-selected exercise along with the cognitive appraisal of environmental cues for the acquisition of food and survival have been postulated to be key features in the development of the human brain (43). However, modern society has removed the need for humans to run/walk for food or shelter. As a result there is an increasing rate of hypokinetic behavior and related diseases such as diabetes, obesity, and hypertension (44, 45). Rational declarative decision-making concerning the volume, intensity, and frequency of exercise has not been sufficient to change sedentary behavior. Therefore, methods are being proposed to promote greater adherence to physical activity regiments, and a psychobiological integrative perspective appears to be a promising approach to achieve this goal (46, 47).

Cognitive and affective regulation of exercise intensity have been suggested to play a key role in both tolerance and adherence to exercise programs. For instance, homeostatic disturbances caused by high-intensity exercise have been associated with negative affective states and lower pleasure during exercise in sedentary individuals (45), leading to lower rates of adherence (48). Conversely, self-selected exercise intensity has been associated with positive affective states and higher levels of pleasure during exercise (45). Self-selected exercise intensity emphasizes the brain as the central governor of exercise intensity fluctuations (46), whereas the decision-making to increase and decrease velocity or tolerate or terminate the exercise session is controlled by the PFC through a bi-directional mind/body integration (49). Within this framework, top-down mechanisms are those initiated *via* declarative or non-declarative mental processing at the PFC level, which regulates muscle recruitment and alters physiological and behavioral responses. On the other hand, bottom-up mechanisms are initiated by sensitizing the ubiquitous somato-, viscero-, chemo-, and mechanical sensory receptors that influence central neural processing from the periphery to the brainstem, limbic system, and cerebral cortex (50). While performing any physical activity with self-selected intensity, the cognitive interpretation of the physiological state may be constantly working to preserve body homeostasis in order to reach the established goal (46, 51). In other words, fluctuations in pace while running are a behavioral outcome monitored by the brain (52). This behavioral modification results from integrating the task cognitive appraisal with afferent information related to biochemical and biophysical changes, such as temperature, heart and respiratory rate, blood pressure, blood concentrations of metabolites (e.g., PO_2, PCO_2, H^+, HCO_3^-, and lactate), intramuscular H^+, and energy substrate availability during the exercise (53).

Furthermore, feelings of fatigue and self-defeating thoughts demand inhibitory control mediated by the PFC in order to maintain physical activity (54). In this context, decision-making might be based on feelings such as perceived exertion (i.e., how hard the exercise is), affect (i.e., generic valence for good and bad feelings), and internal conversations such as "I cannot do it," "I will give up," or "it is very difficult" (53, 55). Therefore, self-selected exercise intensity emphasizes cognitive control (top-down) under the physiological changes (bottom-up) during physical effort (**Figure 1**), and it can be used as a strategy to develop self-monitoring and self-control abilities during the treatment of individuals with SUD. For instance, when setting a goal during an exercise session, such as running for a specific time or distance (i.e., time trial exercise), individuals need to regulate their pace to successfully complete that task. Thus, during the exercise, the decision to regulate the pace (running velocity) will be influenced by several environmental stimuli (i.e. weather, terrain, competitors, verbal instructions, and time or distance feedbacks) combined with the physiological state.

Several therapies focusing on this mind-body interaction through the top-down and bottom-up bi-directional mechanism have been suggested as promising rehabilitation tools in regulating stress and the immune system (56, 57). Therefore, we hypothesize

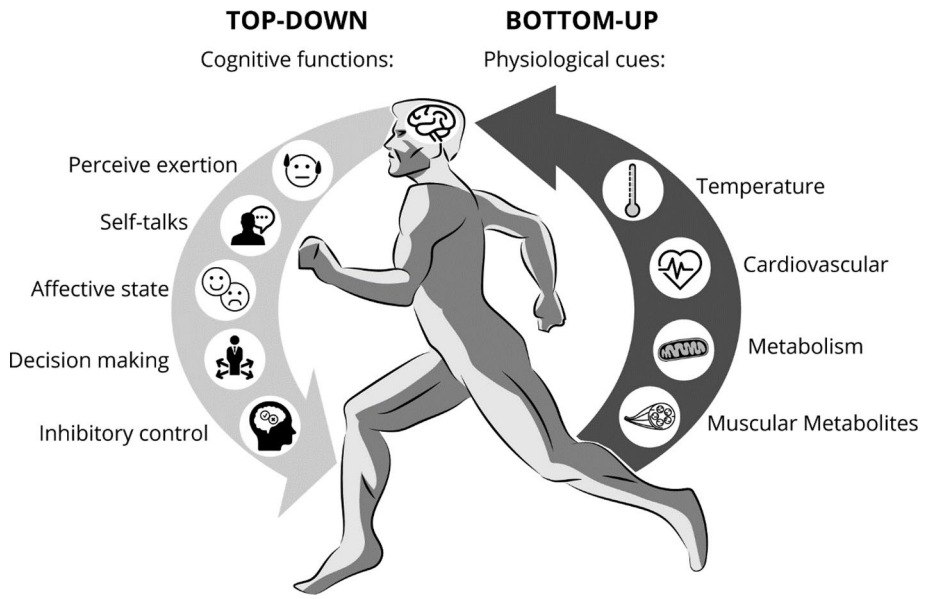

FIGURE 1 | Pace control during continuous exercise while integrating top-down (cognitive functions) and bottom-up processing factors (physiological responses).

that self-selected exercise intensity employs the bi-directional mechanism enabling improvements in self-control abilities associated with brain exercise-induced neuroplasticity. This cognitive regulation can be tested in humans while investigating perceptual responses, exercise-induced effects, and PFC function using neuroimaging methods (e.g., fMRI, PET scan, and fNIRS) and/or electroencephalogram. In addition, the brain responses can be associated with tests that evaluate the executive constructs of SUD-specific decision-making and inhibitory control, such as cue-reactivity go/no-go tests in which individuals have to inhibit their responses to salient stimuli relating to drug-related cues (e.g., drug behavior pictures). This cue-reactivity response has been shown to activate areas of the PFCand to predict relapses in different substances disorders (58, 59). Thus, we suggest that randomized clinical trials could follow the neuroscience paradigm and cognitive methodologies to test this hypothesis. In addition, the implementation of a control group would play a key role in these experimental designs in order to compare the self-selected intensity of exercise with other types of exercise intensity regulation to demonstrate its efficacy.

CONCLUSION

Despite the need for further prospective studies and clinical trials to test the efficacy of the psychobiological model of exercise as an intervention and treatment for SUD, physical exercise has been shown to be an effective and promising additional therapeutic tool for individuals with SUD. Here, we have described the brain areas affected by chronic substance use in patients with SUD as well as those improved by aerobic exercise. Some of these areas are primarily related to executive functions, which refer to a set of self-regulatory processes associated with the control of thoughts and behavior, including inhibitory control and decision-making. Therefore, in the same way that physical exercise is advised for treating other diseases, the neuroplasticity promoted by aerobic exercise may indicate its usefulness as a potential additional treatment for individuals with SUD. Specifically, these benefits may be seen in brain areas related to executive control, such as those areas involved in inhibition of drug-seeking behavior and impulsivity, as well as in decision-making regarding drug consumption. Furthermore, individuals with SUD who improve their fitness levels may enhance PFC function and cognition. These benefits should improve an individual's ability to inhibit drug consumption behavior when exposed to environmental cues and, consequently, their ability to maintain abstinence. However, this is still a hypothesis, and further studies are necessary to provide evidence of the effectiveness of exercise on maintaining drug abstinence, specifically exercise of self-regulated intensity. Thus, we propose an integrative cognitive-psychobiological model of exercise for future research and provide practical guidance to optimize its potential benefits during rehabilitation programs.

AUTHOR CONTRIBUTIONS

KC and EF conceived the idea, draft, figure and final revision. DC reviewed literature for table, described the results and final revision. RH reviewed manuscript and added theoretical framework, practical application and final revision.

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Resonance-Paced Breathing Alters Neural Response to Visual Cues: Proof-of-Concept for a Neuroscience-Informed Adjunct to Addiction Treatments

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Conscious attempts to regulate alcohol and drug use are often undermined by automatic attention and arousal processes that are activated in the context of salient cues. Response to these cues involves body and brain signals that are linked via dynamic feedback loops, yet no studies have targeted the cardiovascular system as a potential conduit to alter automatic neural processes that maintain cue salience. This proof-of-concept study examined within-person changes in neural response to parallel but unique sets of visual alcohol-related cues at two points in time: prior to versus following a brief behavioral intervention. The active intervention was resonance breathing, a rhythmical breathing task paced at 0.1 Hz (6 breaths per minute) that helps normalize neurocardiac feedback. The control intervention was a low-demand cognitive task. Functional magnetic resonance imaging (fMRI) was used to assess changes in brain response to the cues presented before (A1) and after (A2) the intervention in 41 emerging adult men and women with varying drinking behaviors. The resonance breathing group exhibited significantly less activation to A2 cues compared with A1 cues in left inferior and superior lateral occipital cortices, right inferior lateral occipital cortex, bilateral occipital pole, and temporal occipital fusiform cortices. This group also showed significantly greater activation to A2 cues compared with A1 cues in medial prefrontal, anterior and posterior cingulate, and precuneus cortices, paracingulate, and lingual gyri. The control group showed no significant changes. Thus, following resonance breathing, activation in brain regions involved in visual processing of cues was reduced, while activation in brain areas implicated in behavioral control, internally directed cognition, and brain–body integration was increased. These findings provide preliminary evidence that manipulation of the cardiovascular system with resonance breathing alters neural activation in a manner theoretically consistent with a dampening of automatic sensory input and strengthening of higher-level cognitive processing.

Keywords: alcohol, biofeedback, cardiovascular, neural reactivity, functional magnetic resonance imaging, heart rate variability, respiration, resonance breathing

INTRODUCTION

Moment-to-moment changes in internal states (e.g., cognition, emotion, visceral processes, moods) and environments (e.g., cues, persons) influence decisions to use alcohol and other drugs (1). These dynamic, intra-individual change processes derive from the body's ability to collect and relay information to the brain about the environment (afferent neural traffic), as well as from the brain's ability to integrate this information and generate a behavioral response (efferent neural traffic). In other words, behavior is influenced by both body and brain signals that are linked via reflexive and predictive bidirectional feedback (2, 3).

In the case of the cardiovascular system, this feedback loop (**Figure 1**) has been extensively documented in terms of its neurophysiology and functional anatomy in rodent and primate models [e.g., (4, 5)]; parallel functional anatomy emerged in a meta-analysis of human neuroimaging studies (6). The loop maintains signaling between the brain and heart via the vagus and sympathetic nerves, baroreceptors located on the aortic arch, carotid artery, and other vessel walls, and a network of brain regions referred to as the central autonomic network (4). These bodies of literature reveal how the brain elicits cardiovascular signals that promote arousal (e.g., increasing heart rate and blood pressure) that, in turn, prepare the organism for goal-directed behavior to respond to in-the-moment demands. Through this loop, feedback from the heart and vasculature is integrated with other autonomic information and relayed to forebrain structures that mediate cognitive and emotional experience

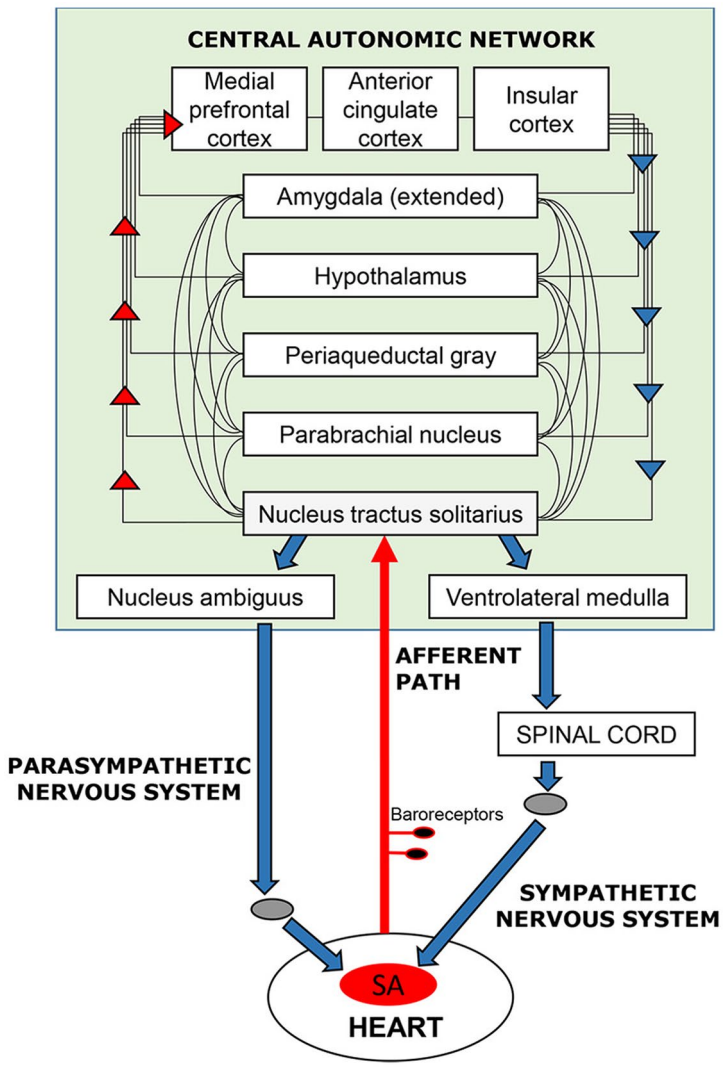

FIGURE 1 | Schematic overview of the neurocardiac feedback loop. Efferent information (blue arrows) emanates from cortical, subcortical, and brain stem structures of the central-autonomic network and flows to the sinoatrial (SA) node of the heart via the sympathetic and parasympathetic branches of the autonomic nervous system. Afferent information (red arrows) from the heart and blood vessels is conveyed back to the brain via baroreceptors located mainly in the walls of the aortic and carotid arteries. Afferent signals enter the brain (shaded in green) via the nucleus tractus solitarius in the brain stem and are integrated with other sensory, cognitive, and affective information as it ascends to cortical regions, including the medial frontal, cingulate, and insular cortices.

(7–9). Consideration of cardiovascular processes as embedded components of affect and cognition implies that these processes contribute to motivated human behavior, including behavioral flexibility toward alcohol and other drugs (10–12). This is important because several non-invasive, low-cost behavioral interventions that help normalize cardiovascular functioning have demonstrated efficacy across various mental and physical health conditions (13–20).

Two compelling qualities of the neurocardiac feedback loop for intervention development are its plasticity and responsivity to relatively simple behavioral interventions. Afferent stream activation of the neurocardiac feedback loop can be accomplished by manipulating peripheral functions, such as respiration and muscle flexion (21–24). Breathing paced at 6 breaths per minute (0.1 Hz) is slower and more rhythmical than typical breathing (12–20 breaths per minute). It creates resonance within the cardiovascular system by synchronizing cardiac oscillations driven by respiratory sinus arrhythmia (i.e., the phenomena of heart rate acceleration with inhalation and deceleration with exhalation) with cardiac oscillations driven by the baroreflex, which links heart rate acceleration/deceleration to corresponding changes in the blood pressure (21, 25). As shown in **Figure 2**, breathing at this frequency lowers systolic blood pressure, increases variability in the time intervals between R-spikes of the electrocardiogram (ECG) (i.e., heart rate variability), generates large oscillations in pulse transit time (i.e., vascular tone variability), and increases the sensitivity of heart rate to changes in blood pressure (i.e., baroreflex gain) (12, 21). A recent meta-analysis found that clinical interventions involving paced breathing at a resonance frequency of the cardiovascular system resulted in large effect size reductions in anxiety and stress (26). Preliminary evidence also suggested paced breathing may reduce craving for appetitive substances (27).

The brain structures of the central autonomic network that participate in cardiovascular signaling overlap considerably with those that process reward, emotion, and habit formation (28), including medial prefrontal, cingulate, and insular cortices, and amygdala. These structures also figure prominently in current translational models of putative addiction neurocircuitry (29–31), with the brain stem serving as the first point of neural integration of afferent autonomic and somatic signals from the body. Psychophysiological evidence suggests that the neurocardiac feedback loop may participate in substance use behaviors through its contribution to attention capture by stimulating cues, affective modulation, and relay of visceral reactivity to the brain [e.g., (32–36)], but little research has extended these findings to the neural structures that comprise the central autonomic network. Nonetheless, converging lines of evidence suggest that ineffective or maladaptive functioning of this feedback loop can set into motion a cascade of biological events that alter one's ability to adaptively modulate affect, arousal, and stress response (2, 37, 38).

Neural cue reactivity studies, wherein brain activation is measured while participants are exposed to salient alcohol- or drug-related cues, have received significant attention in the neuroscience and psychology of addiction literatures (39, 40). Cue reactivity studies typically compare within-person differences in

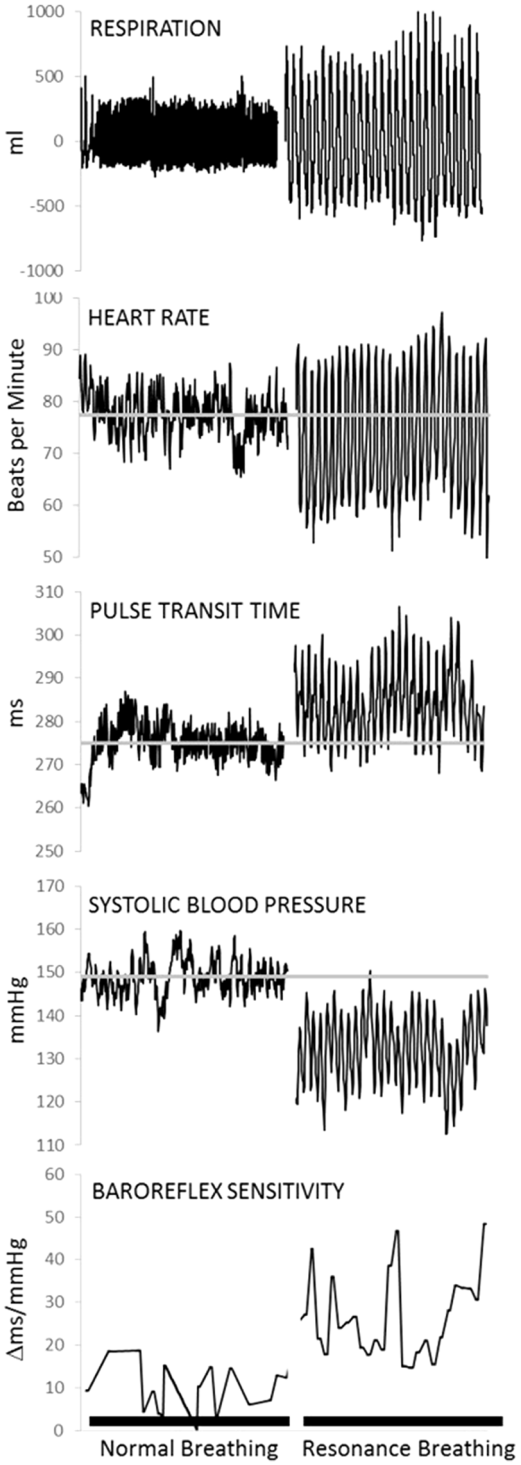

FIGURE 2 | Physiological data from one representative individual collected during a 5-min baseline task (normal breathing) and a 5-min resonance breathing task. Resonance breathing elicited instantaneous changes in respiration, heart rate, pulse transit time (i.e., vascular tone), systolic arterial pressure, and baroreflex sensitivity such that oscillations were magnified and more rhythmic across all measures. In addition, resonance breathing decreased systolic pressure, improved vascular tone, and increased the sensitivity of the neurocardiac feedback loop (i.e., baroreflex). Adapted from (12). Used with permission.

brain activation to alcohol or drug cues versus control cues (40). There is substantial evidence that elevated alcohol and drug cue neural reactivity is found in individuals with substance use disorders (40–42). Increased neural (43) and cardiac (44) cue reactivity also has been associated with increased drug craving (2, 37, 38). Experimental evidence suggests that heightened neural (45) and cardiovascular (46) reactivity to alcohol and drug cues is related to high risk substance use in non-clinical populations. Thus, altered reactivity to affective and appetitive stimuli appears to increase the likelihood that individuals will be susceptible to contextual influences on substance use, even following extended periods of abstinence (47, 48). This raises the question of whether behavioral interventions that enhance the efficiency of neurocardiac signaling might be used to alter neurocardiac activation to contextual challenges that promote substance use and relapse (49, 50).

This proof-of-concept study examined whether stimulating the afferent stream of the neurocardiac feedback loop with a 5-min course of resonance breathing can affect subsequent neural activation to visual alcohol cues. In contrast to cue reactivity paradigms that compare neural activation to alcohol versus control cues, this study examined within-person changes in neural response to alcohol cues at two points in time. We compared neural activation with unique sets of alcohol cues viewed prior to versus following the breathing task. Because this is the first study of its kind, there is no empirical literature to guide predictions about brain activation changes when participants are exposed to visual cues following resonance breathing. Based on the anatomy of the central autonomic network (4, 5) and drug cue salience networks (28, 40), we hypothesized that significant changes in activation may be observed in brainstem, medial prefrontal, cingulate, and insular cortices, as well as in the amygdala. We further allowed for the possibility of spreading activation, wherein structures within the central autonomic network that share additional network circuitry with regions outside the central autonomic network (e.g., the mesocorticolimbic circuit, ventral striatum) may exhibit activation changes as well. Significant changes in neural response were not anticipated in the group that viewed alcohol cues before and after completing a low-demand cognitive task.

METHODS

Participants

Forty-nine men and women, ages 18 to 25 years, were recruited at a large, northeast U.S. university and in the surrounding community through advertisements targeting alcohol drinkers. Initial inclusion criteria for all participants assessed via self-report were fluency in English, right-handedness, near 20/20 vision (corrected), and alcohol consumption at least once per month. Exclusion criteria assessed via self-report included: MRI contraindications (e.g., permanent metal in the body, claustrophobia), abnormal hearing, any serious medical condition (e.g., epilepsy, diabetes), cardiovascular problems (e.g., hypertension, heart murmur), current learning disability or attention difficulties, loss of consciousness for longer than 30 min, and, for women, pregnancy. To reduce heterogeneity related to psychiatric comorbidities and poly-substance use, lifetime diagnosis of a bipolar disorder or psychosis (e.g., schizophrenia, schizoaffective disorder), past year psychiatric/psychological treatment, past year cannabis use exceeding four times per month in the past year, other past year illicit drug use more than twice per month, past or current substance use treatment (including Alcoholics Anonymous/Narcotics Anonymous), and substance use during pregnancy on the part of the biological mother also were exclusionary.

Half of the participants were recruited based on meeting the National Institute on Alcohol Abuse and Alcoholism (NIAAA) "low risk" drinking criteria [i.e., no more than 5 drinks per day for men (4 drinks per day for women), no more than 14 drinks per week for men (7 drinks per week for women)], as well as an additional criterion of not binge drinking more than once in the past 6 months. The other half met DSM-IV-TR criteria (51) for alcohol dependence. This proof-of-concept examination of resonance breathing as a neurally active intervention included all participants with the exception that data from eight participants were excluded due to excessive motion in the scanner. The final sample (n = 41) had a mean age of 21.4 (SD = 1.9) years and was racially and ethnically diverse (27% Asian, 27% black/African American, 29% white, 17% other/multiple race; 11% Latino/a); 46% of the participants identified as female.

Procedures

Potential participants who gave verbal consent completed a telephone screening interview to determine initial eligibility. Eligible participants were asked to abstain from alcohol and drug use (except caffeine and nicotine) for 24 h prior to the experimental session. After screening, they were randomized into the active intervention (i.e., resonance breathing) or the control intervention (i.e., vanilla task), with drinking profiles being approximately equally distributed in both groups.

Upon arrival at the imaging center, participants provided written informed consent, supplied a breath sample to verify zero blood alcohol concentration, and completed a MRI safety screener and self-report questionnaires regarding alcohol use, mood state (Positive and Negative Affect Scale) (52), and stress (Perceived Stress Scale) (53). Basic physiological measures (e.g., temperature, blood pressure, weight) and a urine sample were collected; participants with a positive urine screen for cocaine, methamphetamine, opiates, and/or benzodiazepines (One Step Multi-Drug Screen Test Panel) were excluded. Participants with a positive urine screen for marijuana were asked additional follow-up questions about their drug use, and those with marijuana use exceeding four times per month were excluded. Women were screened for pregnancy using a standard urine dipstick. All participants were trained to use an MRI-compatible response box and to perform their assigned intervention task. Task training lasted approximately 2 min. Participants then were fitted with ECG sensors and a respiration belt and positioned in the scanner.

The overall paradigm (**Figure 3A**) involved four 5-min tasks: 1) viewing a set of nature picture cues, 2) viewing a set

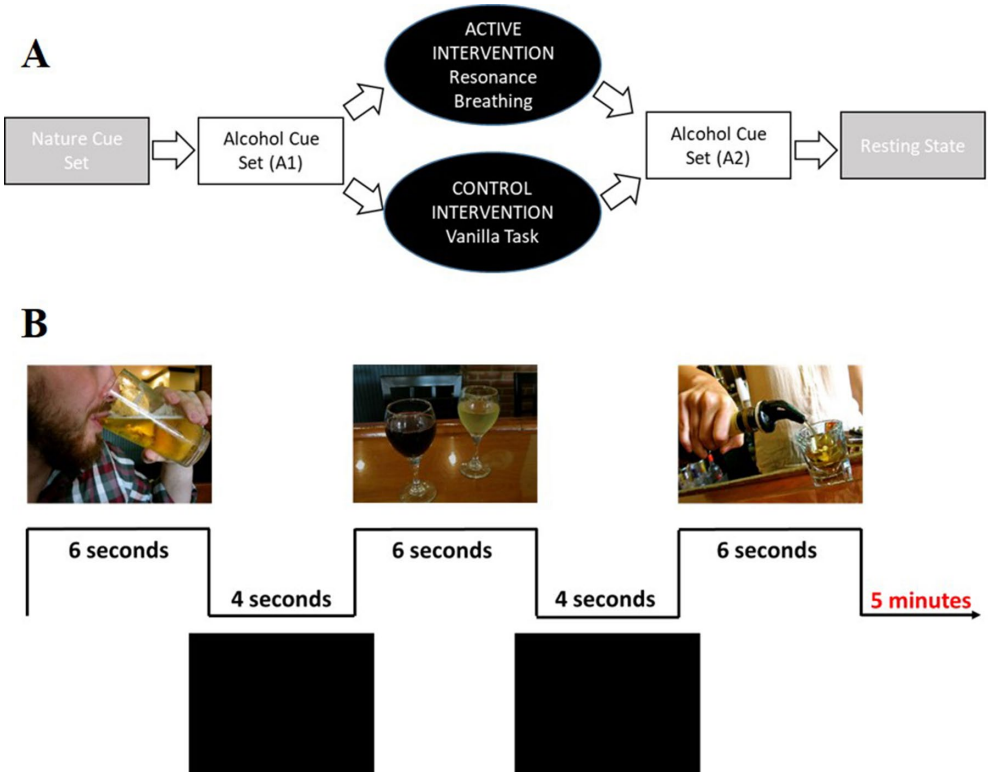

FIGURE 3 | Visual depiction of the study and cue task design. Panel **(A)** shows the complete study design. Participants first viewed a set of nature picture cues (data not shown). Participants then viewed a set of alcohol picture cues (A1), followed by a 5-min intervention task (active condition: resonance breathing; control condition: vanilla task). They then immediately viewed a second, distinct set of alcohol picture cues (A2). The study ended with a 6-min resting state task (data not shown). Panel **(B)** shows representative images from the alcohol cue tasks, both of which involved viewing 30 unique images that were presented for 6 s, with 4-s inter-stimulus intervals.

of alcohol picture cues (A1), 3) performing the intervention task, 4) viewing a second, distinct set of alcohol picture cues (A2); a 6-min resting state task was then performed. After each task, participants responded to the question, "How much are you currently craving alcohol right now?" using a track ball on a visual analogue scale (VAS, 43) anchored from "not at all" (0) to "extremely" (100). Stimulus cues were presented using E-Prime software (Psychology Software Tools Inc.). Images were projected onto a screen positioned at the rear of the scanner bore and viewed through a mirror attached to the head coil. A trigger pulse synchronized the start of each task with the E-Prime software. Total scan time was approximately 45 min.

Data from the two alcohol cue tasks (A1, A2) were analyzed in the present study. Each task included 30 unique images that were presented for 6 s with 4-s inter-stimulus intervals (**Figure 3B**), a design driven by the larger study's broader goal of characterizing the relationship between cardiovascular and neural reactivity. The alcohol cues were drawn from prior studies in our and others' laboratories (34, 54, 55). Each participant's self-reported preferred beverage (i.e., beer, wine, "straight" liquor, or mixed drinks) made up approximately 50% of the images to which they were exposed. Participants were instructed to pay attention to the images and to press a response box button when they saw an image that contained their preferred drink.

Between the A1 and A2 cue sets, participants in the active intervention (resonance breathing) synchronized their breathing with a visual pacer at the rate of 0.1 Hz (i.e., 6 breaths per minute). Compliance to the breathing task was verified via analysis of the respiratory signal. Time series respiratory frequency data were Fourier transformed, and the shape of the spectrum was visually inspected; all participants showed a respiratory peak at 0.1 Hz and spectral characteristics consistent with resonance breathing. Participants in the control intervention group completed a low-demand cognitive "vanilla" task wherein different colored rectangles were presented for 10 s each; they were instructed to silently count the number of blue rectangles (56).

After exiting the scanner, participants were compensated for their time. Those who met the criteria for alcohol dependence were given an informational brochure on alcohol use disorders and treatment options. This study was approved by the university's institutional review board for the protection of human subjects involved in research.

Imaging Parameters and Pre-Processing

Imaging data were collected using a 3T Siemens Trio scanner and 12-channel head coil. Standard localizer, anatomical, scout, and field map scans were collected. High-resolution anatomical

images were acquired using a T1-weighted MPRAGE protocol with parameters: repetition time (TR) = 1,900 ms, echo time (TE) = 2.51 ms, matrix = 256 × 256 voxels, field-of-view (FOV) = 256 mm, voxel size = 1 × 1 × 1 mm, 176 1-mm sagittal slices (.5 mm gap). Functional blood oxygen level-dependent (BOLD) data were acquired using single-shot gradient echo-planar imaging (EPI) sequences with parameters: TR = 2,000 ms, TE = 25 ms, flip, angle = 90°, matrix = 64 × 64 voxels, FOV = 192 mm, voxel size = 3 × 3 × 3 mm, 35 contiguous 3-mm sagittal slices (1 mm gap). ECG and respiration data were collected using a MRI-compatible BIOPAC acquisition system (Biopac Systems, Goleta, CA) as part of the larger study.

FSL 5.0.9 software was used to conduct image preprocessing and data analysis (FMIRB's Software Library, https://fsl.fmrib.ox.ac.uk). Non-brain tissue was removed from all anatomical and BOLD images using FSL's Brain Extraction Tool (BET, 57) by estimating each image's center of gravity and manually adjusting BET parameters as necessary until an optimal result was obtained. BOLD data were motion-corrected using FSL's MCFLIRT (58), and the output was reviewed to identify participants with excessive motion during the resting-state scan. Excessive motion was defined conservatively as mean absolute and/or relative displacement greater than .5 mm. A paired t-test was performed to compare mean framewise displacement between the randomized intervention groups. No significant differences were observed in motion between the groups ($p > 0.05$). BOLD images were segmented into gray matter, white matter (WM), and cerebral spinal fluid (CSF) using FSL's FAST (59). Probability maps of CSF and WM were derived, and time-series data for these signals were extracted from each participant. These nuisance parameters (i.e., WM, CSF) along with extended head motion parameters were used as covariates in the linear regression models implemented in FSL to decrease the effects of signals-of-no-interest. BOLD data were registered to standard space with a two-step process using FMRIB's Linear Image Registration Tool (FLIRT) (60). The data were first registered to the T1-weighted anatomical image and then to MNI-152 standard space using 9 degrees-of-freedom and SINC interpolation. All data were visually inspected for gross errors in registration. A high pass temporal filter was set to 50 s, and spatial smoothing was set to a 6-mm full-width at half-maximum Gaussian kernel.

Statistical Analyses

Analyses of the BOLD data from the A1 and A2 cue reactivity tasks were performed using a two-step process. Subject-level effects were calculated using first-level analyses in FSL's FEAT, and group effects were determined using higher-level analyses. In the first-level analysis, each alcohol image event was modeled and convolved with a double-gamma hemodynamic response function (HRF), and the mean task activation for A1 and A2 was calculated for each participant. In the higher-level analysis stage, two sets of analyses were performed using Randomise, the non-parametric permutation-testing tool implemented in FSL (61). First, one-sample *t*-tests were conducted to characterize neural activation in each intervention group before (A1) and after (A2) the intervention. Next, to examine intervention effects on neural activation to visual stimuli, paired *t*-tests with two contrasts were conducted on each intervention group (i.e., resonance breathing, control) separately (61). For each contrast, 5,000 permutations were calculated. One contrast (A1 > A2) was designed to determine brain areas that demonstrated greater activation pre- compared to post-intervention task, and the second contrast (A2 > A1) was designed to determine brain areas that demonstrated greater activation post-intervention compared to pre-intervention task. Threshold-free cluster enhancement was employed (62), and activation was considered significant at $p < 0.05$ (corrected for multiple comparisons using FSL Randomise).

A repeated-measures mixed model was used to assess the effect of resonance breathing on VAS craving scores. Craving data for one participant was missing due to equipment failure; thus, data from 40 participants were available for analysis. A between-subjects factor of intervention group (resonance breathing, control) and a within-subjects factor of craving scores following A1 and A2, as well as their interaction, were modeled. To examine the relationship between VAS craving scores and brain regions that exhibited significant pre-intervention to post-intervention changes, regions-of-interest (ROIs) were defined by creating 6-mm spheres around the peak voxel of each significant cluster of activation for the A1 > A2 and A2 > A1 contrasts. Mean activation values of these ROIs were extracted for each participant from the subject-level A1 and A2 cope images. Pearson correlations were then used to test the associations between ROI activation and VAS craving scores at A1 and A2. Point biserial correlations were used to examine the relationship of binary drinking status (low-risk = 0, alcohol dependent = 1) to ROI activation at A2 in the resonance breathing group. These analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC, USA).

RESULTS

Neuroimaging

Both intervention groups exhibited widespread neural activity in response to the visual alcohol cues, including in bilateral posterior parahippocampal gyri, temporal occipital fusiform cortices, lateral occipital cortices (inferior and superior divisions), postcentral gyri, and cerebellum at A1 and A2. The resonance breathing group (n = 22) additionally showed significant activation in bilateral inferior frontal gyri, left insula, left pallidum, left putamen, left amygdala, and left thalamus (A1, A2), and left precentral gyrus (A1). The control group (n = 19) additionally showed significant activation in the right thalamus (A1) and left precentral gyrus (A2). These results are shown in **Figure 4**.

Participants in the resonance breathing group demonstrated greater activation in response to alcohol cues pre-breathing compared with post-breathing (A1>A2) in left inferior and superior lateral occipital cortices and right inferior lateral occipital cortex, as well as bilateral occipital pole and temporal occipital fusiform cortices. They also demonstrated greater activation post-breathing compared with pre-breathing (A2 > A1) in

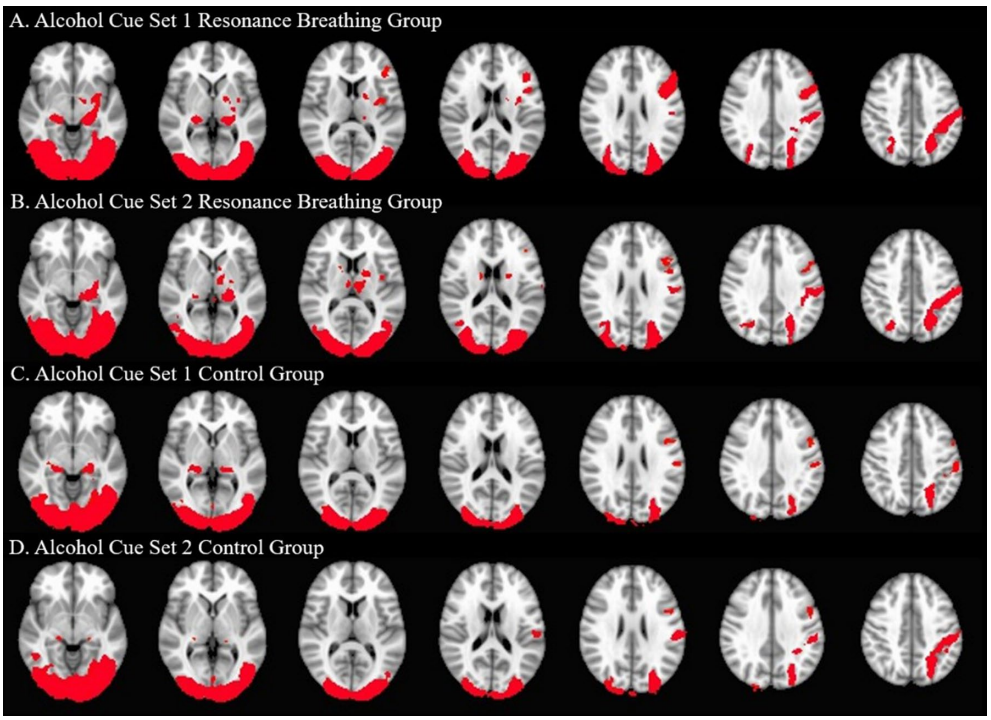

FIGURE 4 | Significant Neural Activation to Visual Alcohol Cue Sets. One-sample *t*-tests were used to identify areas of significant neural activation during alcohol cue set viewing. The neural responses of the active intervention (resonance breathing) group are shown in Panels **(A)** (A1 task, cues viewed prior to the intervention) and **(B)** (A2 task, cues viewed after the intervention). The neural responses of the control intervention (vanilla task) group are shown in Panels **(C)** (A1 task, cues viewed prior to the intervention) and **(D)** (A2 task, cues viewed after the intervention). Axial slices are shown in MNI standard space at z = −6 (first slice) and every fourth subsequent slice. Images are oriented using radiological convention. Areas of significant activation are shown in red.

voxels spanning precuneus cortex, posterior cingulate gyrus, and bilateral lingual gyri, as well as in medial prefrontal cortex (MPFC), paracingulate gyrus, and anterior cingulate cortex (ACC). These results are shown in **Table 1** and **Figure 5**.

The control group analysis yielded no significant activation in either the A1 > A2 or A2 > A1 contrasts, indicating that there were no statistically significant changes in brain activation in response to visual alcohol cues in the group that performed the control task.

Self-Report

Surveys administered prior to the neuroimaging session revealed that the sample as a whole had low-moderate perceived stress (mean ± standard deviation = 17 ± 6), and positive (mean ± standard deviation = 30.7±9.7) and negative (mean ± standard deviation = 13.9 ± 6.2) affect scores that were similar to those reported from the original general adult normative sample (52). There were no differences in affect or stress between the intervention groups nor between the drinking groups (all $p > .05$).

Craving was measured in the scanner after exposure to each cue block. The results of a repeated-measures (A1, A2) mixed model indicated that there was a significant main effect of group on craving, but no main effect of task (i.e., from pre- to post-intervention). Participants randomized to the resonance breathing intervention group reported lower levels

TABLE 1 | Anatomical location at peak voxel coordinates in significant clusters of activation in resonance breathing group.

A1>A2 Contrast					
		MNI Coordinates			
Cluster Size	**Z**	**x**	**y**	**z**	**Peak Voxel Anatomical Location**
2,433	6.80	−30	−96	10	Occipital pole (L)
1,339	6.95	28	−90	4	Occipital pole (R)
10	4.74	28	−38	−24	Temporal fusiform cortex (R)
A2>A1 Contrast					
		MNI Coordinates			
Cluster Size	**Z**	**x**	**y**	**z**	**Peak Voxel Anatomical Location**
2,141	7.81	2	−78	42	Precuneus Cortex
283	5.89	−2	50	0	Paracingulate Gyrus/ Medial Prefrontal Cortex
150	4.74	−16	−50	−2	Lingual Gyrus (L)
16	5.35	6	−24	40	Posterior Cingulate Cortex
15	4.44	2	−22	32	Posterior Cingulate Cortex
2	3.81	0	−56	10	Precuneus Cortex
1	6.87	−2	−6	36	Anterior Cingulate Cortex

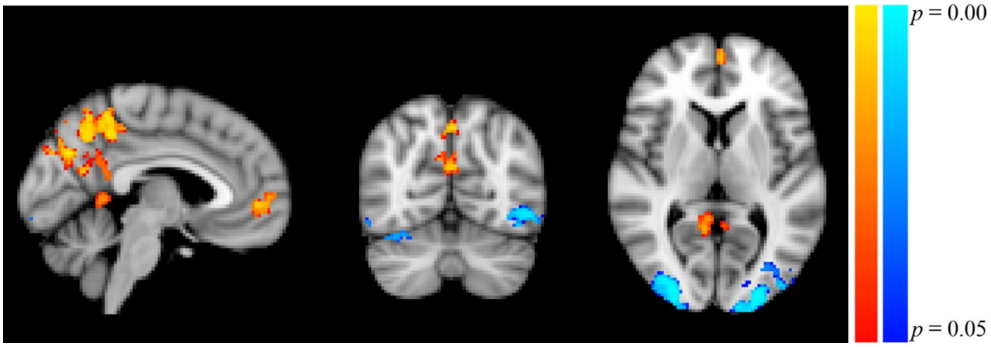

FIGURE 5 | Significant Clusters of Activation in Resonance Breathing Group. Blue-cyan clusters represent regions with greater activation during A1 compared to A2 (A1 > A2), and red-yellow clusters represent regions with greater activation during A2 compared with A1 (A2 > A1). Voxels were thresholded at $p < 0.05$. Image is shown in MNI standard space at x = −4, y = −66, z = 6, and oriented using radiological convention.

of in-the-moment craving compared to those randomized to the control intervention group [$F(76,1) = 5.76$, $p = 0.0188$; least square mean ± standard error of resonance breathing group = 28.1 ± 4.5 and of control group = 43.7 ± 4.7]. The group–task interaction was not statistically significant, suggesting that changes in subjective reports of craving pre- to post-intervention did not significantly differ between the two groups.

No significant correlations were observed at A1 between VAS craving scores and the ten cluster activation scores in the full sample (r range, −0.24 to 0.09, all $p > .05$). In addition, there were no significant correlations at A2 between craving scores and the ten cluster activation scores within either group (resonance breathing group r range, −0.32 to 0.28, all $p > .05$; control group r range, −0.42 to 0.44, all $p > .05$). Lastly, there were no significant correlations at A2 between drinking status (AUD vs. low risk) and the ten-cluster activation scores in the resonance breathing group (r range, −0.27 to 0.28, all $p > .05$).

DISCUSSION

Evidence that visceral afferent signaling influences stimulus processing argues for intervention development aimed at manipulating cardiovascular signals to alter detection and neural processing of affective stimuli (63). The results of the present study provide the first proof-of-concept evidence that a brief behavioral intervention of resonance breathing can significantly alter drinkers' neural activation to visual alcohol cues. The observed changes in brain activity included both decreases and increases in the activation of distinct brain regions.

In the group that performed resonance breathing between the visual cue tasks, but not in the control group, there was reduced activation in occipital regions from the first set of alcohol cues to the second, different set of alcohol cues. This pattern of results suggests that the breathing intervention prompted a subsequent decrease in visual cortex activation when individuals were confronted with alcohol-related visual stimuli. The specificity of these changes to alcohol-related content is unclear as this proof-of-concept study did not include a cue set of non-alcohol–related images presented before and after the intervention. Indeed, visual cortex activation to many types of images, including faces, is modulated by their emotional and social significance (64–66). Multiple lines of evidence also support the involvement of the visual cortex in appetitive cue processing. Several meta-analyses found that drug users consistently showed increased activation in occipital regions in response to drug-related cues compared to controls, even when non-visual drug-related stimuli were presented (41, 67–69). Increased visual cortex activation has been observed in individuals with behavioral addictions, such as pathological gambling, as well (70–72). Thus, although the literature suggests that the role of the visual cortex in alcohol and drug cue reactivity is not specific, decreased activation in the lateral occipital cortices following resonance breathing would be consistent with decreased perception, representation, and recognition of the images (73) and/or may potentially reflect less attention being directed toward the cues by the amygdala (66) or higher cortical areas (74).

In parallel with reduced visual processing of the cues, we observed increased activation in bilateral medial prefrontal, anterior and posterior cingulate, and precuneus cortices during the second alcohol cue task, only in the resonance breathing group. The ACC and MPFC, as regions of the central autonomic network, bi-directionally influence, and are influenced by, afferent cardiovascular signaling. Resonance breathing increases cardiovascular input to the brain via activation of brainstem nuclei that share connectivity with the ACC and MPFC (4) and are thought to give rise to the visceral experience of emotion (75). Functionally, the ACC is a part of the mesocorticolimbic circuit, which is thought to be involved in conflict monitoring and the regulation of cognitive and emotional processing by integrating input and modulating processing in other regions (76, 77). The MPFC is considered to be part of a cognitive control system in the brain that promotes goal-directed behaviors (78) by using incoming information to predict the most adaptive response based on past experience (79).

