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INSIGHTS IN ADDICTIVE DISORDERS: 2021

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Quality of Life and Its Correlates in Alcohol Use Disorder Patients With and Without Depression in China

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Objective: Alcohol use disorder (AUD) is a serious issue worldwide and frequently co-occurs with depression. However, the quality of life (QOL) of AUD patients with and without depression is not well studied in the Chinese Han population. The aim of this study was to investigate QOL and its correlates in AUD patients with and without depression in China.

Methods: Five hundred and fifteen psychiatric patients diagnosed with AUD were recruited. All these patients completed the Beck Depression Inventory (BDI) to assess depression, the Medical Outcome Study 36-Item Short Form Health Survey (SF-36) to evaluate QOL and the Alcohol Use Disorders Identification Test (AUDIT) to measure the severity of drinking.

Results: Compared with AUD patients without depression, those with depression had a lower QOL in all eight domains of the SF-36 (all $P < 0.001$), but were more willing to have alcohol-related treatment ($P < 0.05$). Negative correlations were noted between (i) the BDI total score and all eight domains of the SF-36 (all $P < 0.001$); and (ii) between the AUDIT total score and six domains of the SF-36 (all $P < 0.05$).

Conclusions: Depression impairs QOL in patients with AUD in China. Early intervention in comorbid depression to improve QOL is needed.

Keywords: alcohol use disorder, depression, quality of life, BDI, SF-36

INTRODUCTION

Alcohol use disorder (AUD) is a severe public health and medical issue in China. According to the latest survey, lifetime AUD in China is among the top three most prevalent classes of mental disorders, at 4.4% for adults, following anxiety disorders (7.6%) and mood disorders (7.4%) (1). Although AUD has caused enormous medical, social and economic burdens and costs in China,

the treatment rate for AUD is dramatically low (2). Considering the high prevalence of AUD, its effect on quality of life (QOL) is important and needs to be investigated.

QOL is a critical parameter that reflects the impact of a disease on the individual's well-being and includes physical, mental and social dimensions. The QOL of patients with AUD has received considerable attention. Accumulated research evidence has shown that AUD impairs QOL and causes faculty loss. Many studies found that AUD patients reported poorer QOL compared with the general population (3–7), particularly in the emotional (8–12), mental health (13, 14) and social functioning domains (11). However, the scores in the physical functioning domain were not significantly different between the AUD patients and the reference population (13, 14). Moreover, studies have also revealed that AUD is a risk factor (15, 16) or even a primary cause of low QOL (17), which means that AUD might be used to predict subsequent QOL. Moreover, evidence indicated that the higher alcohol consumption or longer heavy drinking days, the lower levels of QOL (5, 18, 19). Importantly, studies have reported that alcohol abstinence and its maintenance could improve QOL in AUD patients (8, 20–23).

The relationship between QOL deterioration and AUD was moderated by many factors, such as comorbidity with psychiatric disorders (4, 21). Previous studies reported a significant association between depression and diminished QOL in AUD patients (17, 24–26). For example, both Lee et al. and Saatcioglu et al. reported that AUD patients with depressive symptoms had poorer QOL compared with those without depressive symptoms (24, 25). According to the study from Ponizovsky et al., depression was associated with impaired QOL in alcohol-dependent patients (26). Moreover, Levola et al. conducted a review and found that depression considerably impacted QOL among patients with alcohol dependence (17). Interestingly, after treatment with escitalopram or memantine, significant improvement in QOL of the social functioning domain in alcohol-dependent patients with comorbid depression was observed (27).

Although AUD is a serious issue in China, the effect of depression on the QOL of AUD patients has not been studied thoroughly. Furthermore, previous studies regarding the impact of depression on QOL in AUD patients were performed in Western or Asian countries except for China (13, 24, 25, 28). To date, no study has assessed QOL in AUD patients with and without depression in China. Thus, we conducted the present hospital-based study to compare the QOL between AUD patients with and without depression and its correlates in the Chinese Han population. Our study will provide a reference for early intervention in QOL deterioration in AUD patients with depression.

METHODS

Samples

The inclusion criteria for the study were patients aged ≥18 years who met the DSM-IV criterion for alcohol dependence or alcohol abuse. Potential participants were interviewed by trained and experienced psychiatrists to assess the inclusion criteria. A total of 546 patients were recruited from consecutive admissions to general psychiatric clinics in China. Thirty-one patients were excluded because they could not complete the entire interview. Ultimately, 515 patients were enrolled and completed the self-developed questionnaire, the Beck Depression Inventory (BDI) for depressive symptoms, the Medical Outcome Study 36-Item Short Form Health Survey (SF-36) for quality of life, and the Alcohol Use Disorders Identification Test (AUDIT) for the severity of drinking. Patients were allocated into two groups according to their BDI total scores: patients with no depression (BDI score ≤13, see below) and patients with depression(BDI score ≥14, see below). The study was approved by the Institutional Review Board of Second Xiangya Hospital of Central South University and informed consent for participating in the study was obtained from all patients.

Instruments

We used a self-developed questionnaire to assess 515 patients for demographic characteristics, drinking patterns, comorbid disorders, drinking-related treatments and patients' attitudes and expectations for treatment. The validated Chinese version of BDI consists of 21 items and was utilized to assess depressive symptoms. The total score of the BDI ranges from 0 to 63. A cutoff point of 13 on the BDI total score was used to distinguish between AUD patients with (BDI score ≥14) and without (BDI score ≤13) depression (29). The validated Chinese version of the SF-36 was used to measure QOL (30). The SF-36 is a multidimensional instrument with 36 items that address eight QOL domains, including physical function, role physical, body pain, general health, vitality, social function, role emotional, and mental health. According to previous studies, each domain score was normalized to obtain a value between 0 and 100 inclusive [100*(score obtained - minimum score possible)/(maximum score possible - minimum score possible)], and a high score indicated a good QOL (5, 8). The AUDIT-Chinese version with 10 items was used to estimate the severity of drinking. Each item has a score ranging from 0 to 4. Thus, the maximum score for the total instrument is 40 points, and the minimum score is zero (31). All of the SF-36, AUDIT and BDI scales were subject to translation procedures, cultural adaptations and psychometric properties. No significant difference was found between the Chinese version and the original English version. Hence, these scales were suitable to the Chinese cultural context (30–32). All patients were diagnosed with alcohol dependence or alcohol abuse based on the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) (33). We merged alcohol dependence and abuse and labeled it as "alcohol use disorder (AUD)" in our study. The self-developed questionnaire, the BDI, the SF-36, the AUDIT, and the structured interview on AUD were administered by trained and experienced psychiatrists.

Statistical Analysis

All statistical analyses were performed by SPSS version 20.0. Continuous data were described as the mean ± standard deviation, and categorical data were described as frequencies and percentages. The Kolmogorov-Smirnov one-sample test was used to measure the normality of distribution. Comparisons between

the depression and non-depression AUD patients were made using Student's *t*-test (continuous variables), chi-squared test (categorical variables) and Mann-Whitney U test (nonnormally distributed data). In Mann-Whitney U test, Standardized Test Statistic (Z value) was reported. Pearson correlations were used to examine the relationship between QOL and clinical data. A value of $P < 0.05$ was considered significant. Bonferroni correction was used for the multiple comparison correction.

RESULTS

Demographic Characteristics, Drinking Patterns and Comorbid Disorders of AUD Patients With and Without Depression

A total of 254 (49.3%) of 515 AUD patients met the criteria for depression, and 261 (50.7%) did not. The demographic characteristics and drinking patterns of the two groups were presented in **Table 1**. Compared with the non-depression group, the depression group had more females, was younger, and had more unstable marital status (all $P < 0.05$). No significant differences in other variables, including years of education, employment status, monthly family income, age at first drink, daily consumption of pure alcohol, drinking frequency, types of alcoholic beverages, and drinking-related treatments, were found (all $P > 0.05$). Comorbid disorders of AUD patients with and without depression were presented in **Table 2**.

QOL and Its Correlation of AUD Patients With and Without Depression

Table 3 shows that AUD patients with depression had a lower QOL than those without depression in all domains. Significant differences in the physical functioning, role physical, role emotional, bodily pain, general health, vitality, social functioning, and mental health domains were noted (all $P < 0.001$). The Pearson correlation suggested that the BDI total score and the AUDIT total score was negatively correlated with each domain of the SF-36 (**Table 4**). After Bonferroni correction ($0.05/16 = 0.003125$), the BDI total score was still negatively correlated with each domain of the SF-36. Except for the bodily pain and mental health domain, all other domains were still negatively correlated with the AUDIT total score.

Patients' Attitudes and Expectations for Treatment in AUD Patients With and Without Depression

One hundred and forty-nine patients had been treated for alcohol intoxication or alcohol withdrawal or alcohol-related liver injury. Pharmacotherapy primarily included vitamin B_1 (84.5%), benzodiazepines (79.8%), hepatinica (65.1%) and naloxone (10.7%). No significant difference in drinking-related treatments was found between AUD patients with and without depression($\chi^2 = 3.401, P = 0.065$). Two hundred and twenty-two (87.4%) depressed AUD patients thought they needed treatment, whereas the rate was 76.9% in non-depressed AUD patients. The difference was significant ($\chi^2 = 9.600$, $P = 0.002$). Expectations for the treatment of depressed AUD patients were alcohol abstinence (70.4%), alcohol reduction (27.3%) and others (2.3%); these rates in non-depressed AUD patients were 59.8, 39.2, and

TABLE 1 | Demographic characteristics and drinking patterns of AUD patients with and without depression.

Characteristics	Depression ($n = 254$)	Non-depression ($n = 261$)	$t/\chi^2/Z$	*P*
Gender			8.122	0.04
Males	228 (89.8%)	251 (96.2%)		
Females	26 (10.2%)	10 (3.8%)		
Age (years)	41.0 ± 10.3	43.0 ± 10.5	2.242	0.025
Education (years)	11.0 ± 3.5	11.2 ± 3.7	0.537	0.591
Marital status			12.297	0.006
Married/cohabiting	185 (72.8%)	222 (85.1%)		
Single	39 (15.4%)	24 (9.2%)		
Divorced/separated	29 (11.4%)	15 (5.7%)		
Widowed	1 (0.4%)	0 (0.0%)		
Employment status			2.267	0.132
Employed	184 (72.4%)	204 (78.2%)		
Unemployed	70 (27.6%)	57 (21.8%)		
Monthly family income(US$)			1.928	0.381
<$423	111 (44.0%)	128 (49.6%)		
$423–705	103 (40.9%)	99 (38.4%)		
>$705	38 (15.1%)	31 (12.0%)		
Age at first drink	18.4 ± 5.0	18.3 ± 4.9	0.119	0.905
Daily consumption of pure alcohol(g)	110.9 ± 102.5	100.0 ± 83.2	1.327	0.185
Drinking frequency			7.584	0.108
≥1/day	152 (59.8%)	147 (56.3%)		
4–6/week	43 (16.9%)	53 (20.3%)		
2–3/week	33 (13.0%)	47 (18.0%)		
2–4/month	25 (9.8%)	14 (5.4%)		
≤1/month	1 (0.4%)	0 (0.0%)		
Types of alcoholic beverages			0.524	0.769
Spirits	208 (81.9%)	217 (83.1%)		
Beer	37 (14.6%)	33 (12.6%)		
Others	9 (3.5%)	11 (4.2%)		
Drinking-related treatments			3.401	0.065
Present	64 (25.2%)	85 (32.6%)		
Absent	190 (74.8%)	176 (67.4%)		

TABLE 2 | Comorbid disorders of AUD patients with and without depression.

Comorbid disorders	Depression ($n = 254$)	Non-depression ($n = 261$)	χ^2	*P*
Schizophrenia	8 (3.1%)	14 (5.4%)	1.544	0.214
Bipolar disorder	12 (4.7%)	6 (2.3%)	2.245	0.134
Major depressive disorder	47 (18.5%)	4 (1.5%)	41.555	<0.001
Anxiety disorder	15 (5.9%)	17 (6.5%)	0.082	0.775
Drug use disorder	6 (2.4%)	3 (1.1%)	1.103	0.294
Others	13 (5.1%)	16 (6.1%)	0.248	0.618
Total	101 (39.8%)	60 (23.0%)	16.857	<0.001

TABLE 3 | Quality of life of AUD patients with and without depression.

Domains of the SF-36	Depression	Non-depression	Z	*P*
Physical functioning	80.5 ± 21.4	88.4 ± 15.5	4.579	<0.001
Role physical	49.8 ± 28.9	71.3 ± 25.1	8.169	<0.001
Role emotional	41.5 ± 25.2	71.0 ± 22.2	11.909	<0.001
Bodily Pain	64.7 ± 27.2	79.5 ± 21.8	6.181	<0.001
General health	31.9 ± 19.7	50.6 ± 23.1	8.889	<0.001
Vitality	37.3 ± 20.7	60.3 ± 18.7	11.305	<0.001
Social functioning	44.0 ± 23.1	68.9 ± 23.2	10.746	<0.001
Mental health	41.8 ± 17.6	69.6 ± 16.5	14.564	<0.001

TABLE 4 | Correlations between the SF-36 and the BDI and AUDIT total score.

Domains of the SF-36	BDI total score(r, *P*)	AUDIT total score(r, *P*)
Physical functioning	−0.23, <0.001	−0.25, <0.001
Role physical	−0.41, <0.001	−0.27, <0.001
Role emotional	−0.59, <0.001	−0.20, <0.001
Bodily Pain	−0.38, <0.001	−0.10, 0.016*
General health	−0.44, <0.001	−0.23, <0.001
Vitality	−0.61, <0.001	−0.17, <0.001
Social functioning	−0.56, <0.001	−0.22, <0.001
Mental health	−0.71, <0.001	−0.08, 0.047*

**Not statistically significant after Bonferroni adjustment.*

1.0%, respectively. The difference between these two groups was significant ($\chi^2 = 7.102$, $P = 0.029$).

DISCUSSION

To the best of our knowledge, the present study is the first hospital-based survey to investigate QOL and its correlates in AUD patients with and without depression in the Chinese Han population. We found that depressed AUD patients had a lower QOL in all eight domains of the SF-36 and were more willing to take alcohol-related treatment than non-depressed AUD patients. We also observed that the BDI total score were negatively correlated with all eight domains of the SF-36 and the AUDIT total score were negatively correlated with six domains of the SF-36.