Hypothetically, increased activation of MPFC and ACC in response to alcohol cues following the breathing intervention would be consistent with heightened internal monitoring of cognitive-emotional state and enhanced cognitive control. At the same time, some studies have identified these regions as sites of

heightened reactivity to alcohol and other drug cues (42), and heightened reactivity in these regions has been related to post-treatment drinking and relapse, although the results in this area have not been consistent (80). Thus, it is unclear whether or under what circumstances these and other brain regions accentuate or restrain cue-elicited craving and substance use behaviors. Evidence for individual differences in brain areas most reactive to appetitive cues (42) and inconsistencies in replication add further complication to interpretation. More nuanced examination of intra-individual changes in neural activation across brain areas, and perhaps also across simultaneously operating psychological and physiological systems involved in motivated behavior, are needed.

The posterior cingulate cortex (PCC) and the precuneus showed increased activation to visual alcohol cues following the breathing intervention, but not the control task. Both of these regions are considered core nodes of the default mode network, a functional brain network involved in self-referential thought and mind-wandering (81) that shows preserved connectivity during cognitive load (82). The lingual gyrus, a brain region involved in visual encoding and higher-order analysis of complex visual stimuli (83), also showed increased activation only in the resonance breathing group. This gyrus has been implicated in spontaneous thought and often co-activates with the default mode network (84). Whether increased activation in these regions potentially plays a role in promoting self-regulation in response to alcohol or other affectively valenced cues is unknown, but warrants further investigation. One possibility is that following resonance breathing the brain reverts to its "baseline" resting state (85) for some amount of time despite activation by salient cues, rather than transitioning to a heightened state of arousal.

We did not observe acute changes in self-reported craving levels in the resonance breathing group following the second presentation of alcohol cues (absence of significant cue task by group interaction), nor were craving levels related to brain clusters of activation in response to cues at A1 or A2. Several factors likely contributed to these null findings. Randomization into resonance breathing and control groups in the present study did not result in equivalent mean craving rating scores; the resonance breathing group reported significantly lower craving levels throughout the study. Failures of randomization in small samples are common (86), and future studies may benefit from selecting participants with high levels of self-reported craving and/or matching on craving levels across intervention groups. It may also be that the brief 5-min duration of resonance breathing did not affect conscious self-estimates of craving in the present sample, or that resonance breathing works in a way that affects a different pathway, such as the operation of cue salience (50), rather than consciously experienced craving levels. The present data are limited in not speaking to these alternative speculations.

Implications for Clinical Translation

If replicated and extended, the current findings that a brief, 5-min bout of resonance breathing changed neural activation in brain areas implicated in affective and appetitive stimulus processing could have clinical implications for individuals who show elevated neural reactivity in response to appetitive cues (44). Resonance breathing is the active mechanism of heart rate variability biofeedback, an empirically supported behavioral intervention for disorders with core features of affective and emotional dysregulation (13, 14, 17, 26) including alcohol use disorders (44, 87, 88). Emerging evidence suggests that heart rate variability biofeedback and paced breathing interventions reduce self-reported craving for alcohol and other appetitive stimuli, such as food (27, 89). While standard heart rate variability biofeedback delivery protocols include five to ten 1-h sessions and home practice (90, 91), resonance breathing itself produces immediate physiological effects (see **Figure 2**). This proof-of-concept study was novel in examining whether resonance breathing also elicits immediate neural effects. The findings provide an initial step in validating resonance breathing as an in-the-moment behavioral tool that potentially could be used ad lib in the natural environment to alter neural activation, both before and during contexts of heightened risk for substance use. Accessible smart phone applications are available to self-administer resonance breathing and HRV biofeedback, suggesting promise for a scalable intervention tool if future research is successful in demonstrating that such effects are linked to reduced alcohol and drug use behaviors.

Limitations and Directions for Future Research

As a proof-of-concept study, these findings should be interpreted with caution and used for the generation of future hypotheses regarding the effects of resonance breathing on neural activation to alcohol-related visual stimuli, behavioral correlates of alcohol use such as in-the-moment craving, and actual use behaviors. Importantly, the changes observed in neural activation to the cues following the resonance breathing intervention should not be considered specific to alcohol-cue reactivity, as this study did not include a comparison condition of matched, non-alcohol cues presented before and after the intervention. This study also was limited in not being sufficiently powered to examine sensitively the relation of individual differences in alcohol use behaviors to changes in neural activation following resonance breathing. We note that the cue presentation paradigm of the present study was designed in line with the goal of better understanding afferent cardiovascular input to neural reactivity and thus was not typical of those used in many other fMRI studies of cue reactivity. A recent meta-analysis found that cue paradigm and type did not significantly influence neural response patterns associated with cue reactivity however (28), suggesting the fMRI assessment of neural activation is robust to multiple cue presentation approaches. Future studies should include larger samples to link current and chronic substance use behaviors to cue reactivity, and a design that counterbalances and compares neural response to alcohol-related and non-alcoholic beverage cues. Specificity may be addressed also by comparisons to non-alcohol or drug-related, yet positive or negative affectively valenced, visual cue sets.

Conclusion

In summary, this study presents preliminary evidence that individuals ranging in drinking behaviors from low-risk to alcohol-dependent may be less visually engaged by alcohol cues and initiate greater top-down cognitive processing of cues following resonance breathing. This is consistent with the broader literature on resonance breathing that shows it normalizes neurocardiac feedback and improves autonomic nervous system regulation (25). Moreover, it points to a potential neural foundation for the effects of resonance breathing and adds to the scientific premise for the use of heart rate variability biofeedback as an intervention for brain-based mental and physical health conditions. More highly powered studies are needed to replicate and extend these neural activation results. Critical next steps are to understand how the cardiovascular and neural changes elicited by resonance breathing are linked to changes in the subjective experience of craving and alcohol use behaviors.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the National Institutes of Health guidelines for ethical treatment of human subjects with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Rutgers University Arts and Sciences Institutional Review Board for the Protection of Human Subjects Involved in Research.

AUTHOR CONTRIBUTIONS

MB and JB designed the study. MB and LL wrote the first draft of the article. All authors contributed to writing sections of the manuscript. LL and SU collected all data. LL and SU post-processed the imaging data. LL, SU, and SG performed the data analyses. All authors read and approved the final manuscript.

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SYSTEMATIC REVIEW
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The Interplay of Inflammatory Processes and Cognition in Alcohol Use Disorders—A Systematic Review

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Rationale: Of late, evidence emerges that the pathophysiology of psychiatric diseases and their affiliated symptomatologies are at least partly contributable to inflammatory processes. Also in alcohol use disorders (AUD), this interaction is strongly apparent, with severely immunogenic liver cirrhosis being one of the most critical sequelae of chronic abusive drinking. This somatic immune system activation negatively impacts brain functioning, and additionally, alcohol abuse appears to have a direct detrimental effect on the brain by actively stimulating its immune cells and responses. As cognitive decline majorly contributes to AUD's debility, it is important to know to what extent impairment of cognitive functioning is due to these (neuro-)inflammatory aberrations.

Method: We hereby summarize the current existing literature on the interplay between AUD, inflammation, and cognition in a systematic review according to the PRISMA-P guidelines for the systematic review.

Main findings: Although literature on the role of inflammation in alcohol use-related cognitive deficiency remains scarce, current findings indicate that pro-inflammatory processes indeed result in exacerbation of several domains of cognitive deterioration. Interestingly, microglia, the immune cells of the brain, appear to exert initial compensatory neuroprotective functionalities upon acute ethanol exposure while chronic alcohol intake seems to attenuate these responses and overall microglial activity.

Conclusion: As these results indicate inflammation to be of importance in cognitive impairment following alcohol consumption and might as such provide alternate therapeutic avenues, a considerable increase in research efforts in this domain is urgently required.

Keywords: inflammation, alcohol use disorder, cognition, alcohol addiction, psychiatry

INTRODUCTION

Alcohol is the most commonly (ab)used substance worldwide with high-risk drinking occurring in up to 30% in Western populations (1). On a global scale, the WHO estimates the prevalence of alcohol use disorder (AUD) to be as high as 16% (WHO, 2004[1]) being equally present across almost all sociodemographic classes (1) WHO, 2004). Both excessive alcohol use and AUD have a profound (public) health impact as they strongly increase morbidity and mortality through inducing cardiovascular diseases, hypertension, diabetes, liver cirrhosis, and many other somatic comorbidities (1).

AUD is associated to different cognitive deficits, such as abnormalities in working memory, attention, and executive functions like response inhibition (2). As thoroughly investigated in a meta-analysis by Stavro et al. (3), these deficits remain considerable in the first 12 months of sobriety but improve after 1 year of abstinence. Nonetheless, they impact decision making in patients and thus interfere with readiness to change drinking behavior and the ability to attain abstinence (4). Moreover, poorer cognitive functioning predicts increased relapse risk over a 12-month follow-up period (5).

The specific etiopathogenesis of these AUD-related cognitive impairments is rather complex, as it may be an inherent pre-morbid trait vulnerability, but may also result from alcohol-related brain damage (ARBD). As alcohol has major neurotoxic effects, its abuse is related to mild brain atrophy that seems mostly driven by white matter loss and changes in cortical neuronal dendritic arborization (6). ARBD can either be the consequence of a direct molecular impact of the substance on the brain and/or may result from impaired liver functioning, malnutrition (vitamin B1 deficiency), and risk-taking behavior potentially associated with head injury (7). As such, cognitive alterations in AUD patients result from central as well as peripheral abnormalities (7, 8). Nonetheless, Davies et al. (9) demonstrated in a sample of abstinent (750 days) alcohol-dependent subjects without any hepatic, neurological, or other somatic impairments that deficit in visuospatial scanning, verbal memory, and processing speed were still present. These findings suggest enduring, alcohol-induced cognitive impairments. However, it should be noted that it is very likely that these cognitive impairments can both be the result of chronic alcohol use but can also reflect pre-existing cognitive impairments underlying vulnerabilities for escalating alcohol use and subsequent development of AUD. Parsons' (10) analysis of previous studies on the relationship between alcohol consumption and cognitive deficits showed that increase in alcohol use resulted in more pronounced cognitive impairments, suggestive of a dose–response relation. Finally and most importantly, evidence is growing that not only alcohol use but also alcohol withdrawal is a neurotoxic process. Repeated detoxifications have been associated with progressive cognitive decline and impairments (11). With regard to the underlying processes responsible for the many cognition-related dysfunctions following alcohol abuse, cerebral edema, neuronal cell loss, and dysfunction of the blood–brain barrier (BBB) have been demonstrated in the brain of deceased AUD patients (12). These physiological abnormalities have further been linked to a higher concentration of CNS ammonia, mitochondrial damage, and oxidative stress caused by increased levels of reactive oxygen species (ROS) in relevant brain regions (13–15). Recently, also neuroinflammation gains more attention as to playing a role in the above neurodetrimental effects. In the last few years, neuroinflammation has been associated to cognitive decline in several pathological situations, including old age (16, 17), Alzheimer's disease (18), schizophrenia (De Picker et al., 2018, submitted), and bipolar disorder (Van den Ameele et al., submitted). Also in AUD patients, increasing evidence points toward an aberrantly activated immune system. Excessive production of cytokines and chemokines and altered activation of microglial cells—the immune cells of the brain—have been documented in both acute and chronic phases of AUD (7, 8).

As changes in immune system activation may result in cytotoxic effects, thereby impacting neurotransmission, neuroendocrine function, and neural plasticity (19, 20), neuroinflammation presumably also at least partly contributes to cognitive deficits linked to alcohol exposure.

These findings are supported by animal studies linking inflammation to alcohol disorders and related cognitive dysfunctioning. For instance, elevated levels of the pro-inflammatory cytokines interleukin 6 (IL-6), IL-1b, and tumor necrosis factor alfa (TNF-a) have been found in the rodent brain after chronic alcohol consumption (21, 22).

Moreover, Marshall et al. (23) demonstrated (chronic) ethanol exposure in the rat to activate microglia, the brain's most prominent immune cells, and to induce a 26% increase in anti-inflammatory cytokine IL-10 and an even larger increase (38%) in the neurotrophic factor transforming growth factor beta (TGF-b1) up to 7 days after exposure. Finally, the cellular and molecular immune system alterations induced by ethanol consumption are primarily found in the prefrontal cortex and the hippocampus of the rats; these brain regions are known to play a substantial role in several cognitive functions like memory and executive functioning (24, 25).

With this systematic review, we document the influence of AUD-related inflammation on decreased cognitive functioning observed in AUD patients.

METHOD

This systematic review was conducted and reported according to the PRISMA-P (preferred reporting items for systematic review and meta-analysis protocols) guideline (26). We aimed to investigate all types of cognitive aberrations in individuals consuming any amount of alcohol units provided that the study discussed any type of inflammatory mediation in relation to cognition. In order to obtain original studies investigating the impact of the immune system on cognitive functioning of alcohol use and AUD, a PubMed search (January 1946–October 2018) for English language articles was conducted using the following search terms: (alcohol* OR ethyl* OR ethanol) AND (cognit* OR attention OR memory OR "executive function*") AND (immun* OR microglia* OR

[1] http://www.who.int/gho/substance_abuse/burden/alcohol_prevalence/en/

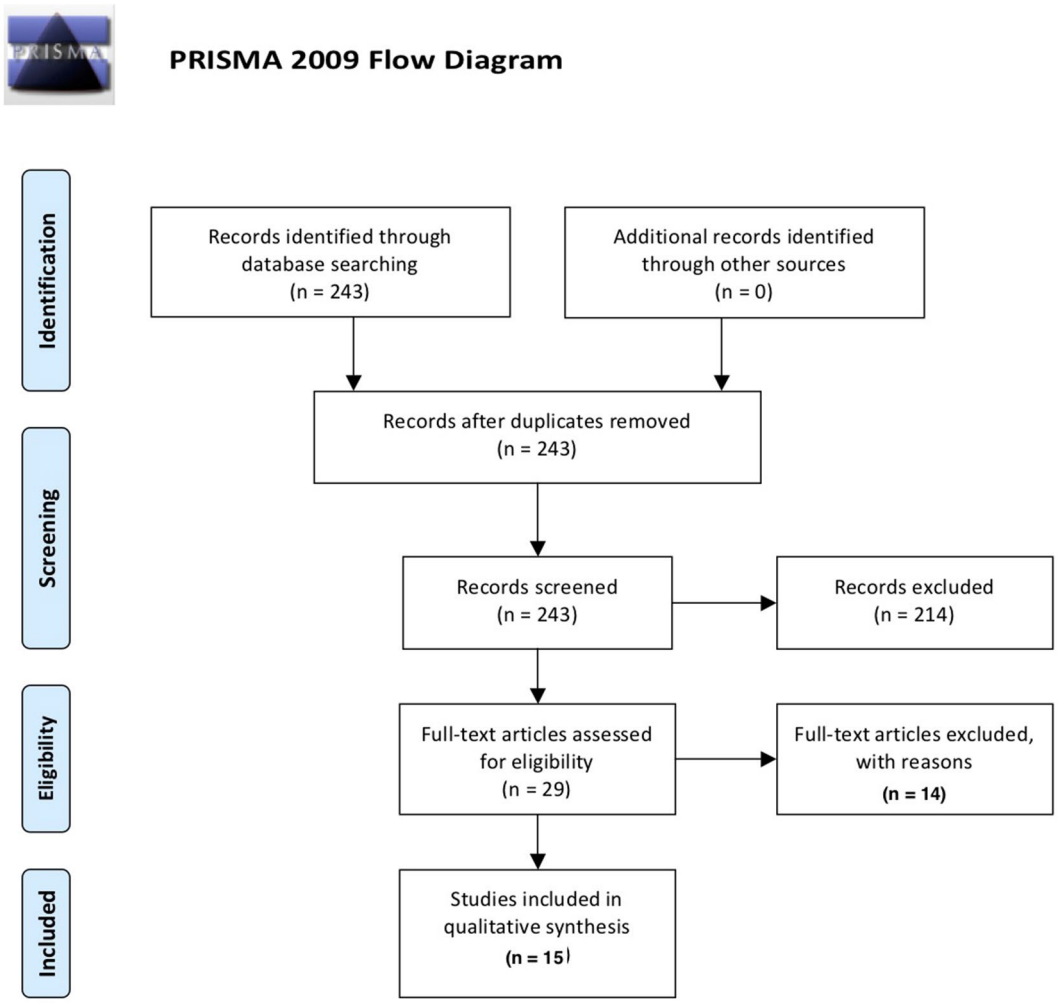

FIGURE 1 | Overview of the selection process of included papers according to PRISMA guidelines (26).

inflamm* OR cytokine* OR kynuren*) NOT review[publication type] AND english[language]. The papers were filtered for human studies exclusively. An overview of the inclusion process can be found in **Figure 1**. Briefly, the above PubMed search yielded 243 results; abstract screening led to exclusion of 214 papers, leaving 29 papers that were read entirely. Of these, 16 manuscripts were deemed eligible for inclusion in the review. Of the 14 papers excluded after full-text analysis, 6 were excluded based on the absence of statistical analyses of the effect ethyl had on cognition/inflammation; 3 studies were not performed in humans; 3 studies did not concern the interaction between the immune system and cognition; 1 paper did not concern alcohol consumption; and 1 paper did not concern cognition.

Of note, the latest edition of DSM (V) refers to the disorder of being dependent on alcohol consumption as "alcohol use disorder, AUD." However, this terminology is rather recent, and literature predating this overarching term mostly refers to this or similar conditions with "alcohol dependence" or related expressions. In order to avoid rephrasing bias in this work, we opted to retain the terminology as applied in the original paper. As such, terminology applied throughout this review remains somewhat heterogeneous in its definition of alcohol consumption disorders.

RESULTS

The PubMed database search resulted in an initial 243 records. Following removal of duplicates and screening of abstracts for relevance, 28 records remained. Eligibility of these 28 records was assessed by detailed evaluation of the full texts. Eight papers were deemed not relevant, and three papers concerned preclinical research, resulting in a final selection of 17 papers included in the current review.

Relation Between the Immune System and Cognitive Functioning

Alcohol abuse has been associated with cognitive impairment in humans, mainly by deleterious effects on memory function and on executive functions including cognitive flexibility and response inhibition (27). In addition, preclinical findings link ethanol consumption to altered immune signaling and to

decreased cognitive capabilities (24, 25). Also in humans, a three-way interaction between an affected immune system, alcohol use, and cognitive decline has been suggested: Miguez-Burbano et al. (28) showed that memory functioning is more severely decreased in alcohol abusing HIV-infected individuals compared to sober HIV-infected peers. Hazardous alcohol consumption was related to thymus size, and the authors suggested that the negative impact of alcohol on thymus volume was the mediating mechanism underlying impaired cognitive performance (28).

The Association Between Alcohol Consumption, Dysregulated Cytokines, and Cognitive Functioning

In a large group of alcohol-dependent male patients (n = 78), Yen et al. (29) looked for associations between plasma cytokine concentrations and cognitive functioning. They showed that, at the start of the withdrawal period, patients display elevation of all investigated cytokines [TNF-alpha (TNF-α), interferon gamma (IFN-γ), interleukin 1 (IL-1), IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, and granulocyte-macrophage colony-stimulating factor (GM-CSF)]. Although the patients displayed reduced information processing speed, these abnormalities did not correlate with cytokine levels. Nonetheless, cognitive dysfunctioning improved after 4 weeks of abstinence, which was mirrored by normalization of the cytokine levels. Felipo et al. (17) did demonstrate peripheral levels of IL-6, together with hyperammonemia, to be a driving factor for cognitive impairment, as assessed by a series of tasks addressing psychomotor and processing speed. In this line, Hanak et al. (2) recently investigated the impact of alcohol detoxification on IL-6 in a small group of patients with AUD (n = 27). They showed that when craving is caused by stress, but not when caused by alcohol or mood, IL-6 decreases after 3 weeks of detoxification. Given the small sample size in each group (n = 5) and the suboptimal statistical analysis strategies used (lack of *post hoc* exploratory analyses), these findings need to be confirmed approached with caution. The authors also aimed to find associations with cognitive functioning, and in line with the findings of Felipo et al. (17) results pointed toward more pronounced working memory deficits in the subgroup with highest levels of IL-6. Here again, methodological problems hamper interpretability. These findings thus corroborate with the previous finding that pro-inflammatory cytokines are correlated to craving in alcohol-dependent individuals (n = 52) (30). Moreover, reductions in selective attention as assessed by a self-developed validated computerized task appeared to be inversely related to the anti-inflammatory cytokine IL-10 after 3 weeks of abstinence, suggesting that reductions in protective levels of anti-inflammatory markers may lead to cognitive impairments.

Wilhelm et al. (31) investigated plasma levels of the pro-inflammatory compound tissue inhibitor of metalloproteinases (TIMP-1) and found them to be associated to self-reported memory complaints in a small sample of female (but not male) alcohol-dependent patients.

More indirect findings come from Duivis et al. (32), who demonstrated that cognitive symptoms of depression and anxiety like negative emotional state, concentration/decision making capacity, thoughts of death or suïcide,… correlate with several peripheral markers of inflammation (namely, higher levels of CRP, IL-6, and TNF-α). Interestingly, when controlling for several lifestyle factors including alcohol use, these correlations disappeared, suggesting that, at least partially, alcohol consumption mediates inflammation-associated cognitive deficiencies.

Boyer et al. (33) found a weak correlation between alcohol abuse in schizophrenic patients and cognitive dysfunctioning (mainly attention), but this was not associated to plasma CRP concentrations.

Although only a handful of studies looked into the associations between cytokines and cognitive dysfunctioning in alcohol-dependent patients, early results suggest impairments (in several cognitive domains including attention, processing speed, and memory) are associate to increases in pro-inflammatory markers and reductions in anti-inflammatory cytokines. Alcohol abstinence may partially remediate some of these deficits as mirrored by normalization of cytokines.

The Association Between Alcohol Consumption, Altered Glial Cells, and Cognitive Dysfunctioning

Kalk et al. (34) recently investigated microglial activation *via* PET tracer imaging in newly abstinent (< 1 month) alcohol-dependent patients (n = 9). In contrast to their expectations, they found less microglial activation than healthy controls, which they suggested to be the result of a potential loss of microglia cells. Although microglia appeared to be less activated in patients, tracer binding strongly correlated with delayed verbal memory, pointing toward poor memory performance in those patients with low microglia activation. This would intuitively contrast with the report of Marshall et al. (23), who showed increased PET tracer binding/microglial activation after acute 4-day ethanol administration in rats. However, both findings can be reconciled by indications from Marshall's study suggesting that activated microglia adopt a neuroprotective (the so-called *M2 phenotype*) rather than a neurotoxic (M1) profile in response to ethanol and that chronic alcohol abuse decreases the number of these safeguarders.

The literature investigating the impact of alcohol use and abstinence on glial activation patterns and their functionality is too scarce to be informative. However, the little preliminary data that are available suggest this to be a research avenue of interest for future studies focusing on the role of inflammation on cognitive deterioration by alcohol use.

The Role of the Gastrointestinal System and Liver Pathologies in Inflammation and Cognitive Dysfunction in Alcohol Disorders

Many of the articles included in this review pointed toward an important role of the liver function and gut permeability and its relation with alcohol (ab) use and subsequent inflammatory processes.

Alcohol use has well known pathological effects on the liver; as such, alcoholic liver disease (ALD) is the most prevalent

type of chronic liver disease worldwide. ALD is accompanied by an inflammatory presentation characterized by increases in pro-inflammatory cytokines and chemokines (35, 36). Alcohol dependence has also been associated with a leaky gut, resulting in increased permeability, which has been associated to increases in plasma lipopolysaccharides (LPS) levels, which in their turn are known to have a proinflammatory stimulating nature. These gut abnormalities and associated LPS increases normalized after a 3-week abstinence period (30). The neuroinflammation described in patients with AUD therefore results from both direct proinflammatory effects of alcohol on the brain and indirect immunological damage *via* the liver (7, 8).

Hepatic encephalopathy (HE) implies the deterioration of brain functioning arising from acute and chronic liver failure as a result of chronic alcohol abuse (7, 37). This may result in cognitive symptoms such as deficitary judgment, memory impairment, and confusion. Excess brain ammonia levels have been put forward as a strong leading factor, although *postmortem* findings suggest that a pro-inflammatory state, abnormal astrocyte, and microglial activation also seem to be involved (7, 37, 38). Dennis et al. (7) showed that HE is associated to increases in cortical IL-6 levels compared to controls or non-HE alcoholic patients, which was partly associated to microglial proliferation and activation in neuroplasticity associated brain regions (including the subventricular zone). This proinflammatory, cytotoxic environment was reflected in reduced neuronal cell counts (7). Cagnin et al. (39) investigated PK11195-binding, reflecting activated glial cells (microglia and astrocytes), in a very small sample (n = 5) of patients with HE (three of which were alcohol-induced), and found significant increases in glial activation, especially in pallidum, right putamen, and right DLPFC. Of note, the patients with the most severe cognitive impairment had the highest increases in tracer binding (including two of the alcohol-induced HE).

HE has also been shown to increase plasma IL-6 levels (40), but it should be noted that it is not clear to what extent IL-6 is able to pass the blood–brain barrier in normal physiological conditions and in HE brains (7, 41).

Furthermore, the cognitive impairments inversely related to levels of the anti-inflammatory cytokine IL-10 in AD patients as described by Leclercq et al. (30) appeared to be partly associated to increased intestinal permeability.

So, although associations between alcohol-induced immune dysregulations and cognitive dysfunctioning in the absence of liver pathology have been shown, affected liver functioning may further fuel a pro-inflammatory state peripherally and in the CNS, thereby negatively impacting cognitive functioning in AUD patients.

DISCUSSION

The current body of evidence suggests that acute exposure to alcohol leads to an anti-inflammatory response of the immune system (42), while chronic exposure seems to be associated more to pro-inflammatory reactions that remain present during abstinence (30). This seems to point toward an initial protective or homeostatic response of the central immune system to alcohol, whereas chronic alcohol consumption rather induces damaging pro-inflammatory states as reflected by elevation of pro-inflammatory signaling molecules (30, 43). Few studies looked into the associations between immune markers and cognitive dysfunctioning in AUD patients, and while these findings suggest that cognitive impairments (including deficits in attention, processing speed, and memory) are associated to increases in pro-inflammatory markers and reductions in anti-inflammatory cytokines, these findings are rather modest and even contradictory in nature. For example, while Cagnin et al. (38, 39) demonstrated *via* PET imaging an increase in glial cell activation in patients with HE, Kalk et al. (34) found the opposite to be true in newly abstinent alcohol-dependent patients. These discrepant findings might be allocated to the differing pathologies but might also reflect technological variability as the tracer used by Kalk et al. (34) is thought to be more specific for microglia, while that of Cagnin et al. (39) rather binds to all glial cell types in equal proportions. An overview of the findings on the interplay between inflammatory processes, ethanol exposure, and cognitive effects can be found in **Table 1**.

A hypothetical mechanistic link between neuroinflammation and cognitive decline in AUD might stem from the tryptophan catabolism (TRYCAT) pathway. This inflammatory degradation process catabolizes the essential amino acid tryptophan to kynurenine and its metabolites. It mainly occurs in microglia and astrocytes and is activated by pro-inflammatory cytokines (44). Several receptors of neuroactive kynurenine metabolites have been associated to cognitive functioning (45) (Van den Ameele et al., 2018, submitted) and might as such be of hypothetical interest to further explore the relationship between inflammation and cognitive functioning in AUD. A single study investigated the impact of retrospectively established alcohol use before, during, and after pregnancy in mothers on the cytokine and kynurenine levels in children with ADHD (mean age 10.4 +/−2.5 years), but no associations between kynurenine levels in the children on one hand and alcohol use on the other was found (46). Sadly, potential effects or correlations in the mother were not scrutinized, and no additional studies exist so far assessing the potential interaction between kynurenine and/or other TRYCAT metabolites in patients with AUD.

The relationship between immune dysregulation and cognitive deficits in AUD patients seems to be further modulated by hepatic and alcohol use–induced gastro-intestinal pathologies (38, 39), although a direct effect of alcohol on the brain will additionally contribute to this interaction. Further research should elucidate the complex interaction of alcohol use, its central and peripheral effects driving immune dysregulations, and these accumulating effects on cognitive deficits in AUD patients. Moreover, it should be investigated to what extent these effects remain after abstinence, and more importantly, to what extent immune regulatory treatment options may be protective toward cognitive functions or remediate already existing cognitive deficits in chronic users. Finally, future studies need to look into the role of potential confounding or mediating factors. First, chronic tobacco smoking has been on itself related with neuro-inflammatory processes (47). About 60% of

TABLE 1 | Overview of the current literature on the interplay between inflammatory processes, ethanol exposure, and cognitive effects (NM = not mentioned in publication).

Clinical findings				
Reference	**Patient population**	**State of ethanol exposure**	**Type of inflammatory response**	**Effect on cognition**
(29)	Alcohol dependence	Early withdrawal	↑ Pro-inflammatory cytokines in peripheral blood	Reduced information processing speed
		4w abstinence	Normalization of cytokine levels	Improvement in cognitive dysfunctioning
(17)	Liver cirrhosis	NM	↑ Pro-inflammatory cytokines in peripheral blood	Reduced psychomotor and processing speed
(2)	AUD	Alcohol detoxification	↑ Pro-inflammatory cytokines in peripheral blood	Increased working memory deficits
(30)	Alcohol dependence	3-week abstinence	↑ Anti-inflammatory cytokines in peripheral blood	Reduction in selective attention
(31)	Alcohol-dependent women	Current alcohol dependence	↑ Pro-inflammatory TIMP-1	Association with memory complaints
(32)	Depression and anxiety	Alcohol use	↑ Pro-inflammatory cytokines in peripheral blood	Cognitive deficiencies
(33)	Schizophrenia	Alcohol abuse	Pro-inflammatory acute phase protein CRP	No association with attention
(34)	Alcohol dependence	Early abstinence	↓ Microglial activation	Delayed verbal memory
(39)	Cirrhosis	NM	↑ Microglial activation	More severe cognitive impairment
Post-mortem findings				
Reference	**Patient population**	**State of ethanol exposure**	**Type of inflammatory response**	**Effect on brain**
(7)	Hepatic encephalopathy (HE)	Chronic alcohol abuse	↑ Cerebral pro-inflammatory cytokines ↑ Microglial proliferation and activation	Reduced neuronal cell counts

↑, *Increased;* ↓, *Decreased.*

alcohol-dependent individuals are also lifetime (heavy) smokers (48). So, the role of tobacco smoking needs to be differentiated from that of alcohol. Second, comorbidity between AUD and other mental disorders is highly prevalent. Often, these mental disorders themselves are associated with cognitive decline and neuroinflammation. For example, the prevalence of affective disorders in AUD is estimated to be 22.9% (49). Next, the most important metabolite of alcohol, acetaldehyde, has been implicated within inflammatory processes, gut permeability, and liver disease (50, 51). Alcohol metabolization is strongly influenced by genetic differences in acetaldehyde dehydrogenase activity, leaving individuals significant differences in alcohol metabolization (and acetaldehyde accumulation) between individuals and different ethnic groups. These genetic difference may represent an important aspect of the alcohol X inflammation X cognition three-way interaction.

Although we attempted to reflect on the existing literature as accurately as possible, this review contains several study- and review design–inherent limitations.

First, the DSM-V categorizes all alcohol-related disorders under the same flag of "AUD." However, as some literature described in this review predates this novel classification, investigated populations over the included studies are often differentially defined. As such, this literature overview might encompass a heterogeneous population with differing levels of alcohol abuse as papers scrutinize "alcohol dependence" or "chronic alcohol abuse" while data were piled in this work as hallmarking the whole of AUD. Second, in addition to "classical" cognitive functions like working memory and processing speed, alcohol dependence is dependent on more complex cognitive reasonings like the sociocognitive ability to infer other's thoughts (theory of mind). Although we did not ambition to exclude papers on the relation of inflammation with these more complex cognitions, no works were found on this topic. Likewise, although extensive literature is available on the considerable role of different domains of cognitive impairment on patient prognosis, therapeutic outcome, relapse rate,… [for review see Ref. (52)], no reports are available on the role of inflammation in AUD prognosis and outcome. As such, these relevant areas of interest remain a lacunae in this review as well. Additionally, we did not take into account potential differences in the amount of ethyl units consumed. However, we can expect the interaction between different AUD, cognition, and inflammatory parameters to be increasingly affected with increasing alcohol dosage and thus increasing inflammation.

Lastly, while extensive preclinical literature provides strong evidence for this three-way interaction between AUD, its cognitive impairments, and immune system aberrations, the actual number of studies investigating it is surprisingly low.

This evidently renders making hard statements on the nature of the interactions somewhat difficult. However, this review aimed at providing sufficient indications that addressing this research avenue more in depth might vastly elucidate inflammatory pathways to be of importance in cognitive deficits marking AUD.

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VC and MM performed literature search and wrote the article. MD and GD acted as advisory board on included papers and reviewed the manuscript.

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REVIEW
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Molecular Imaging of Opioid and Dopamine Systems: Insights Into the Pharmacogenetics of Opioid Use Disorders

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Opioid use in the United States has steadily risen since the 1990s, along with staggering increases in addiction and overdose fatalities. With this surge in prescription and illicit opioid abuse, it is paramount to understand the genetic risk factors and neuropsychological effects of opioid use disorder (OUD). Polymorphisms disrupting the opioid and dopamine systems have been associated with increased risk for developing substance use disorders. Molecular imaging studies have revealed how these polymorphisms impact the brain and contribute to cognitive and behavioral differences across individuals. Here, we review the current molecular imaging literature to assess how genetic variations in the opioid and dopamine systems affect function in the brain's reward, cognition, and stress pathways, potentially resulting in vulnerabilities to OUD. Continued research of the functional consequences of genetic variants and corresponding alterations in neural mechanisms will inform prevention and treatment of OUD.

Keywords: opioid use disorder, neuroimaging, genetics, positron emission tomography, PET, polymorphism, opioid receptors, dopamine receptors

INTRODUCTION

Opioid use in the United States has steadily risen since the late 1990s, along with staggering increases in overdose fatalities (1). The use of illicit opioids such as heroin and fentanyl has increased dramatically, contributing to opioid-related morbidity and mortality (2). With approximately 115 Americans dying each day from an opioid overdose, this epidemic is now considered a public health emergency (3). The surge in prescription and illicit opioid abuse necessitates further investigation into the genetic risk factors and neuropsychological effects of opioid use disorder (OUD).

The roles of the opioid and dopamine (DA) systems in substance use disorders (SUDs) are well recognized (4). Drug reward and incentive salience develop during the acute effects of drug-taking and correspond to changes in opioid and DA signaling in the basal ganglia (5). Incentive salience is defined by the association of previously neutral stimuli with drug use, which promotes compulsive drug-seeking (4). Stress responses associated with withdrawal involve decreased DA signaling along reward pathways, increased dynorphin-mediated kappa opioid (KOP) receptor signaling, and increased corticotropin-releasing factor (CRF) signaling in the amygdala (4). These same principles apply to OUD. For example, Wang et al. (6) used positron-emission tomography (PET) imaging with

[^{11}C]raclopride to demonstrate lower dopamine receptor 2 (D2R) and 3 (D3R) availability in the striatum of opioid-dependent patients compared to controls. Another [^{11}C]raclopride PET study found low striatal D2/3 receptor availability and low presynaptic DA in OUD patients compared to controls (7), which has also been found for other SUDs including cocaine, alcohol, methamphetamine, and cannabis [reviewed in Refs. (8, 9)]. Low D2R levels have also been associated with sleep deprivation (10–12) and lower socioeconomic status (13, 14). These factors may contribute to lower D2R availability found in SUDs, particularly since SUDs and sleep deprivation are highly comorbid (15). Other preclinical studies have found dynorphin-mediated KOP receptor signaling inhibits dopaminergic signaling and modulates aversive emotional states that maintain drug dependence (16–18). Based on these studies, both the opioid and DA signaling systems are implicated in OUD.

However, there are opposing views on these systems' involvement in addiction. For example, there are studies that report no disruption of D2R in OUD, including no difference in baseline D2R availability in methadone-maintained OUD patients compared to controls (19). Moreover, PET studies of opioid-dependent patients on medications for OUD (MOUD) found no increase in striatal DA release in response to opioid administration (19, 20). Studies of other SUDs also present slight inconsistencies in their effects on the dopamine system. Imaging studies in individuals with alcohol use disorder (AUD) have reported marked reductions in dopamine release and in striatal D2R, and most preclinical studies have documented significant reductions in dopamine neuronal firing and tonic dopamine release (9, 21–27). However, studies in rodents have also reported dynamic changes in dopamine release with increases and decreases in accumbens at various days post alcohol withdrawal (28). The discrepancies in the preclinical studies are likely to reflect in part time at which the measurements were made (early versus late withdrawal) as well as the alcohol models used (active versus passive administration). Thus, further research is required to understand the complex relationship between opioid and DA systems in SUDs.

While it has long been postulated that genetics influence an individual's susceptibility to addiction, there has been little success in pinpointing genes with well-defined, causal roles in SUDs (29). Nevertheless, OUD is highly heritable, with an estimated 50% genetic contribution (30–32). The use of candidate gene studies and genome-wide association studies has revealed several polymorphisms that reliably associate with SUDs; however, addiction is a polygenic disease with complex genetic interactions and therefore individual polymorphisms will likely only account for a fraction of the total genetic risk for OUD (33–35). Polymorphisms in the opioid signaling system have been associated with addiction, as well as addiction treatment response (29). For example, several studies have identified a single nucleotide polymorphism (SNP) in the *OPRM1* gene that associates with improved response to naltrexone treatment in individuals with AUD (36–39). Other *OPRM1* SNPs may also play a role in nicotine dependence and treatment response (40–42). Additionally, genetic variations in the DA system have been linked to various SUDs as DA modulates reward and aversion pathways central to addiction (29, 43). For example, polymorphisms in the genes coding for dopamine 1 receptor (D1R) and D2R are associated with OUD, cocaine use disorder (CUD), and AUD (6, 22, 44). In addition, polymorphisms in the gene *DAT1*, which codes for dopamine transporters (DAT), have been associated with CUD and AUD (45–47). In line with this, reduced striatal DAT availability has been associated with OUD (48–53) and DAT availability has been associated with various other SUDs (51, 54–62).

In this review, we compiled findings related to the genetics of the opioid and DA systems and corresponding changes in brain and behavior as evidenced by PET neuroimaging. Functional and structural magnetic resonance imaging (MRI) is another useful tool in examining altered neural circuits in individuals with SUDs, as well as in polymorphism carriers. However, we will limit the scope to molecular imaging as the literature on MRI in OUD was recently reviewed (63–66). Integrating genetics with regional changes in receptor binding may help uncover circuits relevant for the pathophysiology of OUD, and thereby inform precision-based prevention and treatment.

THE OPIOID RECEPTOR SYSTEM

OPRM1

OPRM1 Background

The *OPRM1* gene codes for the MOP receptor, an inhibitory G-protein coupled receptor (GPCR) that binds endogenous opioid peptides such as β-endorphin and enkephalins as well as exogenous opioids such as morphine and heroin (67). MOP receptors are required to establish morphine place preference and physical dependence (68). MOP receptors are expressed throughout the brain's reward pathways including the mesocorticolimbic network as illustrated in **Figure 1**; their proposed mechanism for positive reinforcement in OUD is through disinhibition of DA neurons that trigger drug reward upon DA release (69, 70). Originally it was thought that MOP receptor agonists hyperpolarize GABAergic interneurons of the ventral tegmental area (VTA), reducing GABA-mediated inhibitory input to DA neurons and thereby increasing DA signaling by disinhibition (69). However, most evidence now suggests that the rostromedial tegmental nucleus mediates opioid-induced disinhibition of DA neurons (71–73). There is preclinical evidence of DA-independent opioid-induced reward, but the mechanism is not well understood (74, 75).

The effects of prolonged opioid exposure on MOP receptors, whether in the context of chronic pain management or substance abuse, are not fully understood. Bolger et al. (76) demonstrated an upregulation in MOP receptor in rat brain after chronic heroin administration. However, several other studies have demonstrated that both morphine and buprenorphine administration downregulate MOP receptors in rat brain (76, 77) including striatum (78). Clinically, prolonged exposure to opioids results in tolerance and increased opioid dose requirements; several proposed mechanisms may explain this phenomenon, including phosphorylation and arrestin-driven uncoupling of the GPCR and receptor internalization and degradation

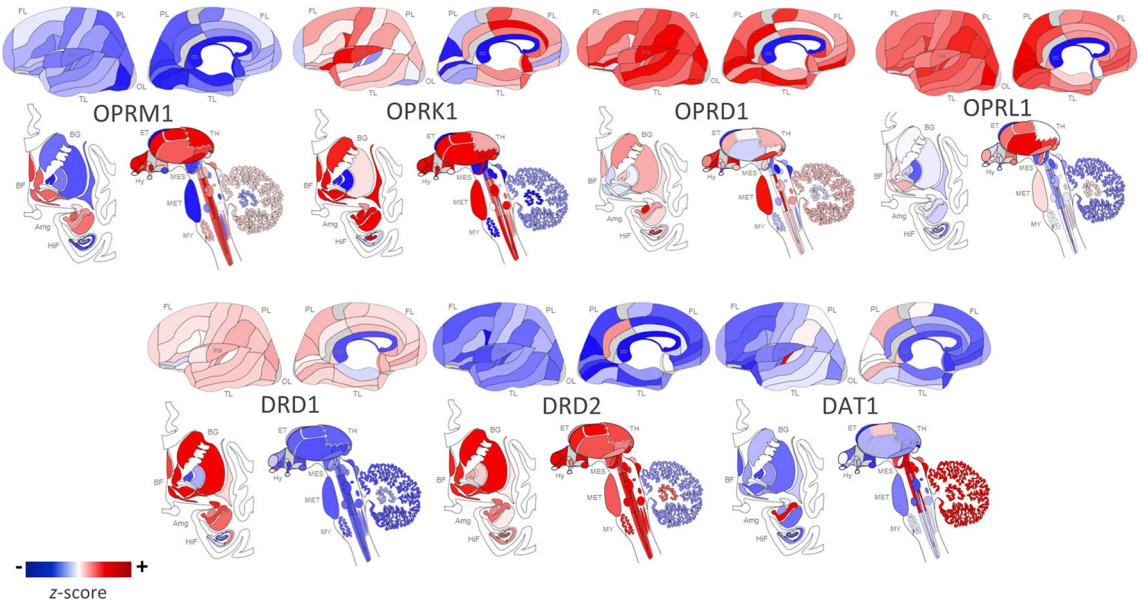

FIGURE 1 | Regional distribution of receptor types in the human brain. Opioid and dopamine receptor gene expression in the human brain [Opioid Receptor Mu 1 (OPRM1), Opioid Receptor Kappa 1 (OPRK1), Opioid Receptor Delta 1 (OPRD1), Opioid Related Nociceptin Receptor 1 (OPRL1), Dopamine Receptor D1 (DRD1), Dopamine Receptor D2 (DRD2), Dopamine Active Transporter 1 (DAT1)]. Images constructed using Allen Human Brain Atlas. Data displayed are from one donor: H0351.2002, 39 years, M, Black or African American. The color bar displays expression values using *z*-score normalization. Color scale was altered to highlight regional differences in gene expression per receptor type; therefore, the absolute scale differs across each of the receptor subtypes. For quantitative results from all six postmortem donor brains, visit http://human.brain-map.org/static/brainexplorer.

(79–82). However, several studies cloned MOP receptors in human embryonic kidney cells and found that morphine does not promote MOP receptor endocytosis (80, 83–85), which results in protracted desensitization that could contribute to tolerance (86). Yet, several opioids including methadone, etorphine, and [D-Ala2, N-MePhe4, Gly-ol]-enkephalin (DAMGO) induced the expected receptor sequestration in cell line models (79, 80, 87, 88). A study in rats also showed MOP receptor internalization in the striatum and habenula after acute etorphine, but not morphine administration (80). These findings were replicated in the rat's locus coeruleus where neurons showed MOP receptor internalization in response to DAMGO and methadone, but not morphine (89). Downregulation of MOP receptors is agent-specific as some opioids are more effective at activating the G-protein response than others (87). The concept of biased agonism explains differential activation patterns and intracellular signaling cascades based on ligand structure and GPCR conformations (90, 91). In the case of MOP receptors, ligands may preferentially activate G-protein coupling or β-arrestin recruitment (92). Schmid et al. (92) reported that fentanyl promotes bias toward β-arrestin recruitment, while morphine is relatively unbiased in mouse models and cell lines. Given that β-arrestin drives MOP receptor internalization and is associated with respiratory suppression and tolerance, these findings have clinical significance and may explain the differences in ligand-mediated MOP receptor internalization (92–95). Specifically, the increased lethality of fentanyl and structurally related synthetic opioids may not be due solely to greater potency, but also due to the preferential activation of an intracellular pathway that promotes respiratory depression (92, 96).

OPRM1 Polymorphisms

Genetic variations of *OPRM1,* the gene encoding for MOP, have been studied in the context of vulnerabilities to SUDs, treatment response, and relapse. Whole genome sequencing has identified 3,324 *OPRM1* polymorphisms, the most commonly studied of which, rs1799971 (A118G), has a global minor allele frequency of 19% (97). Located on exon 1 of *OPRM1*, this SNP results in an asparagine replaced by an aspartate at position 40, which is in the amino-terminus of the receptor (98, 99). In preclinical studies, the G allele was associated with lower MOP receptor expression in transfected cell lines (100–103). In [^{11}C]carfentanil PET scans, the G allele was also associated with lower global MOP receptor expression (104) and lower expression in anterior cingulate cortex (ACC), nucleus accumbens (NAc), and thalamus compared to the common genotype (105). One proposed mechanism suggests that the amino acid substitution removes an extracellular glycosylation site, potentially interfering with the protein's folding or incorporation into the cell membrane (101). Other studies found that the G allele results in reduced levels of MOP receptor mRNA expression, although the underlying mechanism remains unknown (103). For example, a post-mortem study of heterozygotes for A118G found the wild-type A allele had twice the mRNA expression than the G variant in cortical and pons tissue samples (103). An *in vitro* study of G allele-transfected cells also showed reduced mRNA and lower receptor protein

levels when compared to the wild-type allele (103). Oertel et al. (106) propose that rs1799971 creates a novel methylation site that suppresses transcription of *OPRM1*.

Interestingly, an initial *in vitro* study reported increased binding affinity of β-endorphin to the variant receptor (107); though subsequent *in vitro* studies were unable to replicate this finding (100, 108).

Genetic Association Studies: *OPRM1* and OUD

Several studies have investigated the effects of genetic variations in *OPRM1* on susceptibility to SUDs, including OUD. A systematic review and meta-analysis of 13 studies of the A118G polymorphism in OUD found significant associations of the G allele with CUD and OUD in Asian populations, but not in African American, Caucasian, or Hispanic populations (109). However, a behavioral study linked the G allele with increased addiction severity in Caucasian males with OUD (110). This could be attributable to the varying prevalence of the rs1799971 minor allele across ethnicities; for example, the G allele frequency is greater in Asian populations than in Caucasians (30–40% and 11–15%, respectively), and it is less than 5% in African American populations (107, 111, 112). Another study examined four low-frequency SNPs of *OPRM1* in a cohort of European Americans and African Americans; only one polymorphism, rs62638690, was associated with both cocaine and heroin addiction in European Americans; however, it did not withstand correction for multiple testing (113). This may suggest that while *OPRM1* polymorphisms alter vulnerability to OUD, the effects are race- and/or ethnicity-dependent. Finally, an intron 2 polymorphism, rs9479757, was not associated with OUD in a Chinese population, but OUD patients with the minor allele were found to consume higher levels of opioids (114). Further, Xu et al. (115) found the rs9479757 minor allele associated with addiction severity among Chinese OUD patients (115). These findings are outlined in **Table 1**.

Additionally, the A118G polymorphism may have relevance for OUD treatment. In a mouse model of A118G, the analgesic, anxiolytic, and hyperlocomotor effects of buprenorphine were attenuated in carriers of the minor G allele (162). In a study of opioid-dependent chronic pain patients, carriers of the minor G allele required higher morphine equivalent daily doses than AA homozygotes (163). This may be attributed to reduced MOP receptor functioning in carriers of the G allele that results in an increased opioid requirement for pain management (163, 164). However, a meta-analysis of the association between rs1799971 and methadone treatment response among OUD patients was inconclusive (165).

Several studies have examined associations between *OPRM1* polymorphisms and stress response, as MOP receptors help regulate stress levels *via* tonic inhibition of the hypothalamic–pituitary–adrenal (HPA) axis (166). Naloxone is an opioid receptor antagonist with highest affinity for MOP receptors, thus eliciting an HPA axis stress response upon binding (167). Several studies demonstrate that healthy heterozygotes of A118G have increased stress response to naloxone compared to non-G allele carriers (168–170). Given the role of stress dysregulation in vulnerability to SUDs, this provides a potential mechanism for this SNP as a risk factor for OUD (167).

The A118G SNP has also been associated with personality traits relevant to SUDs (171). Several studies assessed participants with the five-factor NEO, a personality inventory that scores in domains of "Openness to Experience, Conscientiousness, Extraversion, Agreeableness, and Neuroticism" (172). High Neuroticism, low Conscientiousness, and low Agreeableness scores are associated with SUDs (173–176). Specifically, higher scores on Neuroticism and lower scores on Conscientiousness, Agreeableness, and Extraversion have been associated with OUD (177, 178). Compared to A118 homozygotes, carriers of the G allele scored lower on the Conscientiousness factor (170), which is associated with task organization and execution, and reflects control over impulsivity (179). Moreover, Pecina et al. (105) found that G carriers had higher Neuroticism scores than non-carriers, which negatively correlated with baseline MOP receptor availability in the anterior insula and subgenual ACC as assessed with [^{11}C]carfentanil PET. However, Hernandez-Avila et al. (180) found no association between A118G and NEO personality dimensions in healthy and substance-dependent volunteers; thus, the role of this polymorphism in moderating personality is uncertain. Love et al. (181) used [^{11}C]carfentanil PET in a study of healthy volunteers and assessed participants with the Revised NEO Personality Inventory, which includes domains "Impulsiveness" and "Deliberation," that have been associated with negative risk-taking, including drug use (182, 183). Participants with high Impulsivity and low Deliberation scores showed higher baseline MOP receptor availability in several brain regions including the ACC and amygdala (181). Further, in response to a pain stress challenge, subjects with high Impulsivity/low Deliberation scores demonstrated a larger reduction in MOP receptor availability from baseline compared to low Impulsivity/high Deliberation scores in regions including the orbitofrontal cortex and amygdala (181). This suggests a possible mechanism for the role of personality traits in shaping vulnerabilities to SUDs.

Molecular Imaging: MOP Receptor and OUD

Several studies have used PET imaging to investigate MOP receptor availability in OUD patients receiving MOUD. The radioligand [^{11}C]carfentanil is widely used in PET studies as it is a highly potent MOP-selective receptor agonist (184). [^{18}F] cyclofoxy is less frequently used as it is both a MOP receptor and KOP receptor agonist, with some preliminary evidence of MOP receptor preference (185–188).

A number of studies have examined the effects of buprenorphine, a high-affinity MOP receptor partial agonist and KOP and delta opioid (DOP) receptor antagonist (189–191) in the treatment of OUD. Using [^{11}C]carfentanil PET imaging, Greenwald et al. (192) investigated the duration of binding of buprenorphine at MOP receptor and the corresponding effects on withdrawal in 10 OUD patients. They found that 50–60% MOP receptor occupancy by buprenorphine was required for withdrawal suppression (192). At 28 h after buprenorphine, 46% of whole-brain MOP receptors were

TABLE 1 | Polymorphisms associated with OUD in the opioid system and molecular imaging correlates.

Gene	Polymorphism	Location	Finding	Author	Year	n	Ethnicity	Imaging Correlates
OPRM1	**rs1799971**	Exon 1	Risk factor for OUD	Kumar et al. (116)	2012	330	Indian	-Lower baseline
				Kapur et al. (121)	2007	282	Indian	MOP receptor
				Deb et al. (122)	2010	169	Indian	binding potential in
				Tan et al. (123)	2003	137	Indian	NAc and amygdala
				Nagaya et al. (124)	2012	160	Malaysian males	of tobacco smokers
				Szeto et al. (111)	2001	296	Chinese	(117–119)
				Bart et al. (125)	2004	309	Caucasian	-Greater DA release
				Drakenberg et al. (126)	2006	65	Caucasian	in the right caudate
			No significant association with OUD	Bond et al. (107)	1998	31	African American	and ventral pallidum
				Luo et al. (127)	2003	100	African American	in response to
				Gelernter et al. (112)	1999	288	African American	smoking (120)
				Crowley et al. (128)	2003	195	African American	
				Zhang et al. (40)	2006	600	Caucasian	
				Bond et al. (107)	1998	52	Caucasian	
				Gelernter et al. (112)	1999	492	Caucasian	
				Franke et al. (129)	2001	652	Caucasian	
				Luo et al. (127)	2003	231	Caucasian	
				Crowley et al. (128)	2003	229	Caucasian	
				Levran et al. (130)	2008	596	Caucasian	
				Nikolov et al. (131)	2011	3,283	Caucasian	
				Bond et al. (107)	1998	67	Hispanic	
				Gelernter et al. (112)	1999	94	Hispanic	
				Li et al. (132)	2000	434	Chinese	
				Zhang et al. (133)	2007	332	Chinese	
				Shi et al. (114)	2002	145	Chinese	
				Tan et al. (123)	2003	208	Chinese	
				Tan et al. (123)	2003	156	Malay	
			No significant association with methadone dose	Crettol et al. (134)	2008	238	Caucasian	
			Prolonged abstinence without agonist therapy	Levran et al. (135)	2017	596	Caucasian	
	rs62638690	Exon 2	Protective against OUD	*Clarke et al. (113)	2013	1,377	European American	
	rs510769	Intron 1	Risk factor for OUD	*Levran et al. (130)	2008	596	Caucasian	
	rs3778151	Intron 1	Risk factor for OUD	*Levran et al. (130)	2008	596	Caucasian	
	rs9479757	Intron 2	Higher opioid consumption	Shi et al. (114)	2002	145	Chinese	
			Addiction severity	Xu et al. (115)	2014	332	Male Chinese	
OPRD1	**rs569356**	Promoter	Risk factor for OUD	*Zhang et al. (136)	2008	1,063	European American	
			No significant association with OUD	Nelson et al. (137)	2014	2,954	Australian	
	rs4654327	3' UTR	Risk factor for OUD	Gao et al. (138)	2017	774	Chinese	
			No significant association with OUD	Nelson et al. (137)	2014	2,954	Australian	
	rs1042114	Exon 1	Risk factor for OUD	Nagaya et al. (139)	2018	1,002	Malay males	
				Zhang et al. (136)	2008	1,063	European American	
				Crist et al. (140)	2013	566	Caucasian males	
			No significant association with OUD	Nelson et al. (137)	2014	2,954	Australian	
	rs2234918	Exon 3	Risk factor for OUD	Huang et al. (141)	2018	1,331	Chinese	
				Mayer et al. (142)	1997	218	Caucasian	
			No significant association with OUD	Xu et al. (143)	2002	754	Chinese	
				Levran et al. (130)	2008	596	Caucasian	
				Zhang et al. (136)	2008	1,063	European American	
				Franke et al. (144)	1999	406	Caucasian	
				Crist et al. (140)	2013	2,502	Mixed	
			No significant association with methadone dose	Crettol et al. (134)	2008	455	Caucasian	
	rs508448	Intron 1	Earlier onset OUD	Gao et al. (138)	2017	774	Chinese	
			No significant association with OUD	Nelson et al. (137)	2014	2,954	Australian	
	rs581111	Intron 1	Risk factor for OUD	Crist et al. (140)	2013	1,006	African American	
			Higher relapse rates on buprenorphine	Clarke et al. (145)	2014	582	Caucasian females	
			No significant association with OUD	Nelson et al. (137)	2014	2,954	Australian	

(Continued)

TABLE 1 | Continued

Gene	Polymorphism	Location	Finding	Author	Year	n	Ethnicity	Imaging Correlates
	rs678849	Intron 1	Risk factor for OUD	Sharafshah et al. (146)	2017	404	Iranian	
			Abstinence-induced withdrawal severity	*Jones et al. (147)	2016	19	Mixed	
			Higher relapse rates on buprenorphine	Crist et al. (148)	2013	77	African American	
				Crist et al. (149)	2018	55	African American	
			Lower relapse rates on methadone	Crist et al. (148)	2013	77	African American	
			No significant association with relapse rates on methadone	Crist et al. (149)	2018	55	African American	
			No significant association with OUD	Nelson et al. (137)	2014	2,954	Australian	
				Zhang et al. (136)	2008	1,063	European American	
	rs2236857	Intron 1	Risk factor for OUD	Sharafshah et al. (146)	2017	404	Iranian	
				Nelson et al. (137)	2014	2,954	Australian	
				*Levran et al. (130)	2008	596	Caucasian	
			No significant association with OUD	Zhang et al. (136)	2008	1,063	European American	
			Protective against stress response in OUD	Huang et al. (141)	2018	1,331	Chinese	
	rs2236857[+] rs581111 haplotype[†]	Intron 1	Risk factor for OUD	Nelson et al. (137)	2014	2,954	Australian	
	rs2236855	Intron 1	Risk factor for OUD	Sharafshah et al. (146)	2017	404	Iranian	
				Nelson et al. (137)	2014	2954	Australian	
			No significant association with OUD	Zhang et al. (136)	2008	1,063	European American	
				Crist et al. (140)	2013	566	Caucasian males	
	rs760589	Intron 1	Risk factor for OUD	Sharafshah et al. (146)	2017	404	Iranian	
				*Nelson et al. (137)	2014	2,954	Australian	
	rs2236861	Intron 1	Risk factor for OUD	Beer et al. (150)	2013	284	Western European	
				*Levran et al. (130)	2008	596	Caucasian	
				*Nelson et al. (137)	2014	2,954	Australian	
	rs529520	Intron 1	Higher methadone requirement	Luo et al. (151)	2017	257	Chinese	
			Higher relapse rates on buprenorphine	Clarke et al. (145)	2014	582	Caucasian females	
			Risk factor for OUD	*Nelson et al. (137)	2014	2,954	Australian	
			No significant association with OUD	Zhang et al. (136)	2008	1,063	European American	
	rs10753331	Intron 1	Abstinence-induced withdrawal severity	Jones et al. (147)	2016	19	Mixed	
			Risk factor for OUD	Crist et al. (140)	2013	566	Caucasian	
	rs3766951	Intron 1	Risk factor for OUD	Nelson et al. (137)	2014	2,954	Australian	
				*Levran et al. (130)	2008	596	Caucasian	
	rs2298897	Intron 1	Risk factor for OUD	Nelson et al. (137)	2014	2,954	Australian	
OPRK1	**rs1051660**	Exon 2	Risk factor for OUD	Yuferov et al. (152)	2004	291	Mixed	
				Gerra et al. (153)	2007	176	Caucasian Italian	
	rs702764	Exon 4	No significant association with OUD	Nagaya et al. (139)	2018	1,002	Malay males	
				Zhang et al. (136)	2008	1,063	European American	
	rs997917	Intron 2	Risk factor for OUD	Albonaim et al. (154)	2017	404	Iranian	
			No significant association with OUD	Zhang et al. (136)	2008	1,063	European American	
	rs6985606	Intron 2	Risk factor for OUD	Albonaim et al. (154)	2017	404	Iranian	
			No significant association with OUD	Zhang et al. (136)	2008	1,063	European American	
	rs6473797	Intron 2	Protective against OUD	*Levran et al. (130)	2008	596	Caucasian	
			Naloxone-precipitated withdrawal severity	Jones et al. (147)	2016	29	Mixed	
			No significant association with OUD	Albonaim et al. (154)	2017	404	Iranian	

(Continued)

TABLE 1 | Continued

Gene	Polymorphism	Location	Finding	Author	Year	n	Ethnicity	Imaging Correlates
PDYN	**rs35286281 H allele**	Promoter	Risk factor for OUD	Yuanyuan et al. (155)	2018	1,107	Chinese	
				Wei et al. (156)	2011	604	Chinese	
			No significant association with OUD	Hashemi et al. (157)	2018	435	Iranian	
	rs1997794	Promoter	Risk factor for OUD	Clarke et al. (158)	2012	2,618	European American females	
				Clarke et al. (159)	2009	858	Chinese females	
			No significant association with OUD	Nagaya et al. (139)	2018	1,002	Malaysian males	
	rs2281285	Intron 2	No significant association with OUD	Hashemi et al. (157)	2018	435	Iranian	
	rs910080	3' UTR	Risk factor for OUD	Nagaya et al. (139)	2018	1,002	Malaysian males	
				Clarke et al. (158)	2012	2,618	European American females	
				Wei et al. (156)	2011	604	Chinese	
				Hashemi et al. (157)	2018	435	Iranian	
			No significant association with OUD	Clarke et al. (158)	2012	2,618	European American males	
	rs1022563	3' UTR	Risk factor for OUD	Clarke et al. (158)	2012	2,618	European American females	
				Clarke et al. (159)	2009	858	Chinese females	
				Wei et al. (156)	2011	604	Chinese	
			No significant association with OUD	Nagaya et al. (139)	2018	1,002	Malaysian males	
	rs2235749	3' UTR	Risk factor for OUD	Wei et al. (156)	2011	604	Chinese	
			No significant association with OUD	Hashemi et al. (157)	2018	435	Iranian	
OPRL1	**rs6512305**	Intron 1	Risk factor for OUD	*Xuei et al. (160)	2008	1,923	European American	
	rs6090043	Intron 1	Risk factor for OUD	*Xuei et al. (160)	2008	1,923	European American	
			No significant association with OUD	Briant et al. (161)	2010	447	African American	
	rs6090041	Intron 1	Risk factor for OUD	Briant et al. (161)	2010	447	Caucasian	
			No significant association with OUD	Briant et al. (161)	2010	447	African American	
				Xuei et al. (160)	2008	1,923	European American	
	rs6090043+ rs6090041 haplotype‡1	Intron 1	Risk factor for OUD	Briant et al. (161)	2010	447	Mixed	
	rs6090043+ rs6090041 haplotype‡2	Intron 1	Risk factor for OUD	Briant et al. (161)	2010	447	Caucasian	
			No significant association with OUD	Briant et al. (161)	2010	447	African American	

SNP associations refer to the minor allele.

**Nominal significance.*

† rs2236857 + rs581111 GA haplotype (coupled minor alleles).

‡[1] rs6090043 + rs6090041 AT haplotype.

‡[2] rs6090043 + rs6090041 GC haplotype.

occupied, indicating inadequate withdrawal suppression (192). This may reflect the half-life of oral buprenorphine, which ranges from 28 to 37 h (193). Plasma concentrations of buprenorphine were time-dependent and correlated with levels of MOP receptor occupancy in brain (192, 194). Considering the minor allele of rs1799971 may lower MOP receptor expression, it stands to reason that this SNP may influence the dose of buprenorphine required to achieve adequate withdrawal suppression.

In two studies, heroin-dependent patients maintained on varying doses of buprenorphine underwent several [^{11}C]carfentanil PET scans (194, 195). Buprenorphine was shown to reduce MOP receptor availability in a dose-dependent manner, and decreased MOP receptor availability correlated with decreased heroin craving and withdrawal symptoms (194, 195). After detoxification from buprenorphine, OUD participants demonstrated higher regional binding potential of MOP receptor particularly in the inferior frontal and anterior cingulate cortex compared to healthy controls (195). Yet, an animal study found buprenorphine maintenance down-regulates MOP receptor in rat brains (77). The higher MOP receptor binding potential among OUD participants found by Zubieta et al. (195) could reflect opioid or buprenorphine induced downregulation of enkephalins and β-endorphins in brain with a consequent reduced competition for [^{11}C]carfentanil binding to MOP.

Another study used [^{18}F]cyclofoxy PET scans in 14 methadone-maintained patients and 14 healthy controls (185).

The methadone-maintained patients demonstrated 19–32% lower cyclofoxy binding than the controls in thalamus, caudate, anterior cingulate cortex, middle temporal cortex, and the middle frontal cortex (185). The lower [^{18}F]cyclofoxy binding in the brain of OUD participants correlated with plasma methadone levels, likely reflecting the steady-state methadone occupancy of MOP receptors (185). These findings contrast with those obtained in OUD patients treated with buprenorphine who showed much greater levels of MOP occupancy consistent with the partial agonist effects of buprenorphine as compared to the full agonist effects of methadone (192). This discrepancy could also reflect less receptor internalization associated with a partial agonist and, therefore, greater levels of receptor occupancy by the radioligand.

PET studies have also investigated the effects of A118G on MOP receptor availability in individuals with SUDs. For example, the G allele has been associated with lower baseline MOP receptor binding potential in NAc and amygdala of smokers (146–148). Thus, A118G may shape predispositions to substance abuse by affecting MOP receptor availability, which could contribute to aberrant dopaminergic signaling. A [^{11}C]raclopride PET study of tobacco smokers found that the G allele associated with greater DA release in the right caudate and ventral pallidum in response to smoking compared to the A allele (120). This is further evidence of the association between A118G and drug reward, which may increase vulnerability to SUDs (120). Longitudinal studies are needed to clarify the link between opioid receptor availability and SUDs.

OPRK1

OPRK1 Background

OPRK1 codes for the KOP receptor, an inhibitory GPCR that is implicated in the brain's stress or anti-reward system (196). KOP receptors are the most abundant opioid receptors in the human brain and are highly expressed in key brain regions of the stress axis such as the prefrontal cortex and amygdala (197) as well as in reward-related regions including the VTA, NAc core, dorsal striatum, and substantia nigra as seen in **Figure 1** (187, 198–201). KOP receptors are coupled with calcium channels and are localized in presynaptic terminals of dopaminergic cells; activation of KOP receptors inhibits adenylyl cyclase and calcium currents, thereby inhibiting DA release (199, 202–204). Prodynorphin (*PDYN*) codes for the precursor to the dynorphin peptide, which is the endogenous ligand to the KOP receptor. Using a phospho-selective antibody against KOP receptors, Land et al. (16) demonstrated that both stress paradigms and CRF injections elicit dynorphin-dependent KOP receptor activation in the basolateral amygdala, NAc, and hippocampus of mice. This indicates the key role KOP receptor signaling plays in stress and dysphoria. In general, KOP receptor agonists have anxiogenic properties in humans (205, 206) while KOR antagonists demonstrate anxiolytic properties in animal models (207, 208). However, there is evidence of dose-dependent effects; in a mouse study, KOP receptor agonist, U50,488H, was anxiolytic at high doses but anxiogenic in low doses (209). KOP receptor signaling may also influence stress responses associated with relapse; for example, heroin-dependent rats treated with KOP receptor antagonists show reduced anxiety- and stress-induced reinstatement of drug-seeking behavior (210, 211).

KOP receptor signaling is also involved in an array of physiological functions such as mood modulation, pain perception, learning and memory, and behavioral response to drugs of abuse (212, 213). Within the NAc, dynorphin signaling inhibits DA release, which leads to aversive effects on mood (214). In individuals with SUDs, KOP receptor-mediated dynorphin signaling drives negative affective states during drug withdrawal (215). One [^{11}C]raclopride PET study showed blunted DA release with a methylphenidate challenge in recently detoxified OUD patients compared to healthy controls (7). This hypodopaminergic response may be explained by dynorphin-mediated withdrawal. This is consistent with a rodent study that found chronic exposure and subsequent withdrawal from morphine led to prolonged (15 day) decreases in spontaneous dopaminergic neuron activity (216). This hypodopaminergic state may underlie dysphoria that drives compulsive drug-seeking (216).

Interestingly, post-mortem brain samples of heroin abusers showed lower levels of PDYN mRNA expression in the amygdalar nucleus of the periamygdaloid cortex compared to controls (217). Further, a post-mortem study reported elevated dynorphin levels in heroin abusers with reduced striatal PDYN mRNA expression, suggesting upregulation of PDYN mRNA translation despite reduced PDYN mRNA levels (126). These results corroborate findings of reduced PDYN mRNA expression and elevated expression of the brain stress marker, CRF, in the periamygdaloid cortex of heroin-dependent rats that were euthanized following 24 h of abstinence (217). Increased CRF may reflect the dynorphin-mediated withdrawal response in the heroin-dependent rats despite seemingly reduced *PDYN* expression (217).

Preclinical studies have found that KOP receptor agonists, including salvinorin A, cause KOP receptor internalization *in vitro* (218, 219). A [11C]GR103545 PET study in rodents found that a dose of 0.60 mg/kg of salvinorin A resulted in a prolonged decrease in [11C]GR103545 binding that persisted even after salvinorin A had cleared from the brain, consistent with KOP receptor internalization (220). This study provides insight into the neurochemical adaptations to KOP receptor agonist exposure, which may contribute to opioid tolerance (18).

OPRK1 Polymorphisms

A few *OPRK1* polymorphisms have been described in the context of SUDs, although the majority of them are silent and have no effect on gene expression (221). One example is rs1051660 (G36T), a synonymous SNP in exon 2 (153). These polymorphisms may affect KOP receptor signaling indirectly by altering mRNA stability or translation (222).

PDYN polymorphisms are associated with aberrant dynorphin expression and signaling (223) that may contribute to dysphoria and relapse during opioid withdrawal (155). Intronic variants may alter gene expression *via* splicing mechanisms or may be in linkage disequilibrium with neighboring variants that have

more direct downstream effects (146, 224). Mutations within the 3' tail of mRNA transcripts could alter important sequences like the polyadenylate tail and may disrupt transcription termination (225), translation, and stability of mRNA (226–228). For example, rs910080, a polymorphism in the 3' untranslated region of *PDYN*, is in high linkage disequilibrium with two other 3' untranslated region SNPs, rs910079 and rs2235749; in a post-mortem analysis, this haplotype block was associated with levels of PDYN expression in the striatum (229). Other polymorphisms may alter gene expression directly. The 68-base pair variable number tandem repeat (VNTR) polymorphism, rs35286281, ranges from two to five repeats in the promoter region of *PDYN*, with each repeat containing one binding site for a transcription factor (230, 231). Thus, high dynorphin expression alleles (H alleles) contain three or more repeats and are associated with higher *PDYN* transcription and translation compared to low dynorphin expression alleles (L alleles) with one or two repeats (230).

Genetic Association Studies: *OPRK1, PDYN,* and OUD

There has been little consensus regarding the role of *OPRK1* polymorphisms in OUD. The minor alleles of two intronic polymorphisms, rs997917 and rs6985606, were reported as risk factors for OUD in an Iranian population (154) but were not associated with OUD in a European American population (136). These conflicting findings are likely explained by ethnicity-dependent effects. Interestingly, the rs6473797 minor allele was found to be protective against OUD in a Caucasian population (130), but not in an Iranian population (154). However, rs6473797 did associate with withdrawal severity among OUD patients who underwent naloxone-precipitated withdrawal in an American population of mixed ethnicities (147). Additionally, Wang et al. (232) found that two *OPRK1* haplotype blocks associated with withdrawal symptoms such as joint aches, gooseflesh skin, and yawning in Taiwanese methadone-maintained OUD patients. Lastly, rs1051660 was initially linked to OUD (152), and this finding was replicated by Gerra et al. (153) in a Caucasian Italian population.

Given the critical role of dynorphin signaling in the negative emotion states of SUDs, several studies have examined *PDYN* polymorphisms in the context of OUD. One polymorphism, rs910080, has been associated with OUD across a wide range of ethnicities (139, 156–158). Additionally, there is evidence of sex effects on the association between another two *PDYN* polymorphisms and OUD. That is, both rs1997794 and rs1022563 were found to associate with OUD among European American females, but not males (158). In a prior study of Chinese females, Clarke et al. (159) found the rs1997794 minor allele associated with OUD. Further, these two polymorphisms were not associated with OUD in a study of Malaysian males (139). Together, these findings suggest sex- and ethnicity-specific effects of the *PDYN* genotype on susceptibility to OUD.

Two studies found that the H allele of the *PDYN* VNTR polymorphism was a risk factor for OUD in Chinese populations (155, 156). It was also associated with greater instances of withdrawal and subsequent relapse among heroin-dependent Chinese patients on methadone therapy (155). However, Hashemi et al. (157) did not find an association between the *PDYN* genotype and OUD in an Iranian population. While evidence exists that the H allele upregulates *PDYN* expression (230), further research is required to understand its functional consequences as it relates to OUD.

Despite preclinical and clinical evidence of KOP receptor signaling modulating anxiety and stress response (16, 205, 206, 210, 211, 233, 234), few studies have investigated the effects of *OPRK1* polymorphisms on personality or behavior. One study using the five-factor NEO found the minor allele at rs963549, in exon 3 of *OPRK1*, was associated with higher Neuroticism scores among participants with SUDs but not among healthy controls (235). While this SNP was found to not be a risk factor for SUDs in an Indian population (116), its effects may be ethnicity-dependent or potentially mediated by opioid use. Future studies on the functional effects of *OPRK1* polymorphisms and their associated changes in neurochemistry and behavior would clarify the link between KOP receptor signaling and OUD.

One study examining the effects of the *PDYN* VNTR polymorphism on behavior found that the L allele is associated with disinhibited behavior as assessed with the Zuckerman Sensation Seeking Scale (236). Given that higher scores on this scale correlate with a preference toward risky behavior, this finding suggests L allele carriers are at increased risk for SUDs, contradicting findings from genetic association studies described above (155, 156) but perhaps corroborating post-mortem findings of reduced *PDYN* expression in individuals with OUD (217).

Molecular Imaging: KOP Receptor and OUD

At this point, no studies have used PET to examine *OPRK1* polymorphisms among patients with OUD. Only recently have radiotracers been developed to target KOP receptors, including the agonist tracers [^{11}C]GR103545 and [^{11}C]EKAP and the antagonist tracer [^{11}C]LY2795050. These radiotracers have been evaluated in primates (237–240) and humans (241–244).

In a [^{11}C]LY2795050 PET study, patients with AUD showed lower KOP receptor availability in the amygdala and pallidum compared to healthy controls (245). It is possible that the reduction in KOP receptor availability helps restore dopaminergic signaling and thus alleviates the aversive effects of drinking. However, reduced [^{11}C]LY2795050 specific binding to KOP receptors in AUD could also reflect increased competition for radiotracer binding from upregulation of dynorphin. Another [^{11}C]LY2795050 PET study found that healthy male subjects had greater KOP receptor availability in several brain regions including ACC, frontal cortex, insula, and ventral pallidum compared to females (246). According to the "simple occupation theory," the robustness of a drug response is directly proportional to the number of receptors occupied by the drug (247). This is consistent with the finding by Vijay et al. (246) that greater KOP receptor availability may mediate stronger responses to KOP receptor antagonists such as naltrexone treatment. Among patients with co-occurring cocaine and alcohol dependence, one study showed that naltrexone treatment reduced cocaine and alcohol use in men, but increased substance use in women (248). While sex differences in KOP receptor availability were not examined by Pettinati et al. (248), the authors suggest that receptor bioavailability and naltrexone treatment response

may be sex-dependent. A potential non-neurochemical basis for the poorer treatment response in women compared to men is that women report higher rates of naltrexone-induced nausea, which results in lower medication compliance (249). However, it is important to note that other clinical studies found no sex differences of naltrexone treatment response in AUD (250, 251). Overall, these findings suggest that KOP receptor availability is associated with alcohol use and could potentially mediate the efficacy of KOP-targeted pharmacotherapies for AUD (245). Given the high comorbidity between AUD and OUD (252–254), these findings might have implications for opioid-antagonist treatment response in OUD.

OPRD1

OPRD1 Background

OPRD1 codes for DOP receptors, which are also involved in the negative affect and withdrawal stage of addiction, albeit with inverse effects than KOP receptors. Specifically, greater DOP receptor signaling leads to improvements in negative emotional states (255). DOP receptor agonists have demonstrated antidepressant and anxiolytic effects in rodent models (256, 257). DOP receptors are highly expressed in cortical and limbic areas such as the hippocampus and amygdala, as well as basal ganglia and hypothalamus (258–260). DOP receptors are located on presynaptic terminals of GABAergic interneurons and have region-specific effects on cAMP production (261). While striatal DOP receptor activation is inhibitory and results in increased extracellular dopamine (262), DOP receptors located in the olfactory bulb, medial prefrontal cortex, and primary cultures of hippocampal neurons stimulate cAMP production thereby inhibiting dopamine release (263–265).

Studies suggest DOP receptors modulate the rewarding effects of drugs of abuse. Le Merrer et al. (197) report DOP receptor knockout has no effect on morphine self-administration but does impair place conditioning in mice. In another rodent study, DOP receptor knockout resulted in reduced morphine reward and tolerance (266). Further, DOP receptor antagonists block sensitization to conditioned rewarding effects of opioids (267), whereas agonists enhance conditioned place preference to morphine (268). In a mouse model of OUD, DOP receptor knockout was associated with increased anhedonia and dysphoria during heroin abstinence compared to the wild-type genotype (269). Thus, *OPRD1* polymorphisms that alter DOP receptor signaling may influence opioid withdrawal-associated stress response and relapse.

OPRD1 Polymorphisms

Several polymorphisms of *OPRD1* have been studied in the context of SUDs. One, rs1042114 (G80T), results in an amino acid substitution from cysteine to phenylalanine in the N-terminus of the DOP receptor, and is proposed to disrupt DOP receptor maturation, leading to increased internalization of the receptor compared to wild type (270). The coding-region variant rs2234918 (T921C) is a synonymous polymorphism, that is, it does not cause a change in the coding amino acid, and has conflicting evidence for a role in OUD. Finally, rs569356, located in the promoter region, has been implicated in altered OPRD1 expression; Zhang et al. (271) found the G allele increased *OPRD1* transcription in transfected cell lines. Few other *OPRD1* polymorphisms have been described in terms of their functional effects; however, several have been assessed in genetic association studies.

Genetic Association Studies: *OPRD1* and OUD

Two polymorphisms in the coding region of *OPRD1* have been associated with OUD. The rs1042114 polymorphism has been found to be a risk factor for OUD in Malaysian males (139) and in Caucasian populations (136, 140). However, Nelson et al. (137) did not replicate these findings in Australian OUD patients. Rs2234918, a synonymous *OPRD1* polymorphism, has also been studied in OUD with conflicting findings. The minor C allele of this polymorphism was initially reported as a risk factor for OUD in a German (142) and Chinese population (272). However, several studies have failed to replicate this association (130, 136, 140, 143) including a study that examined a German population but used a family-based association approach to control for population stratification (144). Thus, it is uncertain what role, if any, these *OPRD1* polymorphisms play in increasing vulnerability to OUD.

Several polymorphisms in intron 1 of *OPRD1* have been studied in OUD, although their functional effects remain largely unknown. Two studies found an association between rs2236861 and OUD among Caucasian patients (137, 150). Levran et al. (130) also found that the rs2236861 minor allele increases the risk of heroin dependence; however, the association did not survive multiple testing, perhaps due to a small sample size. Another intron 1 polymorphism, rs2236857, was associated with OUD in Iranian- and European-descent populations (130, 137, 146). However, Zhang et al. (136) were unable to replicate this association in a study of European Americans. Interestingly, among Chinese OUD patients, carriers of the rs2236857 minor allele were found to have higher subjective stress responses than non-carriers as assessed with the Life Event Questionnaire (272). This suggests that *OPRD1* polymorphisms may disrupt stress responses that increase addiction vulnerabilities. The minor allele of rs581111, located in intron 1, has also been reported as a risk factor for OUD among Australians (137) and African Americans but not European Americans (140). Additionally, the minor allele of rs581111 has been associated with poor response to buprenorphine treatment among Caucasian females, but not males, suggesting ethnicity- and sex-dependent influences on genetic associations (145). Lastly, the minor allele of an *OPRD1* intron 1 polymorphism, rs3766951, was reported as a risk factor for OUD in Caucasian populations (130, 137).

In addition, several studies have investigated the effects of *OPRD1* polymorphisms on treatment outcomes in OUD. For example, the major allele of rs678849 has been associated with higher relapse rates among African American OUD patients undergoing buprenorphine treatment, as indicated by positive opioid urine tests (148, 149). Interestingly, the major allele was initially associated with lower relapse rates among African American OUD patients on methadone treatment (148), but this association was not replicated (149). Jones et al. (147) reported an association between rs678849 and abstinence-induced opioid withdrawal severity; however, it did

not withstand a multivariate analysis. While the mechanism of action is unknown, these findings suggest that rs678849 may affect OUD treatment outcomes by potentially mediating withdrawal symptoms.

Several other *OPRD1* polymorphisms have been studied in association with OUD with conflicting results as seen in **Table 1**.

OPRD1 polymorphisms have also been associated with behaviors related to the negative affect and withdrawal stage of OUD. In one study of Pakistani OUD patients, the minor G allele of rs569356 was strongly associated with increased serum cortisol levels, a marker of stress response (273). Given the preclinical evidence that this minor allele may increase *OPRD1* transcription (271), the minor G allele may affect DOP receptor expression and stress responses that could contribute to OUD. While Zhang et al. (136) found a nominally significant association between rs569356 and OUD in a European American population, no significant association was found in Australian and Pakistani populations (137, 273).

Molecular Imaging: DOP Receptor and OUD

No PET studies have examined neurochemical differences between carriers of *OPRD1* polymorphisms in OUD. The only DOP-selective radiotracer that has been developed for PET imaging in humans is N1'-([^{11}C]methyl)naltrindole ([^{11}C]MeNTI) (274).

PET studies investigating DOP receptor availability in healthy controls and AUD patients may provide insight into the functional effects of *OPRD1* polymorphisms in OUD. One [^{11}C]MeNTl PET study found that patients with AUD had slightly greater DOP receptor availability compared to healthy controls in the cingulate, amygdala, insula, ventral striatum, putamen, caudate nucleus, globus pallidus, and thalamus; however, group differences did not reach statistical significance (275). Within the AUD group, DOP receptor availability in the caudate showed a positive association with recent alcohol drinking (275). However, Weerts et al. (275) did not report associations between DOP receptor availability and other behavioral measures of alcohol dependence or withdrawal. Another PET study in abstinent AUD patients demonstrated that while naltrexone completely blocked MOP receptor radioligand binding, it only partially blocked [^{11}C]MeNTl binding and there was high interindividual variability in DOP receptor blockade (276). These findings could underlie interindividual differences in responses to naltrexone treatment in AUD that could translate to naltrexone treatment responses in OUD.

Additionally, one [^{11}C]MeNTl PET study found a negative correlation between mesolimbic DOP receptor availability and total cortisol output over a 4-h period following naloxone in healthy controls, but not in recently abstinent AUD patients (277). Given that endogenous DOP receptor signaling improves negative emotional states (278), the dissociation of DOP receptor availability from naloxone-induced cortisol response in AUD may suggest that chronic alcohol abuse disrupts DOP-mediated stress signaling during alcohol withdrawal. Whether this is the case for OUD remains to be determined. Notably however, Lutz et al. (269) reported that DOP receptor signaling ameliorates opioid withdrawal in rodents, so together, these findings may suggest a shared mechanism for negative emotional states in opioid and alcohol withdrawal.

OPRL1

OPRL1 Background

The nociceptin opioid peptide (NOP) receptor is an inhibitory GPCR encoded by the Opioid Receptor-Like 1 gene (*OPRL1*) that has MOP, KOP, and DOP receptor structure homology and similar signaling cascades (279). However, the NOP receptor is pharmacologically distinct from classical opioid receptors. The NOP receptor is activated by nociceptin, and its effects are not blocked by the universal opioid antagonist naloxone (280, 281). NOP receptors are distributed throughout the amygdala, hippocampus, thalamus, and cortical processing areas (282) and have roles in both analgesia and hyperalgesia [reviewed in (283) and (284)]. NOP receptor signaling is also involved in processes including stress, anxiety, depression, cognition, and addiction (285–289).

Given the distribution of NOP receptors along the limbic region (290), it follows that NOP signaling is tied to stress signaling. For example, central injections of nociceptin in rats result in increased plasma stress hormone levels, reflecting activation of the HPA axis (291). However, there is also evidence that NOP receptors in extrahypothalamic brain regions exert anti-stress effects. For example, nociceptin injections in the central nucleus of the amygdala reduce anxiety behaviors in rodents exposed to restraint stress (292). Further, body restraint stress upregulates NOP receptor mRNA in the central nucleus of the amygdala and basolateral amygdala (292). In an electrophysiological study, nociceptin blocked CRF-induced GABAergic transmission in slices from the central nucleus of the amygdala; these effects were more pronounced in neurons from ethanol-dependent rodents (293). Additionally, nociceptin injections in the bed nucleus of the stria terminalis block CRF-induced anxiety behaviors in rodents (294, 295). Thus, the role of NOP receptors in stress is likely complex and may be relevant in OUD, particularly due to the high co-occurrence of anxiety and SUDs [reviewed in (296)].

NOP receptor signaling also seems to have an anti-reward effect. In microdialysis studies, nociceptin administration was found to decrease extracellular DA levels in the NAc of anesthetized mice (297) and to decrease morphine-induced DA release in the NAc of rats (298). Further, in several rodent studies, NOP receptor agonists reduced conditioned place preference to alcohol, amphetamines, cocaine, and morphine, suggesting NOP receptor signaling may reduce the rewarding effects of these substances (299–304). However, Walker et al. (305) found nociceptin administration failed to reduce heroin self-administration in rodents. There is also preliminary evidence that the NOP receptor antagonist, LY2940094, could be efficacious in treating AUD in rodents and humans, perhaps by blocking stress-induced relapse (306, 307). While an initial post-mortem analysis demonstrated individuals with AUD had lower *OPRL1* expression in the central amygdala compared to controls (308), no difference in *OPRL1* expression was detected in another

post-mortem study in individuals with SUDs including AUD (309). Thus, the NOP receptor is likely implicated in substance abuse and poses a potential therapeutic target, but further research is required to clarify its roles in reward and stress-related behaviors.

OPRL1 Polymorphisms

The functional effects of several *OPRL1* polymorphisms have been studied. For example, two adjacent SNPs in intron 1, rs6512305 and rs6090043, are in high linkage disequilibrium and there is evidence that variants in rs6090043 may alter transcription factor binding sites, which could affect *OPRL1* gene expression (161). Further, the minor G allele at rs6090041, another intron 1 variant, and the minor C allele at rs6090043 provide additional transcription factor binding sites that could result in increased *OPRL1* transcription and NOP receptor availability (161). Given that NOP receptor signaling has been implicated in decreasing drug reward, there may be a role of *OPRL1* polymorphisms in susceptibility to SUDs.

Genetic Association Studies: *OPRL1* and OUD

Xuei et al. (160) assessed correlations between SUDs and polymorphisms in *OPRL1* as well as in the prepronociceptin gene (*PNOC*), which encodes the NOP receptor precursor, in a European American population; rs6512305 and rs6090043 were nominally associated with opioid dependence; however, no SNPs proved significant (160). Briant et al. (161) found that minor alleles at rs6090043 and rs6090041 were risk factors for OUD among Caucasians but not African Americans. One haplotype (AT) of these variants was found to be a risk factor in both Caucasians and African Americans, while another haplotype (GC) was a risk factor in Caucasians only (161). While there is preliminary evidence that *OPRL1* may influence vulnerability to OUD, further analysis is required to determine the potential ethnicity-dependent effects.

Molecular Imaging: NOP Receptor and OUD

NOP receptor antagonist PET radioligands have been developed; [^{11}C]NOP-1A has been tested in humans (290, 310, 311) and [^{18}F]MK-0911 has been tested in rhesus monkeys (312). To date, no molecular imaging of NOP has been done in participants with OUD; however, studies of other SUDs may provide insight. Using [^{11}C]NOP-1A, Narendran et al. (313) found no difference in NOP receptor availability between healthy controls and recently abstinent AUD subjects, nor did NOP receptor availability correlate with clinical measures of addiction severity. This conflicts with preclinical evidence that NOP receptor signaling is involved with AUD (289, 299, 300, 308). However, the subjects with AUD in this study were abstinent for 16 to 54 days before the PET scan, and there is preclinical evidence that prolonged abstinence may recover NOP receptor levels in rats (313, 314). In another PET study, recently abstinent CUD participants demonstrated a significant increase in [^{11}C]NOP-1A distribution volume notably in the midbrain, ventral striatum, and cerebellum compared to healthy controls (315). This increased NOP receptor availability may reflect a compensatory response to increased CRF transmission or decreased endogenous nociceptin associated with CUD (315). Further studies are required to evaluate NOP in OUD, for while studies in CUD have shown upregulation in brain, studies in AUD showed no differences (313), which suggests that there might be differences between SUDs. Also, research is needed to clarify changes during the different stages of the addiction cycle and to assess if there is recovery of NOP receptor availability with treatment.

THE DOPAMINE SYSTEM

DRD2

DRD2 Background

The gene *DRD2* codes for D2R, an inhibitory GPCR distributed throughout the brain. Expression of D2R is concentrated in the basal ganglia nuclei, including the caudate, putamen, NAc, substantia nigra, and VTA, as shown in **Figure 1** (316). As such, D2R signaling plays an important role in cognition, reward, motivation, and drug addiction, including OUD (317, 318). MOP receptors are expressed on DA neurons in the reward pathway; thus, with opioid use, MOP receptor binding leads to a release of DA, which then binds striatal D2Rs, leading to a decrease in intracellular cAMP production (69, 319). This D2R signaling inhibits the indirect ventral striatal pathway, which is connected to punishment (320).