We found that AUD patients comorbid with depression had a lower QOL compared to those without depression and that the level of QOL negatively correlated with the severity of depression, suggesting that depression might be a significant predictor of poor QOL. Our main findings were consistent with previous studies in other Asian countries (24–26). For example, two studies conducted in South Korea reported that the score of QOL negatively correlated with the BDI score in patients with alcohol dependence (34) and that depression could impair QOL in AUD patients (24). Moreover, surveys from Turkey and Israel also revealed that depressive symptoms were significantly associated with QOL in alcohol-dependent patients (25, 26). Despite of socio-cultural and economic differences, similar results have also been observed in European and American countries (13, 14, 19, 35). For example, Malet et al. found that comorbid with depressive disorder was correlated with diminished QOL among patients diagnosed with alcohol dependence in France (13). According to the study from Daeppen et al., alcohol-dependent individuals in Switzerland with comorbid depressive symptoms was 21–127% lower than that among patients without comorbid depressive symptoms, especially in the psychosocial domain (14). Furthermore, Rosenbloom et al. found that depressive symptoms were associated with decreased QOL in American patients with alcohol dependence and that QOL was lower in individuals who had recovered from depression compared with those who had not (28). Importantly, Levola et al. conducted a systematic review and summarized that depression deteriorated the QOL of these patients (17). Taken together, studies in different countries around the world have consistently found that depression diminishes the QOL of AUD patients, suggesting the urgent need to provide interventions for comorbid depression.

Although many studies have reported that depression diminishes QOL in AUD patients, the mechanism of this phenomenon remains unclear. One study showed that alcohol-dependent patients comorbid with depression had poorer QOL in the social functioning domain compared with patients without depression due to the lack of socioeconomic resources and social support (24). Furthermore, self-confidence and self-esteem were significantly associated with QOL (26); alcohol-dependent patients with depression had much lower self-confidence and self-esteem than patients without depression, contributing to lower QOL (35). Importantly, depression itself deteriorates QOL. Major depression exhibited significant adverse effects on QOL in all domains: psychological functioning, physical functioning, social functioning, and role functioning (36). In addition, major depressive disorders accounted for 55% of QOL loss at the population level (37). Because QOL was impaired in AUD patients with depression, depression probably triggered alcohol relapse (25). Interestingly, we were surprised to find that compared with AUD patients without depression, those with depression were more willing to take alcohol-related treatment. This result is consistent with one previous study which reported that patients who were depressed were more likely to seek treatment (38).

The recovery goal for AUD has traditionally been alcohol abstinence. Nevertheless, abstinence might discourage patients from seeking treatment and does not generate changes in other fields of life (17). The improvement in QOL has gradually become a major indicator of recovery from AUD and is recognized as an ultimate treatment goal (25) and assessment of QOL would help to identify treatment demand in alcohol-dependent patients (39). Studies showed that reducing alcohol consumption or receiving treatment initiation could improve QOL in AUD patients (8, 19–23), especially in the mental health (9, 11, 40) and social functioning (11, 41) dimensions. For instance, according to the studies from Daeppen et al. and Dawson et al., the mental health domain of QOL was significantly improved after full or partial remission among alcohol-dependent patients (9, 40). Furthermore, Muhonen et al. conducted a double-blind randomized controlled trial among alcohol-dependent

outpatients with major depressive disorder and found that the domain of social functioning was improved after treatment with escitalopram or memantine (27). Taken together, QOL may be used as an important outcome indicator of treatment and recovery from AUD.

Several limitations of our study should be mentioned. First, given the cross-sectional design of the study, it was unable to ascertain causality between comorbid with depression and impaired QOL in AUD patients. Second, the depression and non-depression group were not matched, especially for gender and age. Third, although the severity of depression was measured with the BDI, the diagnosis of depression was not established based on the DSM-IV. Fourth, information about family history and psychotropic drug treatment, which were potential factors associated with QOL, was not collected.

In conclusion, depression impairs QOL in all eight domains among patients with AUD in the Han Chinese population. Moreover, QOL negatively correlates with the BDI total score and the AUDIT total score. Early detection and intervention for comorbid depression and its correlates to improve QOL are needed.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Second Xiangya Hospital of Central South University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WH designed the study. HH, HS, KN, RZha, WS, BL, HJ, WW, JD, MZ, ZY, JL, RZhu, SL, SX, XW, WF, and CG collected the sample and performed the literature review. HH conducted the analyses and wrote the initial version of this manuscript. All authors edited, read, and approved the last version of this manuscript.

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Characterizing Pathways of Non-oral Prescription Stimulant Non-medical Use Among Adults Recruited From Reddit

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Objective: Prescription stimulant non-medical use (NMU) is a national predicament. While the risks of prescription stimulant NMU have been considered, less is known about non-oral use. To focus on this gap, a sample of adults with non-oral prescription stimulant NMU within the last 5-years was recruited. The purpose of the present study was to characterize the pathways and substance transitions associated with prescription stimulant NMU and non-oral prescription stimulant NMU in this unique sample of adults.

Methods: Adults (n = 225) reporting non-oral prescription stimulant NMU within the last 5 years were recruited to complete an online survey by banner ads placed on the Reddit website between February and September 2019. After completion of the survey, a second study consisting of an in-depth telephone interview was conducted with 23 participants: interviews took place between July and September 2019. Data reported here include substance, route of administration and class transitions, as well as qualitative data from the interviews.

Results: Approximately 1 in 5 began their substance use trajectory with prescription stimulants (19.1%). Other than marijuana, most exposures to illicit substances occurred after both initial prescription stimulant NMU and initial non-oral prescription stimulant NMU. The most frequently reported route of administration transition was from oral use to snorting (n = 158, 70.2%), however, other route of administration transitions included oral use to injection drug use (n = 14, 6%). In-depth interviews elaborated upon these transitions and indicated that prescription stimulant NMU was consequential to substance use pathways.

Conclusions: Oral prescription stimulant NMU was a precursor to non-oral prescription stimulant NMU. Non-oral prescription stimulant NMU was a precursor to illicit substance use, suggesting that prescription stimulant NMU impacts substance use pathways and revealing opportunities for intervention.

Keywords: ADHD, prescription stimulants, prescription stimulant non-medical use, prescription stimulant non-oral use, transitions

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INTRODUCTION

Prescription stimulant non-medical use (NMU) is a persistent, national dilemma (1–4). Medications containing amphetamines (e.g., Adderall, Vyvanse) or methylphenidate (e.g., Ritalin, Concerta, Focalin) are considered the most widely prescribed stimulants in the United States (5, 6), and are regarded as the most efficacious drugs in the management of ADHD symptomatology (7). These medications lead to regional elevations in brain dopamine (8–10) rendering them as potential candidates for non-medical use (NMU) and diversion (8, 11–17).

Non-oral NMU of prescription stimulants—use that involves alternate routes of administration including intranasal or intravenous routes—has been reported in adolescents (18–21), college students (22–25), and adults (26–28). While the physical and psychiatric risks as well as mortality associated with prescription stimulant NMU have been considered (29–34), less is known about *non-oral* prescription stimulant NMU, which can include adverse physical outcomes, such as toxicity or tissue damage (35–40), and adverse mental health outcomes, such as anxiety or depression (41) or even psychosis (33).

The transition from oral to non-oral NMU of prescription stimulants is not yet well-documented. However, there is an analogous framework to be found in the study of opioid use pathways and transitions (42–47). For example, an opioid class transition is the precursory use of prescription opioids before the use of heroin (48–51). This class transition has been related to age, availability/supply, drug quality, and surrounding environments (52–56). An opioid route of administration (ROA) transition (e.g., swallowing intact tablets then transitioning to crushing the tablet and snorting or injecting) is thought to occur when individuals develop tolerance to effects of a substance and desire stronger effects, more rapid onset of effects, or a more economical way of achieving them (42, 43, 57). Initial route of administration can also affect subsequent ROA choices and overall pattern of drug use (58, 59).

Substance transitions are broadly captured by polysubstance use or substitutions, i.e., when one substance is not available, another is used (54, 55). In addition to switching from one substance or route of administration to another, where previously used substances or routes of administration are no longer used, a substance transition can also mean that new substances (and by extension routes of administration) are simply added to the current repertoire. Which is to say, substance use trajectories are not necessarily linear.

Prescription stimulant NMU class transitions would include prescription stimulant NMU leading to illicit stimulant use, such as cocaine or non-prescription methamphetamine. Prescription stimulant NMU route of administration transitions may include moving between oral and non-oral routes of administration (26, 60). Prescription stimulant substance transitions would involve moving on to other substances after prescription stimulant NMU, a trajectory that is possible among individuals with polysubstance use; a characteristic reported in individuals endorsing prescription stimulant NMU (61–66).

The purpose of this paper is to inform future hypothesis generation by identifying substance transitions, route of administration transitions and class transitions that were reported by a sample of adults who undertook prescription stimulant non-oral NMU within the last 5 years. This convenience sample was recruited from Reddit. The study employed a mixed-method design incorporating quantitative and qualitative data analyses.

MATERIALS AND METHODS

For purposes of this study, NMU included ANY of the following: (1) use for any reason, even once, without your own prescription, (2) use in ways other than prescribed (such as taking more than prescribed, more often than prescribed, or for any other reason or way than prescribed), and (3) use for the feeling or experience the medication caused (such as a feeling of being high, enhancement of other drugs, prevention or treatment of withdrawal symptoms, or other feelings).

Procedure

Advertisement banners appeared on Reddit (http://www.reddit.com) from February through September 2019 for purposes of study recruitment. Banner ads stated that adults (aged 18 years or older) who were English-speaking, had personal experience of non-oral prescription stimulant NMU within the last 5 years, able to give informed consent and were interested in taking an online survey could click on an embedded survey link. The link took them to an online web survey hosting site (YouGov) for survey completion.

Respondents were first asked to provide written, informed consent to participate. Survey completion took ∼10–15 min; participation could be stopped at any time. Respondents who completed the online survey were compensated with a $20 e-gift card upon completion. Compensation was managed by a third party to reduce privacy concerns.

After completion of the online survey, individuals were presented with the option to participate in a more in-depth, semi-structured, follow-up telephone interview to further elucidate their experience with prescription stimulant medications. If respondents agreed to complete the follow-up interview, a designated time was confirmed for interviewers to call them.

Verbal informed consent was acquired at the beginning of each telephone interview; interviews were audio recorded with the participant's permission. Interviewers used an interview guide with open-ended questions that were designed to elicit in-depth responses about participants' substance use. Participants were compensated an additional $25 for their participation, and again, compensation was managed by a third party. After the interviews were transcribed, audio recordings were deleted. This study was approved by the New England Institutional Review Board (NEIRB): 120180324 #137173.0.

Survey and Follow-Up Interview Description

The online survey consisted of four sections: demographics, medical history, history of prescription medication NMU, and history of illicit substance use with 15 broad topic areas. To ensure reliable and accurate prescription medication

identification, product images were displayed and participants were asked to indicate those they had used. To determine use characteristics, such as motivations for use, respondents were asked to select among pre-determined, categorical responses, however, "Other" with a write-in response area was always an option. Skip logic was employed so that number of survey items varied depending on number of prescription medications that were identified as having been used non-medically. Follow-up interviews were ∼1 h in duration. At the outset, after informed consent had been provided, participants were asked to confirm the use of prescription stimulants that had been described in their online survey. After confirmation that this information was, indeed, accurate, participants were asked a series of open-ended questions detailing their use, a series of questions about their patterns and pathways to substance use and a series of questions about their experiences regarding manipulation deterrent formulations. For purposes of this report, the patterns and pathways of substance use are of interest.

Data Handling and Analyses

Survey data were uploaded to and stored on a password protected Inflexxion server that was only accessible by authorized study personnel. The server resided in a climate-controlled, locked facility with nightly backups. Audio recordings were destroyed after a transcription was made from the recordings.

All analyses were carried out using SAS Enterprise Guide Version 7.1 (Cary, NC). Self-reported responses to quantitative survey questions were analyzed with descriptive frequency analyses or ordered categorically. Interviews from the follow-up interview were transcribed using an AI transcription platform. Interview results were categorically combined and summarized on an individual level.

RESULTS

Between February and September 2019, 225 participants were recruited from Reddit and completed the online survey. The sample was primarily male (86.2%), not of Spanish, Latino or Hispanic origin or descent (92.4%), White (78.2%), and 25+ years of age (52.0%), with some amount of college education (81.3%). Most were single (67.6%) and working full-time or part-time (60.4%) with an annual family income between $30,000 and $99,999 (49.3%). The majority reported at least one psychiatric diagnosis in their lifetime (55.1%), most of which were depression (32.9%), anxiety (28.9%), or ADHD (27.6%). Participants were on average, 18.7 (±3.7) years of age when they first initiated prescription stimulant NMU.

Twenty-three participants from the original sample (10.2%) were contacted and completed follow-up interviews, between July and September 2019. This subset of participants was primarily male ($n = 20$, 87.0%) and 28.2 (range 19–36) years of age. Almost half had obtained prescription stimulants through a healthcare provider ($n = 11$, 47.8%) and almost all had obtained prescription stimulants through diversion ($n = 22$, 95.7%). Qualitative follow-up interview results are presented in the latter half of this paper.

Among the full sample, lifetime prescription stimulant NMU included amphetamine ($n = 209$, 92.9%) or methylphenidate ($n = 103$, 45.8%). Other reported lifetime prescription drug use (with or without prescriptions, for any reason) included opioids (44.4%), sedatives (40.9%), muscle relaxants (24.4%), sleep aids (23.6%), and/or diet aids/appetite suppressants (8.0%). In addition to lifetime prescription stimulant NMU, participants reported prescription stimulant NMU within the past year ($n = 171$, 76.0%) and/or within the past month ($n = 81$, 36.0%), while some reported their last use as being longer than a year ago ($n = 54$, 24.0%). Past year and past 30-days prescription drug use were also reported, although to a lesser degree.

Substance Transitions, Stimulant Class Transitions

Slightly more than 3 of 4 began their substance use pathway with marijuana ($n = 173$, 76.9%), while almost 1 in 5 began this pathway with prescription stimulants ($n = 43$, 19.1%). **Figure 1** summarizes the mean age and 95% Confidence Interval (95% CI) at which various illicit substances were initially used by the sample in relation to prescription stimulants. **Figure 1** reveals that marijuana use began earlier than other illicit drug use (95% CIs do not cross with any other substance). Otherwise, the 95% CIs of the means overlap, revealing that the mean age of initiation did not substantially differ between prescription stimulant NMU and the use of remaining illicit substances, other than illicit fentanyl, that was initiated at a significantly later age than prescription stimulants.

Stimulant Class Transitions

Even though the differences were not statistically significant, chronologically, prescription stimulant NMU preceded illicit stimulant use (age of first prescription stimulant NMU: 18.7 ± 3.7 years, age of first cocaine/crack use: 19.7 ± 3.3 years, age of first illicit amphetamine use: 20.1 ± 4.6 years). Three respondents (1.3%) reported using only prescription stimulants non-medically without any illicit substance use.