Ankyrin Repeat and Kinase Domain Containing 1 (*ANKK1*) is a gene directly downstream of *DRD2* on chromosome 11 that expresses a serine/threonine kinase (321). The protein product of *ANKK1* upregulates the expression of the transcription factor NF-κB (322). Increased NF-κB expression results in increased *DRD2* transcription (323).

Several studies have shown that OUD is associated with a disruption of the mesolimbic dopaminergic pathway, which underlies the behavioral response to opioids (4). Koob and Volkow (4) suggest that D2Rs contribute to drug seeking behaviors, but not drug reward directly (324, 325). A conditioned place preference study of *DRD2*-null mice demonstrated that D2Rs are in part responsible for the reinforcing nature of morphine (326).

Lower D2R levels observed in SUDs may reflect a homeostatic downregulation of D2R after excessive drug use (29), and some evidence exists that D2R levels increase after pronounced abstinence (327). Alternatively, lower D2R availability may be an inherent risk factor for drug abuse, even before the initiation of drug taking (328, 329).

DRD2 Polymorphisms

A wide range of *DRD2/ANKK1* polymorphisms have been studied in the context of SUDs. One of the most well studied of these SNPs is *Taq*IA, located on exon 8 of *ANKK1*, adjacent to *DRD2* (321). Many studies have supported the role of *Taq*IA in addictive behaviors including various SUDs, obesity, and pathological gambling (330–333). Thus, the *Taq*IA1 variant, which alters ANKK1 substrate binding specificity, could lead to decreased D2R expression downstream (321). Indeed, [^{11}C]raclopride and [^{11}C]NMB PET studies have shown that minor alleles of *ANKK1* *Taq*IA and *Taq*IB, a linked *DRD2* SNP, are associated with low D2R availability in healthy controls (334–336). However,

*Taq*IA is in linkage disequilibrium with several functional *DRD2* polymorphisms (337); thus, it is unclear if reduced D2R expression is associated with *Taq*IA directly.

Lesser studied *DRD2* variants may also contribute to OUD *via* a diminution of D2R expression (338). SNPs in the 5' untranslated region of *DRD2*, including rs1799732, an insertion/deletion (*Ins/Del*) variant at position -141, have been shown to cause decreased promoter strength in an *in vitro* -141C *Del* luciferase construct (339). While one [^{11}C]FLB-457 PET study found no association between rs1799732 and extrastriatal D2R in healthy volunteers (340), one [^{11}C]raclopride PET study demonstrated higher striatal D2R availability in those with the combined minor variants of rs1799732, *Ins/Del* and *Del/Del*, compared to *Ins/Ins* (334). Until more studies are performed, the role of rs1799732 in D2R expression cannot be concluded.

Other *DRD2* polymorphisms produce splicing errors of the *DRD2* gene, resulting in altered D2R expression (341). For example, the minor allele of rs1076560, located in intron 6, is associated with a decreased ratio of short form D2 receptors (D2S) to long form receptors (D2L) (342). Preclinical studies have demonstrated that D2L knock-out mice have a loss of morphine preference in a conditioned place preference paradigm (343). Thus, this altered D2S/D2L ratio could help elucidate the mechanism of this SNP-OUD relationship. [^{123}I]IBZM SPECT imaging revealed that in healthy volunteers, minor T allele carriers of this SNP showed lower levels of striatal D2R availability compared to G/G (344). However, another [^{123}I]IBZM SPECT study in healthy volunteers did not replicate this finding (345). These findings may implicate *DRD2/ANKK1* polymorphisms in the lower D2R levels observed in individuals with OUD (6).

Genetic Association Studies: *DRD2* and OUD

Several polymorphisms in *DRD2/ANKK1* have been suggested to predispose OUD, as outlined in **Table 2**. Indeed, a recent meta-analysis across 11 studies, with a total sample of 4,529 OUD patients and 4,168 healthy controls, found that the *Taq*IA1 allele is a risk factor for (OUD) (354). Further, several other minor alleles of *Taq*IA and *Taq*IB are more frequent among OUD patients compared to healthy controls (353, 355, 356, 360, 351).

There is less robust evidence for other *DRD2* polymorphisms in OUD. For example, despite preclinical evidence that rs1076560 may alter D2R expression, genetic association studies between rs1076560 and OUD have been inconsistent (44, 341, 348, 352, 354). In contrast, while the role of rs1799732 on D2R expression is uncertain, subjects with the minor variant have shown to be at higher risk for OUD in the Jordanian Arabic population (352).

The extent to which *DRD2* polymorphisms affect the response to MOUD in patients with OUD is inconsistent across studies. Lawford et al. (372) first reported that the *Taq*IA1 allele was associated with poorer treatment outcomes among Caucasian patients on methadone maintenance therapy. Since then, no group has replicated these findings in Caucasian populations (44, 134, 358, 361). Similarly, no association was found between *Taq*IB and methadone maintenance therapy response nor *Taq*IA and buprenorphine maintenance therapy response (44, 272). However, Crettol et al. (134) did report an association with rs6277 and patients' response to methadone maintenance therapy; patients with the major CC genotype were more likely to abuse illicit opioids on methadone therapy than those with CT or TT genotype. Interestingly, in two [^{11}C]raclopride PET studies, the major C allele of rs6277 was associated with lower striatal D2R availability in healthy volunteers (373, 374), while another [^{11}C]FLB457 PET study found the C allele predicted high extrastriatal D2R availability across the cortex and hypothalamus (340). However, several studies found no association between rs6277 and OUD (44, 134). Further, Doehring et al. (44) found no relationship between rs6277 and methadone maintenance therapy response. Instead, this group found that minor allele carriers of a different polymorphism, rs6275, required greater methadone doses than non-carriers and took longer to reach their maximum methadone dose (44). Thus, genetic studies suggest a role of *DRD2* polymorphisms in treatment response in OUD; however, they remain inconsistent and difficult to replicate.

Several studies have investigated the role of *DRD2* variants on behaviors associated with OUD. The tridimensional personality questionnaire scores personality on harm avoidance, novelty seeking, and reward dependence (375). These scores are used to calculate a borderline index using the equation: borderline index = harm avoidance + novelty seeking − reward dependence (376). Borderline index reflects borderline personality trait, characterized by a fear of abandonment, self-injurious behaviors, and emotional dysregulation (376, 377) (DSM-5). A recent study found that OUD patients had higher harm avoidance and novelty seeking scores and lower reward dependence scores, and thus a higher borderline index, than healthy volunteers (356). Further, Huang et al. (272) found that borderline index scores are inversely correlated with methadone dose, indicating the relevance of borderline index score in OUD treatment. These personality scores have not shown associations with *Taq*IA or *Taq*IB polymorphisms (272, 356). However, the -141C *Del* polymorphism (rs1799732) is associated with higher harm avoidance scores among OUD patients (356). In contrast, Gerra et al. (377) found that OUD patients had lower harm avoidance scores compared to CUD patients and healthy volunteers. However, this study reported that both CUD and OUD patients had higher novelty seeking scores and lower reward dependence scores than healthy volunteers (378). Therefore, this difference in harm avoidance could be rooted in genetic differences between the groups, as -141C *Del* is associated with higher harm avoidance scores in OUD, though Gerra et al. (378) did not report the genetic composition of their cohort (356).

Molecular Imaging: D2R and OUD

[^{11}C]raclopride and [^{123}I]IBZM are widely used radiolabeled D2R antagonists differing *via* regioselectivity used to study D2R distribution, with additional affinity to D3Rs (D2-like inhibitory receptors) (379–381). [^{11}C]NMB is another radiotracer used to study D2R availability with higher affinity for D2Rs over D3Rs than [^{11}C]raclopride and [^{123}I]IBZM (382, 383). Lastly, [^{11}C]FLB-457 is a high-affinity radioligand that targets extrastriatal D2Rs and D3Rs (384).

In contrast to other SUDs, less is certain about D2R availability in OUD. In one [^{11}C]raclopride PET study, OUD participants showed lower D2R availability compared to healthy controls (6). In this

TABLE 2 | Polymorphisms associated with OUD in the dopamine system and imaging correlates.

Gene	Polymorphism	Location	Findings	Author	Year	n	Ethnicity	Imaging Correlates
DRD1	**rs10078866**	Promoter	No significant association with OUD	Zhu et al. (346)	2013	939	Han Chinese	
				Liu et al. (53)	2013	739	Han Chinese	
	rs10078714	Promoter	No significant association with OUD	Liu et al. (53)	2013	739	Han Chinese	
	rs1799914	Exon 1	No significant association with OUD	Zhu et al. (346)	2013	939	Han Chinese	
	rs265975	3' Near	Risk factor for OUD	*Jacobs et al. (347)	2014	286	Caucasian	
	rs265973	3' Near	Risk factor for OUD	*Jacobs et al. (347)	2014	286	Caucasian	
	rs686	3' UTR	Risk factor for OUD	Jacobs et al. (347)	2013	187	African American	
			No significant association with OUD	Zhu et al. (346)	2013	939	Han Chinese	
				Liu et al. (53)	2013	739	Han Chinese	
				Levran et al. (348)	2015	801	African American	
				Levran et al. (349)	2009	369	African American	
	rs267418	3' UTR	No significant association with OUD	Peng et al. (350)	2013	739	Han Chinese	
	rs6882300	3' UTR	No significant association with OUD	Peng et al. (350)	2013	739	Han Chinese	
	rs2168631	3' UTR	No significant association with OUD	Peng et al. (350)	2013	739	Han Chinese	
	rs5326	5' UTR	Risk factor for OUD	*Levran et al. (349)	2009	369	African American	
				Liu et al. (53)	2013	739	Han Chinese	
			No significant association with OUD	Zhu et al. (346)	2013	939	Han Chinese	
				Peng et al. (350)	2013	739	Han Chinese	
	rs4532	5' UTR	No significant association with OUD	Zhu et al. (346)	2013	939	Han Chinese	
				Peng et al. (350)	2013	739	Han Chinese	
				Liu et al. (53)	2013	739	Han Chinese	
			No significant association with methadone dose	Crettol et al. (134)	2008	455	Caucasian	
	rs4867798	5' UTR	No significant association with OUD	Zhu et al. (346)	2013	939	Han Chinese	
				Liu et al. (53)	2013	739	Han Chinese	
	rs10063995	5' UTR	No significant association with OUD	Zhu et al. (346)	2013	939	Han Chinese	
	rs265981	5' UTR	Protective against OUD	Liu et al. (53)	2013	739	Han Chinese	
DRD2	**rs6275**	Exon 7	Risk factor for OUD	Wang et al. (351)	2016	633	Han Chinese	
			Higher methadone dose	Doehring et al. (44)	2009	184	Caucasian	
			No significant association with OUD	Al-eitan et al. (352)	2012	425	Jordanian Arabic	
				Doehring et al. (44)	2009	184	Caucasian	
	rs6277	Exon 7	Higher response rates to methadone treatment	Crettol et al. (134)	2008	455	Caucasian	
			No significant association with OUD	Doehring et al. (44)	2009	184	Caucasian	
				Crettol et al. (134)	2008	455	Caucasian	
	rs1801028	Exon 7	No significant association with OUD	Doehring et al. (44)	2009	184	Caucasian	
	rs1125394	Intron 1	Risk factor for OUD	Wang et al. (351)	2016	633	Han Chinese	
				Al-eitan et al. (352)	2012	425	Jordanian Arabic	
	rs17115583	Intron 1	Protective against OUD	Wang et al. (351)	2016	633	Han Chinese	
	rs1079597 (taqIB)	Intron 1	Risk factor for OUD	Tsou et al. (353)	2017	950	Han Chinese	-Low D2R availability in healthy controls (334, 336*)
				*Zhang et al. (354)	2018	593	Han Chinese	
				Xu et al. (355)	2004	799	Chinese	
				Wang et al. (351)	2016	633	Han Chinese	
				Vereczkei et al. (337)	2013	858	Central European	
			No significant association with methadone dose	Huang et al. (272)	2016	138	Taiwanese	
	rs4648319	Intron 1	Risk factor for OUD	Tsou et al. (353)	2017	950	Han Chinese	
	rs4648317	Intron 1	No significant association with OUD	Doehring et al. (44)	2009	184	Caucasian	
	rs7350522	Intron 1	No significant association with OUD	Wang et al. (351)	2016	633	Han Chinese	
	rs2075654	Intron 2	Risk factor for OUD	Al-eitan et al. (352)	2012	425	Jordanian Arabic	
	rs2734836	Intron 2	Risk factor for OUD	Al-eitan et al. (352)	2012	425	Jordanian Arabic	

(Continued)

study, all OUD patients actively used heroin and most, but not all, were also on methadone therapy (6). In another [^{11}C]raclopride PET study, recently detoxed OUD patients showed lower D2R availability than healthy controls (7). These patients also demonstrated lower levels of DA release in response to a methylphenidate challenge in comparison to healthy controls (7). In a [^{123}I]IBZM SPECT study, the OUD patients were abstinent without maintenance therapy anywhere from 1 to 24 weeks (318). Zijlstra et al. (318) observed a negative correlation in length of opioid use history with striatal D2R availability. In contrast, two [^{11}C]raclopride studies observed no differences in D2R availability between OUD patients receiving methadone therapy and healthy controls (19, 20). These findings suggest the potential therapeutic benefit of MOUD in restoring neurochemical imbalances resulting from substance abuse. These results demand further investigation into the relationship between OUD and D2R availability, particularly in the context of MOUD.

TABLE 2 | Continued

Gene	Polymorphism	Location	Findings	Author	Year	n	Ethnicity	Imaging Correlates
	rs1800498 (taqID)	Intron 2	Risk factor for OUD	Tsou et al. (353)	2017	950	Han Chinese	
				*Xu et al. (355)	2004	799	Chinese	
			No significant association with OUD	Vereczkei et al. (337)	2013	858	Central European	
				Doehring et al. (44)	2009	184	Caucasian	
				Xu et al. (355)	2004	663	German	
	rs2283265	Intron 4	Risk factor for OUD	Al-eitan et al. (352)	2012	425	Jordanian Arabic	
				*Levran et al. (348)	2015	801	African American	
			No significant association with OUD	Zhang et al. (354)	2018	593	Han Chinese	
	rs1076560	Intron 6	Risk factor for OUD	Al-eitan et al. (352)	2012	425	Jordanian Arabic	-Lower levels of striatal D2R availability in healthy controls (344)
				Doehring et al. (44)	2009	184	Caucasian	
				Clarke et al. (341)	2014	2649	African American and European American	
				*Levran et al. (348)	2015	801	African American	-No association with striatal D2R availability in healthy controls (345)
			No significant association with OUD	Zhang et al. (354)	2018	593	Han Chinese	
	rs2734842	3' Near	Risk factor for OUD	*Zhang et al. (354)	2018	593	Han Chinese	
	rs2242591	3' Flanking Region	Risk factor for OUD	*Zhang et al. (354)	2018	593	Han Chinese	
	rs6278	3' UTR	Risk factor for OUD	*Zhang et al. (354)	2018	593	Han Chinese	
	rs6279	3' UTR	Risk factor for OUD	*Zhang et al. (354)	2018	593	Han Chinese	
	rs1799732	5'- UTR	Risk factor for OUD (C deletion)	Al-eitan et al. (352)	2012	425	Jordanian Arabic	-Combined minor variants associated with higher striatal D2R availability in healthy controls (334) -No association with extrastriatal D2R in healthy controls (340)
			No significant association with OUD	Teh et al. (356)	2012	93	Han Chinese	
				Zhang et al. (354)	2018	593	Han Chinese	
				Doehring et al. (44)	2009	184	Caucasian	
	rs12364283	5' UTR	No significant association with OUD	Doehring et al. (44)	2009	184	Caucasian	
	rs1799978	5' UTR	No significant association with OUD	Doehring et al. (44)	2009	184	Caucasian	
				Teh et al. (41)	2012	93	Han Chinese	
			Risk factor for OUD	*Hung et al. (357)	2011	321	Han Chinese	
			Higher methadone doses	Hung et al. (357)	2011	321	Han Chinese	
			No significant association with relapse rates on methadone treatment	Bawor et al. (358)	2015	240	Mixed	
				Doehring et al. (44)	2009	184	Caucasian	
ANKK1	**rs4938013**	Exon 2	Risk factor for OUD	Nelson et al. (359)	2013	3485	Caucasian	
				*Zhang et al. (354)	2018	593	Han Chinese	
	rs7118900	Exon 5	Risk factor for OUD	*Zhang et al. (354)	2018	593	Han Chinese	
				*Levran et al. (348)	2015	801	African American	
	rs1800497 (taqIA)	Exon 8	Risk factor for OUD	Teh et al. (356)	2012	93	Han Chinese	-Low D2R availability in healthy controls (334, 335, 336*)
				Hou and Li (360)	2009	1030	Chinese/East Asian	
				*Vereczkei et al. (337)	2013	858	Central European	
				Tsou et al. (353)	2017	950	Han Chinese	
				*Zhang et al. (354)	2018	593	Han Chinese	
				*Doehring et al. (44)	2009	184	Caucasian	
			No significant association with OUD	Al-eitan et al. (352)	2012	425	Jordanian Arabic	

(Continued)

TABLE 2 | Continued

Gene	Polymorphism	Location	Findings	Author	Year	n	Ethnicity	Imaging Correlates
				Barratt et al. (361)	2006	166	Mixed	
			No significant association with methadone dose	Crettol et al. (134)	2008	455	Caucasian	
			No significant association with methadone or buprenorphine therapy success	Barratt et al. (361)	2006	166	Mixed	
			Improved withdrawal among methadone-maintained patients	Barratt et al. (361)	2006	166	Mixed	
	rs877138	5'- Flanking Region	Risk factor for OUD	Nelson et al. (359)	2013	3485	Caucasian	
DAT1	**9-repeat VNTR**	3' UTR	Risk factor for OUD	Galeeva et al. (362)	2002	287	Caucasian males	-Higher striatal DAT availability (363–365) -No association with striatal DAT availability (366, 367)
			No significant association with OUD	Hou and Li (360)	2009	1030	Han Chinese	
				Yeh et al. (368)	2010	1046	Han Chinese	
	10-repeat VNTR	3' UTR	Risk factor for OUD	Ornoy et al. (369)	2016	158	Israeli Jewish Females	-Higher striatal DAT availability (370, 371) -No association with striatal DAT availability (366, 367)

SNP associations refer to the minor allele.
**Nominal significance.*

DRD1

DRD1 Background

The D1R is the most abundant DA receptor in the brain (380). Coded by *DRD1*, this excitatory GPCR is widespread, but most densely expressed in the dorsal striatum, hippocampus, amygdala, and neocortex, as illustrated in **Figure 1** (385–388). D1Rs influence learning and memory *via* association with N-methyl-D-aspartate (NMDA)-mediated long-term potentiation as well as impact D2R-mediated events and regulate addiction-associated behaviors such as impulsivity (389–396). D1Rs are important mediators of several reward-related processes and there is evidence that D1Rs are required and sufficient for drug reward and conditioning (397, 398).

D1R function is relevant in OUD because DA release triggered by opioid-induced MOP receptor activation indirectly stimulates D1Rs and associated reward circuitry (69). While one post-mortem study showed lower D1R mRNA levels in the putamen and NAc shell in OUD subjects relative to controls (347), another postmortem analysis showed higher D1R mRNA and protein expression in VTA, NAc, and amygdala in the brains of opioid abusers compared to controls (399). This difference may be attributed to the difference in populations studied. Where Sadat-Shirazi et al. (399) studied patients who exclusively abused opioids, Jacobs et al. (347) included polysubstance users.

In addition, pharmacological manipulations of D1Rs in preclinical models of OUD demonstrate alterations in behaviors associated with dependence and withdrawal. For example, infusion of D1R agonist SKF 38393 into the NAc enhances, while antagonist SCH 23390 blunts, conditioned place preference in morphine-addicted rats (400). Additionally, infusions of SCH 23390 into the NAc core reduced cue-induced heroin-seeking in dependent rats (401). Furthermore, D1R agonist SKF 82958 relieved naloxone-precipitated withdrawal symptoms in morphine-dependent rats (402). These findings highlight the importance of D1Rs in OUD and correspond with other SUD models. For example, SCH 23390 infusion blocks reinstatement of cocaine-seeking in rats, while D1R agonist SKF 81297 reinstates cocaine-seeking (403, 404). In addition to pharmacological D1R blockade, D1R knock-out mice fail to self-administer cocaine (397). In models of AUD, NAc shell infusions of SCH 23390 blunt, while infusions of D1R agonist A-77636 enhance, ethanol self-administration in alcohol-preferring rats (405).

D1 and MOP receptors directly colocalize into hetero-oligomers in the rat cortex and striatum (including accumbens nucleus), regions of importance in reward and locomotor activity. Together, they promote locomotor sensitization in rats chronically treated with morphine, suggesting this association may be involved in the long-term neuronal changes associated with addiction (406, 407).

DRD1 Polymorphisms

While less attention has been given to variations in *DRD1* than *DRD2/ANKK1*, there are several functional polymorphisms that have been studied in the context of SUDs. One study demonstrated that rs5326A, located in the 5' untranslated region, correlated with decreased *DRD1* promoter strength in an *in vitro* luciferase model (408). Other *DRD1* polymorphisms may increase vulnerability to OUD by interacting with the glutamatergic system in the brain. Homer scaffold protein 1 (*HOMER1*) encodes HOMER1, a postsynaptic protein that facilitates glutamatergic

transmission (409). Excitatory glutamatergic signaling has been shown to underlie the persistent compulsion to use drugs, suggesting SNPs disrupting this gene interaction may be relevant in OUD (410). In a post-mortem analysis of Caucasian samples, the *DRD1* polymorphism rs265973 associated with HOMER1 expression in the striatum (347). Interestingly, the minor T allele associated with higher levels of striatal HOMER1 mRNA among the OUD cohort, but associated with lower levels of striatal HOMER1 mRNA in the control cohort (347). Thus, it is possible *HOMER1*-associated genetic variants disrupt glutamatergic and dopaminergic signaling and contribute to OUD.

Genetic Association Studies: *DRD1* and OUD

Preliminary findings suggest a role of *DRD1* SNPs in OUD, as outlined in **Table 2**. For example, Liu et al. (411) found that two SNPs located in the 5' untranslated region of *DRD1*, major allele rs265981G and minor allele rs5326A, associated with OUD in a Han Chinese population. Levran et al. (348, 349) also found a trend toward an association between rs5326A and OUD in an African American sample. However, other groups were unable to replicate these findings (346, 350). Jacobs et al. (347) found a nominally significant association between *DRD1* SNP rs265973 and OUD among Caucasians, but not African Americans. This provides further evidence of an association between *HOMER1* and OUD, perhaps with ethnicity-dependent effects.

Several studies demonstrate that *DRD1* variants associate with the duration of transition from the first use to dependence of opioids (346, 350). The duration of transition from the first use to dependence is of clinical significance; patients with a more rapid transition to dependence have poorer treatment outcomes and more severe SUDs (412, 413). Zhu et al. (346) found that the minor alleles of rs686 and rs4532 associated with a longer transition period. Peng et al. (350) were unable to replicate the rs4532 association, but found that homozygotes for the major alleles of rs5326 and rs6882300 had an accelerated transition to OUD. Interestingly, while these SNPS associated with the transition from first use to dependence, neither study found that they were associated with increased risk for OUD (346, 350).

DRD1 variants have also been implicated in subjective ratings of pleasure in response to opioids, both upon first use and after dependence (346). Typically, the pleasurable feeling associated with opioids increases with duration of use: most patients report a negative response upon their first use and a euphoric response after dependence (133, 346). This suggests that chronic opioid use induces changes to reward-related circuitry. One potential mechanism is through D1R-mediated phosphorylation of NMDA, contributing to long-term potentiation (414). *DRD1* variants have been associated with this reward sensitization process in a Han Chinese population (346). This study revealed that *DRD1* SNPs that modulate the subjective response to opioids upon first use are distinct from those that do so after dependence. Specifically, the minor alleles of rs5326, rs10063995, and rs10078866 are associated with a non-pleasurable first use of opioids, but are not associated with the subjective response after dependence. Conversely, the minor variants of rs686 and rs4532 are associated with less pleasurable responses to opioids after dependence, but are not associated with the initial response (346). Findings from a rat study indicate that there is a reward-switching mechanism in opioid response within the basolateral amygdala in which D1R signaling is associated with reward upon first use and D2R signaling with reward after dependence (415). Thus, it is possible that rs686 and rs4532 associate with less pleasurable opioid responses after dependence by modulating D2R activity.

Molecular Imaging: D1R and OUD

No molecular imaging studies have yet assessed D1R availability in OUD or in *DRD1* polymorphism carriers. Few studies have examined the relationship between other SUDs and D1R levels. [^{11}C]NNC 112 and [^{11}C]SCH 23390 are radiolabeled D1R antagonists that differentially distribute throughout the brain; however, both display high affinity in the striatum and extrastriatal regions (416–418). In one [^{11}C]NNC 112 study, D1R availability in CUD patients was not significantly different than in healthy controls (419). In contrast, studies utilizing [^{11}C]SCH 23390 PET reveal individuals with tobacco use disorder have lower D1R availability than healthy controls (420, 421). These limited findings highlight the need for increased investigation into D1R availability in addiction.

DAT1

DAT1 Background

DAT are plasma membrane proteins essential for the clearance of DA from the synapse; they play a critical role in regulating DA neurotransmission, especially in the striatum (422–426). DAT harness the electrochemical gradient to transport two sodium ions with a DA molecule into the cell, thus regulating extracellular DA concentrations (423). DAT are coded by *DAT1*, a gene widely studied for its role in substance abuse (427).

DAT1 Polymorphisms

The most studied polymorphisms of *DAT1* are VNTRs in the 3' untranslated region, which may affect DAT expression (428–431). The most common variants are those with 9 or 10 repeats of the 40 base pair sequence (432) and multiple molecular imaging studies have investigated their functional effects. In several [^{123}I]β-CIT SPECT studies, 9-repeat VTNR carriers demonstrated higher striatal DAT availability than the 10-repeat homozygotes (363–365). In contrast, two [^{123}I]β-CIT SPECT studies found those homozygous for the 10-repeat allele had higher striatal DAT density compared to non-10-repeat carriers (370, 371). Finally, Martinez et al. (366) and Lynch et al. (367) found no effect of VNTR polymorphisms on striatal DAT expression in a [^{123}I]β-CIT SPECT and [^{99m}Tc]TRODAT-1 study, respectively. Lastly, Guindalini et al. (433) found that the rare 6-repeat VNTR genotype reduced DAT1 expression *in vitro*, particularly when cocaine was added to the culture. However, the effects of the 6-repeat VNTR polymorphism on *DAT1* availability has not been assessed *in vivo* with PET methodology. Thus, further research is required to determine these polymorphisms' functional effects on DAT expression and availability.

Genetic Association Studies: *DAT1* and OUD

Genetic association studies of *DAT1* and OUD have yielded inconsistent results. While Galeeva et al. (362) found an association between 9-repeat VNTR allele and OUD in an ethnic Russian and Tartar male population, later studies in Han Chinese populations did not observe any association (360, 368). Ornoy et al. (369) examined the heritability of *DAT1* ADHD risk alleles in Sephardic and Ashkenazi Jewish heroin-dependent individuals and their children. They found that mothers with OUD were more likely to be carriers of the *DAT1* 10-repeat allele than mothers without OUD. This association was not seen in fathers and was not explained by prevalence of ADHD among mothers with the polymorphism. Further, the children of heroin-dependent parents were more likely to inherit the 10-repeat allele than children of healthy volunteers (369). However, it is unclear how these VNTR polymorphisms impact DAT availability and thus vulnerability to OUD, as molecular imaging studies have conflicting results (363–367, 370, 371).

Polymorphisms in *DAT1* have been associated with other SUDs, which may provide insight into their functional effects on DA signaling in addiction. *DAT1* VNTR has been associated with OUD (362) as well as AUD in Western European and Japanese populations (47, 434). A meta-analysis also found that the 9-repeat VNTR was associated with increased withdrawal severity in AUD (435). The 6-repeat VNTR genotype was found to be a risk factor for CUD, but this variant has not yet been studied in OUD (45). Thus, it seems that *DAT1* VNTR polymorphisms may affect DAT expression and contribute to SUDs.

Evidence suggests that the number of VNTR in patients with OUD influences their response to treatment. In each study, a "poor" treatment outcome indicates continued heroin use or treatment drop-out, whereas a "successful" outcome indicates cessation of illicit opioid use. In patients receiving buprenorphine therapy, carriers of the 10-repeat VNTR allele had poor outcomes more often than successful outcomes (436). Conversely, 6-, 7-, and 11-repeat VNTR allele carriers had successful outcomes in response to buprenorphine therapy more often than not (436). Gerra et al. (436) suggest that these variations in *DAT1* may modulate buprenorphine-associated DA transmission and thus affect treatment success. In a study of both oral and implanted naltrexone therapy, Krupitsky et al. (437) found that OUD patients with the 9-repeat VNTR allele had poor outcomes more often than successful ones on both forms of naltrexone. Thus, genotyping *DAT1* VNTR could be useful in OUD therapy selection.

While van Gestel et al. (438) reported an association between *DAT1* VNTR polymorphisms and novelty seeking, a personality trait associated with SUDs (439), other studies have failed to replicate this finding (440, 441).

Molecular Imaging: DAT and OUD

Several molecular imaging studies have assessed DAT availability in SUDs utilizing DAT-sensitive tracers including [^{99m}Tc]TRODAT-1, [^{123}I]β-CIT, [11C]WIN 35,428, [11C]cocaine, and [^{11}C]CFT. There is evidence from molecular imaging studies that DAT availability is altered in SUDs. For example, CUD is associated with higher striatal DAT concentrations compared to healthy controls (54, 55), while methamphetamine-dependent individuals demonstrate lower striatal DAT availability compared to healthy controls (51, 57, 58). Alcohol and tobacco dependence have also been associated with lower striatal DAT levels (59, 60–62); however, other studies have observed no association between DAT levels and alcohol and tobacco dependency (22, 442). Although varied, these results overall suggest that DAT plays a role in SUDs.

PET and SPECT studies suggest that OUD is associated with decreased DAT availability. Chronic heroin users, detoxed abstainers, and methadone-maintained patients all present lower striatal DAT levels than healthy controls (48–53). A [^{99m}Tc]TRODAT-1 SPECT study comparing DAT concentrations between recently detoxed heroin-dependent patients and recently detoxed methamphetamine-dependent patients showed that both had lower striatal DAT availability than healthy controls and had no differences between them (51). In contrast, Cosgrove et al. (443) utilizing [^{123}I]β-CIT SPECT imaging, reported no differences in striatal DAT levels between heroin users and healthy controls, though they acknowledged the limitations of their small sample sizes (443).

DAT availability may also vary based on the use of MOUD. For example, one [^{11}C]CFT PET study reported methadone-maintained OUD patients showed lower DAT availability in the bilateral putamen than abstinent OUD patients, with both presenting lower striatal DAT availability compared to healthy controls (49). Further, while methadone-maintained patients showed lower DAT availability in caudate and putamen compared to controls, abstinent OUD patients showed lower DAT availability in the caudate only, suggesting that abstinence from opioids may partially recover DAT availability (49). However, a [^{99m}Tc]TRODAT-1 SPECT study found similar striatal DAT availability between methadone-maintained and abstinent OUD patients (50). This discrepancy may be due to methodological differences; in one study, patients were at least 6 months abstinent (49), while in the other, patients were abstinent for only 3 months or less (50). In a within-subjects [^{99m}Tc]TRODAT-1 SPECT study, Liu et al. (53) observed a 14–17% increase in DAT levels in the caudate and putamen of 64 heroin-dependent patients after 6 months of treatment with traditional Chinese Jitai tablets, an herbal remedy associated with withdrawal mitigation. No significant increase in DAT levels was observed in the placebo-treated group. However, even among the medication group, DAT availability was not restored to that of healthy control levels (53). Thus, further studies are required to determine the effects of MOUD compared to sustained abstinence on DAT availability.

CONCLUSION

Preclinical and clinical studies have demonstrated the importance of the opioid and DA systems in SUDs, including OUD. Polymorphisms within these systems have functional consequences that may influence a number of modalities in addiction, including vulnerabilities, addiction severity, treatment response, and relapse rates. PET and SPECT methodology allow for the study of these receptor systems in both healthy and substance-dependent populations and provide insight into the neurobiology of OUD.

Within the opioid system, the MOP receptor has been most closely studied in the context of OUD. The minor allele of the *OPRM1* rs1799971 SNP has been widely linked to a reduction in

MOP receptor availability (100–105). The implications of this in OUD, however, remain elusive; findings from genetic association studies are varied and seem largely ethnicity-dependent (109). The KOP and NOP receptors have also been studied in relation to OUD; both play important roles in the dysphoric effects of drug abuse seen during withdrawal, including modulating activation of the HPA axis (16, 291, 294, 295, 444). A number of polymorphisms in *OPRK1* have been associated with OUD and opioid withdrawal severity (147, 155, 156, 232). Similarly, VNTR polymorphisms in *PDYN* have been correlated with opioid withdrawal, suggesting the importance of dynorphin-KOP receptor signaling system in the mediation of stress-induced withdrawal and compulsive drug-seeking (155). Lastly, genetic variants in both *PDYN* and *OPRL1* have been associated with personality traits and behaviors associated with SUDs, another indication of their roles in OUD (235, 236, 445). The DOP receptor has an inverse function to the KOP receptor, in that DOP receptor activation improves negative emotional states (255). While several *OPRD1* polymorphisms correlated with heroin dependence (130, 136, 138–141, 146, 150), it is likely that the effects are ethnicity-dependent, as several other studies found no significant associations between *OPRD1* polymorphisms and OUD (137, 140, 144).

The DA system has several well-studied polymorphisms that have been linked with OUD and other SUDs. For example, polymorphisms in *DRD2/ANKK1*, in particular the *Taq*IA and *Taq*IB SNPs, may result in lower D2R availability (321, 334, 335) and have been associated with addictive behaviors including OUD (330, 332, 354, 446, 447). Less studied *DRD2* polymorphisms may also affect D2R expression (341, 344) but results have been varied. Additionally, *DRD2* polymorphisms may associate with response to medications for OUD; however, there are conflicting reports and further research is required (44, 134, 272, 335, 358, 361, 372). Fewer conclusions can be drawn about *DRD1*; for example, several *DRD1* polymorphisms were initially associated with a rapid transition from first opioid use to opioid dependence, but the results could not be replicated (346, 350). Lastly, lower DAT availability has also been associated with OUD (48–53). Both the 9- and 10-repeat VNTR alleles have been associated with lower DAT availability (363–365, 370, 351); thus, more studies are required to pinpoint the effects of the different repeat VNTR polymorphisms in OUD.

While there is strong preliminary evidence of the role of genetic variants in the DA and opioid systems in OUD, more molecular imaging studies are required in individuals with OUD. In particular, studies utilizing PET tracers that target the less-studied opioid receptors, D1R, D3R, and DAT, would greatly contribute to our understanding of the complex interplay between these receptors in opioid addiction. For instance, as of yet, no imaging studies have examined DOP, KOP, NOP, D1, or D3 receptors in individuals with OUD. One of the most important molecular imaging research questions in OUD is how the different MOUD may alter the dopamine and opioid receptor systems and if these changes are associated with higher rates of successful abstinence. Current imaging studies largely group abstinent and medication-maintained OUD participants together and compare to healthy controls; however, analyses between OUD subgroups would shed light on any neurochemical benefits of MOUD. This would help inform treatment and ultimately improve outcomes for those suffering from OUD. Additionally, opioid receptor antagonist challenge studies would help assess the interaction between drugs like naloxone and semi-synthetic or synthetic opioids, improving safety and efficacy of overdose reversal and prevention. Finally, molecular imaging studies examining the effects of polymorphisms in the DA and opioid systems would help elucidate the genetic components of OUD. The literature relating to genetic association studies in OUD does suggest that certain polymorphisms are risk factors for OUD or may affect treatment outcomes. However, given that these associations are largely ethnicity-dependent, it is important to replicate these findings. Finally, there seem to be sex effects both on genetic association studies and PET/SPECT findings; therefore, future studies could investigate the sex differences in development and outcome of OUD. Further investigation into the underlying genetic factors of OUD and treatment response is critical to help curb the opioid crisis by means of addiction prevention, novel pharmacological targets, and precision treatment.

AUTHOR CONTRIBUTIONS

PM, CW, NV, and G-JW contributed to the conception and design of the study. JB, DK, DF, and CK conducted a literature search and wrote the first draft. All authors contributed to manuscript revision, and read and approved the submitted version.

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Bias Toward Drug-Related Stimuli Is Affected by Loading Working Memory in Abstinent Ex-Methamphetamine Users

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Background: There is a trade-off between drug-related impulsive process and cognitive reflective process among ex-drug abusers. The present study aimed to investigate the impulsive effects of methamphetamine-related stimuli on working memory (WM) performance by manipulating WM load in abstinent ex-methamphetamine users.

Methods: Thirty abstinent ex-methamphetamine users and 30 nonaddict matched control participants were recruited in this study. We used a modified Sternberg task in which participants were instructed to memorize three different sets of methamphetamine-related and non–drug-related words (three, five, or seven words) while performing a secondary attention-demanding task as an interference.

Results: Repeated-measures ANOVA revealed that reaction times of abstinent ex-methamphetamine users increased during low WM load (three words) compared to the control group ($p = 0.01$). No significant differences were observed during high WM loads (five or seven words) (both p's > 0.1). Besides, reaction times of the experimental group during trials with high interference (three, five, or seven words) were not significantly different compared to the control group ($p > 0.2$).

Conclusion: These findings imply that increasing WM load may provide an efficient buffer against attentional capture by salient stimuli (i.e., methamphetamine-related words). This buffer might modify the effect of interference bias. Besides, presenting methamphetamine-related stimuli might facilitate the encoding phase due to bias toward task-relevant stimuli. This finding has an important implication, suggesting that performing concurrent demanding tasks may reduce the power of salient stimuli and thus improve the efficiency of emotional regulation strategies.

Keywords: addiction, dual-process models, working memory bias, working memory interference bias, working memory capacity, abstinent ex-methamphetamine users

INTRODUCTION

Methamphetamine, which is an extremely addictive neurotoxic drug, is the second most used illegal drug after cannabis (1). Prevalence of methamphetamine abuse is 1.2 million people in the United States and 17.2 million people around the world (2). Chronic use of methamphetamine has been associated with multiple physical health problems (e.g., cardiovascular disease), mental health problems (e.g., depression) (3–5), and daily functioning problems (e.g., impulsivity) (6, 7), which can also affect the brain and neurocognitive functions (8–10).

Addiction to methamphetamine—similar to addiction to other substances—is often resistant to conventional interventions (11). Therefore, a critical need exists to address additional and appropriate interventions such as nonpharmacological approaches. In line with this, theoretical models and empirical evidence support a role for the modulation of addiction with cognitive-based approaches (11–17). For example, dual-process models of addiction suggest that addictive behaviors are affected by the dominance of drug-related impulsive processes over the reflective processes (13, 18, 19). Several studies have shown that the drug-related impulsive process is spontaneous, fast, and relatively unconscious, while the reflective process is deliberate, slow, and conscious (13, 18, 19).

There is a trade-off between the drug-related impulsive process and reflective process (11, 13, 15). The drug-related impulsive process is affected by the repeated abuse of drugs (20). Impulsive behaviors in addiction are referred to as behaviors that are associated with selecting an immediate reward, making risky decisions (21), generating memory impairment (22), and showing bias toward salient drug stimuli (12, 23, 24). For example, methamphetamine-related stimuli can involuntarily catch the attention of methamphetamine users (i.e., attentional bias). Attentional bias toward methamphetamine-related stimuli can increase the effect of subjective craving, which may contribute to relapse (25, 26). However, the drug-related impulsive process can be modulated by the reflective system (14, 26). Working memory (WM), which is considered as the main part of the reflective process, can modulate the drug-related impulsive process (14, 26, 27). WM is a temporary storage system that can actively maintain information and manipulate stored information (28). WM is involved in the modulation of the processing of irrelevant information by attentional mechanisms (i.e., the reflective process) (29). However, WM processes can negatively be influenced by emotionally salient stimuli like those related to drugs (18). As a result, the bias toward emotionally salient stimuli can lead to deficits in WM performance (18). Therefore, it is important to understand how WM can modulate the attention given to methamphetamine-related stimuli and vice versa.

Given that WM performance might be impaired in methamphetamine users (10, 30) and in abstinent methamphetamine users, it is plausible that the ability to apply attentional control over methamphetamine-related stimuli is reduced as a result of impaired WM performance. For example, a systematic review on methamphetamine use and cognitive function reported that cognitive domains (e.g., WM performance, attention, cognitive flexibility, inhibitory control, decision making) in methamphetamine users were decreased compared to the control group (31). This reduced cognitive performance was associated with deficits in the brain measures, including lower metabolism, gray matter density, fractional anisotropy, and activation (31). For example, the study of abstinent methamphetamine users showed that WM performance (during a one-back cued response, one- back, two-back, and one-increment tasks) is decreased in abstinent methamphetamine users compared to control group (32). In this study, abstinent methamphetamine users showed increased brain activity in left occipital and right posterior parietal lobe compared to control group, while they showed decreased activity in bilateral putamen/insular cortex and right lateral compared to control group (32). Another study showed a correlation between performance on the delayed recall and increased metabolism in the thalamus in abstinent methamphetamine users compared to the control group (33). Another study also reported a correlation between performance on the word-recall task and hippocampal volume, which was smaller in the abstinent methamphetamine users than in the control group (34). These studies have indicated a decreased cognitive function in methamphetamine users in several domains, including WM performance (31).

Effective cognitive control over addiction encompasses more than simply disengaging attention from methamphetamine stimuli; it is also necessary to maintain attention toward nonmethamphetamine information (14, 35). WM allows us to maintain and prioritize relevant information in the face of irrelevant information (28). Evidence supported the role of WM, and the corresponding processes, in the control of attention (29). To understand effective cognitive control over addiction to methamphetamine, we first need to know the trade-off between the top-down effect of WM in attentional control (reflective process) over methamphetamine-related stimuli and the bottom-up effect of attentional bias in WM (impulsive process) (18).

Studies revealed that automatic attentional mechanisms (i.e., impulsive processes) are not independent of the available processing resources (29, 36). However, investigating the effect of WM capacity (i.e. the ability to actively store information despite ongoing processing, which is an indicator of limited cognitive resources) on the interaction between the reflective process and drug-related impulsive processes is a missing piece in the literature (37–43). Many studies have examined the effect of attentional bias in drug-dependent populations versus control groups (23–24, 25, 44–47). However, according to our knowledge, no study to date has investigated the interactive effect of both bias and WM capacity in abstinent ex-methamphetamine users versus a control group. Therefore, the current study investigated the effect of bias and load on WM maintenance in different ways: first, by showing drug-related words, which are task-relevant stimuli that can facilitate the encoding process; next, by applying an interference task, which can disturb the process of rehearsal and needs to be inhibited; and finally, by increasing WM loads, which can result in greater rehearsal demands. Investigating the effect of these WM manipulations independently in combination with WM load can help determine factors that might contribute

Abbreviations: WM, Working Memory; RTs, Reaction Times.

to dual-process models of methamphetamine addiction and may lead to the development of effective assessment tools and interventions.

METHODS

Ethics Approval

All experimental procedures corresponded to the standards set by the latest revision of the Declaration of Helsinki and were approved by the ethical committee of the Institute for Cognitive Sciences Studies, Tehran, Iran. All participants provided written informed consent, acknowledging their right to withdraw from the experiment without prejudice.

Showing methamphetamine cues to participants may increase the possibility of relapse. Concerning this important ethical issue, we used methamphetamine-related words instead of real substances. In addition, participants were monitored in the following weeks for any signs of drug craving, and they also had access to psychological interventions to manage potential drug cravings.

Participants

Thirty abstinent ex-methamphetamine users (all men, 20–47 years old, experimental group) and 30 participants without a history of addiction or drug abuse (all men, 20–50 years old, control group) were recruited in the current study (**Table 1**). The experimental group was recruited from former methamphetamine-dependent users who were admitted to Vardij Abstinence-Based Residential Centre, Karaj, Iran. This treatment center specializes in amphetamine-type stimulant dependence and is located in a rural area near Tehran—a part of the therapeutic network belonging to Rebirth Society Organization (a nonprofit charity). The abstinent ex-methamphetamine users in this center were relatively homogeneous, and only men were admitted. Participants in the control group (all males) were recruited from employees of Shahid Beheshti University, Tehran, Iran. They reported no history of drug abuse. Both groups were right-handed and were matched for age (20–50 years) and educational level (<12 years of school. Inclusion criteria for the experimental group included having a history of methamphetamine abuse in the past 12 months prior to entering the treatment center (methamphetamine dependence based on *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criteria). The most common mean of drug administration was smoking.

TABLE 1 | Demographic and substance abuse characteristics.