Table 1 examines substance use patterns by mentions of initial exposure with substance and route of administration as one instance, hence more than one instance may be reported by one individual and frequencies may be greater than the sample size. For example, there were 259 mentions of marijuana use in this data set. Of these, $n = 38$ (14.7%) mentions were the first oral use of marijuana and $n = 221$ (85.3%) were the first non-oral use of marijuana. **Table 1**, A columns summarizes how other than marijuana, most exposures to illicit substances occurred after the first episode of prescription stimulant NMU.

Specifically, 77.6% of marijuana exposures occurred prior to initiation of prescription stimulant NMU, while 22.4% occurred after the first prescription stimulant NMU. Further, 57.9% oral exposures were before and 42.1% exposures were after first prescription stimulant NMU, while 81.0% non-oral exposures were before and 19.0% non-oral exposures were after first prescription stimulant NMU. Representing a potential class transition, 77.9% cocaine exposures and 86.7% of illicit amphetamine or methamphetamine exposures occurred after prescription stimulant NMU. This pattern was also found for

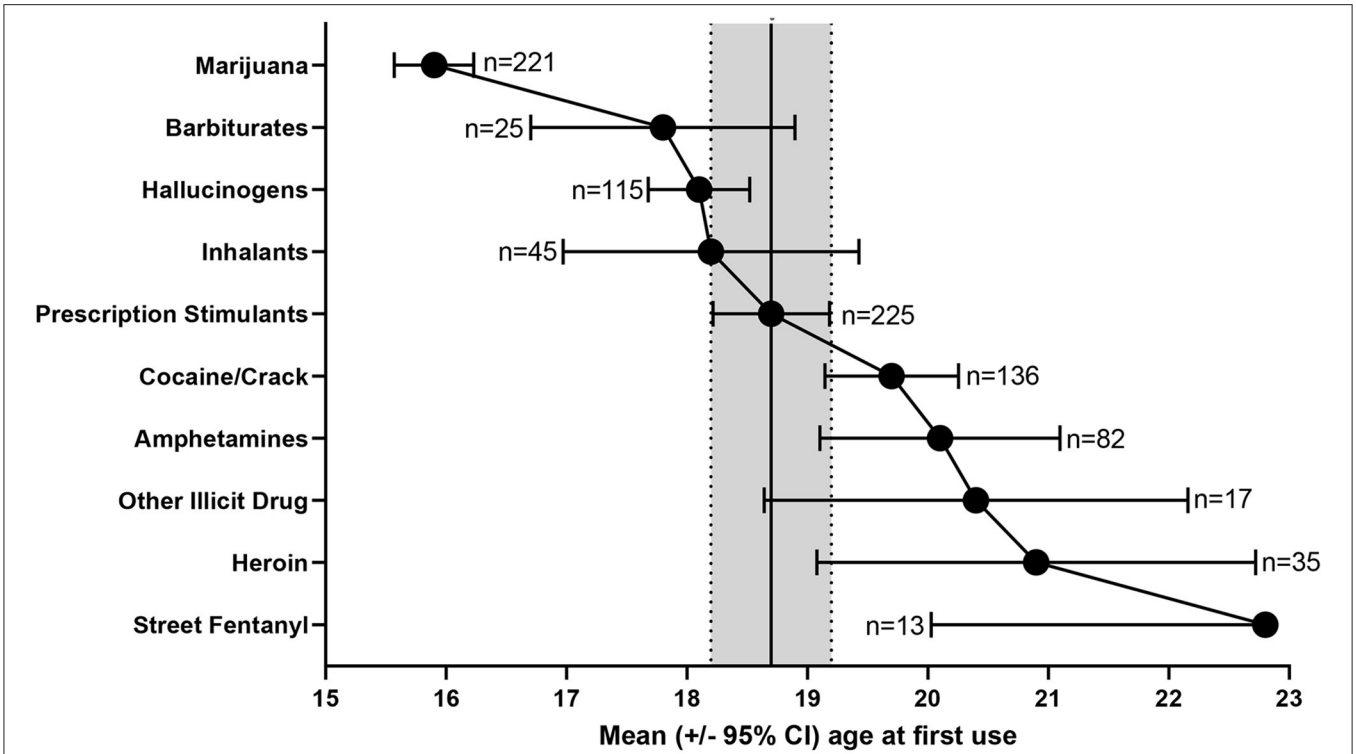

FIGURE 1 | Mean age ± 95% CI of initial prescription stimulant NMU and illicit substance use among individuals reporting non-oral prescription stimulant NMU ($n = 225$).

other initial illicit substance exposures, for example, 62.0% of hallucinogen exposures, 89.7% heroin exposures, 82.1% of barbiturate exposures, etc., occurred after prescription stimulant NMU. This pattern held whether the illicit substance use was oral or non-oral (**Table 1**, A columns).

Table 1, B columns reveals that 80.9% of oral prescription stimulant NMU occurred prior to non-oral prescription stimulant NMU. In addition, most marijuana (85.3%) and hallucinogen (57.7%) exposures occurred prior to non-oral prescription stimulant NMU. Representing a potential class transition, cocaine exposures were almost evenly divided with slightly more exposures (51.4%) occurring before initial non-oral prescription stimulant NMU, while most exposures to illicit amphetamines occurred after initial non-oral prescription stimulant NMU. Most exposures to the remainder of substances (heroin, barbiturates, inhalants, etc.) also occurred after initial non-oral prescription stimulant NMU; all exposures to fentanyl occurred after initial prescription stimulant non-oral NMU.

Substance Transitions: Prescription Stimulant NMU to Prescription Opioid NMU

In addition to prescription stimulant NMU and illicit drug use combinations, ∼38.2% of the sample ($n = 86$, 79.1% male, 20.9% female) reported lifetime prescription opioid NMU. **Table 2** summarizes that a greater proportion of those with a history of prescription opioid NMU than without reported using prescription stimulants via any oral route (91.9 vs. 81.3%) that included cutting and breaking their prescription stimulants into smaller pieces before swallowing (31.4 vs. 5.8%), as well as chewing them before swallowing (20.9 vs. 5.8%). Among non-oral routes of administration, a greater proportion of those with a history of prescription opioid NMU than without reported smoking (8.1 vs. 0.7%) or injecting (10.5 vs. 3.6%) prescription stimulants.

Prescription Stimulant Route of Administration Transitions

Figure 2 depicts transitions among the various routes of administration employed for prescription stimulant NMU among individuals who reported non-oral NMU experience. The first route of administration reported was either oral (swallowing: $n = 173$, 76.9%) or intranasal/snorting (snorting: $n = 52$, 23.1%). **Figure 2A** depicts that the majority, 70.2% ($n = 158$), snorted after initial oral use, and did not transition beyond that experience. Other patterns along this pathway involved oral->snort->inject ($n = 7$, 3.1%), oral->snort->smoke ($n = 2$, 0.9%), or oral->snort->smoke->inject ($n = 2$, 0.9%). Remaining pathways involved oral->smoke (1%), oral->smoke->snort ($n = 1$), or oral->smoke->inject->snort ($n = 1$). One individual reported oral use and transitioning to prescription stimulant injection.

TABLE 1 | Substance transitions: lifetime illicit substance use in relation to prescription stimulant NMU organized by whether initial substance exposure took place before or after the first episode of prescription stimulant NMU (A) or before or after the first episode of prescription stimulant non-oral NMU (B).

			A. First Prescription Stimulant NMU		B. First Non-Oral Prescription Stimulant NMU	
	Total Number Use Mentions		Exposure Before	Exposure After	Exposure Before	Exposure After
Lifetime Use Reported	**n**	**%**	**%**	**%**	**%**	**%**
RX Stim - Any Oral NMU	**262**	--	--	--	80.9	19.1
Swallow Whole	185	70.6	--	--	89.7	10.3
Oral Manipulation	77	29.4	--	--	59.7	40.3
Marijuana	**259**	--	77.6	22.4	85.3	14.7
Any Oral	38	14.7	57.9	42.1	71.1	28.9
Any non-oral	221	85.3	81.0	19.0	87.8	12.2
Hallucinogens	**142**	--	38.0	62.0	57.7	42.3
Any Oral	137	96.5	38.0	62.0	56.9	43.1
Any non-oral	5	3.5	40.0	60.0	80.0	20.0
Cocaine/Crack	**140**	--	22.1	77.9	51.4	48.6
Any Oral	NA	--	--	--	--	--
Any non-oral	140	100.0	22.1	77.9	51.4	48.6
Illicit Amphetamines/ Methamphetamines	**113**	--	13.3	86.7	27.4	72.6
Any Oral	57	50.4	19.3	80.7	38.6	61.4
Any non-oral	56	49.6	7.1	92.9	16.1	83.9
Heroin	**39**	--	10.3	89.7	20.5	79.5
Any Oral	NA	--	--	--	--	--
Any non-oral	39	100.0	10.3	89.7	20.5	79.5
Barbiturates	**28**	--	17.9	82.1	32.1	67.9
Any Oral	24	85.7	16.7	83.3	29.2	70.8
Any non-oral	4	14.3	25.0	75.0	50.0	50.0
Inhalants	**13**	--	23.1	76.9	30.8	69.2
Any Oral	1	7.7	0.0	100.0	0.0	100.0
Any non-oral	12	92.3	25.0	75.0	33.3	66.7
Street fentanyl	**13**	--	0.0	100.0	0.0	100.0
Any Oral	2	15.4	0.0	100.0	0.0	100.0
Any non-oral	11	84.6	0.0	100.0	0.0	100.0
"Other" illicit drugs	**30**	--	10.0	90.0	26.7	73.3
Any Oral	14	46.7	0.0	100.0	21.4	78.6
Any non-oral	16	53.3	18.8	81.3	31.3	68.8

[a]*Analysis includes all oral and non-oral routes of administration reported for substances ever used by respondents reporting lifetime non-oral NMU of prescription stimulants. 'Other' routes reported for substances listed are not included.*

[b]*Initiation before or after prescription stimulant NMU initiation was determined by the respondents self-reported order of first time a route route/substance combination was used.*

[c]*Any oral includes swallowing whole or chewing or dissolving before swallowing.*

[d]*Oral manipulation includes chewing or dissolving before swallowing.*

[e]*Any non-oral includes snorting, smoking, or injecting.*

Figure 2B depicts that the remainder, 23.1% ($n = 52$), snorted prescription stimulants for NMU first. Of those, $n = 32$ (14.2% of the entire sample/61.5% of those who snorted prescription stimulants for NMU first) did not transition to another route of administration. Other patterns involved snorting to oral use ($n = 16$, 7.1%) snort->oral->inject ($n = 2$, 0.9%), or snort->oral->smoke ($n = 1$). One individual reported snorting and then transitioning to prescription stimulant injection.

Follow-Up Interview Depicting Motivations and Transitions

Table 3 summarizes motivations, positive and negative effects of prescription stimulant NMU endorsed by participants who completed the follow-up qualitative study ($n = 23$). Prescription Stimulant NMU was undertaken to enhance school work or work performance ($n = 16$, 69.6%) for recreational substance use, such as to get high or party ($n = 16$, 69.6%), or for the desire to treat

TABLE 2 | Routes of administration for prescription stimulant NMU with or without lifetime prescription opioid NMU.

Characteristics of sample	Prescription stimulant non-oral NMU with prescription opioid NMU ($n = 86$)		Prescription stimulant non-oral NMU without prescription opioid NMU ($n = 139$)	
	n	%	*n*	%
Any oral route	79	91.9	113	81.3
Swallowed whole	74	86.1	111	79.9
Cut or broke into smaller pieces then swallowed	27	31.4	8	5.8
Chewed in mouth then swallowed	18	20.9	8	5.8
Dissolved in liquid then swallowed	9	10.5	7	5.0
Any Non-oral route	86	100.0	139	100.0
Snorted	85	98.8	138	99.3
Smoked	7	8.1	1	0.7
Injected	9	10.5	5	3.6

ADHD when the regular dose was not achieving the effect ($n = 11$, 47.8%). Main positive effects of prescription stimulants included feeling Alert ($n = 18$, 78.3%), Stimulated ($n = 8$, 34.8%), or happy ($n = 7$, 30.4%), whereas main negative effects included feeling tired ($n = 17$, 73.9%), having a decreased appetite ($n = 13$, 56.5%), or feeling anxious ($n = 9$, 39.1%).

Almost all respondents reported oral prescription stimulant NMU ($n = 22$, 95.7%), and most reported that their first episode of prescription stimulant NMU was oral ($n = 20$, 87.3%). Similarly, almost all reported snorting prescription stimulants ($n = 22$, 95.7%) but few indicated that their first episode of NMU involved snorting ($n = 3$, 13.0%). Thirteen percent ($n = 3$) reported injecting prescription stimulants. Participants did not typically endorse snorting or smoking for performance enhancement purposes. The primary motivation for snorting or injecting was to achieve a faster impact of the drug (snorting, $n = 21$, 95.4%; injecting, $n = 2$, 66.7%). Additional motivations for snorting included curiosity/others were doing it ($n = 12$, 54.5%), a friend was doing it ($n = 3$, 13.6%) or the person liked it and thought it was cool ($n = 6$, 27.3%). Additional motivations for injecting were the ritual ($n = 1$) or curiosity ($n = 1$). **Table 4** summarizes representative responses endorsing various motivations to use prescription stimulants via snorting or injecting routes of administration.

Eight participants (34.8%) said that prescription stimulant NMU influenced their subsequent use of illicit drugs. While there were numerous examples of illicit substances (primarily marijuana) influencing other illicit substance use, thirteen respondents (56.5%) indicated that use of illicit substances influenced their decision to try prescription stimulant NMU. Four participants (17.4%) reported that their initial prescription stimulant NMU affected their use of other prescription stimulants. **Table 5** summarizes representative statements of these influential relationships. **Supplementary Tables** present the actual pathways among various substances reported by participants. Slightly more than half (13/23; 56.5%) reported using cocaine after using prescription stimulants, which is a transition within the stimulant class in addition to ongoing polydrug use.

DISCUSSION AND CONCLUSION

The purpose of this investigation was to characterize prescription stimulant NMU class, route of administration and substance transitions. A unique, convenience sample of adults who reported non-oral prescription stimulant NMU within the last 5 years were recruited from Reddit. Qualitative interviews among a subsample provided an opportunity to examine transitions in greater detail. This work reveals a gap not only in the academic literature, but also in general healthcare where prescription stimulant NMU may not be recognized (67).

Illicit Substance Transitions

Almost 77% of the sample initiated an illicit substance use trajectory with marijuana during the ages that typically correspond to sophmore and junior years in high school. National Monitoring the Future surveys have found between 60 and 80% of high school sophmores report that marijuana has been "fairly easy" or "very easy" to obtain since 1992 (68), thus, this finding is not particularly surprising. Recent SAMSHA data indicating that 34.8% of adults from ages 18–25 years of age and 13.3% of adults 26 and older reported using marijuana in the past year further support this finding (2).

Almost 20% of the sample initiated their illicit substance use trajectory with prescription stimulant NMU. Three of those individuals only reported prescription stimulant NMU and did not transition to another illicit substance. The remainder primarily transitioned to marijuana. Marijuana remains a Schedule 1 substance and is illegal at the federal level, however, state-level laws vary with regard to use of medical marijuana, recreational use of marijuana and decriminalization, suggesting varying levels of ongoing access and use across the USA; its ubiquitousness is reflected in this sample.

While prescription stimulants were not always the first substance of the use trajectory, they were also not the last. Most illicit substance use occurred after the initial prescription stimulant NMU. Slightly more than one-third (34.8%) of participants in the qualitative study claimed that prescription stimulant NMU influenced their subsequent use of

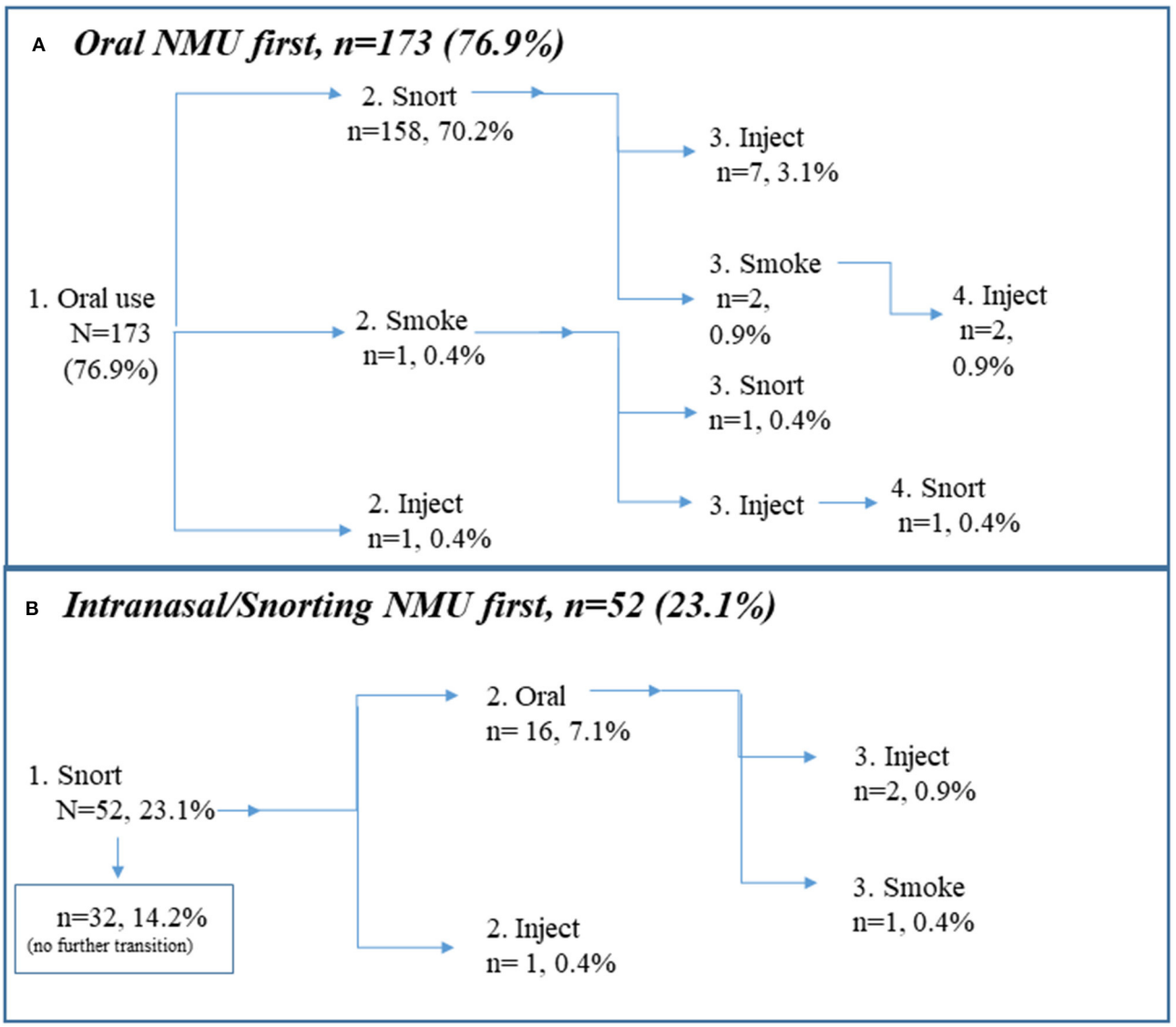

FIGURE 2 | Route of administration transitions for prescription stimulants. Note that linear depiction is only for purposes of illustration. Routes of administration vary as necessitated by access and situation. **(A)** Oral prescription stimulant use first ($n = 173$, 76.9%), **(B)** Intranasal prescription stimulant use first ($n = 52$, 23.1%).

illicit substances, while almost one-half endorsed prescription stimulant NMU when their regular dose was not achieving its effect, a noted risk factor for misuse (69). Recently, among multiple cohorts of high school seniors who were followed longitudinally, it was demonstrated that any reported prescription stimulant misuse (compared to none or rare misuse) was more strongly associated with subsequent substance use disorder symptoms at age 35, including cannabis use disorder, other substance use disorder or any substance use disorder (70).

Prescription stimulants have also been found to be predictive factors in the development of illicit opioid use (48, 71) and increased concurrent use of opioids and stimulants has been represented in overdose deaths (72, 73), revealing a previously underappreciated level of risk associated with this particular trajectory. This finding is particularly important, given the recognition that many college-age students believe the level of risk associated with prescription stimulant NMU is low to non-existent (74).

Route of Administration Transitions

Participants were recruited because they had used prescription stimulants non-orally, a risk factor for substance use severity (57, 66). For example, the speed of transition from first use to daily heroin was faster if the initial use was non-oral (injection) (58). Less is known and reported about the transitions from oral to non-oral prescription stimulant ROAs, other than they are likely to occur during the college years (1, 41, 60), and that they are likely to occur (26–28).

TABLE 3 | Motivations, positive and negative effects of prescription stimulant NMU among follow-up interview respondents*.

Motivations	*n*	%
To enhance school or work performance	16	69.6
Recreational use. To get high/party	16	69.6
To treat ADHD when regular dose wasn't achieving effect	11	47.8
For energy or to stay up	10	43.5
To enhance effect of other drugs	4	17.4
To improve mood, self-medicate for depression, anxiety	3	13.0
To prevent or treat withdrawal symptoms	1	4.3
Positive effects		
Alert, focused, awake, better concentration	18	78.3
High, good buzz, stimulated	8	34.8
Happy, elevated mood, less depressed, less anxious)	7	30.4
Calm	6	26.1
Productive	5	21.7
Social	5	21.7
Energetic	4	17.4
Negative effects		
Insomnia, tired, exhausted	17	73.9
Decreased appetite	13	56.5
Anxiety	9	39.1
Strung out, restless, antsy	6	26.1
Cold sweats, feel terrible after crashing/coming down off stimulants	5	21.7
Rapid heartrate/palpitations	4	17.4
Paranoia and social anxiety	4	17.4
Tense, achy, headaches	3	13.0
Nausea	3	13.0
Depression	3	13.0
Irritable, impatient	3	13.0

**Responses are not mutually exclusive and do not sum to 100%.*

The present study found that the majority of the sample reported oral NMU prior to non-oral NMU. Most, after oral use, transitioned to snorting prescription stimulants (∼70%), or only ever snorted prescription stimulants (23%). These data add to recent findings that most non-oral use of prescription stimulants is intranasal among adults (26–28) and adolescents (19, 41).

However, among some, ROA moved beyond intranasal use to include smoking and injection. Intranasal and injection prescription stimulant NMU are associated with more severe medical outcomes than oral NMU (75), and thus awareness of these potential ROA transitions in prescription stimulant NMU is critical. For example, multiple, non-linear routes of administration have been reported for prescription opioid NMU (76) where approximately half of those interviewed transitioned to snorting or injection of prescription opioids before entering treatment. Similar to prescription stimulant ROA transitions, opioid ROA transitions were mostly to achieve a desired effect or due to social influences, where social influences typically led them to undertake a more dangerous ROA (76). Similar relationships may exist among prescrtipion stimulants, which is an avenue for future investigation.

Class Transitions

The present study found evidence of stimulant class transitions whereby (in addition to most illicit substance use), most illicit stimulant use occurred after prescription stimulant NMU. There is little to no available data on this specific transition. It has been found that early prescription drug NMU is associated with later prescription drug abuse and dependence (77), and prescription stimulant use is associated with subsequent substance use or dependence (24, 78). Similarly, the class transition from prescription to illicit substance has been noted with opioids where prescription opioids have pre-dated the use of heroin (51, 53, 79). When the class transition was made to an illicit stimulant, cocaine, it was snorted, and in 12/2/3 (52%) of those interviewed, this occurred after previous prescription stimulants had been tampered with and/or snorted. Of 16.7% of those with lifetime cocaine use and 11.2% of those with lifetime amphetamine use go on to develop stimulant use disorders (80), and it is possible that the present data capture the initial stages of those trajectories.

Limitations

Data were obtained from a convenience sample of adults who were recruited from Reddit. Although Reddit is advertised as the 5th most visited website in the United States, this may not be a representative sample of adults who undertake non-oral prescription stimulant NMU. Reddit users have been characterized as young, male, regular internet users (81). Subsequent studies targeting non-oral prescription stimulant NMU are needed; the present study can inform hypothesis generation. Increasing attention is being paid to the use of Reddit specifically (82–87) for the conduct of substance use research. One distinct advantage of social media platforms is the potential reach to hidden populations, such as substance users (88). Although data are self-reported, given the nature of the information disclosed, it is possible that anonymous online surveys may increase the likelihood of truthful reporting. In the present study, the self-reported information collected in the quantitative survey was verified and detailed among those who participated in the follow-up interviews.

Temporal relationships alone cannot determine causality. While a mixed methods approach was used to capture motivation and factors that influenced trajectories of substance use, we are unable to quantify the causal relationship between prescription stimulant NMU (or non-oral prescription stimulant NMU) and subsequent drug use patterns. Quantitative data measure study outcomes with precise, numerical data that can be generalized and compared with statistical tests that are widely recognized (89). However, such data can also be overly general and, as a result, decontextualize the environment

TABLE 4 | Motivations for snorting or injecting prescription stimulants for NMU ($n = 23$).

INTRANASAL
Faster impact
• I knew the effect would take on faster and it was just curiosity I suppose. When I was experimenting with that I would swallow one pill whole and then while that was I guess digesting I would crush and snort a different pill
• The immediate effect was definitely the reason. The effects overall were shorter lasting but more powerful in that method of use. I think so that was probably the main reason the immediacy of the effect of the drug
• About 10–20 min faster than swallowing. I mean the oral takes about 10–20 min more than snorting it. Yes. And you when you snort it it's about 5, 5–10 min
• Oh, absolutely I mean you know it hit you in the face like a truck and you feel like the most productive worker in the world. You can get up and you can conquer anything you want it makes you feel empowered if that makes sense
Curiosity/Others were doing it/A friend was doing it
• I was kind of introduced to it for the most part. And like you get that drip on the back of your throat when you do it. The constant reminder kind of higher by the availability and a lot of other methods for quick acting methods and so the constant taste is kind of a reminder, I guess
• So, generally with friends it's a little more of a party thing. You know they all wanted to snort it, and nobody wanted to eat it just because it's cool to snort drugs or whatever. And so that's usually how it would go down. When I was in the company of others
• I was dating a girl that had it and was doing it and I decided to try it
Liked it and thought it was cool
• It was cool to snort
• Pretty much snorting. I mean I did other stuff like coke and stuff like that way before. So, I was kind of already in that mindset
INTRAVENOUS
Faster impact (Intravenous)
• I mean I told you earlier snorting it take maybe a few minutes and then you go on and you feel kind of good. But when you inject, it immediately hits. I mean as soon as you plunge the plunger down it immediately hits, and you get hit stronger and harder than any other way would hit
Ritual
• … As my addiction progressed, I wouldn't do anything if I couldn't shoot it. Basically
• And through it all I feel like I was just as addicted to the using and the like the ritual of preparing the injection and all that just as much. You know it was just part of it
Curiosity (Intravenous)
• That was in part sheer dumb curiosity and reports I've read from the Internet. A lot of people on the Internet dangerously overhype what that's like. And you know it's very tempting once you're that far in: where you're already snorting and you're already taking it every day to say, well … how much more harmful than the next step be. And it is that much harmful because it is it's you know I don't want to say great but it's really great when you do that. ….*(sic)*

TABLE 5 | Examples of influences associated with prescription stimulant NMU among interview respondents ($n = 23$).

Influence of prescription stimulant NMU on illicit substance use
• Oh of course it did. Because it has opened up a world to me of not feeling pain. So, of course I was open to the idea of trying to have the feeling that this thing worked so well that I might as well see what else is out there
• Experience with *methylphenidate product* influenced me to try other 'speedy sort of drugs', in particular cocaine
• *Methylphenidate product* was a substitute for cocaine high
• *Amphetamine product* helped with studying and cramming purposes, partying, enhancing marijuana and alcohol intake, could drink more and party longer
Influence of illicit substances on prescription stimulant NMU
• When (I) couldn't get cocaine (I) would inject prescription stimulants to try and chase that "cocaine high"
• The biggest influence for me to start snorting …was my marijuana use was extreme. I was using the *amphetamine product* to enhance that and get a little bit higher from it. And this all probably played into it as well. But I was having severe depression symptoms and I was kind that was a coping mechanism although temporary
Influence of prescription stimulant NMU on other prescription stimulant NMU
• Positive experience with *amphetamine products* led me to be curious/try other prescription stimulants/fun habit/Positive experience with *long-acting amphetamine products* led me to try other time release stimulants
• Curious to see how it (*methylphenidate product*) felt compared to *amphetamine product*
• Wanted to find something to avoid sundowning/effect of *amphetamine product* wearing off
• Crushed them and snorted or crushed them and ate them….because I was cramming for a test. Extra schoolwork
• I was looking for an effect similar to *amphetamine product* and I was looking for sort of a potent something to keep me awake. It's something to keep me focused while I was doing work and that's why I snorted it instead of swallowing it which I felt like would be a less potent dose
• Experience with *amphetamine product* influenced the use of other prescription stimulants as a result of *amphetamine product* getting too expensive for regular use
• *Amphetamine product* made more comfortable taking prescription stimulants. So, if preference wasn't available, felt pretty comfortable going to another prescription stimulant
• Well yes I did. I suppose if anything it made me more want to acquire *amphetamine product* to keep with that and have a more consistent supply because I saw the value of it both for academically and for partying

in which the outcomes of interest (in this case, substance use behaviors) take place (90). They may not convey the "lived experience" (91). Qualitative data, where the word is the unit of analysis, are employed to examine experiences or processes and can convey meaning and subtlety in a way that numbers alone cannot (90). The mixed method strategy, including quantitative and qualitative data collected together (92) allows for a more nuanced interpretation of each type of data (93) and as such, is a design choice that is particularly useful in the study of non-medical substance use behaviors (74). These behaviors are not only difficult to quantify, but are stigmatized and often difficult to find and detail in the general population, rendering mixed methodology a useful and valuable data collection strategy. In the present study, this strategy enabled a rich characterization of transitions and use pathways.