Descriptive	Experimental group	Control group
Gender (men)	30	30
Age (years)	31.5 ± 1.22	28.07± 1.42
Education (years)	11.97 ± 0.47	12.78 ± 0.5
Duration of meth abstinence (day)	17.26 ± 1.43	—
Duration of meth dependence (months)	45.2 ± 4.87	—

Values are reported as mean ± SEM.

Subjects had to be abstinent from any drugs except cigarettes for at least a week before the experiment, with confirmation by urine testing.

Exclusion criteria for both the experimental group and the control group included any current or past major clinical neurological disorders, central nervous system–effective medication intake, or any major clinical psychiatric disorders (in Axis I, except substance-related disorders). We excluded data of two participants from the experimental group and data of two participants from the control group because of their inaccurate responses to the cognitive task.

The Modified Sternberg Task With Interference

To test WM performance of participants, we adopted a modified Sternberg task with interference. The task was designed with MATLAB (The MathWorks, Inc., Natick, MA, United States) and used the Psychtoolbox ran on a Microsoft Windows 7 operating system. The modified Sternberg task fits in the category of a complex span task. It consisted of three steps: memorizing a list of words (encoding step), performing a secondary task (as an interference step), and selecting the memorized word among presented words (retrieval step). In order to obtain different levels of WM load, the Sternberg task included a list of either three, five, or seven words (**Figure 1**) (19).

We selected a list of words, that were validated in a previous study based on their mean of craving and emotional valence (49). This list consisted of 24 Persian words: 12 were selected randomly from a list of methamphetamine-related words (i.e., experimental; ex: methamphetamine, drugs), and 12 were selected randomly from a list of non–drug-related words (i.e., neutral; ex: scissors, carriage). All words had two syllables with a maximum of four letters. They were presented with the same font in white color on a black background screen.

Proceeding of the Modified Sternberg Task With Interference

The first step (i.e., WM set) consisted of the presentation of a list of three, five, or seven words (encoding step). Participants had to memorize the presented word list. Words were presented randomly according to methamphetamine-related or non–drug-related content. For example, in the 3-word memory set, there were either two methamphetamine-related words and one non–drug-related word or vice versa. In the 5-word WM set, there were either three methamphetamine-related words and two non–drug-related words or three non–drug-related stimuli and two methamphetamine-related words. Each word was presented for 750 ms with an interstimulus interval of 500 ms. Two fixation crosses (++) were presented in the center of the screen to signal the end of this step (**Figure 1**, left panel).

The second step consisted of a secondary task (as an interference step). In this step, four words were presented one after the other. Two of these four words were methamphetamine-related words, and two were non–drug-related. These words were new and different from the words used in the memory set step. Each word was presented for 500 ms, after which time the font

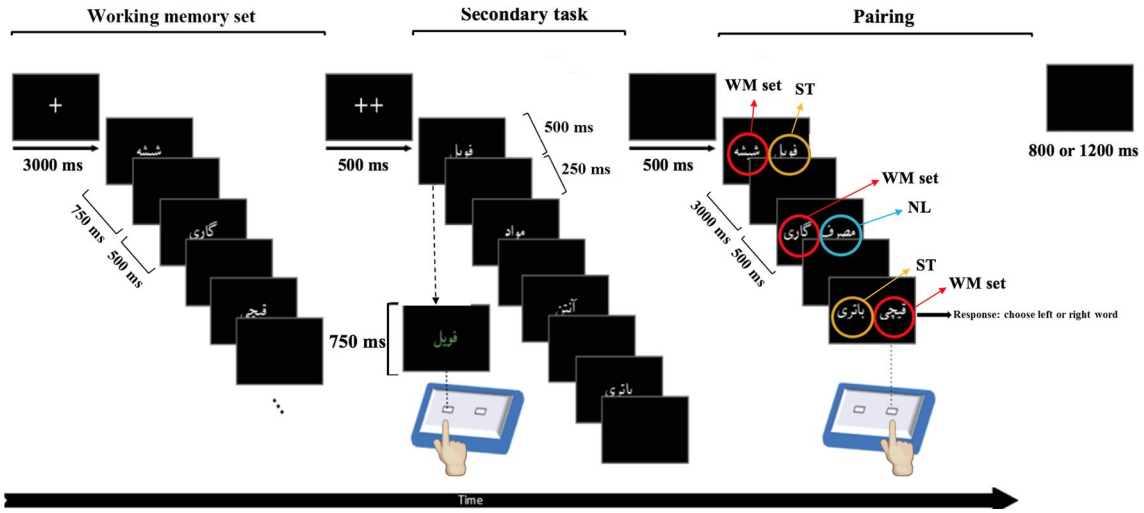

FIGURE 1 | Modified Sternberg task with interference.This Figure is an example of one trial with different responses at different steps of the modified Sternberg task with interference. The modified Sternberg task with interference consisted of three steps. The first step shows a working memory set with three Persian words, out of which one is a methamphetamine-related word (e.g., methamphetamine) and two are non–drug-related words (e.g., cart and scissors). This step is considered as an encoding step. The second step illustrates the secondary task in which the color of the words can change to green or blue (interference step). Subjects have to respond to the color of the word by pressing the corresponding button on the response box (e.g., left for green, right for blue). During the last step, called the pairing step, the participants have to choose the correct word from the working memory set by using the response box (according to their position on the screen; recall step). Numbers represent the display time of the words on the screen (Figure is modified from (48).

color was changed randomly to either blue or green (750 ms). Participants were asked to indicate which font color was used for the words by pressing the corresponding button on the response box (left button for green, right for blue). After the participant's response, a black slide was presented for 250 ms, and the next word appeared. One-third of the trials were null; instead of word stimuli, an empty black screen was presented. The total duration of the secondary task was 6 seconds (**Figure 1**, middle panel).

In the third step (i.e., pairing step), each word from the first step was presented once along with a word from the secondary task (ST trial) or a novel list (NL) of methamphetamine-related and non–drug-related words, which had not been presented in that trial, for 3,000 ms. The participant's task was to choose the word that was presented in the memory set by pressing the corresponding key on the response box (i.e., right button for the word on the right side of the screen, and left button for the word on the left) as fast and as accurate as possible. After the presentation of each pair and response by the participant, the screen was replaced by a black slide for 500 ms, and the next pair appeared on the screen. After all words from the memory set were presented, a single fixation cross was presented in the center of the screen, and the next trial was started. The intertrial time interval was set to be between 800 and 1,200 ms (**Figure 1**, right panel). This pairing step is referred to as retrieval step. A black screen was presented for 500 ms after each probe. At the end of the three probes, a black screen was presented randomly for 800 or 1,200 ms (**Figure 1**, right panel).

Second words (i.e., incorrect words) during the pairing step were selected randomly considering the following restrictions: at least one methamphetamine-related word and one non–drug-related word were required to be among the words. Second words in each probe had a 50% chance of being randomly selected from the ST step of its respective trial (i.e., high interference trials). The remaining second words were again randomly selected among methamphetamine-related and non–drug-related words (NL) not previously presented in its respective trial (i.e., low interference trials).

Regarding the mentioned rules for the presentation of both words, the display in the pairing step included the situations as below:

(A)methamphetamine-related words (WM set) + methamphetamine-related words (ST);
(B) methamphetamine-related words (WM set) + methamphetamine-related words (NL);
(C) methamphetamine-related words (WM set) + non–drug-related words (ST);
(D) methamphetamine-related words (WM set) + non–drug-related words (NL);
(E) non–drug-related words (WM set) + methamphetamine-related words (ST);
(F) non–drug-related words (WM set) + methamphetamine-related words (NL);
(G) non–drug-related words (WM set) + non–drug-related words (ST);
(H) non–drug-related words (WM set) + non–drug-related words (NL).

Experimental Procedure

All subjects participated in one session. The experimental procedure was explained clearly to them at the beginning of the session. Basic demographic information, drug abuse, treatment history, and high-risk behaviors of each subject were recorded during a structured interview by an expert drug counselor. After signing the consent form, participants sat in front of a 13-inch laptop screen at a 60-cm viewing distance in a room with dimmed light to increase their focus on the screen.

The experimental procedure had two different phases: a training phase and a test phase. The goal of the training phase was to learn how to perform the Sternberg task. The training task was designed similarly to the main one, but with different words compared to the main experiment (all of them non–drug-related). After it was sure that participants knew how to perform the task, they proceeded to the testing phase.

Overall, participants performed three conditions, including a condition of three WM words consisting of 72 trials, a condition of five WM words also consisting of 72 trials, and a condition of seven WM words consisting of 72 trials (**Figure 1**). All 24 words appeared equally in the probe; they were also paired with second words (incorrect words) in all types of pairings (i.e., methamphetamine-related words, non–drug-related words, and non–drug-related words from the NL). Each of the 24 words was repeated 27 times during 72 trials. The sequence of words was counterbalanced between participants.

Statistical Analysis

Data analysis was conducted using SPSS 21 and Statistica v13 (Dell Inc., Tulsa, OK, USA). All results are expressed as the mean ± standard error of the mean, and the statistical threshold was set to $p \leq 0.05$. A priori hypotheses were tested with *post hoc* analysis (Tukey test) and planned contrasts. The data from trials with null stimuli were excluded from all statistical tests. To analyze the reaction time (RT), trials with incorrect responses were excluded from relevant statistical tests.

Bias Caused by Difference Sources

Potential bias, caused by the methamphetamine-related words on the performance of experimental participants, was from different sources and should be separated in the current task paradigm.

i. The first bias we considered was the summation of WM interference bias and WM bias during different WM loads (three, five, or seven words). This score was defined as 1/2 * (RT (E − G) + RT (F − H) + RT (G − C) + RT (H − D)). Repeated-measures ANOVA was used to calculate this first bias: the three first bias scores during the different WM loads (three, five, or seven words) were considered as a within-subject factor, and subject group (experimental, control) was considered as the between-subject factor.
ii. The second bias we referred to was the WM interference bias. This score was defined as (RT(E) + RT(F))/2 − (RT(G) + RT(H)/2. Repeated-measures ANOVA tests were used to obtain this second score; three second bias scores during the different WM loads (three, five, or seven words) were considered as a within-subject factor, and subject group (experimental, control) was considered as the between-subject factor.
iii. The third bias we referred to was the WM bias. This score was defined as (RT(G) + RT(H)/2 − (RT(C) + RT(D))/2. Repeated-measures ANOVA tests were used in order to calculate this score: three third bias scores during the different WM loads (three, five, or seven words) were considered as a within-subject factor, and subject group (experimental, control) was considered as the between-subject factor.

The Effect of Different WM Loads on the Performance of Participants During High Interference Trials

The performance of participants during high interference trials (i.e. the high interference effect caused by the words from the secondary task) was measured during different WM loads (three, five, or seven words). High interference trials included trials from A, C, E, and G conditions. To test the effect of presenting different WM loads (three, five, or seven words) on the performance of participants, two separate repeated-measures ANOVA tests were performed on RTs and accuracy of participants during high interference trials. In this analysis, RTs and accuracy during different WM loads (three, five, or seven words) were considered as a within-subject factor, and subject group (experimental, control) was considered as the between-subject factor.

RESULTS

Bias Caused by Difference Sources

The First Bias

Repeated-measures ANOVA test showed a significant interaction effect between WM load and subject group on the first bias of RTs ($F(2, 116) = 3.76$, $p = 0.02$). Planned contrasts analysis revealed that mean scores for the first bias RTs of the methamphetamine user group significantly increased during the performance of the 3-word WM compared to the control group ($p = 0.01$). However, no significant difference was observed in mean RTs during the 5- and 7-word WM sets (both p's > 0.1) (**Figure 2**).

Planned comparisons based on our priory hypothesis revealed that mean scores for the first bias RTs of the control group were significantly increased during the performance of the 3-word WM set compared to the 5- and 7-word memory sets (both p's < 0.001). However, no significant difference was observed in mean scores for the first bias RTs of the control group when comparing the 5-word WM sets to the 7-word sets ($p > 0.2$). Additionally, no significant difference was observed in mean scores for the first bias RTs of the experimental group during the 3-word WM set compared to the 5- and 7-word memory sets (p's > 0.2) (**Figure 2**).

The Second Bias

Repeated-measures ANOVA test showed no significant interaction effect between WM load and subject group on the second bias of RTs of the experimental group compared to the control group ($F(2, 116) = 1.97$, $p = 0.14$). Planned comparisons

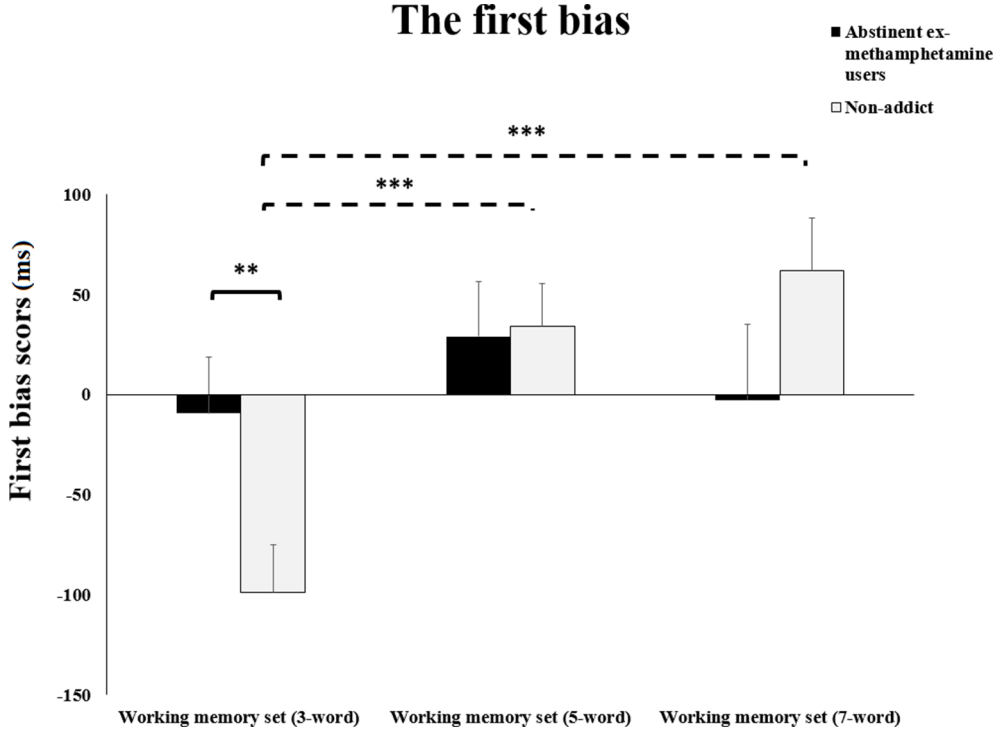

FIGURE 2 | The first bias.The summation of reaction times of working memory interference bias and working memory bias during different working memory loads (three, five, or seven words). Error bars indicate standard error of the mean $^{**}p \leq 0.01$; $^{***}p \leq 0.01$.

based on our priory hypothesis revealed that mean scores for the second bias RTs of the control group were not significantly changed during the performance of the 3-word WM set compared to the 5- and 7-word memory sets (both p's > 0.2). No significant difference was observed in mean scores for the second bias RTs of the control group when comparing the 5-word WM sets to the 7-word sets ($p > 0.2$). Additionally, mean scores for the second bias RTs of the experimental group were not significantly changed during the performance of the 3-word WM set compared to the 5- and 7-word memory sets (both p's > 0.1). No significant difference was observed in mean scores for the second bias RTs of the experimental group when comparing the 5-word WM sets to the 7-word sets ($p > 0.05$).

The Third Bias

Repeated-measures ANOVA test showed no significant interaction effect between WM load and subject group on the third bias RTs of the experimental group compared to the control group ($F(2, 116) = 0.81$, $p = 0.44$). Planned contrasts analysis revealed that mean scores for the third bias RTs of the control group were not significantly changed during the performance of the 3-word WM set compared to the 5- and 7-word memory sets (both p's > 0.1). No significant difference was observed in mean scores for the third bias RTs of the control group when comparing the 5-word WM sets to the 7-word sets ($p > 0.2$). Additionally, mean scores for the third bias RTs of the experimental group were not significantly changed during the performance of the 3-word WM set compared to the 5- and 7-word memory sets (both p's > 0.2). No significant difference was observed in mean scores for the second bias RTs of the experimental group when comparing the 5-word WM sets to the 7-word sets ($p > 0.05$).

The Effect of Different WM Loads on the Performance of Participants During High Interference Trials

Reaction Times During Trials With High Interference

Repeated-measures ANOVA test showed no significant interaction effects between WM load and subject group on the RT of high interference condition ($F(2, 116) = 0.47$, $p = 0.62$). However, priori hypotheses were tested with planned contrasts, and the type I error rate was controlled for using the Bonferroni correction for multiple comparisons. Planned contrasts analysis revealed that the mean RTs of the methamphetamine user group significantly decreased during the performance of the 3-word WM set compared to performing the 5- and 7-word WM sets (p's < 0.001). However, no significant difference was observed in mean RTs during the 5-word WM set compared to mean RTs when performing the 7-word WM sets ($p > 0.2$). The same results were also found in the control group. Mean RTs of the control group during performance of the 3-word WM set compared to the 5- and 7-word memory sets were significantly decreased (p's < 0.001), but no significant difference was observed in mean RTs when comparing the 5-word WM sets to the 7-word sets ($p > 0.2$) (**Figure 3**).

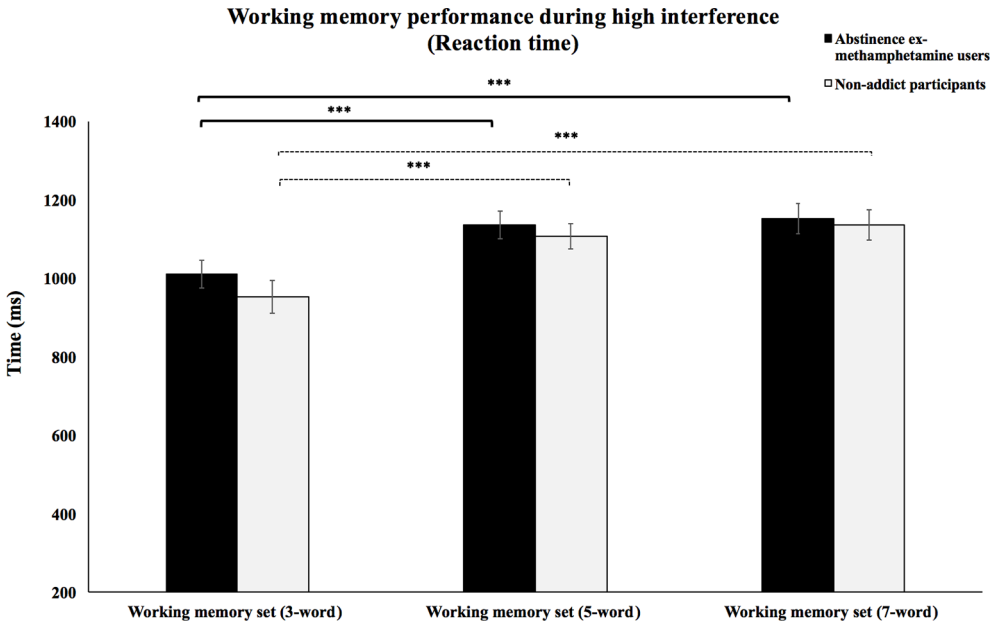

FIGURE 3 | Working memory performance during high interference (reaction times).Mean reaction times of abstinent ex-methamphetamine users and nonaddict control group for the recognition of words from the 3-word working memory sets were compared to the 5- and 7-word working memory sets during trials with high interference. Error bars indicate standard error of the mean ***$p \leq 0.001$.

Accuracy During Trials With High Interference

Repeated-measures ANOVA test showed no significant interaction effects between WM load and subject group on the accuracy of high interference condition ($F(2, 116) = 2.91$, $p = 0.058$). However, priori hypotheses were tested with planned contrasts, and the type I error rate was controlled for using the Bonferroni correction for multiple comparisons. Planned contrasts analysis revealed that the mean accuracy of the methamphetamine user group significantly increased during the performance of the 3-word WM set compared to performing the 5- and 7-word WM sets (p's < 0.001). However, no significant difference was observed in mean accuracy during the 5-word WM set compared to mean accuracy when performing the 7-word WM sets ($p > 0.2$). Mean accuracy of the control group during performance of the 3-word WM set compared to the 5- and 7-word memory sets was significantly increased (p's < 0.001). Besides, mean accuracy was significantly increased when comparing the 5-word WM sets to the 7-word sets ($p = 0.03$) (**Figure 4**).

Demographic information is summarized in **Table 1**.

DISCUSSION

The novel finding of the current study is that abstinent ex-methamphetamine users compared to a nonaddict group showed a bias toward methamphetamine-related stimuli only in in low WM load conditions (3-word WM sets). These results suggest that increasing the load of WM might reduce the effect of interference. In addition, there was no statistically significant difference in WM performance between all three WM load conditions during trials with high interference between both groups. These findings suggest that increasing the load of WM shields the effect of interference. Besides, attentional bias toward methamphetamine-related stimuli, which were presented during the encoding phase of WM, may contribute to optimal WM performance and may increase the availability of the shared cognitive resources.

Bias Caused by Difference Sources

The First Bias

The results showed that abstinent ex-methamphetamine users showed a bias (i.e., the summation of WM interference bias and WM bias) during low WM load (three words) task performance but not during high load WM (five and seven words) compared to the nonaddict group. The impulsive process may trigger cognitive biases such as attentional bias for drug-related stimuli (14, 15, 18). Studies showed that the use of drugs develops a specific reward system in the brain by releasing dopamine in mesolimbic brain areas, which in turn enhance learning by conditioning (26, 50–52). Attentional bias toward drug-related stimuli results in prolonging the disengagement of attention from those stimuli, leading to increased RTs (20, 51, 53). However, following the views that WM protects bias toward distractors, we expected to find a modulation over distraction (i.e. methamphetamine words) under higher WM loads (29).

The Second and Third Bias

Results from the current study showed no significant differences between groups for the second and third biases (i.e., WM

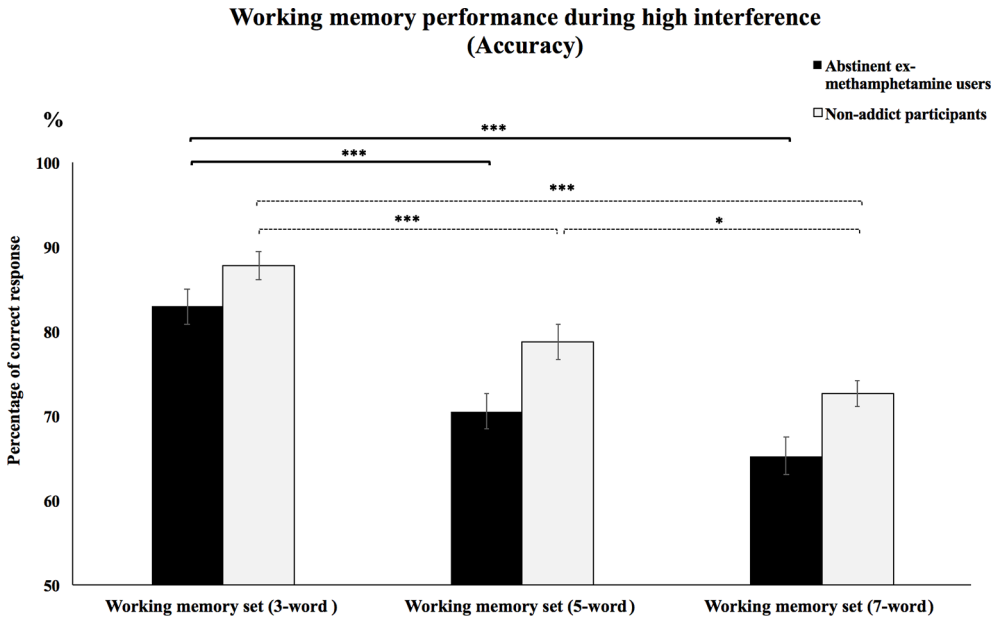

FIGURE 4 | Working memory performance during high interference (accuracy).Mean accuracy of abstinent ex-methamphetamine users and nonaddict control group in recognition of words from the 3-word working memory sets was compared to the five- and seven-word working memory sets during trials with high interference. Error bars indicate standard error of the mean ***$p \leq 0.001$ and *$p \leq 0.05$.

interference bias, WM bias). These results can best be considered with some possible explanations:

i. Abstinent ex-methamphetamine users are probably motivated to quit or stay abstain from drugs (54, 55). This motivation leads individuals to develop avoidance strategies to cope with tempting stimuli, which meanwhile might be effortful for them (54, 56). For example, heavy alcohol drinkers showed an attentional bias toward alcohol-related stimuli, while abstaining alcohol-dependent individuals avoided such stimuli (24, 57, 2, 55). Besides, studies have also indicated that presenting drug-related stimuli long enough (e.g., 500 ms) can give patients enough time to use efficient avoidance strategies; therefore, the effect of attentional bias might be reversed and away from drug-related stimuli (24, 57).
ii. The cognitive effort, which has been closely coupled with concepts of attention, difficulty in concentration, and motivation, can also explain current results (58). Cognitive effort can modulate the cognitive resources dedicated to a particular task (59). Indeed, to accomplish more demanding tasks, we have to exert more effort, which leads to a reduced effect of distractors (59, 60). Although we did not measure cognitive effort during the task, abstinent ex-methamphetamine users might invest more effort to perform WM task.
iii. Drug-related stimuli might elicit an attentional bias toward those stimuli, resulting in an interruption in the performance during the ongoing task. However, it is also possible that drug-related stimuli can elicit a motor response to provide fast and necessary reactions, resulting in avoiding the effect of distractions (61, 62). Besides, according to the literature on anxiety, the shorter RTs for threat stimuli in threat-neutral pairs could indicate an attentional bias away from the threat (61–63). Therefore, it is postulated that salient methamphetamine-related stimuli might lead to increased anxiety, resulting in quicker responses.
iv. The reflective process can moderate the impact of the impulsive process by emphasizing the effect of WM capacity (top-down process) (14, 17, 18, 64–67). For example, studies have supported the moderating effect of WM capacity on alcohol abuse (27, 64). These results indicated that individuals with a lower WM capacity show strong correlations between implicit alcohol associations and the use of alcohol (14, 27, 64). Although traditional models of impulse control have emphasized the adverse effect of increasing cognitive load on self-regulation, emotion-related studies have supported the idea that increased cognitive load can inhibit feelings of temptation (68–71). Regarding this issue, attention toward an emotional target is automatic (i.e., fast and involuntary), but it is also resource-dependent (71–73). It means that an increased cognitive load may lead to a decrease in the motivation to process task-irrelevant stimuli despite their saliency and associated feelings of temptation (71, 74). For example, categorizing the gender of angry faces compared to happy faces—as an index of selective attention to threatening information—was slower during the mental rehearsal of a one-digit number (low cognitive load) compared to the rehearsal of an eight-digit number (high cognitive load) (74). The bottom line is that there is bias variability in the addiction literature, which makes the basic mechanisms still unclear, but this bias might reflect variations in top-down cognitive control (47, 62, 75). In addition to the emotion-related

studies, the WM theory proposed by Andrade et al. (76) also supports the current findings. This theory suggested that retrieving information from WM requires WM capacity, but if the capacity of WM (resource) is occupied during memory reactivation, the emotionality and saliency of new information will be decreased, which will result in updating that information into a less emotional form (67). For example, studies have shown that using a high WM load task (visual-spatial task) during the retrieval of drug-related information could decrease cigarette (77) and food cravings (67, 78).

In summary, studies have indicated that WM and attention processes recruit similar neural networks and share common cognitive resources (79–81). In our case, attentional bias to the methamphetamine-related stimuli, particularly during high WM loads, may bring gain in WM performance (particularly during the encoding phase) and may increase the availability of cognitive resources. The result of the first bias during a task with low WM load indicated that attention was directed toward salient methamphetamine-related stimuli. On the other hand, performing tasks with high WM loads inhibited the effect of bias in abstinent ex-methamphetamine users. Regarding the results of the second and third bias considered, we suggest that presenting methamphetamine-related stimuli and increasing loads of WM were helpful for the experimental group to inhibit the effect of interference. In line with the dual-process models of addiction, which is focused on the trade-off between impulsive and reflective processes, these findings suggest that WM engagement and increased WM load improved avoidance strategy, possibly through reflective processes (71).

The Effect of Different WM Loads on the Performance of Participants During High Interference Trials

Our findings showed that increasing WM load resulted in increased RTs and decreased accuracy in both the abstinent ex-methamphetamine and nonaddict groups. These results were supported by previous studies showing that increasing WM load could decrease WM performance (82–85). However, there was no significant difference between groups, which contradicted our hypothesis.

There are contradictory findings regarding the effect of methamphetamine on WM performance. On the one hand, some studies have revealed overall cognitive deficits in the domains of verbal memory, WM, executive function, and social cognition in methamphetamine users (9, 10, 20, 86–89). For example, one study indicated that chronic methamphetamine users showed a deficit in some CogState battery domains (i.e., evaluated seven cognitive domains including WM) and poor psychological well-being (88). Studies have also revealed that methamphetamine users had deficits in brain function in areas including the dorsolateral prefrontal cortex during performing cognitive tasks that assess executive function (WM) (20, 87). Activity in this brain area can support WM performance and allocation of attentional resources (36, 90, 91).

However, in line with our results, some studies have shown no significant difference in WM performance of abstinent ex-methamphetamine compared to the nonaddict group (30). For example, Boileau et al. (92) asked methamphetamine users and subjects from a control group to perform different cognitive tasks including WM, attention/psychomotor function, and immediate and delayed memory tasks. Their results showed that there was no significant difference in WM performance between both groups, but that in attention/psychomotor function and delayed memory tasks, methamphetamine users showed a deficit. Another study employed attention/psychomotor function tasks (e.g., Stroop), learning/memory tasks, WM tasks, response inhibition tasks, and set-shifting/executive function tasks for both methamphetamine users and a control group (93). The findings indicated no significant difference between groups for all cognitive tasks. Similar results were observed in other studies as well (94, 95); for a review of this topic, see Hart et al. (30).

The use of different kinds of WM tasks in different experiments might explain these contradictory findings. In our study, we utilized the modified Sternberg task, in which methamphetamine-related stimuli were presented during the encoding phase of WM. These salient methamphetamine-related stimuli might cause attentional bias leading to attentional capture and eventually contributing to better performance despite having an interference bias. Indeed, attentional bias to methamphetamine-related stimuli might highlight those stimuli in WM, resulting in enhanced WM performance. Also, type of distractors might be an important factor to explained contradictory findings. For example, the amount of physical separation between targets and distractors might modulate the effects of load on distraction (29).

The availability of cognitive resources for optimal task performance and inhibiting the effect of interference is critical, particularly when WM is highly loaded or saturated (29). Our findings suggest that cognitive resources might be available as they are not dominated by task demands, resulting in optimal performance. Besides, bias toward the methamphetamine-related words (which were task-relevant information) might facilitate the WM process.

Limitations and Future Directions

Only male participants were recruited in the present study to minimize the effect of potentially confounding factors. One noteworthy and currently unexplored direction for future studies might be to examine gender differences. Moreover, participants with the mean of nearly 17-day abstinence from methamphetamine use were recruited. We chose this sample to assess the effect of short time abstinence from methamphetamine on WM performance. However, it is still unclear what may be the effect of long-term abstinence from methamphetamine use on cognitive function. For example, one study revealed that enhanced performance on tests of verbal memory and executive function was observed after approximately 6 months of abstinence from methamphetamine use. In line with this idea, some studies have examined the role of duration of abstinence from methamphetamine use on cognitive function (96, 97). They showed that prolonged greater duration of abstinence from methamphetamine use resulted in better cognitive performance (96–98). Future studies might consider the effect of long-term

abstinence from methamphetamine use on WM biases and WM capacity. In addition, this study did not include a sample of active methamphetamine users who do not want to quit drug use, due to the difficulty in performing the modified Sternberg task. Future studies might add this group to compare the effect of motivation to quit on WM performance between abstinent and active groups. Due to the size of the center and the limited-time permission we have for our study, we could not recruit more participants. In several tests, we realized that the power of analysis is below the optimal level, and for some interactions, there was only a trend toward significance. In the future studies hiring complex tasks, more participants should be recruited to have enough power to run all the required analyses properly. This study sought to examine the neurobiological substrates of the interaction between WM bias, WM capacity, and interference effect using a complex span task in methamphetamine users.

CONCLUSION

We investigated the impulsive effects of methamphetamine-related stimuli on WM performance in abstinent ex-methamphetamine users. The experimental group demonstrated bias toward methamphetamine-related stimuli during a task with low WM load (three words) but not while performing tasks with higher WM loads (five and seven words). This result suggests that increasing WM load may provide an efficient buffer against attentional capture by salient stimuli (i.e., methamphetamine-related words). In line with this findings, investigating the effect of increasing WM load on the performance of abstinent ex-methamphetamine users (i.e., WM capacity) showed that increasing WM load had no significant effect on WM performance of abstinent ex-methamphetamine users compared with the control group. These findings suggest that increasing WM loads modified the impact of the interference bias. Besides, presenting methamphetamine-related stimuli facilitated their encoding due to bias toward task-relevant stimuli.

This finding has an important implication, suggesting that performing concurrent demanding tasks may reduce the power of salient stimuli and thus improve the efficiency of emotion regulation strategies. Further investigation on the interactions between WM interference bias, WM bias, and WM capacity may lead to the development of better tools and alternative therapies, including WM training, for the treatment of addiction.

ETHICS STATEMENT

All experimental procedures corresponded to the standards set by the latest revision of the Declaration of Helsinki and were approved by the ethical committee of the Institute for Cognitive Sciences Studies, Tehran, Iran. All participants provided written informed consent, acknowledging their right to withdraw from the experiment without prejudice.

AUTHOR CONTRIBUTIONS

ZD contributed to all aspects of the research. HE contributed to experimental design and data interpretation. HP contributed to experimental design and data interpretation. AK contributed to all aspects of the research.

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Effects of Opioid Dependence on Visuospatial Memory and Its Associations With Depression and Anxiety

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Introduction: The cognitive impact of opioid dependence is rarely measured systematically in everyday clinical practice even though both patients and clinicians accept that cognitive symptoms often occur in the opioid-dependent population. There are only a few publications which utilized computerized neuropsychological tests to assess possible impairments of visuospatial memory in opioid-dependent individuals either receiving opioid replacement therapy (ORT) or during subsequent short-term abstinence and the effects of anxiety and depression.

Methods: We assessed a cohort of 102 participants, comprising i) a stable opioid-dependent group receiving methadone maintenance treatment (MMT) (n = 22), ii) a stable opioid-dependent group receiving buprenorphine (BMT) (n = 20), iii) a current abstinent but previously opioid-dependent group (ABS) (n = 8), and iv) a control group who have never been dependent on opioids. The Cambridge Neuropsychological Automated Test Battery (CANTAB) neuropsychological tasks undertaken by participants included: Delayed Matching to Sample (DMS), Pattern Recognition Memory (PRM), Spatial Recognition Memory (SRM), and Paired Associate Learning (PAL) tasks. Three clinical measures were used to assess the severity of anxiety and depressive illness: Hospital Anxiety Scale-Hospital Anxiety Depression (HADA)-(HADD), Beck Depression Inventory (BDI), and Inventory of Depressive Symptomatology (self-report) (ISD-SR).

Results: The methadone- and buprenorphine-treated groups showed significant impairments ($p < 0.001$) in visuospatial memory tasks but not the abstinent group. Impairments in visuospatial memory strongly correlated with higher mood and anxiety symptom severity scores ($p < 0.001$).

Discussion: These results are broadly consistent with previous studies. Uniquely, though, here we report a strong relationship between visuospatial memory and depression and anxiety scores, which might suggest common illness mechanisms.

Keywords: memory, opioid dependence, heroin, methadone, buprenorphine, depression, anxiety

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INTRODUCTION

Substance misuse is a chronic condition often characterized by remissions and relapses (1). Individuals with a history of long-term opioid dependence may demonstrate cognitive impairments, primarily within the executive functioning domains (2–8).

These impairments have been linked to grey matter reductions in the prefrontal cortex, anterior mid-cingulate cortex, and basal ganglia (9), brain regions thought responsible for the regulation of cravings, pain, and emotional experience. In addition, other studies have reported how opioids affect memory, learning, and emotional disturbances (2, 3, 10, 11). Depression has long been associated with widespread cognitive deficits (12) which tend to worsen over a life span (13).

Specific memory tasks have shown to be sensitive and useful in detecting brain dysfunction in the temporal and amygdalo-hippocampal regions (14), which are consistently reported as functionally abnormal in mood disorders and sensation-seeking behaviors (15–17).

Importantly, these brain regions are also relevant to the neurobiology of substance misuse (18) with similar symptoms such as mood, anhedonia, and anxiety associated with drug dependence (19). These symptoms may represent a risk factor for the development of dependence and also may constitute a specific factor by which dependence is maintained, as well as strongly associated with major depressive disorder (MDD). However, depressive and anxiety symptoms have rarely been investigated in opioid dependence within a clinical environment.

Previous studies showed impairments in episodic memory (20), visual memory, verbal memory, information processing, problem solving (21), and spatial, tactile, and verbal memory (2) in heroin-, morphine-, and methadone-dependent participants. Curran and colleagues showed that a single dose of methadone could negatively impact on episodic memory in opiate users (20).

Previously, we have shown that visuospatial memory was impaired in chronic heroin and methadone-dependent participants, those maintained on methadone as part of opioid replacement therapy (ORT), or patients prescribed opioids for chronic pain (10). However, to our knowledge, there are no previous studies reporting the impact of opioid dependence on memory during short-term abstinence from opioids.

Here, we tested the following hypotheses:

(i) Visuospatial memory impairments are associated with current opioid exposure. Conversely, we therefore predicted that abstinence would be associated with no significant impairments.
(ii) Cognitive impairments would correlate with mood and anxiety ratings. Specifically, we predicted that participants with higher depression and anxiety symptoms would have greater visuospatial memory impairments.

METHODS

Study approval was granted by the East of Scotland Research Ethics Committee (REC reference number: 06/S1401/32) and written informed consent obtained from all participants. National Health Service (NHS) Scotland Research Governance approval was provided by the NHS Fife Research and Development Department.

A total of 102 participants were *opportunistically* enrolled in this study with four groups: (i) a stable opioid-dependent group receiving methadone maintenance treatment (MMT) (n = 22), (ii) a stable opioid-dependent group receiving buprenorphine (BMT) (n = 20), (iii) a current abstinent but previously opioid-dependent group (ABS) (n = 8), and (iv) controls, with no history of illicit heroin, methadone, or buprenorphine use (n = 52). Patients had a diagnosis of *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*), Opioid Dependence and a history of poly-substance misuse with heroin as the primary "drug of choice" preceding initiation of MMT.

An extensive detailed screening was assessed by two clinicians (A.B. or F.D.), which included sociodemographic information collection and a semi-structured interview to obtain detailed previous histories of drug and alcohol use and current opioid dependence status (**Table 1** and **Supplementary Table 1**). Clinical histories and diagnoses were obtained using the structured Mini International Neuropsychiatric Interview (MINI Plus v 5.0) (22) together with a detailed review of individual clinical care records. The latter included recording the dose of methadone and buprenorphine that each participant received at the time of testing. A morphine equivalent calculation was performed in accordance to a previous publication by Vieweg et al. (23). Each methadone dose was multiplied by 20, and each buprenorphine dose was multiplied by 12 (23). Ongoing abstinence from illicit drug use was also objectively confirmed just prior to scanning with a urine drug test (24) using automated enzyme-mediated immunoassay to classify any detected drug (25). The Clinical Opioid Withdrawal Scale (COWS) was used to quantify the level of opioid withdrawal if present (26). Previous care records from Addiction Services, psychiatric notes, and general practitioners' records confirmed the absence of hepatitis B and C and HIV. Other exclusion criteria included: past or current histories of psychotic disorders; post-traumatic stress disorder (PTSD); antisocial and borderline personality disorders; neurological and neurodevelopmental disorders; significant head injury; confirmed history of non-fatal overdose episodes; and co-occurring benzodiazepine, stimulant, and/or alcohol dependence.

Current and premorbid intelligence was estimated using the Wechsler Abbreviated Scale of Intelligence (WASI) and National Adult Reading Test (NART) (27, 28).

Visuospatial Memory Tasks

The Cambridge Neuropsychological Automated Test Battery (CANTAB, www.camcog.com) comprises a series of computerized memory tasks (29). As previously reported, the following tasks have shown specificity to detect impairments in *visual memory performance* [Delayed Matching to Sample (DMS), Pattern Recognition Memory (PRM), Spatial Recognition

TABLE 1 | Demographic, clinical, and substance use history data.

	MMT (N = 22)	BMT (N = 20)	ABS (N = 8)	HC (N = 52)	Statistics
Number	22	20	8	51	
Age in years	33.6.	37.4	37.6	28.0	P < 0.001 MMT, BMT, ABS > HC***
NART	114.3 (5.2)	98.0 (13.5)	106.4 (15.6)	117.5 (6)	P < 0.001 BMT, ABS < HC***
HADA	6.0 (4.3)	4.8 (2.7)	4.0 (2.3)	3.5 (3.4)	P = 0.04
HADD	4.4 (3.5)	4.4 (2.9)	8.0 (1.5)	1.2 (2.3)	P < 0.001
BDI	12.4 (10)	9.9 (6.3)	9.0 (1.8)	3.7 (5.2)	P = 0.02
IDS-SR	17.8 (12)	12.6 (6.6)	14.0 (3.2)	7.9 (7.3)	P < 0.001
Fagerstrom (total score)	3.4 (2.3)	3.9 (2.3)	3.5 (2.8)		ns
OD (methadone or buprenorphine in mg)	73.4 (60.8)	11.0 (6.7)	–	–	P < 0.001 MMT > BMT***
Daily intake expressed as morphine equivalent dose in mg	1,835.5 (1,277)	888.0 (533)	–	–	P < 0.001 MMT > BMT***
Age when first used heroin in years	20.2 (4.4)	21.7 (5.4)	20.0 (4.7)	–	ns
Age when dependent on opioids in years	20.2 (4.4)	23.6 (5.9)	22.9 (8.5)	–	ns
Age when injecting opioids in years	21.8 (4.2)	24.8 (6)	22.7 (6.9)	–	ns
Years of opioid use	12.9 (4.4)	13.4 (6.7)	13.4 (7.6)	–	ns
Age when first used benzodiazepine in years	17.2 (5.8)	21.7 (7.7)	15.6 (6.6)		P < 0.04 MMT < BMT*
Days of benzodiazepine use in the last 30 days	–	–	–	–	–
Age when first used cocaine in years	17.3 (1)	21.9 (6.6)	18.3 (4.2)	–	ns
Days of cocaine use in last 30 days	–	–	–	–	–
Age when first used cannabis in years	13.3 (3.8)	15.8 (5.3)	13.1 (1.2)	–	ns
Days of cannabis use in last 30 days	–	–	–	–	–
Age when first used alcohol in years	10.5 (7.9)	15.1 (3)	13.0 (1.9)	–	0.04 MMT < BMT*
Days of alcohol use in last 30 days	–	–	–	–	–
Duration abstinence (days)	–	–	102.2 (61.3)	–	–

*Values are mean (SD); MMT, methadone maintenance treatment group; BMT, buprenorphine maintenance treatment group; ABS, abstinent group; HC, healthy control group; N, total number; HADA, Hospital Anxiety Scale; HADD, Hospital Anxiety Depression; BDI, Beck Depression Inventory; IDS-SR, Inventory of Depressive Symptomatology (self-report); NART, National Adult Reading Test; significance * = p = 0.05, *** = p < 0.001; ns, non-significant; mg, milligrams; OD, opioid dose (methadone or buprenorphine).*

Memory (SRM), and Paired Associate Learning (PAL)] and *spatial memory performance* [Spatial Span Task (SSP) and Spatial Working Memory (SWM)] (10).

Depression and Anxiety Rating Scales

Three clinical measures were used to assess the severity of anxiety and depressive illness: the Hospital Anxiety and Depression Scale (HADS) (30), Beck Depression Inventory (BDI) (23), and Inventory of Depressive Symptomatology (IDS): clinician (IDS-C) and self-report (IDS-SR) (31).

HADS is commonly used to determine depression and anxiety. It is a 14-item scale with 7 items that relate to depression (HADD) and 7 items to anxiety (HADA) (30). BDI and IDS are self-report inventories, and they have been mostly used to assess depression and anhedonia (32, 33). BDI demonstrated high internal consistency, with an alpha coefficient of 0.82 (34). Similarly, IDS demonstrated strong internal consistency, with an alpha coefficient of 0.88 (35).

Statistical Analysis

Data meeting assumptions of normality and homogeneity of variance were analyzed using analysis of variance (ANOVA) (36). All other data were compared using Mann–Whitney test. Preliminary analysis of all the experimental and control groups separately indicated that the samples did not come from normally distributed populations with the same standard deviation. We used a *post hoc Bonferroni* correction in order to control for family-wise error for unplanned tests. Mann–Whitney U tests established that NART, age, and smoking history needed to be used as covariates for hypothesis testing.