Conclusion and Future Directions

This study found prescription stimulant NMU to be associated with substance transitions, route of administration transitions and class transitions, which is a novel clarification of the risks associated with this type of substance use. This study was undertaken before the FDA issued the Register notice [FDA-2019-N-3403; Federal Register 84 (183), September 20, 2019], however, some of the findings may inform the questions raised in that document, specifically, whether there may be a role for manipulation resistant formulations in the current misuse and abuse of prescription stimulants. While illicit stimulants are not data presented herein may be used to inform future studies that address whether interventions, such as manipulation resistance formulations of prescription stimulant medications, may disrupt the key transitions that are part of substance use trajectories.

DATA AVAILABILITY STATEMENT

Data are proprietary. Requests to access the data may be considered.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by New England Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SV evaluated early data analyses, suggested subsequent data analyses, wrote the first draft, and revised the manuscript. RR suggested and conducted data analyses and reviewed the manuscript. KA and SF reviewed the manuscript and made significant helpful suggestions and comments. JG acquired funding, designed and oversaw the study, suggested data analyses, and reviewed and commented on the manuscript extensively. All authors contributed to the article and approved the submitted version.

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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.2020.631792/full#supplementary-material

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Impaired Learning From Errors and Punishments and Maladaptive Avoidance—General Mechanisms Underlying Self-Regulation Disorders?

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Self-regulation (SR) is an important human function that relates to quality of life in multiple domains including mental health. Previous studies have found important correlates of low SR including impulsivity and poor emotional regulation; however, underpinnings of low SR are incompletely understood. Individuals low in SR frequently engage in maladaptive behaviors (substance abuse, procrastination, etc.) despite negative consequences. This phenomenon suggests that impaired learning from errors and punishments may be important mechanisms underlying low SR. Consistently, previous studies observed impaired error processing in a wide spectrum of individuals with low SR and impaired learning from errors and punishments in SR-related disorders. We also note a possible role for poor emotional regulation and refer to concepts suggesting that engaging in maladaptive behaviors may serve as short term emotion regulation strategies aimed at avoiding or alleviating negative affect. We speculate on transdiagnostic factors underlying poor SR. We propose that impaired error processing (possibly related to striatal functioning) may prevent subjects with low SR from learning from errors and punishments and thus learning better SR skills or tendencies. Additionally, impaired coping in emotionally challenging situations, possibly related to prefrontal-cortical functioning, may lead to maladaptive avoidance. Moreover, maladaptive behaviors may be reinforced by the temporary decreases in negative affect and rewarding values of behaviors. Given existing knowledge gaps, we call for more extensive research and describe possible directions and challenges for future studies.

Keywords: self-control, impulsive behavior, punishment, emotional regulation, avoidance learning, substance-related disorders, procrastination, addictive behaviors

INTRODUCTION

Self-regulation (SR) is an important human ability or tendency, with the former relating more to cognitive functioning and the latter more to behavioral traits. Levels of SR differ across individuals and correlate with quality of life in many domains including mental health (1). Thus, the topic is gaining attention among researchers in different fields of science. Previous studies have found multiple correlates of low SR including impulsivity and poor executive functioning and emotional regulation (2). Nonetheless, an incomplete understanding of underpinnings of low SR persists. Here we explore the notion that impaired learning from errors and punishments may underlie poor SR, and maladaptive avoidance may result from and perpetuate low SR.

People make many decisions regarding their actions, some of which are perceived at the time or later to be in error and may lead to negative consequences. For most people, such negative consequences serve as punishments and lead to learning and acting differently in similar future situations. However, people with low SR may frequently engage in maladaptive behaviors (e.g., substance abuse, procrastination, binge eating, gambling, etc.) despite negative consequences. Such data suggest that these individuals may have impaired mechanisms of learning from failures and punishments.

The topic of punishment and avoidance learning has arguably been receiving more attention recently (3, 4). While some human studies have focused on avoidance in relation to anxiety disorders (5) and relatively few experimental papers have investigated learning from punishments and/or avoidance learning in relation to broadly understood SR, some data suggest that subject groups low in SR may learn less from errors and punishment (6). These studies complement a more extensive behavioral and neuroimaging research in SR, impulsivity, substance use disorders and behavioral addictions (2, 7–12).

In the following sections, we first review studies suggesting error-processing may be impaired in a range of individuals with low SR. Next, we summarize data relating impaired error-processing to less effective learning from punishments. We then describe studies demonstrating impaired learning from errors and punishment in SR-related disorders and behaviors (in addictive disorders and procrastination). We also consider a role for poor emotional regulation and suggest that short-term avoidance of negative emotions may be a mechanism motivating people to engage in the maladaptive behaviors that may result in long-term negative consequences. Based on striatal and prefrontal systems, we propose a transdiagnostic model connecting impaired coping and learning from errors and punishments with tendencies to engage in maladaptive behaviors. Finally, we describe the need for more extensive research and suggest some possible future directions.

What Is Self-Regulation?

Following (2), we consider SR in a broad sense as, "the intrinsic processes aimed at adjusting mental and physiological state adaptively to context." SR "encompasses cognitive control, emotion regulation, and top-down and bottom-up processes that alter emotion, behavior, or cognition to attempt to enhance adaptation (…) strategic/deliberative as well as reactive/automatized processes and their reciprocal influences." This broad definition encompasses also self-control defined as "top-down aspects of SR" (2). From a clinical perspective, individuals with low SR often engage in maladaptive behaviors like substance abuse, problematic gambling, procrastination, excessive gaming, binge eating and other behaviors, and they will be a focus of the present considerations.

While punishment, negative motivation and negative affect may have different underpinnings and associations, they may also share features relevant to SR. As such, we will consider these processes generally, while noting some unique psychological and neurobiological underpinnings.

ERROR PROCESSING

Error processing is often measured using specific tasks (e.g., Go/No-go, stop-signal or flanker) and assessment of error-related brain activity often employs EEG or fMRI approaches. Commission of an error results in activation of a network of brain regions including the anterior cingulate cortex (ACC); see (13) for a meta-analysis. Multiple studies of substance additions (involving cannabis, opioid, cocaine, or tobacco use) and behavioral addictions (involving gambling or gaming) suggest diminished error-related ACC activity measured with fMRI or as lower amplitude of error-related negativity (ERN) in EEG studies; see (14) for a meta-analysis. Interestingly, however, in people with alcohol dependence, increased ERN was found, possibly in relation to higher anxiety (15). Diminished error-related brain activity has also been found in people with criminal recidivism (16), procrastination (17, 18), and high impulsivity (19). These results suggest impaired error processing may link transdiagnostically to multiple groups with low SR.

Measurement of startle reactions after errors and correct trials suggests that errors are aversive (20). Amplitude of the ERN component related to degree of startle, consistent with a recent study in which assessments of error sensitivity (i.e., the fear of making mistakes) was correlated with ERN measures in children (21). These results suggest that errors may be less salient and arousing in individuals with lower ERNs. A study of impulsivity employing a flanker task with separated reward and punishment conditions found impulsive subjects to exhibit particularly low ERN components in punishment trials (22). Together these results suggest monitoring difficulties, especially in punishment contexts, and/or impaired processing of aversive values of errors and punishments in individuals with low SR.

Noteworthy errors can also be interpreted as conflicts between the assumed goals and the obtained situations [e.g., (23)], and conflicts have also been proposed to represent aversive signals (24). In light of the theory of expected value of control (25), the activity of ACC may be interpreted as a more general signal regulating cognitive control in demanding situations. This could suggest that individuals characterized with lower error-related ACC activity could also show cognitive control deficits in other situations. A recent review (26) has noted correlations between neural correlates of error processing (ERN amplitudes)

and multiple measures of cognitive control. The measures, however, did not assess performance related to learning from errors. Taking the above-mentioned results together, one may hypothesize that lower ERNs and lower SR may concurrently relate to impaired learning from errors and punishments.

LEARNING FROM ERRORS AND PUNISHMENTS

Individual differences exist relating to tendencies to learn from rewards or punishments. A probabilistic cognitive reinforcement learning task used in one study (27) had two stages: learning and inference. In the learning phase, participants were presented with three pairs of stimuli (AB, CD, EF, one pair at a time), were to choose one of the stimuli from a pair, and were provided with feedback. Choosing A resulted in reward in 80% of trials and in punishment with 20% probability, while stimulus B had the opposite contingency. In the CD pair, the probabilities were 70 and 30%, and in the EF pair they were 60 and 40%. During the learning phase, participants learned to choose A over B; however, to check whether they had learned to pursue rewards (choose A) or to avoid punishments (avoid B), a second phase of the task was conducted. During the inference phase, participants again were to choose one of two stimuli, but the stimuli were mixed in different pairs (i.e., AC, AD, AE, AF and BC, BD, BE, BF) and no feedback was provided. Analysis of performance from the inference stage provides insight into whether participants show biases toward learning from rewards (more frequent choices of A) or punishments (more frequent avoidance of B). The authors recorded EEG during the task and found that learning from punishments correlated with ERN amplitudes. Unfortunately, no self-regulation-related questionnaires were employed in the study. However, together with information presented above, the results suggest that subjects with low SR, and thus low ERNs, would show decreased learning from punishments. Several recent studies support this possibility.

An fMRI study employing a spatial paired-associate learning task suggests impaired learning from errors in people who use cannabis (28). In this study, participants were instructed to remember and recall associations of numbers with spatial locations on the screen. After a first round of recall, subjects were presented with the correct numbers, and, if they were unsuccessful, they could improve their performance in a second round of recall. The proportion of corrected errors was significantly lower in individuals who used cannabis vs. those who did not. Neuroimaging results revealed significantly lower error-related brain activity in several regions including the ACC in individuals who used cannabis. Moreover, the ACC was implicated in a group-by-error-type interaction (group: cannabis use vs. non-use; error type: corrected vs. repeated). The interaction suggested higher ACC activity in the non-using group during processing of errors that were later corrected. These results suggest impaired error processing and learning from errors in relation to cannabis use, although disentangling whether impaired learning from errors could have led to cannabis abuse or vice versa would require further studies.

A monetary version of this task, allowing manipulation of the quantity of the monetary outcomes and to separate rewards and punishments, was used to investigate cigarette smoking (29). The study revealed that non-smoking subjects learned better than smoking subjects from small rewards and large punishments. fMRI results showed no error-related group differences in the ACC. The smoking group, however, showed higher activity of the right dorsolateral prefrontal cortex (DLPFC) during recall and during re-encoding of errors corrected in the second round. The authors noted that a "greater need for attentional control, or reduced efficiency in translating DLPFC activation into attentional control" may be evident in individuals who smoke cigarettes.

Impaired learning from punishments has been suggested in opioid addiction during an acquired equivalence task (30). During the first phase of the experiment, subjects were to learn by trial and error associations between antecedent stimuli and consequences. Importantly, learning of associations of two of four antecedent stimuli was reward-based (positive feedback and points gained for correct choices and no feedback for incorrect choices) and learning of the other two was punishment-based (no feedback for correct choices and negative feedback and points lost for incorrect choices). Relative to healthy comparison subjects, opioid-addicted participants needed more trials and committed more errors to reach a desired outcome while learning from punishments. However, no significant group difference was found in reward-based learning. The authors concluded that a "selective deficit in learning from punishment could contribute to processes by which addicted individuals continue to pursue drug use even at the cost of negative consequences."

We have conducted a behavioral study where students high and low in procrastination performed probabilistic reversal learning tasks with separate reward and punishment conditions (31). During the reward condition, participants were to repeatedly choose between two stimuli, where one had higher (75%) and the other had lower (25%) probabilities of monetary reward. Participants were instructed to maximize gains. From time to time, the stimulus-reward contingencies reversed (the previously better stimulus became worse and vice versa). In the punishment condition, the situation was analogous, and participants were instructed to minimize losses. Analysis was based on the Rescorla-Wagner model (32) as applied to human data (33). The model permits calculation of learning rates (i.e., rates of change of conviction about stimuli-reward contingencies) and exploitation-exploration balance of each participant in each condition (reward/punishment). The analysis revealed significantly lower learning rates in students high in procrastination regardless of condition. This group also demonstrated less exploration (or more persistence). A group-by-condition interaction indicated greater persistence in highly procrastinating subjects during the punishment condition. These results suggest that individuals high in procrastination are less flexible in learning than those low in procrastination, especially in punishment contexts.

Taken together, the above-mentioned results suggest impaired learning from errors and punishments across diagnostic boundaries in individuals low in SR.

MALADAPTIVE AVOIDANCE AND IMPAIRED EMOTIONAL REGULATION

The experiments described in the previous section confront subjects with choices and do not allow for or assess avoidance. Employing different experimental paradigms could assess avoidance behaviors that may better resemble real-life situations. Relatively few such studies have been conducted, with several described below.

In one study of heroin-dependent and non-dependent control subjects, participants were asked to perform an escape-avoidance task in the form of a computer game in which they controlled a spaceship with the goal of earning points by shooting enemy spaceships (34). During the first twelve "acquisition trials," a warning signal announcing a bomb coming was periodically displayed for 5 s. Appearance of a bomb resulted in a reduction of points unless subjects hid their spaceship in a "safe box." During the next twelve "extinction trials," no bomb appeared after the warning signal. Women performed significantly worse on the task, and group differences were found only in male subjects. Heroin-dependent males scored significantly fewer points than control subjects because they spent significantly more time hiding in the safe box during the warning signal and a good while after the "bomb period," during both acquisition and extinction trials. This study suggests that heroin-addicted vs. non-addicted males present exaggerated avoidance behavior that may result in reduced opportunities to obtain rewards.

A study employing the same task in alcohol-dependent and healthy men (35) led to similar and different results. Alcohol-dependent men escaped the bomb situation more often than healthy men. They also tended to spend more time hiding during the warning signal in the acquisition but not in the extinction trials. However, alcohol-dependent men scored more points in total as they shot significantly more enemy spaceships than healthy control men, especially during the extinction phase. The authors interpreted the results as, "supporting the idea that both positive and negative reinforcement are important components underlying addictive behaviors."

Maladaptive avoiding may represent an important consideration in addictions. We use the term maladaptive avoidance as reflecting managing stressful situations by not addressing them directly, but by averting attention from them (c.f. "avoidance coping" in APA Dictionary) (36), and this may in turn eventually lead to negative consequences including more stress and negative emotions. Whether behaviors observed in the above-mentioned experimental studies are suitably modeling real-life maladaptive avoidance may be subject to interpretation and further investigation; however, a role for maladaptive avoidance in individuals characterized by poor SR (including those with addictions) was proposed decades ago (37, 38). In related models, engaging in maladapitve or addictive behaviors (e.g., substance abuse, gambling, proctrastination, binge eating) may serve as a short-term emotion-regulation strategy aimed at avoiding or alleviating negative affect [consistent with negative reinforcement motivations and self-medication models of addictions (39), among others (8, 40)]. Previous studies using self-report measures support the notion of engaging in potentially addictive behaviors like substance use (41), gambling (42), procrastination (43), and internet use and gaming (44, 45) for avoiding or alleviating negative mood states.

The described preference to obtain short-term rewards or relief over avoiding possibly larger long-term punishments in people with low SR may also may be interpreted in terms of steep delay discounting or a tendency to value immediate future events higher than more distant ones. Indeed, a recent meta-analysis of delay discounting in addictive behaviors found a small but highly significant correlation (46). Interestingly, delay discounting was correlated with procrastination when measured with questionnaires (47, 48), but not when measured with tasks (49). Most previous studies focused however on delayed reward discounting, and did not include punishments. Future studies should therefore examine delayed punishment discounting, and also consider whether there may be causal relationships between delay discounting and maladaptive avoidance.

The above-mentioned results suggest that maladaptive avoidance may represent a mechanism involved in disorders characterized by low SR. Maladaptive avoidance tendencies may reflect strategies developed to compensate for poor coping in response to challenging situations (for example, to decrease stress when exams approach, students could play computer games instead of studying). Alternatively, both maladaptive avoidance and impaired learning from errors and punishments may indicate impaired cognitive and behavioral control during emotionally challenging situations in which negative emotions and/or threat of punishment are experienced or anticipated.

DISCUSSION AND POSSIBLE MECHANISMS

SR failures related to negative affect may result from imbalances between subcortical and frontal regions; e.g., insufficient frontal top-down control "either due to particularly strong impulses or when prefrontal function itself is impaired" (50). Indeed, both lack of reward and receipt of punishment have led to activation of the right DLPFC in healthy subjects (51). These findings suggest increased behavioral control in such situations. According to the theory of expected value of control (25), cognitive control is implemented by the lateral PFC in response to ACC signaling a potential need for it. Therefore, it may be predicted that activity of these prefrontal brain regions related to punishment or negative affect could differ in individuals high and low in SR. Indeed, abstinent cocaine-dependent participants showed hypoactivity of the ACC and right DLPFC in relation to punished errors in the Go/No-go task (52). We have found similar results (diminished ACC and right DLPFC activity during punishment condition in the Go/No-go task) in individuals high in procrastination (17). These findings are in line with prior theories (50) and suggest that impairment of prefrontal control

by punishment threat or negative emotions may operate for many subject groups characterized by low SR. Note, however, that the previously mentioned study (29) showed higher DLPFC activity in tobacco-smoking individuals during re-encoding of later-corrected errors, possibly reflecting higher difficulty and/or effort needed to correctly perform in the task, or impaired mechanisms of regulation of intensity of implemented control [c.f. (25)].

Prefrontal-striatal mechanisms linked to SR may be amenable to interventions, with transdiagnostic implications. Both regulation of emotion and regulation of motivation (e.g., craving in addictive disorders) have been implicated in groups characterized by low SR. Among individuals who smoke tobacco, regulation of craving has been found to involve prefrontal control over striatal cue responsiveness (53). Prefrontal regions (PFC, ACC) and circuitry (a fronto-cingulo-parietal network) were less activated and engaged, respectively, in individuals with internet gaming disorder vs. those without during emotional regulation (54). Recently, both impaired regulation over responses to primary rewards and addictive cues have been reported in internet gaming disorder (55), and stimulation of the right DLPFC enhanced both regulation of craving and negative emotions in individuals with internet gaming disorder (56). Taken together and in line with prior theories of internet gaming disorder (57) and other addictive behaviors (8, 58), these findings suggest that interventions targeting increased prefrontal control over subcortical emotions/motivations may help multiple groups with low SR.

Concerning the balance between subcortical and frontal regions, dysregulation of dopaminergic circuits may be one mechanism underpinning impaired reward, punishment, and error processing, and thus underlie impulsivity, addictions and possibly low SR in general (59–62), although dopamine may play a more central role in some disorders than in others (63–65). At least two non-exclusive dopamine-related mechanisms may underlie aspects of low SR.

First, a "No-Go" pathway could be deficiently functioning in low SR as has been proposed as one element in some models of addiction (66) and could reflect higher striatal and lower prefrontal activity. However, addictive behaviors have also been linked to lower striatal activation [e.g., in reward anticipation in substance use and gambling disorders (67), with similar findings in binge eating disorder (68, 69) and internet gaming disorder (70)]. In several of these studies, blunted striatal activation was linked to increased impulsivity (71–73), suggesting a relationship to SR. These findings are in line with reward deficiency models of addiction (74) and suggest more complex etiologies relating to SR in addictive disorders. Blunted ventral striatal activation during a prospect phase of reward and loss processing has been linked to disadvantageous decision-making in people with and without gambling disorder, suggesting another route by which reward and loss processing may link to SR impairment (75). Although some models suggest that striatal dopamine may underlie aspects of human addictions (76), findings may be strongest for stimulant use disorders (63), and even in such disorders, dopamine receptor availability may show differential relationships with measures of disease severity (77).

When considering the involvement of the striatum in SR, one should be mindful of complexities involving regions of the striatum and how they may relate to SR, including changes within individuals over time both developmentally and from life experiences including psychopathology (78, 79). For example, data suggest that the ventral striatum may be more linked to impulsive behaviors and dorsal striatum to more habitual behaviors, with these regions components of different parallel cortico-striato-pallidal-thalamo-cortical circuits that are involved in different stages of disorders (e.g., addictions, impulse control disorders) characterized by impairments in SR (79–84). Given these data, a shift from more ventral to dorsal striatal involvement has been proposed for addictions as they become more instantiated (84). More recently, a study of healthy adults performing a naturalistic maze-navigation task identified functionally segregated regions of the ventral striatum that separately encode specific aspects of performance [effort activation, movement initiation and effort discounting of rewards (85)]. Furthermore, opposing patterns of activation related to effort activation and discounting were associated with striatal encoding of effort during effort-based decision-making. The authors suggested that the dorsomedial region of the striatum that has been previously understood as being linked to action may rather be involved in assessing cost of effort, raising questions regarding prior interpretations of striatal "reward" signals. Taken together, the findings indicate that more research is needed to examine involvement of specific striatal regions and circuits in studies of the neurochemical and neurocircuitry underpinnings of SR. Furthermore, additional circuitry should be considered, consistent with recent models of addiction (8, 40).

Second, considering the diminished error-related ACC activity, it could be hypothesized that the errors are less salient in low SR individuals and thus impede learning on errors. Early data (86) suggested that error-related ACC activity influenced learning not to repeat erroneous behaviors, and this may in part reflect dopamine-dependent reinforcement signals from the basal ganglia. This view was supported by data from patients with Parkinson's disease participating in a probabilistic reinforcement learning task (87) similar to the one described above (27). Unmedicated Parkinson's patients, considered characterized by low dopamine, learned better based on punishments than on rewards; application of dopamine-replacement medications reversed this pattern, suggesting that lower levels of dopamine may support D2-like-receptor-dependent "No-Go" learning based on errors and punishments, while high levels of dopamine may shift the balance toward D1-like-receptor-related "Go" behaviors (87). This interpretation is consistent with results of correlations between ERN amplitudes and learning from punishments in healthy subjects (27). This leads to speculation that people with lower ERNs and lower tendencies to learn from punishments may be characterized by higher levels of striatal dopamine, consistent with findings suggesting positive correlation between impulsivity and striatal dopamine measures (88, 89). Buckholtz and colleagues suggested that high levels of striatal dopamine in impulsive subjects may result from lower levels of D2/D3 autoreceptors in the substantia nigra and ventral tegmental area leading to stronger dopamine cell

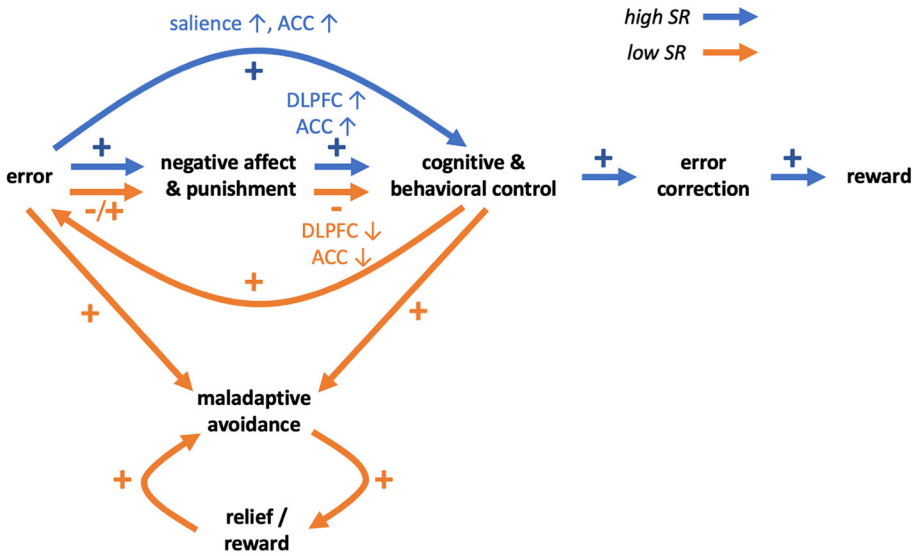

FIGURE 1 | Schematic hypothetical transdiagnostic model of self-regulation behaviors and disorders in relation to impaired coping and learning from errors and punishments. Differences between high SR (blue arrows) and low SR (orange arrows) individuals may involve brain reactions to negative affect and punishments. In individuals high in SR, negative affect and punishments may lead to increased activity of prefrontal control regions (ACC, DLPFC) and increased cognitive and behavioral control. In individuals low in SR, ACC and DLPFC activity in emotionally challenging situations may be relatively lower and result in impairment of cognitive and behavioral control. In individuals high in SR, errors may be processed as more salient events and lead to increased monitoring and control, supporting correction of errors in the future, leading to more rewards and learning of self-regulation. In individuals low in SR, learning from errors and punishments may be impaired. Errors may be processed as less salient and aversive events and not result in increased monitoring and control, potentially leading to repeating of errors. Eventually however errors may result in punishments and negative affect and further decline of cognitive and behavioral control. Both because of error-processing and diminished control, individuals low in SR may preferentially engage in maladaptive behaviors. The behavioral pattern may be reinforced by the relief and rewarding value of substitute behaviors, eventually preventing individuals low in SR from learning self-regulation.

activity and enhanced release of dopamine which could in turn increase impulsivity and promote "Go" behaviors (88). However, given inconsistent findings and complications of synthesizing information across studies [e.g., from Parkinson and non-Parkinson populations that may show important dopamine-related differences given the pathophysiology of the disorder and other factors (90, 91)], additional research is necessary.

Summing up, in emotionally challenging situations prefrontal activity in individuals with low SR may be insufficient to effectively regulate emotional and motivational drives involving the striatum and other regions, and this may lead to difficulties in coping with negative situations. Additionally, individuals with low SR may not learn from errors and punishments, and this may relate to differences or impediments in error processing. Together, these mechanisms may impede coping in negative situations, hinder learning from such situations and impair learning SR (**Figure 1**).

Such maladaptive behaviors may be reinforced over time. In an fMRI study employing a probabilistic reinforcement learning task with separated rewards and punishments (51), the authors showed that both obtaining rewards and avoiding punishments lead to activation of the medial orbitofrontal cortex (mOFC). Given that the mOFC is a component of the ventromedial PFC that has been implicated in processing rewarding outcomes (92), the findings suggest that avoidance of aversive outcome may be rewarding. Similar conclusions were made in a different study employing a repeated acquisition approach-avoidance learning task and showed, among other regions, activations in anterior and posterior cingulate and ventral striatum both for rewards and avoidance of aversive outcomes (93). These studies showed that reward and avoidance learning rely largely on common brain networks, consistent with meta-analytic findings (94). Therefore, negative reinforcement (i.e., avoidance of punishment) may lead to consolidation of avoidance behaviors including maladaptive avoidance. Moreover, engaging in maladapitve behaviors (e.g., substance abuse, gambling, gaming) may be rewarding in and of themselves and thus additionally reinforce such behavioral patterns (**Figure 1**).

Summary and Future Directions

In this manuscript, we discuss possible transdiagnostic mechanisms underlying poor SR. Impaired coping in emotionally challenging situations, related to decreased prefrontal activity, may promote avoidance of such situations in individuals with low SR. Moreover, impaired error processing may prevent individuals with low SR from learning from errors and punishments and impede effective correction of faulty behaviors and learning of SR itself. Additionally, maladaptive behaviors may be reinforced by short-term decreases in negative affect and by rewarding values of behaviors, leading to more persistent engagement (**Figure 1**).

Whether the model is valid and is transdiagnostic should be a subject of future studies, which may involve several challenges. First, regarding learning from errors and punishments, future studies may benefit from novel tasks (ideally applicable in

neuroimaging studies) as many probabilistic reinforcement learning tasks often do not show between-group differences in task performance and require modeling approaches to show differences in learning strategies. Second, new experimental tasks, better mimicking real-life situations, should be developed to address learning of avoidance. Ideally, such tasks should allow participants a choice to avoid engagement in aspects of the task. They should also allow for distinguishing between learning of adaptive and maladaptive avoidance. Such human avoidance research tasks may encounter challenges that should be considered (95). Future studies should also check whether punishments, punishing contexts and negative affects evoked in different ways may lead to similar or different neuronal and behavioral effects. Future research could also refer to the theory of expected value of control and test which of the proposed components of cognitive control may be particularly impaired in individuals low in SR: estimation of expected outcomes, regulation of intensity of control, or monitoring of performance (25). Ideally, future research will address proposed mechanisms in a broad range of disorders characterized by low SR including substance use disorders, behavioral addictions, binge eating disorder, and other conditions, as well as in other relevant behavioral dimensions including procrastination and high impulsivity.