A general linear model was performed with "groups" as a factor and "visuospatial memory task performances" as dependent variables using analysis of covariance (ANCOVA). To explore the potential contribution of the impact of depression and anxiety scores on memory task performance, we added an additional correlational analysis within the ANCOVA.

Data were analyzed using the Statistical Package for the Social Science (SPSS) version 24 (SPSS Inc.) in Windows 10 on a PC computer. P values < 0.05 were considered significant.

RESULTS

Demographic Characteristics

Demographic and clinical characteristics are presented in **Table 1**. Participants and controls were matched on the basis of gender (all males). The MMT, BMT, and ABS groups were older

than the healthy controls (HCs) ($p < 0.001$). The HC group had higher estimated premorbid IQ ($p < 0.001$) according to the NART than the BMT and ABS groups. The mean morphine equivalent daily dose for the MMT group was significantly higher than the BMT ($p < 0.001$). Urine analyses confirmed complete absence of recent heroin, amphetamine, benzodiazepine, and cocaine prior to neuropsychological testing. The MMT group reported they first drank alcohol and consumed benzodiazepine approximately 4.5 years prior to the BMT cohort ($p < 0.04$). There were no significant group differences identified on several clinical substance history data such as: age when they first used heroin ($p = 0.6$), age when dependent on heroin ($p = 0.2$), or age when injecting opioids ($p = 0.3$). The MMT, BMT, and ABS were well matched with regard to age when they first used cocaine ($p = 0.15$) and cannabis ($p = 0.13$).

Visual Memory

Performance on DMS

There was a significant effect of group on the percentage of correct responses for DMS [$F(4, 78) = 7.5$, $p < 0.001$]. *Post hoc* Bonferroni comparisons showed that participants from the MMT and BMT groups made significantly more errors than the ABS and HC groups ($p = 0.03$ and $p < 0.001$, respectively). There was a significant effect of group on the percentage of correct responses for DMS [$F(4, 78) = 7.4$, $p < 0.001$]. *Post hoc* Bonferroni comparisons showed that participants from the MMT and BMT groups made significantly more errors than the ABS and HC groups ($p = 0.02$ and $p < = .001$, respectively).

More details are reported in **Table 2** and **Figure 1**.

Performance on PRM, SRM, and PAL

There was a significant effect of group on the percentage of correct responses for the PRM task [$F(4, 60) = 9.3$, $p < 0.001$] and on the mean correct latency for the SRM task [$F(4, 60) = 6.4$, $p < 0.001$]. Similarly, there was a significant effect of group on the total adjusted errors on the PAL task [$F(4, 75) = 6.1$, $p < 0.001$] and on PAL first trial memory [$F(4, 75) = 5.7$, $p < 0.001$] (see **Figure 2**).

TABLE 3 | Correlations between depression and anxiety and visuospatial performance.

	HADA	BDI	IDS-SR
PAL (total error adjusted)	0.3**	0.25*	0.3**
PAL (first trial memory score)	0.3**	0.28*	0.4***
DMS (% correct)	–	0.3**	–

** indicates p < 0.05, ** indicates p < 0.01, *** indicates p < 0.001.*

Spatial Memory

Performance on SSP and SWM

There was a significant effect of group on the SSP task (span length) [$F(4, 75) = 10.5$, $p < 0.001$]. The BMT and ABS groups (a) made significantly more errors (between errors) [$F(4, 75) = 5$, $p < 0.003$] and (b) presented with a poorer strategy on the SWM task [$F(4, 75) = 9.8$, $p < 0.001$].

Depression and Anxiety and Visuospatial Memory Performance

Higher HADA anxiety, BDI, and IDS-SR depression scores were significantly correlated with PAL (total error adjusted [$r (66) = 0.3$, $p = 0.01$, $r (66) = 0.25$, $p = 0.04$, $r (64) = 0.3$, $p < 0.005$, respectively]). Similarly, higher HADA, BDI, and IDS-SR scores were significantly associated with PAL (first trial memory score) [$r (66) = 0.3$, $p = 0.007$, $r (66) = 0.28$, $p = 0.02$, $r (64) = 0.4$, $p = 0.001$, respectively]. DMS (% correct) significantly correlated with BDI [$r (66) = 0.3$, $p = 0.01$] (see **Table 3**).

TABLE 2 | Summary of neuropsychological findings for visual and spatial memory.

Memory and learning measures	MMT (N = 22)	BMT (N = 20)	ABS (N = 8)	HC (N = 52)	Statistics
Visual Memory					
DMS % correct	84.5 (11.6)	80.0 (15)	92.8 (2.1)	92.5 (5.9)	P < 0.001, MMT, BMT < ABS, HC***
DMS % correct (all delays)	80.2 (14.8)	75.6 (18.5)	91.6 (3.9)	90.7 (7.6)	P < 0.001, MMT, BMT < ABS, HC***
PRM % correct	83.8 (10.1)	80.1 (11.7)	90.2(0.09)	93.2 (4.3)	P < 0.001, MMT, BMT < ABS, HC***
SRM mean correct latency	1,997 (377)	2,743 (1,138)	2,150 (454)	1,882 (555)	P = 0.001, BMT > HC***
PAL total errors adjusted	125.7 (101)	29.9 (34.6)	11.0 (9)	57.0 (90)	P = 0.001, MMT, BMT > ABS, HC***
PAL first trial memory score	8.5 (0.8)	17.9 (4.5)	19.7 (3)	16.4 (9)	P = 0.001, MMT < HC, ABS***
Spatial Memory					
SWM between errors	8.8 (15.9)	33.4 (21.4)	22.7 (16.2)	16.6 (21.9)	P = 0.003, BMT > MMT, HC***
SWM strategy	13.1 (14.9)	32.9 (6.9)	31.7 (6)	21.3 (13.4)	P < 0.001, MMT < BMT, ABS***

*Values are mean (SD); significance *** = P < 0.001; DMS, Delayed Matching to Sample; PRM, Pattern Recognition Memory, SRM, Spatial Recognition Memory; PAL, Paired Associate Learning; SWM, Spatial Working Memory; N, total number.*

DISCUSSION

In this clinically well-characterized study, we have demonstrated that memory for visually presented patterns and spatial locations was impaired in individuals on ORT. This is consistent with previous studies utilizing computerized CANTAB assessment with individuals on ORT and HCs. These studies revealed that individuals on ORT exhibited impairments in comparison to controls on the PRM task (2, 3) and on the PAL task (21). In a recent meta-analysis by Baldacchino and colleagues (37), short-term memory impairments were not present in the abstinence cohorts. This is consistent with our present results, as cognitive impairments were not present in the abstinent group for both visual and spatial memory tasks.

We previously reported that cognitive processes particularly associated with the prefrontal cortex are disrupted during chronic opioid use but not during abstinence (9). Our results could be explained by frontal lobe dysfunction (9, 38–40), which can potentially cause impairments on tasks requiring optimal memory function with patients receiving ORT. In addition, the identified impairments within the opioid-dependent groups on ORT point to specific correlations with depression and anxiety, particularly with tasks sensitive to the anatomical location of the medial temporal lobe.

This is consistent with numerous studies in healthy volunteers identifying the medial temporal lobe, such as the hippocampus and amygdala, as the area where memory-sensitive tasks are encoded (41, 42). Of specific interest, the medial temporal lobe regions have been reported 1) as structurally abnormal in depressive disorder (16) and 2) as one of the main putative candidate regions for both the development and the maintenance of dependence (18) and depression (43).

Regarding possible limitations of the present study, we recruited only males, so these findings shouldn't be generalized to females (44). Drug use and clinical histories were collected based upon self-report, and no blood, hair, or saliva samples were available to confirm the accuracy of the information given; however, our study did acquire urine drug screen analysis to confirm the absence of recent illicit drug use prior to every session. Additionally, the present study recruited well-matched subjects with regard to their previous drug history in the experimental groups and excluded regular and dependent users of most psychoactive substances, such as alcohol and benzodiazepines, as they have been shown to profoundly impact neuropsychological performance (18). We couldn't control the effect of nicotine, which may have influenced our results due to its known neuropsychological effects on visual and spatial memory (45). The burprenorphine group had a significant lower morphine equivalent dose than the methadone group, which may impact our findings; however, no statistically significant correlations were present. Larger studies with long-term abstinence are required to fully validate the observed reversibility and possible extinction of these impairments.

Clinical Relevance

Patients' questions about the effects of opioid dependence on memory and its impact during abstinence cannot comprehensively be answered, due to a current lack of research in this area (10). More data are required on the consequences of opioid dependence on memory in order to evaluate the acceptability of differential treatments, such as methadone and buprenorphine, and perhaps maximize abstinence periods (46). Previous studies have indicated the importance of detecting memory impairments using highly structured and extensive neuropsychological batteries. This is further highlighted in the present study, indicating that opioid-dependent individuals have memory loss in both visual and spatial domains. Early identification of memory impairments associated with opioid dependence could improve the current standard clinical method of assessment. Elucidating the cognitive and neural mechanisms responsible for the formation and maintenance of opioid-related associative dependence has the

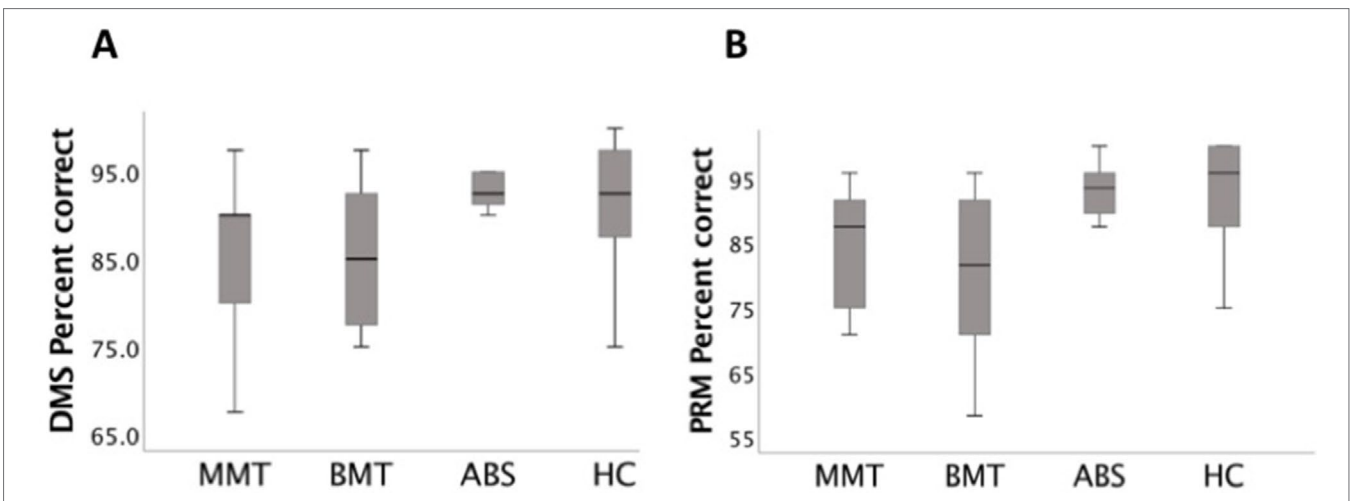

FIGURE 1 | (A) Delayed Matching to Sample (DMS) task (% correct) box plots: the stable opioid-dependent group receiving methadone maintenance treatment (MMT) and that receiving buprenorphine (BMT) made significantly more errors than the abstinent but previously opioid-dependent group (ABS) and healthy controls (HCs) ($p < 0.001$) groups. **(B)** Pattern Recognition Memory (PRM) task (% correct) box plots: the MMT and BMT made significantly more errors than the ABS and HC ($p < 0.001$) groups.

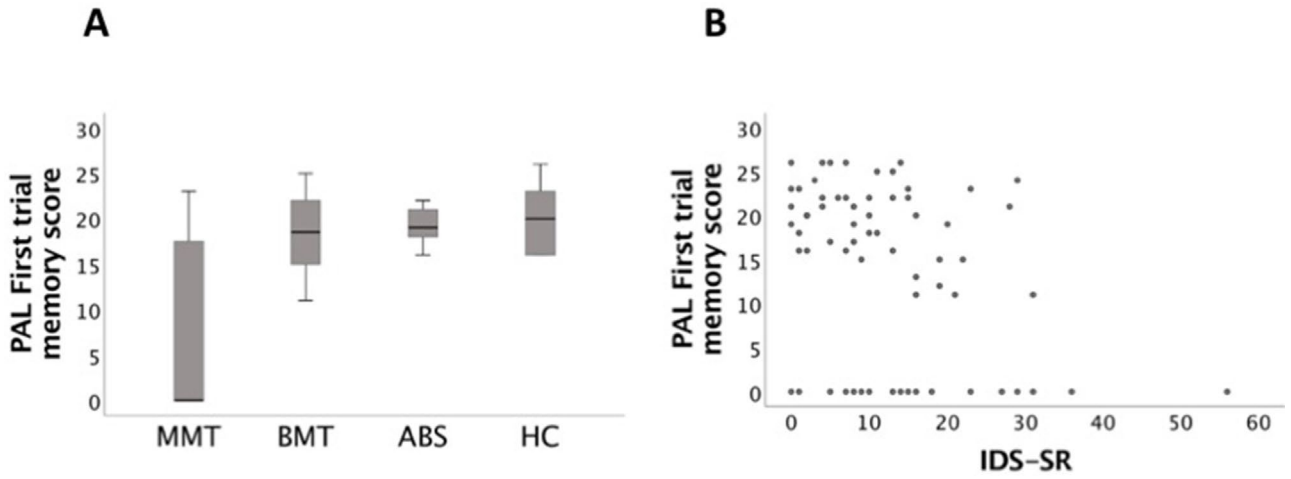

FIGURE 2 | (A) Paired Associate Learning (PAL) (first trial memory score) box plots: those in the MMT group were significant more impaired than the ABS and HC groups ($p < 0.001$). **(B)** PAL (first trial memory score) task significantly correlated with Inventory of Depressive Symptomatology (self-report) (IDS-SR) ($p = 0.005$).

potential for opening up new therapeutic trajectories during both the prevention and/or reversal of the significant effects on memory and learning, which may be a vulnerability for development and maintenance of opioid dependence. Notably, our results highlight the possibility that opioid-dependent individuals may benefit from focused treatments for depression and anxiety symptoms during ORT.

In particular, understanding the underlying neurocognitive and brain substrates linked to a dual close relationship between comorbid substance misuse and mood states may (a) reveal potential new interventions for the treatment of protracted opioid dependence and/or relapse (18) and (b) provide the required biomarkers to create predictive algorithms to detect early dependence and abstinence (6, 7).

CONCLUSION

In summary, our results found that opioid-dependent participants exhibited visuospatial memory impairments closely associated with depression and anxiety scores. These impairments were not present in short-term abstinence, suggesting reversible impairments. Further studies need to explore the effect that mood plays in cognitive impairments observed in this and other dependent populations (e.g. nicotine and alcohol). Indeed, identifying and characterizing the visuospatial memory abilities and their potential mechanisms of action may be of crucial importance in identifying potential common mechanisms controlling the switch from the non-dependent to substance-dependent states and ultimately achieving abstinence in the opioid-dependent population.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

Study approval was granted by the East of Scotland Research Ethics Committee (REC reference number: 06/S1401/32) and written informed consent obtained from all participants. National Health Service (NHS) Scotland Research Governance approval was provided by the NHS Fife Research and Development Department.

AUTHOR CONTRIBUTIONS

ST wrote the first draft of the manuscript with AB's input and created the figures and tables. FD and JS provided revisions to versions of the draft manuscript. ST formatted the manuscript for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00743/full#supplementary-material

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A Roadmap for Integrating Neuroscience Into Addiction Treatment: A Consensus of the Neuroscience Interest Group of the International Society of Addiction Medicine

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Although there is general consensus that altered brain structure and function underpins addictive disorders, clinicians working in addiction treatment rarely incorporate neuroscience-informed approaches into their practice. We recently launched the Neuroscience Interest Group within the International Society of Addiction Medicine (ISAM-NIG) to promote initiatives to bridge this gap. This article summarizes the ISAM-NIG key priorities and strategies to achieve implementation of addiction neuroscience knowledge and tools for the assessment and treatment of substance use disorders. We cover two assessment areas: cognitive assessment and neuroimaging, and two interventional areas: cognitive training/remediation and neuromodulation, where we identify key challenges and proposed solutions. We reason

that incorporating cognitive assessment into clinical settings requires the identification of constructs that predict meaningful clinical outcomes. Other requirements are the development of measures that are easily-administered, reliable, and ecologically-valid. Translation of neuroimaging techniques requires the development of diagnostic and prognostic biomarkers and testing the cost-effectiveness of these biomarkers in individualized prediction algorithms for relapse prevention and treatment selection. Integration of cognitive assessments with neuroimaging can provide multilevel targets including neural, cognitive, and behavioral outcomes for neuroscience-informed interventions. Application of neuroscience-informed interventions including cognitive training/remediation and neuromodulation requires clear pathways to design treatments based on multilevel targets, additional evidence from randomized trials and subsequent clinical implementation, including evaluation of cost-effectiveness. We propose to address these challenges by promoting international collaboration between researchers and clinicians, developing harmonized protocols and data management systems, and prioritizing multi-site research that focuses on improving clinical outcomes.

Keywords: neuroscience, addiction medicine, treatment, substance use disorder, fMRI, neuromodulation, neuropsychological assessment, cognitive rehabilitation

INTRODUCTION

The past two decades have seen significant advances in our understanding of the neuroscience of addiction and its implications for practice [reviewed in (1–3)]. However, despite such insights, there is a substantial lag in translating these findings into everyday practice, with few clinicians incorporating neuroscience-informed interventions in their routine practice (4). We recently launched the Neuroscience Interest Group within the International Society of Addiction Medicine (ISAM-NIG) to promote initiatives to bridge this gap between knowledge and practice. This article introduces the ISAM-NIG key priorities and strategies to achieve implementation of addiction neuroscience knowledge and tools in the assessment and treatment of substance use disorders (SUD). We cover four broad areas: (1) cognitive assessment, (2) neuroimaging, (3) cognitive training and remediation, and (4) neuromodulation. Cognitive assessment and neuroimaging provide multilevel biomarkers (neural circuits, cognitive processes, and behaviors) to be targeted with cognitive and neuromodulation interventions. Cognitive training/remediation and neuromodulation provide neuroscience-informed interventions to ameliorate neural, cognitive, and related behavioral alterations and potentially improve clinical outcomes in people with SUD. In the following sections, we review the current knowledge and challenges in each of these areas and provide ISAM-NIG recommendations to link knowledge and practice. Our goal is for researchers and clinicians to work collaboratively to address these challenges and recommendations. Cutting across the four areas, we focus on cognitive and neural systems that predict meaningful clinical outcomes for people with SUD and opportunities for harmonized assessment and intervention protocols.

COGNITIVE ASSESSMENT

Neuropsychological studies consistently demonstrate that many people with SUD exhibit mild to moderately severe cognitive deficits in processing speed, selective, and sustained attention, episodic memory, executive functions (EF: working memory, response inhibition, shifting and higher-order functions such as reasoning, problem-solving, and planning), decision-making and social cognition (5–10). Furthermore, neurobiologically-informed theories and expert consensus have identified additional cognitive changes not typically assessed by traditional neuropsychological measures, namely, negative affectivity and reward-related processes (e.g., reward expectancy, valuation and learning, and habits-compulsivity) (11–13).

Cognitive deficits in SUD have moderate longevity, and although there is abstinence-related recovery (14–16), these deficits may significantly complicate treatment efforts during the first 3 to 6 months after discontinuation of drug use. Thus, one of the most critical implications of cognitive deficits for SUD is their potential negative impact on treatment retention and adherence, in addition to clinical outcomes such as craving, relapse, and quality of life. A systematic review of prospective cognitive studies measuring treatment retention and relapse across different SUD suggested that measures of processing speed and accuracy during attention and reasoning tasks (MicroCog test battery) were the only consistent predictors of treatment retention, whereas tests of decision-making (Iowa and Cambridge Gambling Tasks) were the only consistent predictors of relapse (1). A later review that focused on substance-specific cognitive predictors of relapse found that long-term episodic memory and higher-order EF (including problem-solving, planning, and decision-making) predicted alcohol relapse, whereas attention and higher-order EF predicted stimulant relapse, while only

higher-order EF predicted opioid relapse (8). Working memory and response inhibition have also been associated with increased risk of relapse among cannabis and stimulant users (8, 17, 18). Additionally, variation in response inhibition has been shown to predict poorer recovery of quality of life during SUD treatment (19). Therefore, consistent evidence suggests that processing speed, attention, and reasoning are critical targets for current SUD treatments, whereas higher-order EF and decision-making are critical for maintaining abstinence. Response inhibition deficits seem to be specifically associated with relapse prediction in cannabis and stimulant users and also predict quality of life (a key non-drug-related clinical outcome) (20).

Practical Considerations: Characteristics and Needs of the SUD Treatment Workforce

The workforce in the SUD specialist treatment sector is diverse, encompassing medical specialists, allied health professionals, generalist health workers, and peer and volunteer workers (21). For instance, in the Australian context, multiple workforce surveys over the past decade suggest that around half the workforce have attained a tertiary level Bachelor (undergraduate) degree or greater (21–24). Similarly, US and European data has shown that education qualifications in the SUD workforce are lower than in other health services (25). Because the administration and interpretation of many cognitive tests are restricted to individuals with specialist qualifications, this limits their adoption in the sector. In addition, when screening does occur in SUD treatment settings, its primary function is to identify individuals requiring referral to specialist service providers (i.e., neuropsychology, neurology, etc.) for more comprehensive assessment and intervention, rather than to inform individual treatment plans.

Two fields in particular have driven progress in cognitive assessment practice for generalist workers: dementia, with an increasing emphasis on screening in primary care (26, 27), and schizophrenia, where cognitive impairment is an established predictor of functional outcome (28) necessitating the development of a standardized assessment battery specifically for this disorder. In the selection of domain-specific tests for the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) standard battery, a particular emphasis was placed on test practicality and tolerability, as well as psychometric quality. Pragmatic issues of administration time, scoring time and complexity, and test difficulty and unpleasantness (such as item repetition) for the client should be considered (28). These domains and issues are particularly relevant for the SUD workforce as well. The dementia screening literature has also emphasized these pragmatic issues, leading to a greater awareness and access to general cognitive screening tools.

Routine Cognitive Assessments in Clinical Practice

To date, the majority of the published literature on routine cognitive screening in SUD contexts has focused on three tests commonly used in dementia screening (29–34): the Mini-Mental State Examination (MMSE) (35), Addenbrooke's Cognitive Examination (ACE) (36), and the Montreal Cognitive Assessment (MoCA) (37). Due to their development for application in dementia contexts, these screening tools placed a heavy emphasis on memory, attention, language and visuospatial functioning (34). Multiple studies have demonstrated superior sensitivity of the MoCA and the ACE scales compared to the MMSE (34, 38). It is possible that this arises from the MoCA and ACE including at least some items assessing EF (letter fluency and trails) which are absent in the MMSE. Indeed, this may demonstrate an important limitation of adopting existing screening tools designed for dementia in the context of SUD treatment. It can be argued that cognitive screening is most beneficial in SUD contexts when focused on SUD-relevant domains, rather than the identification of general cognitive deficits. Therefore, current neuroscience-based frameworks emphasise the importance of assessing EF, incentive salience, and decision-making in SUD (13, 28, 39, 40). As such, there is much to be gained by applying a process similar to the MATRICS effort (28, 39, 40) in the SUD field to identify a 'gold-standard' set of practical and sensitive cognitive tests that can be routinely used in clinical practice.

Cognitive Assessment Approaches in SUD Research

The most commonly used cognitive assessment approach in SUD research has been the "flexible test battery". This approach combines different types of tests to measure selected cognitive domains (e.g., attention, EF). Attention, memory, EF, and decision-making are the most commonly assessed domains, although there is a considerable discrepancy in the tests selected to assess these constructs (41). Even within specific tests, different studies have used several different versions; for example, at least four different versions of the Stroop test have been employed in the SUD literature (1). Another commonly used approach is the "fixed test battery", which involves a comprehensive suite of tests that have been jointly standardized and provide a general profile of cognitive impairment. The Cambridge Automated Neuropsychological Test Battery (CANTAB) (42), the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (43), the Neuropsychological Assessment Battery (NAB) – Screening Module (44) and the MicroCog™ (45) are examples of fixed test batteries utilized in SUD research (30, 46–48), although these too have limited assessment of EF. Another limitation of these assessment modules is the lack of construct validity, as they were not originally designed to measure SUD-related cognitive deficits. As a result, they overemphasize assessment of cognitive domains that are relatively irrelevant in the context of SUD and neglect other domains that are pivotal (e.g., decision-making). A common limitation of flexible and fixed batteries is their reliance on face-to-face testing, normally involving a researcher or clinician, and their duration, which is typically around 60-90 min.

To address this gap, a number of semi-automated tests of cognitive performance have been developed, including the Automated Neuropsychological Assessment Metrics (ANAM, developed by the U.S. Department of Defence), Immediate

Post-concussion Assessment and Cognitive Testing battery (ImPACT), and CogState brief battery, have been used more widely, although validation studies to date suggest they may not yet have sufficient psychometric evidence to support clinical use (49–53). Research specifically in addictions has begun to develop and validate cognitive tests that can be delivered in client/participants' homes or *via* smartphone devices (54) (*scienceofbehaviorchange.org*, 2019). Evaluations of the reliability, validity, and feasibility of mobile cognitive assessment in individuals with SUD have been scarce, but promising (55–57).

Cognitive assessment *via* smartphone applications and web-based computing is a rapidly developing field, following many of the procedures and traditions of Ecological Momentary Assessment (EMA) (56). The flexibility and rapidity of assessment offered by mobile applications makes it particularly suited to questions assessing change in cognitive performance over various time scales (within hours to over months). For example, cognitive performance can be assessed in event-based (i.e., participants-initiated assessment entries), time-based and randomly prompted procedures that were not previously feasible, and or valid, in laboratory testing. While the benefits of mobile testing to longitudinal research, particularly large-scale clinical trials, appear obvious (57), the rapidity and frequency of deployment also provide opportunities to test questions of much shorter delays between drug use behavior and cognition. For example, recent studies have examined if daily within-individual variability in cognitive performance, principally response inhibition, was associated with variable likelihood for binge alcohol consumption (58). Similarly, influencing the immediate dynamic relationship between cognition and drug use has also been used for intervention purposes. Web and smartphone platforms have been used to administer cognitive-task based interventions, such as cognitive bias modification (CBM) training (59–61), where cognitive performance is routinely measured as a central element of interventions that span several weeks. The outcomes of these trials show that mobile cognitive-task based interventions are feasible but not efficacious as in a stand-alone context (58, 61). However, the combination of cognitive bias modification (approach bias re-training) and normative feedback significantly reduces weekly alcohol consumption in excessive drinkers (59).

Summary of Evidence and Future Directions

A substantial proportion of people with SUD have cognitive deficits. Alcohol, stimulants and opioid users have overlapping deficits in EF and decision-making. Alcohol users have additional deficits in learning and memory and psychomotor speed. Heavy cannabis users have specific deficits in episodic memory and attention. Cognitive assessments of speed/attention, EF and decision-making are meaningfully associated with addiction treatment outcomes such as treatment retention, relapse and quality of life (1). In addition, there is growing evidence that motivational and affective domains are also implicated in SUD pathophysiology and clinical symptoms (8). For example, both reward expectancy and valuation and negative affect have been proposed to explain SUD chronicity (13). However, to date, there have been no studies linking these "novel domains" with clinical outcomes. Thus, it is important to explore the predictive validity of non-traditional cognitive-motivational and cognitive-affective domains in relation to treatment response. While flexible and fixed test batteries are the most common assessment approaches, data comparability is alarmingly low and future studies should aim to apply harmonized methods (41). Remote monitoring and mobile cognitive assessment remain in a nascent stage for SUD research and clinical care. It is too early to make accurate cost-benefit assessments of different mobile methodologies. Yet, their potential to provide more cost-effective assessment with larger and more representative samples and in greater proximity to drug use behavior justifies continued investment into their development.

Challenges for Implementation Into Practice

One of the main challenges for the cognitive assessment of people with SUD is the disparity of tests applied across sites and studies, and the lack of a common ontology and harmonized assessment approach (13, 62). Furthermore, harmonization efforts must accommodate clinicians' needs, including brevity, simplicity, and automated scoring and interpretation (10). Mobile cognitive testing is a highly promising approach, although its reliability and validity are influenced by a number of key factors. Test compliance, or lack thereof, seems to be problematic. A recent meta-analysis suggested that the compliance rate for EMA (the standard paradigm to administer mobile cognitive testing) with SUD samples was below the recommended rate of 80% (63). Designs including participant-initiated event-based assessments were associated with test compliance issues, whereas duration and frequency of assessment were not. While the latter finding suggests that extensive cognitive assessment may be feasible with mobile methods, caution is advised with regard to the scope and depth of the data that can be obtained with these brief assessments and the validity of data sets collected (64). Remote methods for assessing confounds such as task distraction, malingering, and "cheating" are not well established or validated. As the capability of smartphones, for example, increases, so will the potential to minimize or control for such variables. Face-recognition and fingerprint technology has been proposed for ensuring identity compliance, although this presents ethical issues regarding confidential and de-identified data collection from samples that engage in illicit drug use (65).

ISAM-NIG Recommendations for Cognitive Assessment

As the authors of this ISAM-NIG roadmap, we give the following recommendations for future work:

1. *Selecting theoretically and clinically relevant constructs*: We recommend prioritizing constructs that are theoretically implicated in current neurobiological models of SUD [reviewed in (66)] and meaningfully related to SUD treatment

response and clinical outcomes [e.g., (1, 67, 68)]. These include attention/processing speed, response inhibition, and higher-order EF/decision-making. Episodic and working memory assessments can be particularly indicated in the case of alcohol and cannabis users (8).

2. *Selecting measures with well-established clinical validity in the SUD population*: We recommend using measures with demonstrated predictive and ecological validity (i.e., their scores predict individual variation in meaningful clinical outcomes such as treatment response, craving, drug use/relapse, and quality of life), in addition to reliability. Unfortunately, few such measures are currently available. The MicroCog test battery and Continuous Performance Test (sustained attention/response inhibition) are highly reliable and excellent predictors of treatment response (1). Delay discounting paradigms and gambling tasks have excellent predictive and ecological validity, but the latter have been criticized for low reliability and construct validity (69). Because the ultimate goal is to incorporate cognitive assessment into clinical practice, we recommend conducting a Delphi consensus study including both cognitive assessment researchers and SUD clinicians to identify a minimum battery of measures with adequate psychometric properties AND clinical significance.
3. *Adopting harmonized cognitive assessment protocols*: We recommend continuing work towards developing a harmonized Cognitive Assessment of Addiction (CAA) battery. This battery should be (1) theoretically grounded in current addiction neuroscience frameworks; (2) brief and easy to administer, to meet the needs and qualifications of the SUD workforce; (3) portable and repeatable, capitalizing when possible on emerging remote monitoring techniques; (4) clinically meaningful in individual-level predictive models, i.e., able to identify risk of cognition-related premature treatment cessation or relapse, cognitive phenotypes relevant for predicting response to different treatment approaches, or changes in cognitive status relevant to treatment progression. The CAA should also address challenges specific to international research collaboration, including culturally-sensitive contents and appropriate translation of instructions.

NEUROIMAGING

The development of functional imaging techniques such as Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI), has allowed the high-resolution mapping of the brain in-vivo, in people with SUD. This body of work has provided increasing evidence that SUD is associated with alterations in the anatomy and the functional brain pathways ascribed to reward, learning, and EF. Importantly, emerging evidence suggests that neuroimaging versus subjective measures in SUD may predict with greater precision addiction-relevant cognitive processes (e.g., attentional biases) and treatment outcomes (e.g., abstinence) (70–72).

Neuroimaging Methods and Techniques Applied to SUD

Functional imaging techniques allowed exploration of whether brain dysfunction is implicated in SUD in humans. These create images of brain function by relying on proxies, including metabolic properties of the brain (e.g., oxygen in PET and fMRI, glucose levels in PET) (73). The application of functional imaging has been crucial to reveal the impact of SUD on human brain function in areas ascribed to cognitive processes (e.g., EF, decision-making) and positive and negative emotions (see "Cognitive assessment approaches in SUD research" in the COGNITIVE ASSESSMENT section).

PET studies have also provided early evidence on the neurobiology of SUD (74–77). PET imaging relies on the movement of injected radioactive material to identify whether the metabolic activity of brain regions is related to cognitive functions (73). PET's invasiveness and high financial costs have resulted in a limited number of studies using it, and its low temporal and spatial resolutions (i.e., 20–40 min required for image generation, with a spatial resolution up to 5 mm^3) prevented the identification of subtle brain activity alterations in SUD samples (73).

The development of fMRI provided a way to overcome these limitations. Unlike PET, fMRI is non-invasive, promoting feasibility in unpacking the neural correlates of SUD (73). Specifically, fMRI generates information about brain activity by exploiting the magnetic properties of oxygenated and deoxygenated blood (73). Further, fMRI provides information on the brain's functional activity with higher temporal and spatial resolutions than those of PET, i.e., within seconds and millimeters, respectively (73). These methodological advantages have allowed many studies to map the neural pathways implicated in SUD, while providing information on brain function within a high spatial and temporal resolution. However, a well-described limitation of fMRI analyses is the difficulty to control for multiple tests (i.e., statistical thresholds) and related false positive errors (78). The neuroimaging community has started to implement several strategies to address this limitation (79), but the use of liberal thresholds has probably inflated false positive rates in earlier studies.

Using multi-modal imaging techniques is warranted to further unpack the neural mechanisms of SUD and abstinence. For instance, integrating structural MRI (sMRI) data with Magnetic Resonance Spectroscopy Imaging, an MRI imaging technique that allows investigation of metabolites in the brain, may provide insight into the biochemical changes associated with volumetric alterations in SUD. Further, conducting brief, repeated task-free fMRI studies during treatment/abstinence could provide a better understanding of the impact of clinical changes on intrinsic brain architecture. An advantage of resting-state functional imaging data is the possibility of investigating patterns of brain function without restrictive "forces" on brain function placed by a specific task. Finally, studying SUD with modalities such as Diffusion Tensor Imaging (DTI) may reveal alteration in white matter pathways that connect brain regions that are volumetrically altered. This approach may inform the pathophysiology of volumetric alterations in SUD-relevant brain circuits.

Brain Systems Implicated in Addiction: Insights From Theory

Table 1 overviews key neurobehavioral pathways implicated by prominent neuroscientific theories of addiction and a growing body of work. These include neurobehavioral systems implicated in positive valence, negative valence, interoception, and EF (80–86). Abstinence may recover and mitigate such brain alterations and related cognitive functions, e.g., increase in response inhibition capacity, lower stress and drug reactivity, learning new responses to drugs and related stimuli. This notion is yet to be tested using robust neuroimaging methods that, in conjunction with treatment-relevant clinical and cognitive measures, measure and track the integrity of specific neural pathways during abstinence (see examples in **Table 1**).

The neurobiology of abstinence has been posited to entail two core processes (99). The first is the *restored* integrity of brain function, as drug levels in the central nervous system and bloodstream clear out with abstinence. The second is the *retraining* of neural pathways implicated in cognitive changes that enable abstinence. These include awareness/monitoring of internal

TABLE 1 | Overview of addiction-related neurocognitive constructs and related brain circuits, tasks, and interventions.

	Positive affect, Response (13), (80), (82), (84)	**Positive affect, Anticipation (13), (83), (84)**	**Negative affect (13), (80), (82),**	**Learning/habit (13), (83), (84)**	**Cognitive control (13), (82), (83), (84)**	**Interoception (83), (86)**
Brain circuit	Medial OFC, ventral striatum	Medial OFC, sgACC (subgenual)	Amygdala	Lateral OFC, Dorsal striatum (Caudate, putamen), Hippocampus	DLPFC, dACC (dorsal), IFG	Insula, posterior cingulate
fMRI tasks	Monetary incentive delay (reward receipt) (87), probabilistic reward task (88), activity incentive Delay task (98)	Monetary Incentive delay (reward anticipation) (87), cue-reactivity (90), attentional bias (89)	Cue reactivity (90) during withdrawal, negative or stress cue reactivity	Instrumental reward-gain and loss-avoidance task (89)	Stop Signal (91), Go-no go (92), Stroop (93), PASAT-M (97)	heartbeat counting task (94), visceral interoceptive attention task (95)
Cognitive	Reward receipt, response to reward, reward satiation	Motivation, saliency valuation, reward anticipation, drive expectancy, approach/attentional bias	Acute/sustained threat	Stimulus-response conditioned habits, compulsivity, learning reward/loss contingencies	Loss of cognitive control, disinhibition, performance monitoring, action/response selection, low distress tolerance	"Momentary mapping of the body's internal landscape" (96) during craving and withdrawal
Behavior	Experience of reward with drug use, response to substance-free reward	Increased: attention/salience of drugs and related stimuli, reward when anticipating drug use.	Experience of withdrawal, stress, anxiety, anhedonia	Drug use as: repetitive, compulsive drive, conditioned response to seek positive affect & avoid/mitigate negative affect, learnt association with people, situations, places	Drug use even when known as harmful and in response to affective distress	Heightened/lowered awareness to drug-related physical & psychological states; increase distance between cue and behavioral response.
Intervention strategies	Decrease reward value of drug (e.g., methadone or nicotine patches), suppression of mPFC with low frequency rTMS or cTBS; increase reward value of drug-free activities (e.g., behavioral activation, physical activity)	Cognitive bias modification, reappraisal training for drug cues, exposure therapy, motivational interviewing, contingency management	Strategies to address negative affect (e.g., behavioral activation and cognitive reappraisal training), medication that counter stress response, rtfMRI neurofeedback on Insula or sgACC	Strategies that weaken conditioned drug behaviors, memory reconsolidation	Strengthen inhibitory/executive control, inhibitory control training (e.g., Go-No-Go), working memory training, goal management training, stimulating DLPFC with anodal tDCS or high frequency rTMS	Mindfulness-based therapies, physical exercise

Columns reflect key neurocognitive constructs for addiction research. Identified constructs also map onto the three domains of the Addiction Neuroclinical Assessment (ANA) (11) framework: Positive affect (response and anticipation), Negative affect, and Cognitive control map directly onto the three domains of ANA (i.e., Incentive salience, Negative affectivity and Executive function). Learning/habit is part of Incentive salience (reward learning); Interoception is at the interface of the three ANA domains. Rows reflect functional neuroimaging methods (e.g., fMRI tasks), cognitive/behavioral assessments, and examples of neuroscience informed intervention strategies aligned with each of the identified constructs.

ACC, anterior cingulate cortex; cTBS, continuous theta burst stimulation; DLPFC, dorsolateral PFC; IFG, Inferior Frontal Gyrus; mPFC, medial PFC; OFC, orbitofrontal cortex; PFC, prefrontal cortex; rtfMRI, real-time functional MRI; rTMS, repeated transcranial magnetic stimulation; tDCS, transcranial direct current stimulation.

psychological/physiological states (e.g., insula), withdrawal and craving (e.g., amygdala); EF (e.g., dorsal prefrontal regions); monitoring conflict between short-term goals (e.g., pleasure from using drugs, ventral striatum) *versus* long-term goals (e.g., abstinence and improved quality of life; anterior cingulate cortex); motivation to use drugs (e.g., orbitofrontal cortex); and learning new responses to drug-related and other stimuli (e.g., lateral prefrontal and dorsal striatal regions) (99).

Summary of Neuroimaging Evidence in SUD

Most neuroimaging studies to date have mapped dysfunctional neural pathways in SUD. There is a significant lack of work that tracks abstinence-related brain changes over time. This evidence gap prevents neuroimaging studies from informing the identification of treatment targets and clinical practice. It is unclear if abstinence (i) leads to recovery of SUD-related brain dysfunction (i.e., return to pre-drug onset level, or comparable levels to non-drug using controls), (ii) engages additional pathways implicated in abstinence-related cognitive, clinical, and behavioral changes, and (iii) is predicted by specific brain measures assessed pre-treatment. Emerging (but mixed) evidence from standard behavioral (e.g., CBT, Motivational Interview, Contingency Management) and pharmacological treatments that directly affect the central nervous system provides preliminary support for these notions, as reviewed in detail in previous work [see (100–102)]. This section provides an overview of early neuroimaging evidence for brain changes related to abstinence and novel interventions (i.e., cognitive training approaches and mindfulness-based therapies).

Neuroimaging Evidence in Abstinence

Abstinence may "reverse" brain dysfunction and volume loss associated with SUD. Studies have observed increased or normalized volumes in global and prefrontal brain regions related to abstinence in people with alcohol use disorder (103) and cocaine and opiate use disorders (104). PET and DTI studies of alcohol and cocaine users showed recovery of brain dysfunction and white matter integrity following heterogeneous abstinence durations, e.g., from about a month (105, 106), to several months (107, 108) and several years (109, 110). Results from fMRI tasks of response inhibition in abstinent users also showed that reduced brain function typically associated with drug use, was "restored" and increased in prefrontal and cerebellar pathways in former *versus* current cigarette smokers (> 12 month abstinent) (111, 112), and in former cannabis users (> 28 day abstinent) *versus* non-users (113).

Emerging (but mixed) evidence showed that abstinence duration was associated with improved integrity (functional and structure) of cortical and prefrontal pathways (109, 111, 114). Additionally, abstinence related neuroadaptations have been associated with substance use levels [e.g., cocaine dose (115)], and performance was improved during cognitive tasks relevant to addiction [e.g., processing speed, memory, EF-shifting (104, 115)]. Thus, abstinence-related brain changes may in part drive treatment relevant outcomes.

Neuroimaging Predictors of Abstinence

Several neuroimaging studies have examined whether (structural and functional) brain integrity in SUD predicts abstinence, with promising results. Studies of *brain structure* in people with nicotine and alcohol use disorders reported that increased volume and white matter integrity in prefrontal regions, followed by parietal and subcortical areas, most consistently segregated abstainers *versus* relapsers (116–119). Studies have examined *brain function* using fMRI tasks that engage cognitive domains relevant to treatment response (cue reactivity, attentional bias, error-related activity, reward, and emotion processing) (71, 72, 111, 116, 117, 120–124). These studies provided evidence that the function of fronto-striatal regions in particular, followed by other regions (e.g., cingulate, temporal, insular cortices) discriminated responders *versus* non-responders, relapsers *versus* non-relapsers in cigarette smokers and people with methamphetamine, cocaine and alcohol use disorders (71, 72, 111, 116, 117, 120, 121, 123, 124). Also, the activity of fronto-striatal pathways have been shown to predict alcohol dosage at 6 month follow-up (122). Studies that used other functional imaging techniques such as spectroscopy and PET imaging consistently reported that frontal blood flow and metabolites (i.e., in prefrontal, insular, and cerebellar areas) and the density of dopamine receptors (i.e., in the dorsal striatum) predicted treatment outcome in alcohol users (125, 126) and relapse in methamphetamine users (127).

Impact of Cognitive Training Strategies

Novel training strategies that target core cognitive dysfunctions in SUD have shown promise to restore cognitive alterations and help maintain abstinence (128). One example includes cognitive bias modification strategies that reduce attentional biases towards substance related cues [see study in tobacco smokers (129)]. Such strategies may target top-down and bottom-up brain pathways (130) implicated in addiction (131). These include increasing the activity of top-down EF regions that enhance inhibitory control and behavioral monitoring (e.g., dorsal anterior cingulate, lateral orbitofrontal cortex), and decreasing reactivity of bottom-up pathways implicated in reactivity to drug stimuli, and craving (e.g., amygdala).

Early neuroimaging evidence has examined the neuroadaptations that occur pre-to-post-cognitive bias modification training. These findings are revised and discussed in the COGNITIVE TRAINING AND REMEDIATION section below. There is a paucity of neuroimaging research on other cognitive training and remediation approaches, despite promising evidence of neuroplasticity-related changes after cognitive remediation in brain injury (132).

Impact of Mindfulness-Based Interventions

Mindfulness-based interventions are being increasingly used for the treatment of SUD (133). Although mindfulness does not use standard cognitive training/remediation approaches, it has shown to improve SUD-relevant cognitive processes such as attention and EF (134) as well as substance use outcomes (i.e., reduced craving, withdrawal) (135). Mindfulness-based interventions

engage two key cognitive processes (i) *focused attention*, which consists of paying attention to a specific stimulus while letting go of distractions (e.g., focus on breathing, while experiencing craving) and (ii) *open monitoring*, which refers to the being aware of internal and external stimuli (e.g., acknowledging the experience of stress, craving, and withdrawal, or environmental triggers) with a non-judgmental attitude and acceptance.