We believe that research addressing learning from negative consequences and coping in negative situations in disorders characterized by low SR may eventually contribute to the improvement of existing and/or development of new therapeutic approaches. Psychological interventions could possibly address emotional regulation, working with internal conflicts and/or training inhibitory control and error-awareness. Pharmacological therapies could aim at the regulation of function of neurochemical systems underlying motivational drives and cognitive control. Neuromodulatory approaches may be well-suited to increase prefrontal control over subcortical drives, particularly given the ability to target prefrontal cortical regions using transcranial direct current stimulation and repetitive transcranial magnetic stimulation.

Limitations

Our proposed model should be considered cautiously. The understanding of individual differences, especially concerning SR, in processes underlying learning based on errors and punishment and avoidance learning is still developing; therefore, the model may currently be considered speculative. Existing data do not typically permit dissection of causes from consequences (e.g., of substance abuse); nevertheless, we believe the model is relevant to SR impairments. In considering a transdiagnostic mechanism underlying low SR, we considered together many disorders and behaviors characterized by low SR. In doing so, the model does not incorporate all mechanisms that may contribute to low SR, for example delay discounting or motivational processes, neither does it include factors relating, for example, to effects of specific substances. Noteworthy, we relate the results of the reported studies to learning of SR, repetitive engagement in maladaptive behaviors, and their long-term negative consequences, while the studies investigated almost exclusively short-term processes. Thus, it is imaginable that the experimental situations do not fully reflect real-life processes, especially with respect to preferring short-term rewards over avoiding of possibly larger long-term punishments, and further research in this area would likely improve understanding of mechanisms and help to refine the model. We also simplified and limited brain considerations largely to the striatum and PFC, and we largely did not discuss roles for particular subregions and other parts of the brain. We also did not discuss the broader range of neurochemical/neurotransmitter systems that may contribute to SR. However, we believe that these simplifications permitted proposing a model for how impaired coping under negative affect and impaired learning from errors and punishments may operate as transdiagnostic mechanisms underlying poor SR. We hope that future studies will test the proposed model, lead to the development of more detailed models and facilitate clinical advances related to poor SR.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

MW conceptualized the manuscript. Both authors reviewed literature, wrote, and approved the submitted version of the manuscript.

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Behavioral Economic Assessment of Alcohol and Cigarette Demand in Smokers With Alcohol Use Disorder

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Background and Objectives: Behavioral economic purchase tasks are widely used to assess drug demand in substance use disorder research. Comorbid alcohol use is common among cigarette smokers and associated with greater difficulty in quitting smoking. However, demand for alcohol and cigarettes in this population has not been fully characterized. The present study addressed this gap by examining alcohol and cigarette demand among treatment-seeking smokers with alcohol use disorder (AUD).

Methods: Alcohol and cigarette demand was assessed among 99 smokers with AUD. We conducted Principal Component Analysis (PCA) and correlational analyses on the demand indices.

Results: Participants showed higher demand for alcohol than for cigarettes, as evidenced lower elasticity (resistance to increasing price) and higher O_{max} (maximum response output for drug). PCA revealed a two-factor structure (Persistence and Amplitude) for both alcohol and cigarette demand indices. Cigarette-related demand indices were positively correlated with nicotine dependence, but alcohol-related demand indices were not associated with alcohol dependence, suggesting dissociation between alcohol demand and use behaviors.

Discussion and Conclusions: Our results suggest that smokers with AUD were more resistant to price elevations in relation to reducing alcohol consumption as compared to cigarette consumption, suggesting preferential demand for alcohol over cigarettes. However, it is unclear how acute substance exposure/withdrawal impacts the demand indices.

Scientific Significance: Potentially differential alcohol and cigarette demands among smokers with AUD should be considered in the concurrent treatment of smoking and alcohol.

Keywords: purchase task, alcohol demand, cigarette demand, latent structure, smokers with alcohol use disorder, alcohol and tobacco co-dependence

INTRODUCTION

Smoking and alcohol misuse often co-occur. In the United States, the prevalence of nicotine dependence among individuals with alcohol dependence is 45.4%, while the prevalence of any alcohol use disorder among adults with nicotine dependence is 22.8% (1). These co-dependent individuals have more difficulty quitting smoking (2). An outstanding problem among those with substance use disorders is their disproportionate valuation of the drug (3) and their disproportionate allocation of resources to obtaining the drug compared to participating in other daily activities (4). This imbalance between drug-related vs. regular activities reflects reinforced drug consumption patterns (5, 6), and the differences in how drugs and nondrug reinforcers (e.g., food) exhibit differential reinforcement strengths can be operationalized using a concept known as Relative Reinforcing Efficacy (RRE).

One validated laboratory approach to measuring the RRE of drugs is hypothetical purchasing tasks, which assess changes in drug purchase and consumption as a function of increasing drug price (7–9). The consumption pattern can yield the demand curve modeled by $Q = Q_0 * 10^{k(e^{-\alpha Q_0 C} - 1)}$ (10), an exponentiated version of the classic equation by Hursh and Silberberg (11). Q represents consumption at price C; Q_0 (also referred to as intensity of demand) represents consumption at or near price zero, α represents the rate of change in demand elasticity, and k is the span of consumption values in log units. Other demand indices derived from the demand curve include: breakpoint (the price at which consumption reaches 0), O_{max} (the maximum response output or the maximum expenditure), and P_{max} (the price associated with O_{max}). P_{max} also indicates the price at which the slope of the demand curve becomes <-1, indicating a shift from relatively inelastic demand where changes in consumption is resistant to increases in price to relatively elastic demand.

Research using the alcohol purchase task (APT) has found alcohol demand to be associated with alcohol use. For example, college students with recent heavy drinking exhibited greater intensity, O_{max}, and breakpoint than recent lighter drinkers (9), and the APT's reliability and validity was further confirmed among college students (12). Importantly, heavy drinking smokers exhibited greater O_{max}, P_{max}, and breakpoint for alcohol compared to heavy drinking nonsmokers (13), suggesting that smoking may increase the demand for alcohol.

Research using the cigarette purchase task (CPT) has suggested that cigarette demand indices are associated with smoking behaviors. Nicotine dependence severity was positively associated with the breakpoint, intensity, P_{max}, and O_{max} among young light smokers (8) and among moderately heavy smokers (14). Cigarette demand is also related to psychiatric conditions among smokers. For instance, it was shown that smokers with schizophrenia reported higher intensity, consumption, and expenditure than smokers without schizophrenia (15).

Researchers have further studied the latent structure of the demand indices to identify higher-level factors in the RRE domain that potentially better explain drug use behaviors. Two latent factors, labeled Persistence and Amplitude, have been identified for different drugs, including marijuana (16), alcohol (17), and cigarettes (18–20). The Persistence factor was found to consist of breakpoint, O_{max}, P_{max}, and elasticity. Higher levels of breakpoint, O_{max}, and P_{max}, and lower elasticity values were associated with higher Persistence scores, reflecting more persistent demand for the studied drug. However, the Amplitude factor appears to be more heterogeneous. The demand index that loads to this factor is the intensity, and thus it may reflect the maximum possible amount acquired and consumed by users, but other demand indices, such as O_{max} (17, 18) and elasticity (19), were found to load on the Amplitude factor.

While many studies have evaluated the RRE of alcohol and cigarettes separately, most were conducted in nonclinical samples, particularly among younger college students. Smokers with alcohol use disorder (AUD) represent a special population known to be more treatment resistant because of their dual dependency (2). Recently, there have been several attempts studying the demand for alcohol and cigarettes among populations with concurrent use of alcohol and cigarettes. For instance, it was found that smokers showed greater demand for alcohol than nonsmokers among a college student sample (13). Extending these results from university settings to communities, Amlung et al. (21) provided further evidence of increased demand for alcohol among smokers compared to nonsmokers. Recently, in a larger community sample ($n = 383$) of nontreatment seeking heavy drinking smokers, Green et al. (22) found that alcohol and cigarette demand indices were positively correlated and more importantly, they found that compared to alcohol-related dependence measures, smoking-related measures accounted for more variance in alcohol demand's Persistence factor, suggesting that smoking may play a reinforcing role in increasing alcohol demand among nontreatment seeking heavy drinking sample.

These three studies have provided important insights for the interrelationships between the demand for alcohol and cigarettes, shedding light on developing interventions for alcohol and tobacco co-dependence. To complement these findings, we evaluated the demand for alcohol and cigarettes among treatment-seeking smokers with AUD, a clinical population that has not been examined previously. Specifically, the current study used the APT and CPT to examine the baseline demand for alcohol and cigarettes among smokers with AUD enrolled in a clinical trial for the concurrent treatment of AUD and smoking. We aimed to (1) compare the alcohol and cigarette demand indices and their latent factor structures and (2) examine each drug's demand metrics' relationship with the dependence severity of alcohol and nicotine.

MATERIALS AND METHODS

Participants

Participants ($n = 101$) were recruited from the Houston metropolitan area to participate in the current study, as part of a multi-center clinical trial (clinicaltrials.gov # NCT01182766) that used topiramate (23) for the concurrent treatment of both smoking and AUD. Key inclusion criteria included: smoking 5 cigarettes/day or more, producing an expired CO level of $\geq$ 10 ppm, drinking at least 15 (men) or 8 (women) standard drink

units (SDUs) per week, and meeting the DSM-5 (24) diagnosis of mild to severe AUD. Key exclusion criteria included having a medical condition (e.g., seizure disorder) that may put subjects at risk when discontinuing topiramate, or daily use of certain medications (e.g., opioids) that could interact with topiramate. Other exclusions included any psychiatric disorders other than AUD or nicotine dependence, any treatment for alcohol and/or nicotine dependence within 30 days, any illicit drug use, and women who were pregnant or lactating.

The parent study was approved by all participating sites' Institutional Review Boards (IRB), and the current study was approved by the IRB at The University of Texas MD Anderson Cancer Center. All participants provided written informed consent when abstinent from alcohol, as indicated by having a breath alcohol content (BAC) of <0.001%. Participants were not required to abstain from smoking. Instead, they were encouraged to smoke *ab libitum* prior to this session to establish their baseline smoking amount.

Measures

We used the DSM-IV-based Mini International Neuropsychiatric Interview (MINI, v6.0.0) (25) plus an added question about cravings to homogenize with DSM-5 criteria to determine the diagnosis of AUD or any other psychiatric disorders. The Alcohol Use Disorders Identification Test (AUDIT) (26) assessed alcohol consumption, drinking behaviors, and alcohol-related problems (range: 0–40). The Fagerström Test for Nicotine Dependence (FTND) (27) measured nicotine dependence (range: 0–10). The Short Alcohol Withdrawal Scale (SAWS) (28) assessed the alcohol withdrawal severity (range: 0–30). The Wisconsin Smoking Withdrawal Scale (WSWS) (29) captured smoking withdrawal severity in various subdomains (e.g., concentration and anger). Specifically, we created a consolidated negative affect score to index smoking withdrawal by using the subscales of Anger, Anxiety, Sadness, and Concentration in WSWS. Timeline follow-back interviews recorded alcohol drinking and cigarette smoking amount (30), and the 30-day period preceding the visit date was used to establish the baseline use patterns for the participants. Breath CO and BAC levels were also collected as biochemical indicators of cigarette and alcohol consumption levels.

The purchase tasks were collected at the same session when consent was obtained, before participants were randomized to treatment. The purchase tasks were administered through in-person interview, which allowed our research staff to review the entire instruction with the participants and clarify any outstanding questions. Order of administration was not systematically fixed or counterbalanced. To facilitate comparisons, the instructions of these hypothetical purchase tasks were similar, in which participants were instructed to "imagine a typical day for you that is not in the hospital" and report how drinks or cigarettes they would buy at each price given the following parameters: (1) participant's financial status was the same, (2) there were no other sources of alcohol or cigarettes, (3) any alcohol or cigarettes purchased must be consumed the same day, and (4) alcohol or cigarette craving was the same as they currently felt. The APT defined "a drink" as a standard sized 12-ounce beer, 5-ounce of wine, or 1.5-ounce (shot) of liquor, while the CPT defined cigarettes as individual cigarettes. It should be noted that the APT's instruction was different from previous studies [e.g., (31, 32)], which typically set up the scenario as at a bar or a party during which heavy drinking may be more likely to happen.

Participants then reported the amount of individual drinks or cigarettes at 19 prices: zero, 0.01, 0.02, 0.05, 0.10, 0.25, 0.50, 1, 2, 3, 4, 5, 10, 20, 50, 100, 250, 500, and 1,000 U.S. dollars in an incremental order (8, 33). Due to an oversight, one participant was not administered the purchase tasks.

Data Processing

We used the "beezdemand" package (34) in the R program (R v3.4.4, The R Foundation for Statistical Computing) to score the purchase tasks.

Non-systematic data were identified using the three-criterion (the trend, bounce, and reversals from zero) algorithm (35). In total, four sessions of APT data and one session of CPT data were identified as non-systematic data and excluded from further analyses. The resulting data were from 99 subjects, consisting of 96 sessions of APT data and 99 sessions of CPT data.

Observed intensity, breakpoint, O_{max}, and P_{max} were calculated using the raw data, and these observed values were more reliable than those estimated from the demand curves (12). To compute elasticity, we used the exponentiated version of the model: $Q = Q_0 * 10^{k(e^{-\alpha Q_0 C}-1)}$ (10). The k values were 3.52 and 2.68 for APT and CPT, respectively, which were computed by subtracting the mean consumption at the lowest price from mean consumption at the highest price with both values $\log_{10}$ transformed (19) and then adding 0.5 (34).

For each price, we calculated Z scores across all available data with values exceeding 3.29 SD of the mean value (17) considered outliers. In total, 18 outliers (1.85%) were identified. To retain these data, these outliers were recoded as one unit higher than the highest non-outlying value, with the exception of elasticity using 0.1 unit, following previous research (19). By calculating the Mahalanobis distance, one session of CPT data was found to be a multivariate outlier and removed from further analysis. All five demand indices were square-root-transformed to reduce skewness and kurtosis for subsequent data processing and analysis, following previous research (19).

Statistics

The final data set had data from 99 participants with 96 sessions of APT and 98 sessions of CPT data. All data analyses were conducted using SAS (v9.4; SAS Institute Inc., Cary, NC, USA). To compare the demand indices between APT and CPT, we conducted one-sample paired t-tests in SAS with a two-sided alternative. For these tests, a significance level of 0.01 was set to adjust for multiple comparisons involving five separate demand metrics (i.e., the Bonferroni correction). To identify the latent factors for the demand curve indices, we conducted principal component analyses (PCA) with the oblique rotation, which allowed the estimation of multifactorial solutions with correlated factors (17, 18). The scree plot for clear discontinuities between succeeding factors was used for factor retention (eigenvalues ≥

TABLE 1 | Demographics and baseline characteristics ($n = 99$).