The effectiveness of mindfulness-based interventions has been ascribed to improved function of prefrontal, parietal, and insula regions that are implicated in EF and autonomic regulation (133, 136), and down-regulation of reactivity in striatal/amygdala regions implicated in reward, stress, and habitual substance use (136). Only a handful of neuroimaging studies have examined brain changes that occur with mindfulness-based interventions in SUD. This includes a fMRI study in tobacco smokers that showed a 10-session mindfulness-oriented recovery enhancement (MORE) *versus* placebo intervention, decreased activity of the ventral striatum, and medial prefrontal regions during a craving task and an emotion regulation task (137). Most evidence on mindfulness and SUD consists of behavioral studies that showed robust effects on cognition, substance use, and craving. Given the widespread use of mindfulness-based interventions in clinical settings, we advocate the conduct of active placebo-controlled neuroimaging studies that map the neurobiology of mindfulness in SUD.

Challenges for Implementation Into Practice

Overall, there is a paucity of neuroimaging studies of treatment and abstinence in SUD. The study methods are very heterogeneous which precludes their systematic integration. *First*, there was significant heterogeneity in treatments, with distinct durations and hypothesized neurobehavioral and pharmacological mechanisms of action, and distinct treatment responses across different individuals, SUD and related psychiatric comorbidities. *Second*, control groups varied substantially (e.g., placebo, active control treatment, no control group) and brain changes related to abstinence were compared to different types of controls (e.g., pretreatment baseline in the same group, control group of non-substance users, separate SUD group also assessed post-treatment). *Third*, repeated measures study designs had varying data testing points (e.g., before, during and at varying times post-treatment) that precluded the integration of the study findings and mapping treatment-related, trajectories of brain changes with abstinence/recovery. More systematic evidence is needed to provide sufficient power to measure brain pathways relevant to treatment response and to inform clinically-relevant treatment endpoints. In order to address this gap, the ISAM-NIG Neuroimaging stream recommends the conduct of harmonized, multi-site, neuroimaging studies with systematic testing protocols of relevance for clinical practice. It is hoped that the ISAM-NIG Neuroimaging approach will generate results that can be readily integrated and that increase the power to detect abstinence-related neuroadaptations.

On one hand, the integration of neuroimaging testing into clinical practice can be challenging. MRI scanners are extremely expensive to buy, setup, and run safely, and the acquisition of high-quality brain images requires extensive specialized technical expertise. On the other hand, the availability of MRI scans in many hospitals, universities, and medical institutions, may provide ideal settings to integrate neuroimaging and clinical expertise. MRI scans can be feasible in that they are non-invasive, safe, and can be relatively quick (e.g., anatomical and resting-state brain scans can take <10 min, and some fMRI tasks can last between 10 and 15 min). Outstanding challenges to address remain funding sources, the lack of integration in the theoretical frameworks between basic research, clinical science, and clinical practice. Discipline-specific specialized language and practices can also create barriers. We advocate using team science to develop a harmonized interdisciplinary framework, so that all stakeholders, including clinicians, neuropsychologists, social workers and neuroscientists interact to inform commonly-agreed testing batteries and most profitable directions for future work.

The present review has focused on neuroimaging data mainly acquired through fMRI, allowing for visualization of the brain networks involved in certain conditions (e.g., abstinence vs. relapse). However, it should be noted that the coarse temporal resolution of such techniques (1–2 s) impedes determination of the temporal activation sequence (in the order of the ms), allowing the specific brain activation patterns to be correlated with the various cognitive stages involved in the investigated processes [e.g., (138)]. Other tools, such as cognitive event-related potentials (ERPs) in particular, might be more suitable for this purpose (139). Nowadays, different studies reveal that specific ERP components tagging specific cognitive functions (mainly cue reactivity and inhibition) may be used as neurophysiological biomarkers for addiction treatment outcome prediction (140). Such data may be of great value to clinicians for the identification of cognitive processes that should be rehabilitated on a patient-by-patient basis through cognitive training and/or brain stimulation. However, despite technical facilities (cheap tool easily implementable in each clinical care unit), several decades of research, and clinical relevance, ERPs like other neuroimaging modalities have yet to be implemented in the clinical management of SUD.

ISAM NIG Recommendations for Neuroimaging

We aim to map how advanced multimodal neuroimaging tools—coordinated with relevant clinical and cognitive measures agreed upon with a large multidisciplinary team of experts in the field—can be used to track the neurobiological mechanisms of addiction treatment. As the authors of this ISAM-NIG roadmap, we give the following recommendations for future work:

1. Neuroimaging testing should be *harmonized* with clinical and cognitive tools mapping overlapping systems (see example in **Table 1**).
2. Neuroimaging testing should be *feasible* and rely on short and robust imaging protocols that recruit specific brain pathways implicated in relevant clinical and cognitive features of addiction (e.g., craving, attentional bias, cognitive control).

3. Neuroimaging protocols may also incorporate *neuroimaging measures of brain integrity other than those included in the harmonized protocols when focused on discovery science* (e.g., new fMRI tasks that target novel cognitive constructs, new neuroimaging techniques that test distinct properties of brain integrity). This would mitigate the risks that complete harmonization around existing neuroimaging measures and neurobiological models of addiction would stifle new knowledge. We cannot exclude that current neuroimaging techniques and theories of addiction may not be an accurate/valid representation of brain changes that occur with SUD treatment.
4. Imaging testing batteries should be *amenable to repeated testing* so that changes over time can be tracked (i) *prospectively*, to examine if baseline imaging measures predict follow up outcomes assessed 1+ times at the end of treatment, (ii) *longitudinally*, to track individual trajectories of brain and behavioral change before, during and after treatment, (iii) using rigorous *double-blind randomized controlled studies* to map treatment-specific effects in distinct substance and behavioral addictions.
5. *Multi-site* neuroimaging studies using shared protocols will be necessary to gain sufficient power to track heterogeneity of treatment responses between individuals SUD, to validate the protocols and test their reliability. There are excellent examples of successful international collaborations that are already in place in this area, such as ENIGMA-Addiction (141). We aim to leverage these existing collaboration initiatives to increase neuroimaging methods reliability and validity and studies sample size and representativity, and to expand them by incorporating more clinical researchers and clinicians.
6. As treatments often consist of individual and combined interventions, the distinct and cumulative effects on brain changes should be examined. In addition, investigating moderating roles of age and sex differences on these abstinence-related neuroadaptations is critical. Indeed, younger and older people with SUD may show lower and greater vulnerability to aberrant neurobiology (142). People with different ages and sex may show distinct neuroplastic changes with abstinence and these are largely unknown (99, 143, 144).
7. Brain indices from neuroimaging testing should be *examined in relation to treatment response variables*, whether measured as categories (e.g., responders vs. non-responders, relapsers vs. non-relapsers) or as discrete measures of addiction (severity of addiction symptom scores, number of relapses, duration of abstinence, amount of substance used) and related mental health, cognitive and quality of life outcomes (e.g., stress, mood, socio-occupational functioning).

COGNITIVE TRAINING AND REMEDIATION

Despite recent advances in psychological and pharmacological interventions for SUD, relapse remains the norm. A recent meta-analysis of 21 treatment outcome studies conducted between 2000–2015 found that fewer than 10% of treatment seekers were in remission (i.e., did not meet SUD diagnostic criteria for the past 6 months) in any given year following SUD treatment (145). The past decade has seen a proliferation of cognitive training (CT) intervention trials aimed at remediating or reversing substance-related cognitive deficits (146). However, their implementation into clinical practice is almost non-existent, despite promising results and now having more flexible, precise, engaging and convenient modes of delivery (i.e., computer, web and mobile application-based approaches). Gathering more data in this still-developing area is essential to facilitate translation. Even the most widely tested training interventions, such as cognitive bias modification, need more data to fully appraise their benefit for addiction treatment (147). This section summarizes recent advances in CT, identifies limitations in the evidence base, and highlights priorities and directions for future research to bridge the gap between science and practice. Current CT approaches can be broadly divided into: general cognitive remediation, working memory training (WMT), inhibitory control (or response inhibition) training (ICT), and cognitive bias modification (CBM).

Cognitive Remediation

In SUD, general cognitive remediation approaches such as cognitive enhancement therapy (CET) and cognitive remediation therapy (CRT) aim to reduce substance use (148–150) and craving (151) by targeting EF and self-regulation. Cognitive remediation has been shown to improve cognition in domains of working memory (WM), verbal memory, verbal learning, attention, and processing speed (151–154). Positive outcomes have also been shown to be associated with increased neuroplasticity in emotion regulation-related fronto-limbic networks in individuals with schizophrenia and co-morbid SUD (155). A recent study delivered 12 two-hour group sessions of clinician-guided CRT and computerized CT (Lumosity) (156) over 4 weeks to a sample of female residents completing residential rehabilitation and found significant improvements in EF, response inhibition, self-control, and quality of life relative to treatment as usual (TAU) (157). Similar research has reported comparable improvements in cognitive functioning following CRT (150, 151) and CET (148), and improved cognitive functioning has been associated with reduced substance use at 3- and 6-month follow-ups (148, 150). Importantly, CET and CRT also demonstrate preliminary efficacy for SUD patients with cognitive impairments (e.g., schizophrenia, past head injury) (148, 157). However, their duration, intensity, and high cognitive demand—coupled with a current paucity of large-scale, methodologically rigorous clinical trials—may currently preclude their widespread implementation in clinical settings.

Another manualized therapist-assisted group intervention is Goal Management Training (GMT), which trains EF and sustained attention and emphasizes the transfer of these skills to goal-related tasks and projects in everyday life. When combined with mindfulness meditation, GMT has been found to significantly improve WM, response inhibition and decision-making in alcohol and stimulant outpatients relative to TAU (158) and more recently also in polysubstance users in a therapeutic

community (159). A meta-analysis of GMT more broadly concluded that it provides small to moderate improvements in EF which are consistently maintained at 1–6 month follow-ups (160). As such, GMT is likely to be an effective candidate cognitive remediation approach for SUD treatment; however, substantially more research is needed to validate this assertion, particularly regarding the translation of cognitive improvements into improved substance use outcomes.

Working Memory Training (WMT)

The most widely researched EF training intervention, WMT (e.g., Cogmed, PSSCogRehab) (161, 162) requires participants to repeatedly manipulate and recall sequences of shapes and numbers through computerized tasks that become increasingly difficult over time (i.e., they are adaptive to the individual's performance). WMT aims to extend WM capacity, so individuals can better integrate, manipulate, and prioritize important information, with the aim of supporting more adaptive decision-making that leads to reduced substance use (163). Relative to many other approaches, WMT is intensive, typically requiring 19–25 days of training and as such, retention is often poor (164). While WMT has been shown to lead to improvements in near-transfer effects (i.e., improved performance on similar WM tasks), there is limited evidence supporting far-transfer effects of WMT on other measures of EF and importantly, on substance-related outcomes (165). Reduced alcohol consumption 1 month after training was reported following WMT in heavy drinkers (163), but most studies have failed to demonstrate or even measure changes in substance use (165). For example, non-treatment seekers with alcohol use disorder who were trained with Cogmed showed improved verbal memory but no clinically significant reductions in alcohol consumption or problem severity (166). While a study of treatment-seekers improved WM and capacity to plan for the future (i.e., episodic future thinking) on a delay discounting task, there was no measurement of substance use outcomes (167). Similarly, studies of methadone maintenance (168) and cannabis (169) have found no evidence of far-transfer effects (e.g., delay discounting), although Rass et al. (168) showed WMT-related reductions in street drug use among methadone users. Other forms of WMT (e.g., n-back training) have reported similar near-transfer but not substance-use-related findings with methamphetamine patients (170) and a mixed group of substance use patients (alcohol, cannabis, cocaine) (164). As such, the greatest limitation in the WMT literature is the failure to consistently examine substance use outcomes and therefore there is insufficient evidence at this time to support the utility of WMT as an effective adjunctive treatment for SUD.

Inhibitory Control Training (ICT)

Since deficits in inhibitory control are associated with increased drug use (171–174), ICT aims to bolster inhibitory control through the repeated practice of tasks [e.g., go/no-go (GNG), stop-signal task]. Such tasks require individuals to repeatedly inhibit prepotent motor responses to salient stimuli (172). In a seminal study, a beer-GNG task which trained heavily drinking students to inhibit responses to "beer" stimuli resulted in significantly reduced weekly alcohol intake relative to students trained towards "beer" stimuli (175). A recent RCT of 120 heavily drinking students found that a single session of either ICT or approach bias modification (ApBM, described below) led to significant reductions in alcohol consumption relative to matched controls (176). Similarly, Kilwein et al. (177) found that a single session of ICT (GNG) reduced alcohol consumption and alcohol approach tendencies in a small sample (n = 23) of heavily drinking men (177). Despite these promising findings, each of the aforementioned ICT studies used community samples, and it has not yet been established whether these results will generalise to treatment seekers.

Two meta-analyses recently concluded that ICT leads to small but robust reductions in alcohol consumption immediately after training (178, 179). Di Lemma and Field (176) reported reduced alcohol consumption in a bogus taste test after a single session of ICT or cue-avoidance training (approach bias modification). Others have observed reduced alcohol consumption 1 and 2 weeks after ICT (163, 177, 180). These findings highlight the promise of ICT though there remains a paucity of research assessing long-term drinking outcomes outside of laboratory settings. Future studies of ICT with clinical populations should consider testing multi-session approaches akin to WMT. To date, few studies have trialled multi-session ICT: One found it to be ineffective (58) for heavily drinking individuals, while another found that 2 weeks of ICT resulted in modest reductions of alcohol consumption among individuals with AUDs, compared to WMT or a control condition (181).

Cognitive Bias Modification (CBM)

CBM aims to directly interrupt and modify automatic processes in response to appetitive cues. Attentional bias modification (AtBM) aims to modify the preferential allocation of attentional resources to drug cues by repeatedly shifting attention to neutral or positive (non-drug) cues and away from drug-related cues. Despite several null findings (182), significant effects have included the reduction of alcohol consumption in non-treatment seeking heavy or social drinkers (183, 184). Among treatment seekers, five sessions of AtBM have been shown to significantly delay time to relapse (but not relapse rates) relative to controls who received sham training (185). Similarly, six sessions significantly reduced alcohol relapse rates at a one-year follow-up relative to a sham training condition in a sample of treatment seekers with AUD (186). Among methadone maintenance patients, AtBM reduced attentional bias to heroin-related words, temptations to use, and number of lapses relative to TAU (187). However, among individuals with cocaine use disorder, it failed to reduce attentional bias, craving, and cocaine use (188). Likewise, 12 sessions of AtBM vs. sham training during residential treatment for methamphetamine use disorder failed to reduce craving and preferences for methamphetamine images (189). A systematic review of alcohol, nicotine, and opioid AtBM studies concluded that despite numerous negative findings in the literature, eight out of 10 multiple-session studies resulted in reduced addiction

symptoms (particularly for alcohol), but without concomitant reductions in attentional bias (190).

Approach bias modification (ApBM), which uses the Approach Avoidance Task, requires an avoidance response to drug cues (pushing a joystick, shrinking image size) and an approach response (pulling a joystick, enlarging image size) to non-drug cues. Several trials have examined alcohol ApBM, with evidence that short-term abstinence is increased by up to 30% with four consecutive training sessions during inpatient withdrawal (32) and by 8%–13% at 12-month follow-up (186, 191, 192). Alcohol ApBM has demonstrated relatively consistent, moderate reductions in drinking behavior when delivered to clinical populations (193), and it was even added to the German guidelines for the treatment of AUD (194).

Early neuroimaging evidence has examined the neuroadaptations that occur pre-to-post-cognitive bias modification training. This work has focused on two samples of abstinent alcoholics undergoing an fMRI cue-reactivity task (alcohol *versus* soft drink stimuli) (61, 195). Participants showed higher baseline reactivity to alcohol cues within the amygdala/nucleus accumbens and the medial prefrontal cortex, respectively (61, 195). The same samples, following a 3-week implicit avoidance task (versus placebo), showed reduced amygdala and medial prefrontal reactivity (61, 195). Notably, these brain changes were associated with reduced craving and approach bias to alcohol stimuli (61, 195) but not abstinence 12 months later. While preliminary, these findings suggest that neuroadaptations associated with cognitive bias modification have clinical relevance and warrant replication in larger SUD samples using robust, active placebo-controlled designs.

To date, only one study has been published that trialled ApBM in an illicit drug-using sample of non-treatment-seeking adults with cannabis use disorder (N = 33). Relative to sham-training, four sessions resulted in blunted cannabis cue-induced craving (196) but not less cannabis use. Overall, evidence suggests that ApBM is associated with reduced approach bias and reduced consumption behaviors for alcohol, smoking, and unhealthy foods (197). Recently, six sessions of ApBM delivered to 1,405 alcohol-dependent patients significantly reduced alcohol relapse rates at a 1-year follow-up relative to a sham-training condition (186). However, as these reductions were also observed following AtBM and a combined AtBM and ApBM condition, the authors concluded that all active CBM training conditions had a small but robust long-term effect on relapse rates.

Finally, a meta-analysis of alcohol and smoking CBM studies (both AtBM and ApBM) showed a small but significant effect on clinical outcomes for alcohol (but not smoking), but a lack of evidence that reduced approach bias led to improved outcomes (198). This assertion was challenged by Wiers et al. (193) who noted that the review conflated proof-of-principle lab-studies and clinical RCTs and different samples (e.g., treatment-seeking alcohol dependent individuals vs non-clinical student populations). Importantly, these populations likely have differences in motivation/awareness for receiving an intervention to reduce alcohol use, which could explain inconsistencies in the reported effectiveness of CBM across populations (193).

Summary of Evidence and Future Directions

Currently CBM, particularly ApBM, appears one of the most promising approaches for individuals seeking treatment for AUDs; however, its effectiveness for other drugs (aside from tobacco) is yet to be established. The most extensively trialled CT approach is WMT, which has shown promising results in alcohol and stimulants users. However, its high cognitive demand, training intensity, and apparent lack of far-transfer effects limit its application to clinical populations. ICT holds much promise for reducing alcohol consumption in heavy drinkers, but requires testing in treatment-seekers. Finally, more intensive group-based approaches such as CRT/CET and GMT may improve EF and quality of life; however, their impact on substance use outcomes remains largely untested. Synergistic approaches now warrant exploration. Indeed, a study that combined WMT and AtBM (199) has shown promising feasibility and improved EF, though substance use outcomes were not assessed. It may also prove fruitful to adopt staggered CT approaches, capitalizing on the brain's capacity to repair itself (neuroplasticity) during withdrawal, early and later abstinence by strengthening cognitive control (e.g., using ICT) and dampening cue-reactivity (e.g., using CBM), prior to engaging in more intensive and cognitively demanding but ecologically valid group training for more extensive remediation (e.g., using GMT).

Challenges for Implementation Into Practice

While there may be logistical challenges to the adoption of CT in clinical practice (e.g., cost, lack of time, training requirements, etc.), the main impediment to implementing CT in clinical practice is the absence of robust evidence for treatment success of any one particular approach. This is largely due to the vast heterogeneity of studies, particularly regarding differences in treatment settings, samples (clinical vs. non-clinical populations), cognitive intervention approaches, number and duration of training sessions, targeted mechanisms, targeted drugs of concern and varying primary outcome measures. Similarly, the absence of brief, ecologically valid, easily-administered measures of cognition precludes the identification of candidates who are most likely to benefit from CT (e.g., individuals with the poorest WM or the strongest attentional bias). As such, the evidence base for CT remains hampered by (1) the marked lack of studies on clinical populations, (2) the counter-intuitive neglect of assessing relevant substance use outcomes, (3) the lack of adequately-powered RCTs, (4) the limitations of research designs, (5) lack of attention to individual-level trajectories of cognitive improvements in relation to substance use and quality of life outcomes (precision medicine approach), and (6) a simple focus on direct relations between cognitive deficits and outcomes without considering person and environmental mediators and moderators of this relation (14). Despite positive signals from proof-of-concept studies and pilot RCTs, they require replication and testing with suitable control conditions in order to demonstrate their applicability in clinical settings. These limitations highlight the need for a harmonization approach that

promotes greater standardization in cognitive training protocols and assessment of its effectiveness (i.e., routine assessment of substance use outcomes). Since the software and manuals of some of the most promising interventions (e.g., CBM, GMT) are well-developed and reproducible, we should advance towards optimized shared protocols that can promote international collaborations and multi-site studies. These recommendations will elucidate what works, for whom and under what conditions (i.e., identifying neurocognitive phenotypes). This knowledge will then guide the adoption of CT to improve outcomes for people seeking treatment for SUD.

ISAM-NIG Recommendations for Cognitive Training and Remediation

As the authors of this ISAM-NIG roadmap, we give the following recommendations for future work:

1. *The a priori publishing of research protocols*: To improve the consistency of cognitive training trials we encourage the publishing of research methodologies and protocols. This will permit replication studies to aid the consolidation of a disparate evidence base and help determine the optimal training duration and frequency to be implemented in real world clinical settings.
2. *Adopting consistent training paradigms and tailored, context-relevant stimuli:* A challenge for CBM research is the absence of consensus on optimal sham training conditions (e.g., matched stimuli with different push-pull contingencies) and optimal approach stimuli (e.g., whether to use neutral stimuli or healthier alternatives such as non-alcoholic beverages) (200). In the context of both CBM and ICT, utilizing personalized/tailored stimuli may increase engagement and effectiveness. For avoidance or "no-go" stimuli this might involve only using beverage types/brands that are regularly consumed by an individual, or images of illicit drug use and paraphernalia reflecting their preferred route of administration. Similarly, approach or "go" stimuli could encompass positive motivational images representing an individual's personal goals, values, and aspirations (family, employment, hobbies, etc.), which are drawn on heavily in most psychosocial interventions. Furthermore, co-design with consumers and end-users is a fundamental step to developing interventions that will be implemented successfully in practice.
3. *Ensuring targeted constructs are measured in cognitive training trials:* Future research protocols must adopt pre- and post-intervention measures that will elucidate changes in targeted mechanisms, thereby integrating neuroscience into addiction treatment. Importantly, these protocols should enable moderation and mediation analyses using psychophysiological measures (e.g., EEG, skin-conductance) in order to address issues regarding the notorious lack of reliability of traditional measures (e.g., the implicit association task and the approach avoidance task) (192, 201, 202) and thereby more accurately identify individuals most likely to benefit from adjunctive approaches.
4. *Adopting and standardizing SUD-related outcome measurement*: Future research needs to test cognitive interventions in real-world clinical settings and assess meaningful SUD clinical outcomes (i.e., reduced substance use, reduced cue-craving). Clear evidence of reduced harm and consumption is likely to appeal to both clinicians and individuals under their care, thus driving this improved addiction treatment effort.

NEUROMODULATION

The exponential growth in our understanding of the neural circuits involved in drug addiction over the last 20 years (3, 203–205) has been accompanied by the introduction of non-invasive brain stimulation technologies (NIBS) capable of modulating brain circuits externally (outside of the skull), such as transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES). Technical advances in NIBS has increased hopes to find clinical applications for NIBS in addiction medicine (206). New FDA approval of NIBS technologies in depressive and obsessive-compulsive disorders, which have overlapping brain circuits with SUD, has raised these expectations to a higher level. There are other emerging areas of NIBS for addiction medicine, such as focused ultrasound stimulation (FUS) and transcranial nerve stimulation (tNS). Furthermore, other technologies exist that target neural circuits noninvasively that can be classified as "neuromodulation", such as fMRI- or EEG-neurofeedback (NF), whereby individuals can change their own brain activity in real time using a brain-computer interface. However, this section will primarily focus on tES/TMS/NF. We will review potential targets, ideal scenarios, and complexities in the field of neuromodulation for addiction treatment and then conclude with a few recommendations for future research.

Potential Targets for Neuromodulation

Targets in the field of neuromodulation should be defined across multiple levels, from behavior, cognitive process, and neural circuit. The NIMH research domain criteria (RDoC) have provided a research framework for mental health disorders that include these levels of targets for neuroscience-informed interventions including neuromodulation. While this framework was not specifically designed for addiction science, it is still a helpful resource. In RDoC terminologies, three main domains are more frequently considered for addiction medicine: *positive valence*, *negative valence*, and *cognitive systems* with a predominant focus on EF (13, 207). Within the positive valence domain, non-drug and drug-related reward processing (drug craving) are the most favorable multi-level targets for addiction treatment. Within the negative valence domain, acute or chronic withdrawal/negative reinforcement, anhedonia, and negative mood/anxiety comorbidities should be considered. EF with a broad definition has also potential to be targeted in neuromodulation (208). For more details, please see **Table 1**.

Brain Stimulation Studies in SUD

There is a trend of reporting positive results in tDCS and rTMS trials in SUD that is being reflected in systematic reviews and meta-analysis. In a meta-analysis published in 2013 on 17 eligible trials, Jansen, et al., reported that rTMS and tDCS on DLPFC could decrease drug craving (209). A meta-analysis of 10 rTMS studies identified a beneficial effect of high-frequency rTMS on

craving associated with nicotine use disorder but not alcohol (210). Another meta-analysis published in 2018 by Song, et al., including 48 tDCS and rTMS studies targeting the DLPFC, reported positive overall effects on reducing drug craving and consumption with larger effect for multi-session interventions compared to single-session interventions (211). A recent meta-analysis with 15 studies using tDCS among nicotine dependents reported positive effect on craving and consumption (212). However, there is a large variation in methodological details (mainly ignored in meta-analyses) that makes it hard to find trials replicating previous findings using same stimulation protocols. Some of these methodological variations are being introduced below with few examples.

Figure 1 depicts the distribution of published tES/TMS studies based on their target areas. Most but not all published tES/TMS studies (90%) have targeted the DLPFC in order to indirectly target other areas within the EF network or other limbic/paralimbic areas through their connections to the DLPFC. As an example, Terraneo et al. showed that applying 15-Hz stimulation to the left DLPFC can reduce self-reported craving [visual analogue scale (VAS)] and cocaine use (urinalysis) among patients with cocaine use disorder randomized to receive active or sham repetitive TMS (rTMS) (213). In another study, Yang et al. showed that electrical stimulation over the DLPFC helps lower cigarette craving in nicotine-dependent individuals (214). Participant smokers underwent 1 session of real and sham transcranial direct current stimulation (tDCS) in a cross-over setting with 30 min duration and 1-mA intensity. There are studies targeting other areas than the DLPFC within the frontal cortex, such as inferior frontal gyrus, ventromedial prefrontal, or middle frontal cortices. As an example, Kearney-Ramos et al. demonstrated that applying continuous theta burst stimulation (cTBS) as a type of TMS to the ventromedial prefrontal cortex could attenuate the cue-related functional connectivity (215). In another study, Ceccanti et al. found out that deep TMS (dTMS) on the medial prefrontal cortex (MPFC) decreased craving and alcohol intake in people with alcohol use disorder. There are also studies targeting motor cortex and temporoparietal areas which have shown that tDCS reduces behavior in tobacco users. To conclude (as shown in **Figure 1**), the distribution of international resources across all these circuit/process/behavior targets provides interesting explorative results to date. Ignoring these methodological variations could result in positive results in meta-analysis reports. However, considering these methodological details would make it hard to introduce a stimulation protocol with enough evidence for clinical use. There is a critical need in the international NIBS research community to focus on one or two main targets to explore any potentially replicable effects that could determine suitable avenues for clinical application.

Application of other areas of NIBS such as FUS, tNS in addiction medicine is limited to a few case reports. Beyond NIBS, invasive brain stimulation technologies like deep brain stimulation (DBS) are only just emerging as approaches in addiction medicine with only a few case reports or pilot trials in the literature. Consequently, the lack of robust evidence for invasive neuromodulation precludes any judgment regarding its clinical utility.

Challenges for Implementation Into Practice

There are 96 original tES/TMS publications in addiction medicine as of May 1, 2019 mainly reporting positive results with one to over 20 sessions of stimulation (**Figure 2**). Large space of methodological parameters to select from, small sample sizes, and lack of replication across different labs make it difficult to draw firm conclusions regarding its effectiveness. Published tES/TMS evidence for addiction treatment has been generated by labs in 14 countries so far (**Figure 3**). To focus these efforts, there is a need for an international roadmap to harmonize the current activities in the field across the world using methodologically rigorous designs. We hope ISAM-NIG along with other international collaborative networks like International Network of tES/TMS

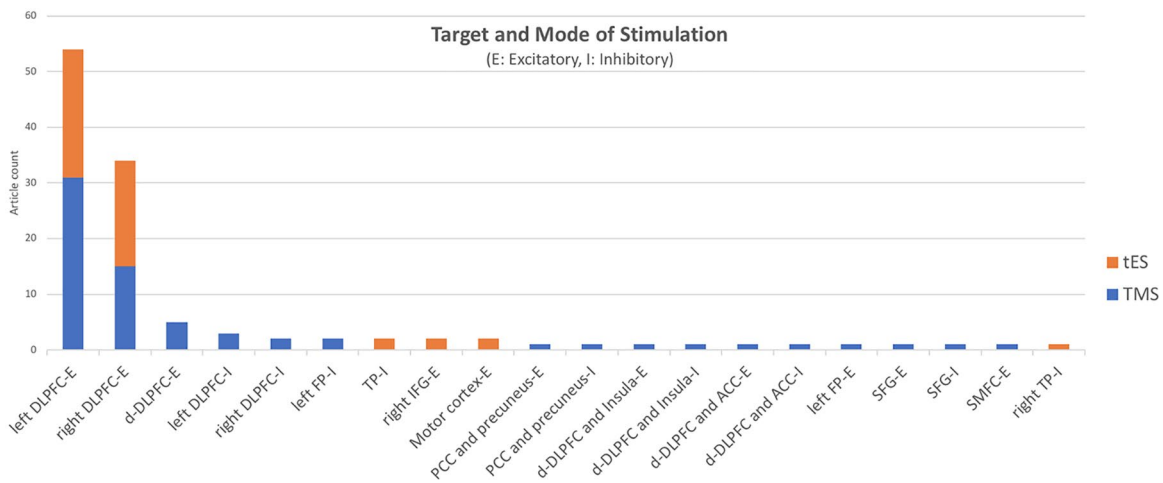

FIGURE 1 | Brain areas targeted with inhibitory (i) and excitatory (e) protocols in 96 tES/TMS studies among people with substance use disorder (as of May 1, 2019) (ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; FP, frontal pole; IFG, inferior frontal gyrus; PCC, posterior cingulate cortex; SFG, superior frontal gyrus; SMFC, superior medial frontal cortex; tES, transcranial electrical stimulation; TMS, transcranial magnetic stimulation; TP, temporoparietal).

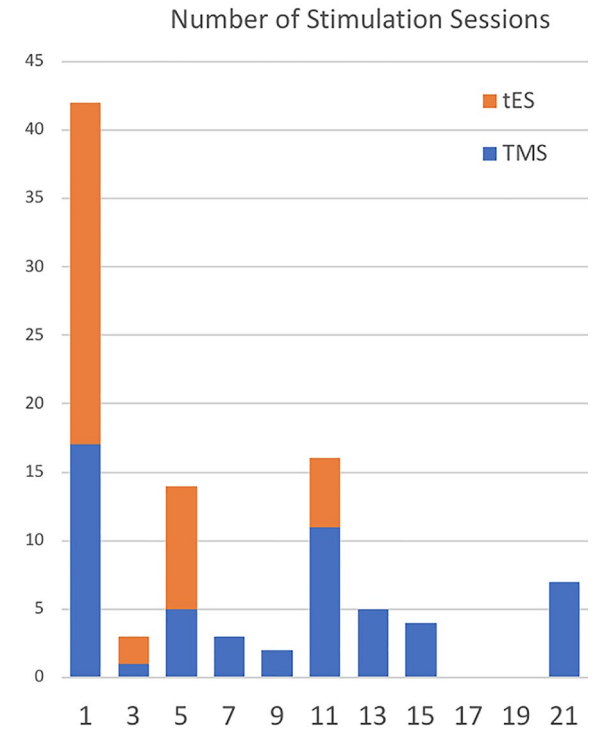

FIGURE 2 | Number of sessions in 96 TMS/tES studies among people with substance use disorder. Around half of the published studies in the field have used just a single session of intervention (as of May 1, 2019). tES, transcranial electrical stimulation; TMS, transcranial magnetic stimulation.

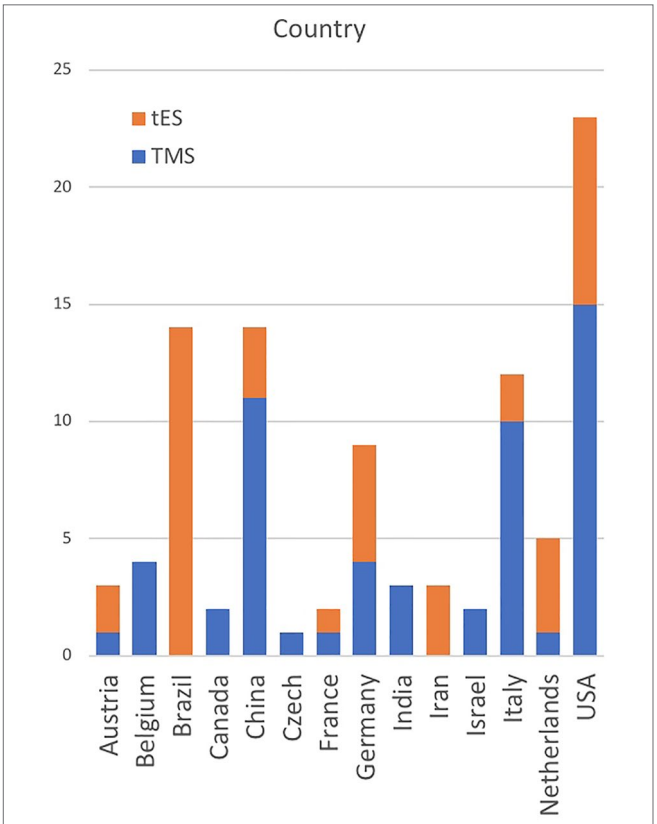

FIGURE 3 | International contribution to the published evidence with tES/TMS in people with substance use disorder. Contribution of 14 different countries (as of May 1, 2019) in the filed confirms the importance of international partnership to improve quality of research in the field. tES, transcranial electrical stimulation; TMS, transcranial magnetic stimulation.

Trials for Addiction Medicine (INTAM) can serve to develop and navigate this roadmap. The ISAM-NIG neuromodulation roadmap should also align with ISAM-NIG roadmaps in other areas like brain imaging, cognitive assessments or cognitive training, and this publication is the first attempt at this initiative. These domains of clinical addiction neuroscience can then work hand-in-hand to create tangible outcomes in daily clinical practice. The challenges for implementing neuromodulation studies into practice are summarized below:

1. *How to move beyond single session interventions:* 44% of the tES/TMS studies have recruited a single session of intervention to investigate potential effects to then move forward to multiple session studies (**Figure 2**). By comparison, most of the medications, we use in daily clinical practice in psychiatry today probably do not show significant effects with a single dose. Even adding a sensitive biomarker like a human brain mapping measure using fMRI will not be sufficient for a "no-go" or "fast-fail" decision. In a recent trial with NIMH fast-fail framework, 8 weeks of medication was being considered as the minimum dosage of intervention (216). Meanwhile, running multi-session trials is costly and decisions between the wide range of available parameters to apply and measure are complex.
2. *How to narrow down key brain targets and relevant SUD-relevant cognitive processes/behaviors:* There is a wide range of potential targets for neuromodulation. There is not a consensus on a framework that specifically defines (i) key neuromodulation targets, (ii) their relevant substance use, cognitive, and clinical outcomes, as different brain pathways are ascribed to heterogeneous neurobehavioral processes (**Table 1**), (iii) measurement instruments of desired outcomes with highest psychometric properties.
3. *How to find the best target population/timing for intervention/contextual treatment:* Timing of neuromodulation intervention [before treatment, before initiating abstinence, during early abstinence (detoxification), after early abstinence (maintenance)] and contextual treatment (pharmacotherapies, psychosocial interventions, cue exposure, cognitive remediation, etc.) in parallel to neuromodulation are important areas for future explorations with specific considerations in different SUDs.
4. *How to optimize the large parameter space within each NIBS technology at the individual level:* There is a new effort to optimize the stimulation parameter for each individual subject based on their subjective responses or objective biomarkers in closed-loop stimulation. Bayesian optimization protocols have introduced an interesting area with initial positive response

with transcranial alternating current (tACS) stimulation (217). Additionally, personalized brain treatment targets can be identified using neurofeedback machine learning approaches that discriminate distinct patterns of brain function within each individual, instead of *a priori* brain regions (or their connectivity) across various individuals (218).

Neurofeedback Studies in SUD

Real-time neurofeedback allows online voluntary regulation of brain activity and has shown promise to enhance ascribed cognitive processes in health and psychopathology (219–221). Participants can monitor their brain function in real time through a brain computer interface (BCI), typically showing a thermometer representing the "temperature" of which increases/decreases in real time, to reflect changes in the level of brain function. Neurofeedback aids participants to voluntarily change brain function online using distinct cognitive strategies (e.g., focus on and away from drug-related stimuli). Neurofeedback has been most consistently tested in ADHD and other psychopathologies, with very early evidence being available in SUD.

Neurofeedback is a promising tool that enables mapping of the causal mechanisms of SUD. As core brain dysfunction is identified within a SUD, neurofeedback can be used as a personalized intervention to enhance and recover underlying dysfunctional neurocognitive pathways. Neurofeedback can source and target brain activity using distinct brain imaging techniques including EEG and fMRI (222).

EEG-based neurofeedback allows individuals to modulate the intensity of brain oscillations at specific frequencies (e.g., alpha, beta, theta, alpha-theta, theta-alpha). These protocols have often been used in conjunction with sensorimotor rhythm training (223) to improve efficacy in SUD. EEG-based neurofeedback studies have targeted brain function in varying SUD groups including alcohol, opioid, and stimulant use disorders [see detailed review here (224)]. This body of work led to mixed evidence of effects (and lack of) on abstinence in the week and months following neurofeedback training, as well as reduced disinhibition, craving, and severity of dependence symptoms. A paucity of studies has shown that these effects were stronger when EEG neurofeedback was used in conjunction with existing standard psychological, pharmacological, and rehabilitation treatments.

Real-time fMRI (rtfMRI)-based neurofeedback has the potential to provide insight in understanding the mechanisms of SUD underpinned by deep brain nuclei [e.g., striatum, amygdala (80)] the activity of which is unlikely to be robustly measured *via* surface EEG. Feedback can be provided on the level of activity of single or multiple *a priori* regions of interest, the strength of the connectivity between multiple regions, and patterns of brain activity identified with machine learning methods (e.g., support vector machine) (218). A handful of studies have used rtfMRI neurofeedback in SUD [for a review, see (12)]. This body of work focused largely on nicotine (225–230) and alcohol use disorders (231, 232).

Most of these studies focused on *a priori* brain regions of interest, most commonly the anterior cingulate cortex, medial prefrontal cortex, and other regions—as well as brain connectivity—were used as source for feedback from single studies (OFC, dorsomedial and dorsolateral prefrontal regions, insula and ventral striatum). Several neurofeedback studies required participants to modulate brain function during craving tasks (e.g., largely cue reactivity tasks that entail watching drug-related pictures). This body of work shows that patients could modulate brain function in the target regions, and provides mixed evidence on the presence and absence (226, 227, 229) of associations between changes in brain activity/connectivity and the severity of drug craving.

In EEG and rtfMRI neurofeedback studies, the significant lack of active placebo controlled and well-powered studies (e.g., comparison with a group with sham feedback) warrants the conduct of more systematic work to determine the efficacy of rEEG and rtfMRI-based neurofeedback.

ISAM NIG Recommendations for Neuromodulation

As discussed above, there is a growing hope that neuromodulation can play a role in the daily practice of addiction medicine. However, the lack of rigorous designs does not provide strong enough evidence to give a green light for clinical use. With frequent negative trials for new pharmacological interventions in addiction medicine, governmental agencies across the world are seriously looking for new hopes for any intervention that can bring positive results in well-powered double-blinded sham/active controlled randomized trials. As the authors of this ISAM-NIG roadmap, we give the following recommendations for future work:

1. Creating international platforms that facilitate consensus on key targets for neuromodulation and outcome measures of efficacy: Addiction neuroscience suffers from the lack of international collaborations based on shared matrix of multilayer targets and outcome measures. We hope that ISAM NIG can bring together a critical mass of expert multidisciplinary scientists across the world to contribute in development of this international consensus.
2. Setting an agreed-upon minimum international standards to produce high quality evidence on the efficacy of neuromodulation in SUD: An overview on the scientific rigor in the published trials on tES/TMS for addiction medicine shows many methodological gaps (233). New potential solutions to address this may include shared protocols across labs internationally with leadership of expert scientists in the field, the development of quality control checklists and Delphi initiatives to reach a consensus on minimum standards.
3. Increase the power of neuromodulation experiments: Over 80% of tES/TMS/NFB studies reported 30 or less subjects in each of their arms. Sample sizes can be boosted using multi-site studies with shared protocols with or without shared funding and replication of previous and ongoing studies and trials across distinct laboratories. Larger samples will be instrumental to (i) increase the power to detect existing effects (or lack of), (ii) increase external validity (while accounting for inter-individual variability), (iii) make predictive modeling for responders and non-responders possible.

4. We also need to have studies with multi-session interventions and long term follow-up to examine the efficacy in tES/TMS/NF over time, particularly if it increases prolonged abstinence.
5. Strategize research efforts to focus available resources to examine the clinical feasibility/efficacy of neuromodulation: Huge parameter space in almost all areas of neuromodulation prevent providing high quality evidence necessary to inform clinical practice. Pharmaceutical companies are one of the main drivers of drug developments. There is no big company in the field of non-invasive neuromodulation and few new ones for TMS are still considered as "small businesses" (less than 250 employees). Efforts that pool sources of research support, e.g., targeted governmental funds and/or "crowd sourcing"-type collective international efforts may support the development and testing of harmonized neuromodulation protocols/target sites for intervention, in order to provide high quality, well-powered evidence.

CONCLUSIONS

We reason that incorporating cognitive assessment into clinical practice in addiction treatment requires identification of constructs that predict meaningful clinical outcomes, streamlining of measures for clinical usability while improving retest reliability and ecological validity, and application of technology for remote monitoring and scalability. Translation of neuroimaging measures to clinically meaningful treatment outcomes requires developing imaging biomarkers that have mechanistic, diagnostic, and prognostic value. It also requires testing the cost-effectiveness of introducing brief, targeted brain scans, and deriving quantitative predictors of successful treatment outcome. Application of cognitive training/remediation and neuromodulation requires additional evidence from randomized trials and clear pathways to implementation. These translation efforts need to address all substance-related disorders. To date, most neuroscience studies have focused on alcohol, nicotine, cannabis, and stimulants, whereas opioids have been underrepresented. The promise of translational neuroscience will only be fulfilled if we can provide novel and effective solutions to pervasive addiction problems, for example, the current opioid crisis. Translation efforts should also factor in the heterogeneity of SUD populations in terms of principal drug of choice, patterns of polysubstance use and psychiatric comorbidities. In this regard, assessment and intervention protocols need to advance towards personalized approaches, by capitalizing on advanced machine learning applications.

Cognitive assessments and neuroimaging methods can elucidate mechanistic multi-level targets (biomarkers) with neural/cognitive/behavioral levels for neuroscience-informed individualized interventions (**Figure 4**). Neuromodulation and cognitive training interventions along with neuropharmacological agents could form multilevel adjunctive interventions based on these targets. The effects of these multilevel interventions in successfully targeting these mechanisms (biomarkers) should be assessed using cognitive and neural mapping measures. There remain many challenges to implementing neuroscience-informed

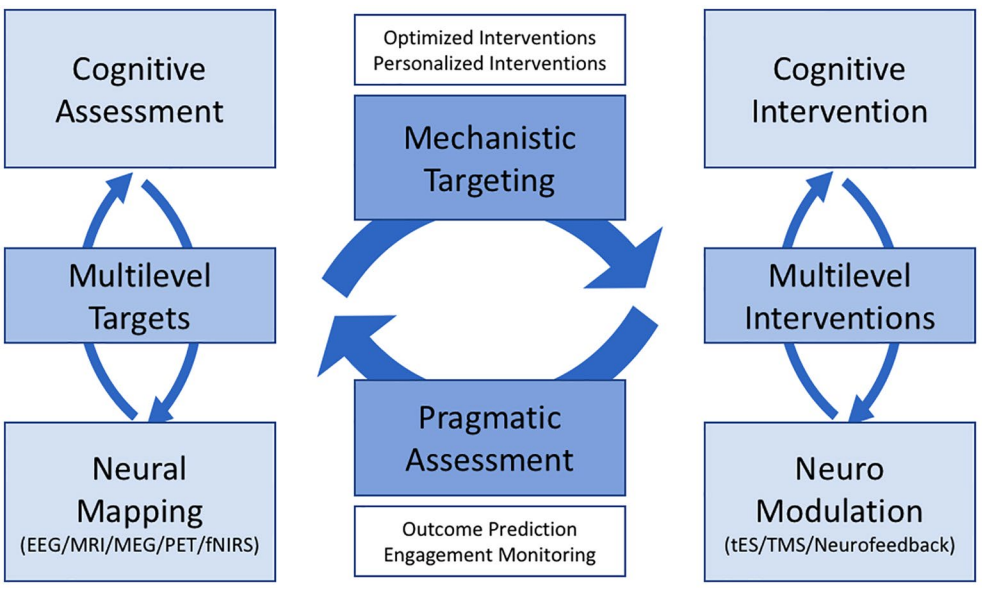

FIGURE 4 | Neuroscience-informed addiction medicine in closed-loops. Cognitive assessments and different neural mapping technologies will introduce mechanistic targets (biomarkers) with neural/cognitive/behavioral levels for a combination of neuromodulation and cognitive interventions. Effects of interventions in successfully modifying these targets (biomarkers) are assessed with cognitive and neural mapping measures. Predictive models for treatment efficacy are optimized with Bayesian algorithms based on the pragmatic multilevel assessments. Interventions can be optimized in closed-loops to engage targets and consider personalized variations toward precision addiction medicine. Psychopharmacological interventions are not included in this roadmap paper; however, they could be delivered alongside and potentially augment cognitive training and neuromodulation.

addiction treatments. We propose to address these challenges by promoting international collaboration between researchers, clinicians, and industry, developing harmonized protocols and data collection/sharing platforms, and prioritizing research that focuses on improving clinical outcomes in SUD.

AUTHOR CONTRIBUTIONS

All authors have contributed in design and preparation of the manuscript. RH, RB, AV-G, VL, VM, DP, and HE created the first draft of assessment, imaging, training, and neuromodulation sections, respectively. AV-G and HE integrated all feedbacks from authors. All authors have agreed on the final manuscript before submission.

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Cognitive Function Impairments Linked to Alcohol and Cannabis Use During Adolescence: A Study of Gender Differences

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Major neurocognitive changes occur during adolescence, making this phase one of the most critical developmental periods of life. Furthermore, this phase in life is also the time in which youth substance use begins. Several studies have demonstrated the differential associations of alcohol and cannabis use concerning the neurocognitive functioning of both males and females. Past and contemporary literature on gender-specific effects in neuroscience of addiction is predominantly based on cross-sectional datasets and data that is limited in terms of measurement variability. Given the importance of gender-specific effects in addiction studies, and in order to address the two above-mentioned gaps in the literature, the present study aimed to compare neurocognitive functioning of male and female adolescents in the context of cannabis and alcohol use, while employing a longitudinal design with multiple repeated measurements. Participants were 3,826 high school students (47% female; mean age, 12.7), who were recruited from 31 high schools in the greater Montreal area. Participants were requested to complete annual surveys for five consecutive years, from 7th to 11th grade, assessing their alcohol/cannabis use and neurocognitive functioning (working memory, delayed recall memory, perceptual reasoning, and inhibition control). The analytical strategy focused on the longitudinal association between each predictor (female, male) and each of the outcomes (domains of neurocognitive functioning). Multilevel linear models assessed the association of alcohol and cannabis consumption and the four domains of neurocognitive functioning. Results revealed a gender by within-subject interaction, suggesting a weaker effect of yearly fluctuation of cannabis use on working memory among males compared to females. Our findings suggest a different pattern of neurocognitive impairment of female and male working memory after using cannabis over the course of adolescence. Early initiation of cannabis use potentially results in more spatial working memory deficits in female adolescents. This may negatively influence young females' capacity in academic settings and lead to significant impairment in adulthood, which critically decreases the individual's quality of life.

Keywords: cognitive function, alcohol, cannabis, gender difference, adolescent

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INTRODUCTION

Given the increased rate of substance use from early to late adolescence (Duncan et al., 2006), it is becoming more and more critical to understand the effects of substance use on teens' neurocognitive functioning. Alcohol and cannabis are the most commonly used psychoactive substances in Canada (Statistics Canada, 2015). Heavy drinking during adolescence has been indicated as a significant factor for declined memory (Mahmood et al., 2010) and impaired neurocognitive functioning (Mahmood et al., 2010), while cannabis use has been demonstrated to be associated with short-term and long-term cognitive deficits, such as impaired inhibitory control and working memory (Volkow et al., 2016; Morin et al., 2019). The proportion of males aged 12 years and over using alcohol or cannabis is approximately 5% to 10% higher than that of females in the same age group (Leatherdale and Burkhalter, 2012; Statistics Canada, 2018). Although the rate of substance use is different for male adolescents than for female adolescents, contemporary knowledge concerning gender-specific trajectories of substance use is limited. In particular, research distinguishing between different neurocognitive outcomes attributed to alcohol and cannabis use in adolescence, as well as taking into account potential gender-specific varying effects, is scarce.

The developmental phase of adolescence is, among others, marked by a multitude of neurocognitive and psychosocial changes, making the phase of adolescence one of the most critical developmental periods of life (Giedd, 2015). Furthermore, experimentation with substance use often starts in adolescence and so does the process of addiction (Volkow et al., 2016). For example, more than 90% of people who have an addiction today started to use various substances before they were 18 years old (Public Health Agency of Canada, 2018). This could reflect normal adolescent-specific behaviors (risk-taking, novelty-seeking, response to peer pressure) that increase the probability of someone experimenting with substances, and perhaps could also reflect the incomplete development neurocognitive functioning (Sowell et al., 2004).

The latter has been demonstrated by previous work showing that, relative to young adults and older people, the balance between adolescents' reward motivation and executive control is not fully developed, therefore making adolescents more prone to engaging in health-risk behaviors such as alcohol use and cannabis use (Hammond et al., 2014). This disturbed balance has also been shown to accentuate the difference between adolescents who frequently engage in health-risk behaviors and those who do not (Squeglia et al., 2009). However, this differing balance has not only been found between adolescents and older people, and adolescents who frequently engage in health-risk behavior and those who do not, but also between male and female adolescents, predominantly because male and female adolescents do not share the same brain structure and neurodevelopmental pace (Lenroot and Giedd, 2010). That is, it has been suggested that early exposure to alcohol and cannabis use affects male and female adolescents' neurocognitive development differently. Therefore, identifying gender-specific influences of alcohol and cannabis use separate for male and female adolescents could be beneficial to explain differential proneness to substance use in adolescents. Although, while within the realm of research on substance use, the importance of standard reporting on gender differences has been well acknowledged, only one-fourth of all studies on adolescent substance use have reported on this (Karlsson Lind et al., 2017). Thus, the results of this longitudinal study could potentially contribute in moving a step forward within this specific field of research.

To date, several studies have demonstrated differential associations of alcohol use, brain structure, and neurocognitive functioning for male and female adolescents. Specifically, Medina et al. (2008) examined the role of gender concerning the association of alcohol-use disorder and prefrontal cortex (PFC) morphometry in adolescents. Despite similar patterns of alcohol use, and even after controlling for variables such as conduct disorder and family history of substance-use disorders, Medina and colleagues found that gender moderated the association of alcohol-use disorder and PFC morphometry in adolescents. Also, it was revealed that, compared to same-gender controls, females showed smaller volumes of PFC morphometry, whereas males showed larger volumes (Medina et al., 2008). These findings are in line with previous work on functional neuroimaging, reporting that males suffering from alcohol-use disorder had increased superior frontal activation while female drinkers had limited superior frontal activation during spatial working memory tasks (Caldwell et al., 2005). The latter indicates, and has been supported by other works, that the fronto-parietal network regions could be particularly susceptible to alterations due to alcohol misuse/use, with females portraying greater adverse effects than males (Caldwell et al., 2005; Squeglia et al., 2012). Moreover, it has been proposed that regions in the brain network develop sooner among females than males (Giedd et al., 1996), implying that females may experience a stronger impaired working memory than males, if alcohol use has its onset in early adolescence (Wager and Smith, 2003).

Another brain region that might show a differing developmental trajectory for male and female adolescents when it concerns substance use is the PFC. The PFC has been shown to have protracted development and has been identified to be the last region of the brain to develop in adolescence. Several pre-clinical studies suggested that exposure to cannabis products during adolescence impacts neuromaturational processes in this region (Miller et al., 2019). Furthermore, functional neuroimaging studies found abnormal PFC activation patterns among adolescent marijuana users compared to controls, when it concerned an inhibition related go/no-go task (Tapert et al., 2007), as well as verbal memory (Jacobsen et al., 2007) and spatial working memory (Schweinsburg et al., 2008) tasks. Despite these valuable study results, when it concerns the moderating role of gender on the association of PFC structure and function and cannabis use in adolescents, past and contemporary findings are rather inconsistent. Whereas Pfefferbaum et al. (2002) found increased myelination of the PFC among young women, another study by Nagel et al. (2006) revealed contrasting results. Specifically, Nagel et al. (2006) found that women had reduced PFC white matter volume than men, of which the white matter volume of men remained moderately unaffected. Finally, in a

study of PFC morphology, Medina et al. (2009) reported that, after 28 days of abstinence, female cannabis users showed higher volumes of PFC as well as a poorer performance on executive functioning tasks, whereas the control group demonstrated the opposite pattern.

To date, there is a strong body of research on the potential consequences of alcohol and cannabis use on brain structure and cognitive function in clinical, adult populations (Adger and Saha, 2013; Kuntsche and Gmel, 2013; Volkow et al., 2016). However, many previous studies utilized cross-sectional designs, which do not allow for causal modeling of associations (McHugh et al., 2018). However, to our knowledge, there is one notable exception. Using a longitudinal design, Morin et al. (2019) investigated the time-varying association of substance use (cannabis and alcohol) and neurocognitive functioning (inhibition control, perceptual reasoning, working memory, and delayed recall memory). The result of this study demonstrated that cannabis use has potential neurotoxic effects on inhibitory control and working memory of all the participants (Morin et al., 2019). Although, we value the study of Morin et al. (2019), they did not take into account the role of gender, which is rather striking given the previously presented work on the differences concerning neurocognitive functioning between female and male adolescents. Therefore, in extending the work by Morin et al. (2019), the present study aimed to explore potential differences in male and female adolescents concerning the development of neurocognitive functions in the context of alcohol and cannabis use over the course of adolescence.

In doing so, while also extending previous and contemporary cross-sectional works, we developed a longitudinal study in which we compared male and female adolescent neurocognitive functioning (i.e., working memory, recall memory, perceptual reasoning, and inhibitory control) in the context of alcohol and cannabis. We analyzed this prospective data using a multi-level statistical framework allowing for the dissociation of three different, yet potentially additive (or interacting), associations of low neurocognitive functioning and substance use: common vulnerability, time-varying concurrent (same year) relationships, and time-varying lagged relationships. Based on previous works on the different levels of vulnerability of females and males to substance use in samples of adults and adolescents (Medina et al., 2008; Squeglia et al., 2009, 2011, 2012; Alfonso-Loeches et al., 2013; Ewing et al., 2014; McHugh et al., 2018), we hypothesized that there is a difference between neurocognitive functioning of males and females linked to alcohol and cannabis use over the course of adolescence.

MATERIALS AND METHODS

Participants

Participants were 3,826 high school students [47% female; mean age, 12.7 years (SD = 0.5)] from the Co-Venture study (NCT01655615; Landry et al., 2004; O'Leary-Barrett et al., 2017). A more detailed description of this study has been published elsewhere (O'Leary-Barrett et al., 2017). Participants were recruited from 31 public or private (French/English) high schools in the greater Montreal area, and were requested to participate in annual surveys for five consecutive years, from 7th to 11th grade. Among others, those surveyed had their alcohol and drug use, neurocognitive functions, and personality dimensions assessed. Our sample of high school students consisted of 15% of the entire population of 7th grade high school students in the greater Montreal area and they epidemiologically matched the size and socioeconomic status of each school district. Participant inclusion criteria consisted of providing informed assent and parent consent. Participants were excluded if they had unusual response patterns (e.g., same answer, sham drug item) or were reacting faster than usual (Reaction Time). Among the participants who completed the annual surveys, 3,659 (95.6%) of them were included in the analysis based on the minimal response to the questions and demographic information. The Co-Venture study obtained ethical approval from the ethics committee of the Sainte-Justine Hospital and the school boards of the schools that were recruited.

Measures

Substance use and disorders (alcohol and cannabis) were evaluated by the modified version of the "Detection of Alcohol and Drug Problems in Adolescents" questionnaire (Landry et al., 2004). Participants were asked to rate the frequency of their substance consumptions on a scale of 0–5 (never to everyday). There was a specific question for the quantity of alcohol consumed, but not for cannabis consumption. In line with previous studies in the field of substance use, assessing the quantity of used cannabis is still a challenge (Piontek et al., 2008).

More details regarding the frequency and quantity of alcohol use and frequency of cannabis use can be found in **Tables 1**, **2**. Self-reports measuring substance use during adolescence can be more accurate than biological measures (such as urine tests) when the confidentiality is guaranteed (Clark and Winters, 2002), as there is a higher chance of reporting any episodic substance use. In the Co-Venture study, confidentiality was guaranteed unless there was a risk of harm to self or others.

Outcomes

Utilizing a computerized neuropsychological assessment battery, the following cognitive functions were assessed. The detailed description of measures can be found in the original study protocol (O'Leary-Barrett et al., 2017).

Spatial working memory: like the spatial working memory sub-test of the Cambridge Neuropsychological Test Automated Battery (Owen et al., 1990), "Find the Phone" task was the measurement tool for assessing spatial working memory. This task is based on the Self-Order Pointing Task (Cragg and Nation, 2007) and the subjects are asked to search through a number of phones which are supposed to ring. The measure of spatial memory deficit is the number of times that the participant reselects the items that have already rung. The task had good internal reliability, with Cronbach α coefficient of 0.88 (Cragg and Nation, 2007).

Delayed recall memory: to assess the delayed recall memory, the computerized version of the "Dot Location" test as a part of Child Memory Scales (Cohen, 1997) was used. In this task, the participants memorize the location of circles in eight different

TABLE 1 | Frequency distribution for substance use variables in females over 5 years.

Substance and assessment for girls[a]	Frequency or quantity					
Frequency	**Never**	**Occasionally**	**Once a month**	**Once or twice per week**	**Three times or more per week**	**Every day**
Cannabis use						
Year 1	47.19%	1.27%	0.21%	0.11%	0.08%	0.08%
Year 2	37.51%	2.67%	0.82%	0.50%	0.24%	0.16%
Year 3	30.44%	4.45%	1.14%	1.43%	0.42%	0.32%
Year 4	26.39%	6.56%	1.51%	1.11%	0.48%	0.56%
Year 5	21.65%	8.02%	2.09%	1.75%	0.48%	0.42%
Alcohol use						
Year 1	33.35%	13.79%	1.06%	0.66%	0.03%	0.05%
Year 2	20.14%	17.73%	2.86%	1.03%	0.13%	0.00%
Year 3	12.78%	18.08%	4.79%	2.46%	0.05%	0.03%
Year 4	7.89%	17.76%	6.99%	3.79%	0.16%	0.03%
Year 5	5.24%	15.96%	7.62%	5.29%	0.29%	0.00%
	Number of standard drinks on a drinking occasion					
Quantity[b]	**<1**	**1–2**	**3–5**	**6–8**	**>8**	
Alcohol use						
Year 1	2.65%	5.29%	1.27%	0.11%	0.08%	
Year 2	2.49%	9.40%	3.10%	0.50%	0.21%	
Year 3	1.59%	11.86%	5.69%	1.03%	0.40%	
Year 4	1.40%	11.86%	9.11%	2.17%	0.56%	
Year 5	0.85%	11.41%	11.59%	2.33%	0.48%	

[a]Year 1: assessment in 7th grade, year 2: 8th grade, and so on. [b]Alcohol use quantity variables were categorized here for presentation purposes; in the analyses, alcohol use quantity was used as a continuous variable.

TABLE 2 | Frequency distribution for substance use variables in males over 5 years.

Substance and assessment for boys[a]	Frequency or quantity					
Frequency	**Never**	**Occasionally**	**Once a month**	**Once or twice per week**	**Three times or more per week**	**Every day**
Cannabis use						
Year 1	47.41%	1.48%	0.53%	0.34%	0.24%	0.32%
Year 2	38.22%	2.57%	0.50%	0.45%	0.16%	0.16%
Year 3	31.18%	4.95%	0.64%	0.93%	0.45%	0.58%
Year 4	25.36%	6.51%	1.16%	1.43%	0.77%	1.01%
Year 5	19.90%	6.91%	2.22%	1.83%	1.06%	1.24%
Alcohol use						
Year 1	29.27%	18.03%	1.99%	0.74%	0.16%	0.13%
Year 2	20.12%	17.68%	3.18%	0.87%	0.13%	0.08%
Year 3	14.06%	18.10%	4.21%	2.12%	0.16%	0.08%
Year 4	9.16%	15.11%	6.75%	4.61%	0.37%	0.24%
Year 5	6.14%	12.73%	6.70%	6.88%	0.53%	0.19%
	Number of standard drinks on a drinking occasion					
Quantity[b]	**<1**	**1–2**	**3–5**	**6–8**	**>8**	
Alcohol use						
Year 1	4.42%	6.62%	1.16%	0.29%	0.21%	
Year 2	4.02%	8.52%	1.88%	0.42%	0.26%	
Year 3	3.02%	10.01%	4.10%	0.98%	0.48%	
Year 4	1.80%	10.03%	7.41%	2.99%	0.56%	
Year 5	1.14%	8.58%	8.71%	4.16%	1.32%	

[a]Year 1: assessment in 7th grade, year 2: 8th grade, and so on. [b]Alcohol use quantity variables were categorized here for presentation purposes; in the analyses, alcohol use quantity was used as a continuous variable.

colors on the screen. Thirty minutes later, the subjects are asked to relocate the circles as they were placed on the previous image. Test-retest reliability ranged from 0.71 to 0.91 for subscales (Cohen, 1997).

Perceptual reasoning: to measure perceptual reasoning, an abbreviation of the original Cattell's Culture Fair Intelligence Test was used. In this nine-item task, the adolescents were asked to complete a series of puzzles with an increasing level

of difficulty (Bilker et al., 2012). The scores from this test are highly correlated with that of Raven's 60-item perceptual reasoning matrices, with the correlation of 0.98 for the short form (Bilker et al., 2012).

Inhibitory control: to assess the cognitive control and response inhibition, an adopted version of Go/No-Go PALP (Passive Avoidance Learning Paradigm), which requires individuals to inhibit a rewarded response in order to prevent further punishment (Newman et al., 1985; Castellanos-Ryan et al., 2011), was used. By trial and error, subjects learn to react to "good" numbers and not react to "bad" numbers. The poorer response inhibition is the number of errors on trials involving a No-Go response. Confirming the previous studies, response inhibition is correlated with other functional imaging measures of PFC activities in Go-No-Go tasks (Whelan et al., 2012).

We controlled for socioeconomic status measured by the family affluence scale (Currie et al., 1997) and school-cluster effects in all of our analysis.

Statistical Analysis

The analytic strategy was focused on the longitudinal association between each predictor (female, male) and each of the outcomes (domains of cognition). Multilevel linear models assessed the association of alcohol (quantity by frequency) and cannabis (frequency) consumption and the four domains of cognition (working memory, delayed recall memory, perceptual reasoning, and inhibitory control). Two separate multilevel linear models were estimated for longitudinal effects of cannabis and alcohol as time-varying predictors of perpetration. The levels were time (nested in individuals) and individuals (nested in schools). The time parameter was coded from one to five (the survey waves). Predictors were person-mean centered. For both outcomes, the predictor terms were as follows: gender, socioeconomic status, linear and quadratic effects of time, between-subject differences in consumption measured by average substance use (alcohol or cannabis) over all waves, within-subject difference in consumption measured by current year change in use with regards to participant's mean use, and lagged within-subject measured by past year change in use with regards to participant's mean use. As the results of these effects were reported in a previous publication (Morin et al., 2019): interaction of gender by average use over all assessments, interaction of gender by change in use current year compared with the participant's mean use, and interaction of gender by past year's substance use compared with the participant's mean use. Between-subject effects were interpreted as a common vulnerability between consumption and poor neurocognitive performance, while within-subject effects were interpreted as potentially neurotoxic effects of substance use. The interaction of gender with within-person effects were interpreted as a potential sensitivity in one gender relative to the other with respect to the neurotoxic effects of substances on cognitive development. The intraclass correlation coefficient (ICC) function from the psych package in the R statistical environment was used to estimate the within-subject stability of cognitive data over time; ICCs were 0.74 for working memory, 0.80 for perceptual reasoning, 0.58 for delayed memory recall, and 0.68 for response inhibition.

RESULTS

Overall, 3,826 students [2,028 boys (53%); mean age, 12.7 years] were involved. Analyses included the interactions of cannabis/alcohol use and gender, time, and SES. For socioeconomic status, the participants with lower SES revealed worse perceptual reasoning. Considering the main variables, the quantity of alcohol use and the frequency of cannabis use increased yearly for both genders (**Tables 1**, **2**).

Cannabis Model

Table 3 presents results for the cannabis model. The results indicated a significant between-person effect of cannabis (the general level of cannabis use) on inhibition control ($\beta = 2.10$, SE = 0.71, $p = 0.001$). Furthermore, it was shown that the past year fluctuation in cannabis use was significantly associated with females' perceptual reasoning ($\beta = 0.12$, SE = 0.05, $p = 0.02$). When we included the interaction with male-gender in our model, cannabis use revealed differential association of cannabis use and working memory among

TABLE 3 | Estimated parameters for cannabis model in a school sample of adolescents assessed over 5 years[a].

	Working memory			Perceptual reasoning			Delayed recall memory			Inhibition control		
	Estimate	SE	*p*	Estimate	SE	*p*	Estimate	SE	*p*	Estimate	SE	*p*
Intercept	21.04	1.50	0.00	15.48	0.42	0.00	17.86	0.48	0.00	34.80	3.00	0.00
Time	−6.76	0.97	0.00	1.25	0.27	0.00	−9.58	0.32	0.00	−8.92	1.96	0.00
Time squared	0.83	0.16	0.00	−0.10	0.04	0.02	2.00	0.05	0.00	0.88	0.33	0.01
SES*	0.10	0.08	0.20	−0.06	0.02	0.03	−0.03	0.02	0.16	0.31	0.15	0.04
Gender (female)	1.22	0.61	0.05	0.07	0.19	0.72	0.10	0.16	0.51	1.93	1.16	0.10
Cannabis, B*	0.23	0.37	0.54	−0.18	0.12	0.11	−0.08	0.10	0.42	**2.10**	**0.71**	**0.00**
Cannabis, W*	0.05	0.18	0.79	0.00	0.05	0.92	−0.09	0.06	0.12	−0.40	0.38	0.29
Cannabis, W (lagged)	−0.23	0.18	0.20	**0.12**	**0.05**	**0.02**	0.11	0.06	0.05	−0.13	0.38	0.73
Gender (male) × cannabis, B	0.25	0.49	0.61	−0.09	0.15	0.56	−0.01	0.13	0.93	−0.35	0.96	0.72
Gender (male) × cannabis, W	**−0.51**	**0.25**	**0.04**	−0.05	0.07	0.52	0.08	0.08	0.32	0.02	0.53	0.97
Gender (male) × cannabis, W (lagged)	0.40	0.25	0.12	0.00	0.07	0.98	−0.09	0.08	0.25	0.22	0.54	0.69

[a]*Significant effects are indicated by boldface. Performance on working memory and inhibitory control tasks was measured by counting number of errors; a lower score indicates a better performance. *SES, socioeconomic status; B, between-subjects; W, within-subjects. Bold values correspond to significant predictors.*

TABLE 4 | Estimated parameters for alcohol model in a school sample of adolescents assessed over 5 years[a].

	Working memory			Perceptual reasoning			Delayed recall memory			Inhibition control		
	Estimate	**SE**	***p***	**Estimate**	**SE**	***p***	**Estimate**	**SE**	***p***	**Estimate**	**SE**	***p***
Intercept	21.54	1.49	0.00	15.12	0.42	0.00	17.71	0.48	0.00	37.80	2.97	0.00
Time	−6.50	0.99	0.00	1.18	0.27	0.00	−9.57	0.33	0.00	−9.41	1.98	0.00
Time squared	0.79	0.17	0.00	−0.09	0.05	0.04	2.00	0.05	0.00	0.95	0.33	0.00
SES*	0.12	0.08	0.15	−0.07	0.03	0.01	−0.04	0.02	0.05	0.38	0.16	0.02
Gender (female)	1.74	0.47	0.00	0.24	0.15	0.11	0.23	0.12	0.06	1.21	0.92	0.19
Alcohol, B*	−0.41	0.32	0.20	−0.03	0.10	0.74	0.06	0.08	0.49	0.22	0.61	0.72
Alcohol, W*	−0.20	0.18	0.26	0.08	0.05	0.13	0.03	0.06	0.62	0.28	0.35	0.42
Alcohol, W (lagged)	−0.10	0.18	0.57	0.02	0.05	0.75	−0.03	0.06	0.66	**−0.80**	**0.35**	**0.02**
Gender (male) × alcohol, B	0.62	0.43	0.15	0.00	0.14	0.97	0.00	0.11	0.97	0.28	0.85	0.74
Gender (male) × alcohol, W	0.12	0.24	0.61	−0.12	0.07	0.08	0.00	0.08	0.98	−0.16	0.49	0.75
Gender (male) × alcohol, W (lagged)	0.03	0.24	0.90	0.08	0.07	0.23	0.04	0.08	0.59	0.67	0.50	0.18

[a]*Significant effects are indicated by boldface. Performance on working memory and inhibitory control tasks was measured by counting number of errors; a lower score indicates a better performance. *SES, socioeconomic status; B, between-subjects; W, within-subjects. Bold values correspond to significant predictors.*

TABLE 5 | Estimated parameters for combined alcohol-cannabis model in a school sample of adolescents assessed over 5 years[a].

	Working memory			Perceptual reasoning			Delayed recall memory			Inhibition control		
	Estimate	**SE**	***p***	**Estimate**	**SE**	***p***	**Estimate**	**SE**	***p***	**Estimate**	**SE**	***p***
Intercept	20.65	1.53	0.00	15.62	0.43	0.00	17.79	0.49	0.00	35.39	3.05	0.00
Time	−6.49	0.99	0.00	1.20	0.27	0.00	−9.56	0.33	0.00	−9.35	1.98	0.00
Time squared	0.80	0.17	0.00	−0.09	0.05	0.04	1.99	0.05	0.00	0.94	0.33	0.00
SES*	0.14	0.08	0.09	−0.08	0.03	0.00	−0.04	0.02	0.04	0.42	0.16	0.01
Gender (female)	0.96	0.67	0.15	0.10	0.21	0.62	0.17	0.17	0.32	1.68	1.29	0.19
Cannabis, B*	0.61	0.45	0.17	−0.27	0.14	0.06	−0.17	0.12	0.15	**3.06**	**0.86**	**0.00**
Cannabis, W*	0.14	0.18	0.45	−0.02	0.05	0.71	−0.11	0.06	0.08	−0.33	0.38	0.39
Cannabis, W (lagged)	−0.31	0.19	0.09	0.13	0.05	0.01	**0.13**	**0.06**	**0.03**	−0.22	0.38	0.57
Alcohol Frequency, B	**−0.94**	**0.38**	**0.01**	0.24	0.12	0.05	0.19	0.10	0.06	**−1.73**	**0.73**	**0.02**
Alcohol Frequency, W	−0.20	0.18	0.26	0.06	0.05	0.19	0.04	0.06	0.51	0.42	0.35	0.23
Alcohol Frequency, W (lagged)	−0.03	0.18	0.88	−0.02	0.05	0.63	−0.05	0.06	0.40	−0.67	0.36	0.06
Gender (male) × Cannabis, B	0.25	0.58	0.67	−0.10	0.18	0.57	0.03	0.15	0.86	−1.08	1.14	0.35
Gender (male) × Cannabis, W	**−0.65**	**0.26**	**0.01**	−0.03	0.07	0.68	0.09	0.08	0.29	−0.15	0.54	0.78
Gender (male) × Cannabis, (lagged)	0.50	0.26	0.06	−0.01	0.07	0.94	−0.10	0.08	0.22	0.33	0.55	0.55
Gender (male) × Alcohol, B	0.49	0.51	0.34	−0.02	0.16	0.89	−0.04	0.13	0.75	1.22	0.99	0.22
Gender (male) × Alcohol, W	0.32	0.24	0.19	−0.12	0.07	0.09	−0.02	0.08	0.84	−0.21	0.50	0.67
Gender (male) × Alcohol (lagged)	−0.09	0.25	0.73	0.09	0.07	0.20	0.06	0.08	0.44	0.64	0.51	0.21

[a]*Significant effects are indicated by boldface. Performance on working memory and inhibitory control tasks was measured by counting number of errors; a lower score indicates a better performance. *SES, socioeconomic status; B, between-subjects; W, within-subjects. Bold values correspond to significant predictors.*

genders (β = −0.51, SE = 0.25, p = 0.04), implying potentially different neurotoxic effects of cannabis use for male and female adolescents. There were no significant interactions between time and gender, or time and gender and cannabis use (**Supplementary Table S1**).

Alcohol Model

Table 4 presents results for the alcohol model. When including the interaction with male-gender, the results indicated that alcohol use did not significantly interact with any of the neurocognitive domains. However, at the lagged-person level, it was shown that past year fluctuations in alcohol use were significantly associated with female adolescents' inhibition control (β = −0.80, SE = 0.35, p = 0.02). Furthermore, at the between-person level, it was shown that alcohol use (general level of alcohol use) was not significantly associated with any of the neurocognitive domains when it concerned female adolescents.

Combined Alcohol-Cannabis Model

Table 5 presents the results of an integrated model of the simultaneous effect of alcohol and cannabis. The results revealed a male-gender by within-subject interaction, suggesting that the effect of yearly cannabis use fluctuation on working memory among males compared to females is weaker (β = −0.65, SE = 0.26, p = 0.01), meaning that females make more errors in working memory task than males. Furthermore, at the between-person level, it was revealed that alcohol use (general level of alcohol use) was significantly associated with perceptual reasoning (β = −0.94, SE = 0.38, p = 0.01) and inhibition control (β = −1.73, SE = 0.73, p = 0.02) of female adolescents only. Regarding the general level of cannabis use, the models revealed significant between-person associations of cannabis use and inhibition control, for female adolescents only (β = 3.06, SE = 0.86, p = 0.00). In addition, the past year fluctuation of cannabis use was shown to be significantly associated with female adolescents' delayed recall memory (β = 0.12, SE = 0.05, p = 0.02).

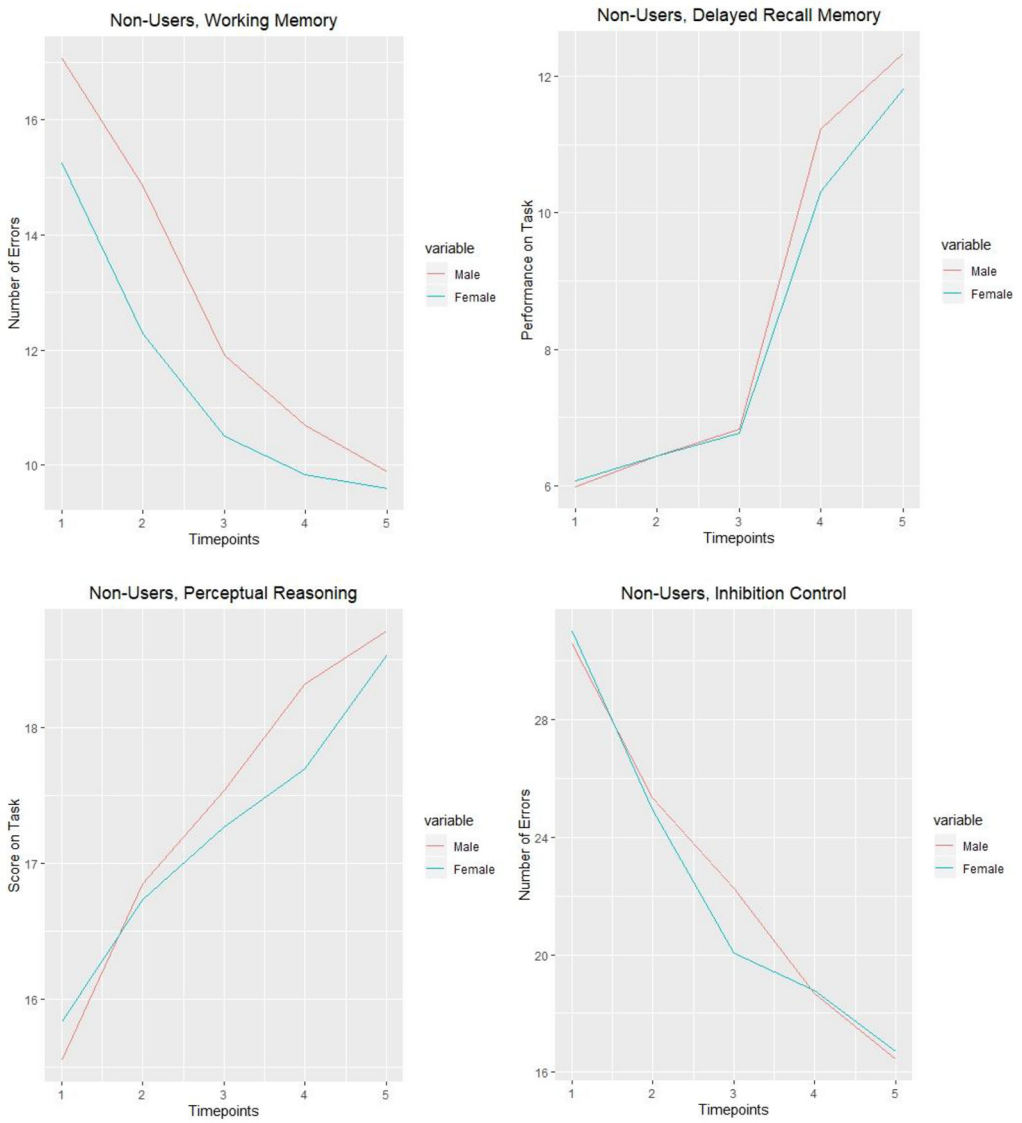

FIGURE 1 | Non-user students' cognitive tasks performance over 5 years (grade 7–11).

To facilitate interpretation of these results, the mean of cognitive tasks performance of non-user adolescents are presented in **Figure 1**. In general, across all time points, non-using female adolescents were making fewer errors than boys during the working memory task. However, when it concerned the other cognitive tasks, no significant differences between male and female adolescents were observed. Furthermore, **Figure 2** represents the working memory performance of those who were cannabis users and who used in a particular year. It was shown that female adolescents using cannabis displayed higher initial levels of errors concerning the working memory task than male adolescents using cannabis across time points 1 and 2, indicating that although non-cannabis using male adolescents made more errors during the working memory task, female cannabis users were shown to be more sensitive to the negative consequences of cannabis on working memory. However, these effects were shown to disappear over time.

DISCUSSION

This study examined the gender differences in female and male adolescents' neurocognitive functioning (working memory, perceptual reasoning, delayed recall memory, and inhibition control) utilizing a longitudinal design among a large sample of nearly 4,000 North-American adolescents, distinguishing between three time-varying effects of predictor variables: between-person effect, within-person effect, and lagged within-person effect. Based on the results, several important conclusions can be drawn. First, among the studied neurocognitive functions,

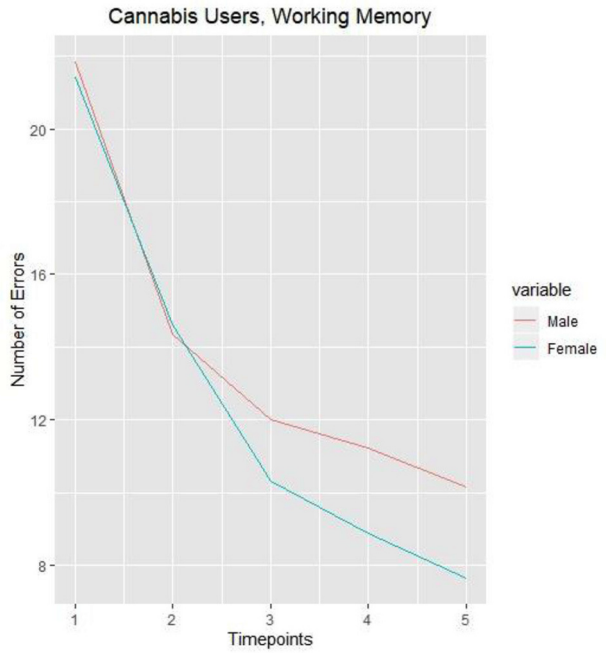

FIGURE 2 | Number of errors on working memory task in male and female cannabis users (once a month and more) measured over 5 years.

female cannabis users had significantly different levels of working memory impairments than males. We also found robust male/female differences in the combined model of alcohol and cannabis use, confirming the different effects of cannabis use on females and males working memory even after controlling for the effect of alcohol use. We did not observe such an effect for alcohol users. While significant alteration in the brain regions responsible for working memory have been reported in previous findings (Kanayama et al., 2004; Jager et al., 2006; Becker et al., 2010), results from this study revealed a new gender-specific developmental effect. Therefore, the gender-specific impairments related to cannabis use in females were limited to early stages of adolescent development, in line with the hypothesis that there are gender differences concerning the effects of cannabis on neurocognitive functioning in early adolescence.

Given the shifting policy of cannabis use laws, the prevalence of adolescents' misuse/use is rising. Meanwhile, having a better understanding of the neurocognitive functions after exposure to cannabis for boys and girls separately is the key to leading future research on the optimal treatment methods for cannabis dependency. The current evidence on gender-specific underlying neurobiological mechanisms of executive functioning and decision making regions of the brain, can be a possible explanation for the "Telescoping" phenomenon, which narrates a faster progression from the first exposure to a substance to the addiction phase in women (Hernandez-Avila et al., 2004). To be more specific, working memory is an essential component in academic success at school (Aronen et al., 2005). At least 10% of females 15 years and above report using cannabis in the past year (Health Canada, 2018) which increases the risk of school drop out up to 2.3 times more than non-user students (Bray et al., 2000). Students' cognitive function level decreases significantly for days after cannabis use (Crean et al., 2011) and for a considerable period, it affects their performance at school. In addition, the long term effects of cannabis on attention and memory are more long-lasting and severe when the individuals start using cannabis during adolescence (Schweinsburg et al., 2008) or are heavy-regular users (Solowij et al., 2002). Consequently, a secondary effect of acute intoxication, cannabis user students fail to learn at school, which in the long term leads to poorer grades and higher school drop out rates (Lynskey and Hall, 2000).

Working memory involves the ability to process and store information over a short time period and has been found to be predominantly associated with PFC and parietal cortex activities (van Asselen et al., 2006). In many studies, cannabis use was related to significant alterations in brain activity during functional magnetic resonance imaging (fMRI) tasks measuring spatial working memory (Jager et al., 2006; Becker et al., 2010). On the other hand, strong evidence on neurodevelopmental trajectories of the PFC shows discrepancy by gender. Due to sexual dimorphism during brain development, the full maturation process of female brain volumes is almost reached at the age of 10–11, while maturation could be as late as 14–15 years for male adolescents (Lenroot et al., 2007). Female PFC maturation peaks size 1 to 2 years earlier than for males (Giedd et al., 1996; Lenroot et al., 2007). As a result, females may experience more impairments in working memory than males, under the condition that cannabis use has its onset in adolescence.

Several studies have highlighted the importance of assessing the interaction between gender and age of onset after exposure to THC. In animal studies, while both male and female adolescent rats had impaired spatial working memory after cannabis exposure (O'Shea et al., 2006; Rubino et al., 2009), it was only the male rats with lasting memory deficit in adulthood (O'Shea et al., 2006). Also, in human subjects, gender can be a moderator in the association of brain structure, cognitive functioning, and cannabis use. For example, a number of studies highlighted that higher executive functioning (Medina et al., 2009) and memory performance impairments were linked to cannabis use (Gruber et al., 1997; Crane et al., 2013) in female adolescents. In contrast, as an acute effect of THC, Makela et al. found improved spatial working memory in young adult females (Makela et al., 2006). Those inconsistencies in the previous studies (Ketcherside et al., 2016) can be the result of differences in developmental stage, design of study (longitudinal/cross-sectional), levels of THC exposure and intoxication (Morin et al., 2019), and age of initiation (Gorey et al., 2019).

When considering gender differences in alcohol and cannabis effects on neurocognition, it is first important to account for the developmental sensitivity in neurocognitive performance. Considering the late maturation of brain substrates related to working memory among boys, there is a neuroplastic effect that decreases cannabis-related impairment among male adolescents compared to female adolescents. In contrast, as the maturation of prefrontal regions related to working memory happens earlier

in girls, the negative effects of cannabis on working memory appears to be more pronounced during early adolescence. We can conclude that initiation of cannabis use during early adolescence might effect males and females differently due to these gender-based differences in neuromaturation (Lenroot and Giedd, 2010). Whether these drug-related changes are implicated in females' elevated risk for substance use disorders is a question worthy of further investigation.

The current study has some limitations. First, we looked into the effects of alcohol and cannabis use, but not the substance use disorder as it is defined in the DSM-5 (American Psychiatric Association, 2013), or polysubstance use. As we did not have the clinical substance use data, the results from this study could not be generalized to clinical population. Second, like other studies on cannabis use, we could not identify the cannabis exposure quantity (Piontek et al., 2008). Cannabis legalization in North America might provide the opportunity to use a standard scale for cannabis intake in the future studies. Third, we applied a self-report scale for measuring alcohol and cannabis use and our assessment did not include more objective observation methods such as biological tests. Regarding the sensitive nature of reporting substance use, those behaviors might have been underreported. Fourth, even though cognitive functioning was assessed with valid and reliable instruments, the results could be different in clinical settings due to its limitations (e.g., false-positive/negative results, over-diagnosis; Roebuck-Spencer et al., 2017). As cognitive tests used in the current study were done in school and they were administrated with other tests, fatigue and boredom could affect the students' cognitive functioning and neuropsychological status. In addition, we have not considered possible neurological or neurocognitive disorders of the participants. Finally, although observing the interaction of some other demographic variables such as SES (Johnson and Novak, 2009), sexual orientation (Medley et al., 2016), and racial/ethnic (Guerrero et al., 2014) differences with gender could be significant, this study was not intended to thoroughly explore those effects. Nevertheless, the current study was designed to report the association of gender differences and cognitive impairment due to alcohol and cannabis use during early ages.

In conclusion, the current study carried out one of the first analysis of gender differences in patterns of adolescents' neurocognitive impairments, using a longitudinal design from the Co-Venture study across five consecutive years. The results from this study provide a more detailed understanding of gender-specific processes in addiction vulnerability that could be used to inform public health messaging and targeted drug and alcohol prevention for young people (Conrod, 2016). Spatial working memory deficits could negatively influence young females' capacity in academic settings and could lead to significant impairment in adulthood, which critically decreases the individual's quality of life.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Sainte-Justine Hospital and all administrative school board of involved high schools in Montreal. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

SN and PC conceived the presented idea. MA developed the theory and performed the computations. PC verified the analytical methods. PC encouraged SN to investigate the cognitive developmental trajectories of male and female adolescents and supervised the findings of this work. EB critically reviewed and revised the manuscript. All authors discussed the results and contributed to the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2020.00095/full#supplementary-material.

TABLE S1 | Estimated parameters for cannabis model in a school sample of adolescents assessed over 5 years, interaction with TIME.

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Corrigendum: Cognitive Function Impairments Linked to Alcohol and Cannabis Use During Adolescence: A Study of Gender Differences

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In the original article, part of Figure 1 was included in **Figure 2** by mistake. The corrected **Figure 2** appears below.

The authors apologize for this error and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

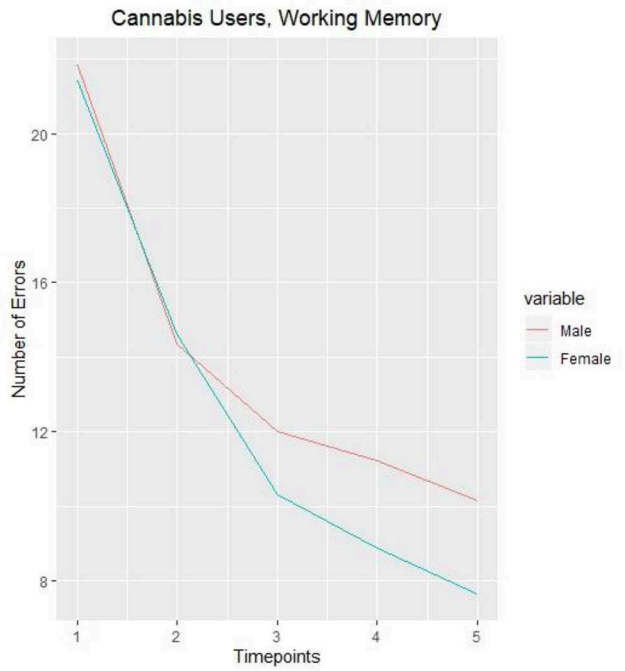

FIGURE 2 | Number of errors on working memory task in male and female cannabis users (once a month and more) measured over 5 years.

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