Variable	Mean (SD)
Age in years	47.0 (10.6)
Cigarettes per day	18.3 (8.4)
Cigarettes per smoking day	18.4 (8.3)
CO in ppm	16.9 (9.2)
Hours since last cigarette	1.8 (1.9)
Drinks per day in SDU	7.9 (4.3)
Drinks per drinking day in SDU	10.1 (5.6)
Heavy drinking days	12.9 (11.4)
FTND total score	5.6 (2.2)
AUDIT total score	19.7 (6.8)
WSWS, negative affect	20.8 (12.0)
SAWS	1.22 (0.62)
	***N* (%)**
Women	30 (30.3)
Race/ethnicity	
African American	38 (38.4)
European American	51 (51.5)
Hispanic	8 (8.1)
Other	2 (2.0)
Married/cohabitating	30 (30.3)
Employed	63 (63.6)
Alcohol use disorder	
Moderate or severe	90 (90.9)
Mild	9 (9.1)

CO, Carbon Monoxide; ppm, parts per million; FTND, Fagerström Test for Nicotine Dependence; AUDIT, Alcohol Use Disorders Identification Test. Cigarettes per smoking day, drinks per drinking day, and heavy drinking days (men: >4 daily SDU; women: >3 daily SDU) were calculated over the 30-day period before the visit; WSWS, Wisconsin Smoking Withdrawal Scale; SAWS, Short Alcohol Withdrawal Scale.

TABLE 2 | Means of alcohol and cigarette demand indices.

Index	APT	CPT
Intensity	8.72 (1.49)	21.29 (1.26)
Elasticity	0.0048 (0.0031)	0.011 (0.0051)
O_{max}	18.80 (2.46)	13.80 (4.73)
P_{max}	5.99 (1.52)	2.23 (1.29)
Breakpoint	18.10 (5.28)	6.22 (3.19)

The parentheses list the standard deviations for each index. All the values have been transformed back to their raw values for better interpretability.

TABLE 3 | Latent structures of the alcohol purchase task and cigarette purchase task.

	APT		CPT	
	Factor 1	**Factor 2**	**Factor 1**	**Factor 2**
Intensity	0.218	**0.937**	−0.176	**0.954**
Elasticity	**−0.791**	−0.276	**−0.382**	**−0.658**
O_{max}	**0.952**	0.221	**0.727**	**0.342**
P_{max}	**0.692**	**−0.538**	**0.983**	−0.111
Breakpoint	**0.799**	**−0.386**	**0.955**	−0.070

Factor loadings are shown in this table and those >0.32 are highlighted in bold. For both tasks, square-root-transformed values were used for the Principal Component Analysis. Each task yielded a two-factor solution.

1.0). A loading of 0.32 was considered to load significantly on a given factor (19).

To examine the correlations between various dependence variables and demand indices, we conducted bivariate correlation analysis. The correlation analysis also included factor scores, which were computed from the five demand indices using the regression method.

RESULTS

Sample Characteristics

On average, participants were in their late forties ($M = 47.0$, $SD = 10.6$), mostly male (70%), and moderately dependent on alcohol and nicotine, with a mean score of 19.7 ($SD = 6.8$) and 5.6 ($SD = 2.2$) for the AUDIT and FTND, respectively (see **Table 1**). At baseline, participants smoked 18.3 ($SD = 8.4$) cigarettes per day and drank 7.9 ($SD = 4.3$) SDUs per day. **Table 1** also lists other baseline characteristics, including withdrawal scores and other drinking and smoking behaviors. Overall, our participants represent a heavy drinking and smoking sample.

Alcohol and Cigarettes Demand Indices

The five demand indices for APT and CPT are listed in **Table 2**. We found that the breakpoint ($t = 7.89$, $p < 0.0001$), O_{max} ($t = 3.01$, $p < 0.005$, and P_{max} ($t = 6.65$, $p < 0.0001$) of the APT were all significantly higher than those of the CPT, while both the elasticity ($t = -5.39$, $p < 0.0001$) and the intensity ($t = -10.52$, $p < 0.0001$) of the APT was lower than that of the CPT.

Latent Structure of the Demand Indices

For the APT, the PCA revealed a two-factor structure, which in total accounted for 80.65% of the variance (**Table 3**). The first factor explained 52.55% of the variance, and included breakpoint (factor loading: 0.799), O_{max} (0.952), P_{max} (0.693), and elasticity (−0.791), while the second factor explained 28.10% of the variance, and included intensity (0.937), P_{max} (−0.538), and breakpoint (−0.386).

For the CPT, the PCA revealed a two-factor structure, which in total accounted for 73.32% of the variance (**Table 3**), but had differential loadings from the demand indices of the APT. The two factors explained 46.67 and 26.65% of the variance. The first factor was mainly loaded by breakpoint (0.955), O_{max} (0.727), P_{max} (0.983), and elasticity (−0.382), while the second factor was mainly loaded by O_{max} (0.342), elasticity (−0.658), and intensity (0.953).

Despite differential loadings of the demand indices to their respective factors, these two-factor solutions for both tasks have qualitative similarities. Specifically, the first factor had significant loadings from breakpoint, O_{max}, P_{max}, and elasticity, which reflect the persistent drug use pattern, and thus we referred to Factor 1 as the Persistence factor. The second factor had significant loadings from intensity, which reflects

the drug consumption levels, and thus we termed Factor 2 the Amplitude factor.

Correlation Analysis

As shown in **Table 4**, baseline drinking levels were significantly correlated with AUDIT scores and BAC levels (both Pearson's $r > 0.35$, $p < 0.01$). Cigarette-related dependence measures (i.e., FTND scores, baseline smoking levels, CO) were also correlated with each other ($p < 0.05$). However, the alcohol withdrawal measure SAWS scores were not correlated with any other alcohol-related dependence measures, and the smoking withdrawal measure WSWS negative affect scores were not correlated with any other cigarette-related dependence measures. We did not find any correlations between alcohol- and cigarette-related dependence measures with the exception that WSWS negative affect scores were correlated with AUDIT and SAWS scores.

Most of the bivariate correlations between alcohol and cigarette demand metrics were significant. However, alcohol demand metrics were not correlated with any alcohol-related dependence measures except for the SAWS scores (Pearson's $r > 0.25$, $p < 0.01$). In light of these null findings, we also examined alcohol demand metrics in relationship with the MINI-based (25) categorical alcohol diagnosis measure, but found that alcohol diagnostic category had no relationship with alcohol demand indices.

By contrast, most of the cigarette demand metrics were significantly correlated with smoking-related dependence measures, particularly FTND scores (Pearson's $r > 0.20$, $p < 0.05$), baseline smoking levels (Pearson's $r > 0.21$, $p < 0.05$), and WSWS negative affect scores (Pearson's $r > 0.20$, $p < 0.05$).

DISCUSSION

Our finding that participants had higher O_{max} (expenditure) and elasticity (insensitivity to price increase) in the APT than in the CPT suggests that they were willing to allocate more economic resources toward alcohol than cigarettes and were less sensitive to the price escalation of the alcohol than that of cigarettes. These results suggest that alcohol had relatively greater RRE than cigarettes among smokers with alcohol use disorder. Our results were consistent with an earlier study among alcohol-dependent individuals (36). They used a multiple-choice questionnaire to assess the crossover point between drug (alcohol or cigarettes) and monetary values and found that the crossover point for the monetary option was higher for a drink than for a cigarette, suggesting that alcohol had greater RRE than cigarettes did among a similar population.

The greater values of O_{max} and lower elasticity scores in the APT than those in the CPT suggested that smokers with AUD had greater demand for alcohol than cigarettes. Consistent with difference in elasticity between alcohol and cigarette demand, our findings support the notion that smokers with AUD were more resistant to the price elevation in terms of reducing their alcohol consumption compared with their cigarette consumption. Notably, greater and more sustained demand for alcohol may be related to one's smoking status *per se*, as previous research showed that heavy drinking smokers reported greater alcohol demand than heavy drinking nonsmokers (13, 21). Although our participants reported lower intensity of alcohol than that of cigarettes, this difference in intensity may reflect the inherent difference in characteristics between alcohol and cigarettes, such as packaging and consumption patterns specific to the products. The relative difference in intensity between alcohol and cigarettes demand, as well as their relative difference in baseline consumption patterns (i.e., less alcohol consumption measured in daily SDU than cigarette consumption measured in cigarettes per day) is consistent with previous research using a similar sample—heavy drinking smokers (22).

Our PCA suggested a robust two-factor latent structure for the APT that accounted for 80.65% of the variance. This finding is consistent with previous research that identified a two-factor solution for marijuana (16), alcohol (17), and cigarettes (18–20). Moreover, consistent with these studies, the first factor includes breakpoint, O_{max}, P_{max}, and elasticity for both alcohol and cigarette demands. These four indices reflect the sensitivity to the increasing prices of alcohol and cigarettes. Thus, this factor indicates the persistence of alcohol and cigarette use behaviors among this population.

The second factor has been commonly referred to as Amplitude (16–18, 20), which reflects individuals' consumption levels when the cost was minimum. This factor was mainly attributable to the intensity index. However, previous research identified differential contributions from a second demand index. Three studies found extra loading from O_{max} (17, 18, 20), one study found elasticity (19), and one found no extra indices (16). Unlike these studies, we found that the Amplitude factor had extra loading from the breakpoint and P_{max}, although three studies found similar nonsignificant negative loadings from P_{max} (16, 19, 20). These results highlight the heterogeneity of the second factor, despite the consistent loading from intensity.

For the cigarette demand's PCA, we replicated a two-factor (18–20). Overall, the loadings to the first factor were similar to our findings with the APT's PCA. However, the Persistence factor accounted for 52.55% of the variance in alcohol demand vs. 46.67% of the variance in cigarette demand, which suggests that smokers with AUD are characterized by higher persistence use of alcohol than cigarettes, consistent with the differences of O_{max} and elasticity between APT and CPT.

Perhaps the most interesting finding with the cigarette demand's PCA was the second factor. This factor pattern is unique because it has been partially reported. For example, Bidwell et al. (18) and O'Connor et al. (20) reported O_{max}, while González-Roz et al. (19) reported elasticity to load to the second factor. Except for the same factor (i.e., intensity) loading to the second factor, the loading from the other four demand indices have a complementary pattern (breakpoint and P_{max} for APT vs. O_{max} and elasticity for CPT). These differential loading patterns highlight the heterogeneity of the Amplitude factor, and distinct latent factors may contribute to the observed differential demand for alcohol and cigarettes.

We found that cigarette demand indices were significantly correlated with FTND scores, baseline smoking rate, and smoking withdrawal (i.e., WSWS negative affect scores). These

TABLE 4 | Bivariate correlations between demand metrics and dependence measures.

Measure	Dependence Measures								Demand Metrics														
	Alcohol				Cigarettes				APT							CPT							
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)	(19)	(20)	(21)	(22)
(1). AUDIT	–	0.36**	0.09	0.17	0.05	0.06	0.02	0.27**	0.07	0.09	0.03	−0.04	0.05	0.08	0.02	−0.04	−0.02	−0.01	0.02	0.001	−0.03	−0.01
(2). Baseline Drinking			0.39**	0.02	0.06	0.17	−0.18	0.02	−0.05	0.05	−0.02	−0.05	0.11	0.02	0.11	−0.04	−0.03	−0.10	−0.05	0.03	−0.06	0.05
(3). BAC				0.08	0.05	0.06	0.05	0.07	0.007	0.11	0.04	−0.06	−0.05	0.06	−0.02	−0.07	−0.03	−0.10	−0.02	0.10	−0.09	0.08
(4). SAWS					−0.004	−0.08	−0.08	0.41**	0.29**	0.32**	0.18	−0.16	0.08	0.30**	−0.001	0.19	0.15	0.15	−0.02	0.01	0.17	0.01
(5). FTND						0.59**	0.20*	0.13	0.20*	0.07	0.18	−0.14	−0.04	0.16	−0.10	0.24*	0.42**	0.20*	−0.35**	0.49**	0.28**	0.51**
(6). Baseline Smoking							0.30**	0.11	0.26*	0.13	0.28**	−0.23*	−0.15	0.25*	−0.20	0.14	0.34**	0.07	−0.44**	0.55**	0.17	0.60**
(7). CO								−0.04	0.19	0.06	0.12	−0.14	−0.14	0.13	−0.15	0.15	0.16	0.07	−0.19	0.12	0.13	0.17
(8). WSWS									0.34**	0.28**	0.38**	−0.09	−0.11	0.31**	−0.23*	0.19	0.26*	0.22*	−0.20*	0.16	0.24*	0.20*
(9). APT Breakpoint										0.70**	0.87**	−0.42**	−0.22*	0.86**	−0.52*	0.44**	0.39**	0.41**	−0.32**	0.22*	0.44**	0.27**
(10). APT O_{max}											0.58**	−0.64**	0.25*	0.92**	0.07	0.32**	0.33**	0.31**	−0.37**	0.18	0.35**	0.28**
(11). APT P_{max}												−0.35**	−0.35**	0.78**	−0.65**	0.37**	0.38**	0.33**	−0.34**	0.19	0.39**	0.27**
(12). APT Elasticity													−0.12	−0.75**	−0.15	−0.19	−0.23*	−0.14	0.47**	−0.18	−0.23*	−0.33**
(13). APT Intensity														0.07	0.90**	0.09	−0.002	0.08	−0.08	0.13	0.06	0.10
(14). APT Persistence[a]															−0.16	0.40**	0.40**	0.36**	−0.45**	0.24*	0.42**	0.36**
(15). APT Amplitude[b]																−0.09	−0.14	−0.09	−0.004	0.03	−0.11	0.01
(16). CPT Breakpoint																	0.65**	0.88**	−0.46**	0.13	0.93**	0.23*
(17). CPT O_{max}																		0.71**	−0.66**	0.33**	0.83**	0.57**
(18). CPT P_{max}																			−0.42**	0.09	0.95**	0.20
(19). CPT Elasticity																				−0.45**	−0.59**	−0.78**
(20). CPT Intensity																					0.12	0.90**
(21). CPT Persistence[a]																						0.31**
(22). CPT Amplitude[b]																						–

AUDIT, Alcohol Use Disorder Identification Test; BAC, Breadth Alcohol Concentration; SAWS, Short Alcohol Withdrawal Scale; FTND, Fagerstrom Test for Nicotine Dependence; CO, Carbon Monoxide in ppm; WSWS, Wisconsin Smoking Withdrawal Scale, Negative Affect Score; APT, Alcohol Purchase Task; CPT, Cigarette Purchase Task; [a]Persistence Factor Score; [b]Amplitude Factor Score.

*$p < 0.05$; **$p < 0.01$.

positive correlations have been reported in several studies (8, 14, 15, 37, 38), and suggest that smokers who were more dependent on nicotine have more demand for cigarettes. Notably, the correlations between cigarette demand indices (i.e., O_{max}, P_{max}, elasticity) and WSWS negative affect scores have not been previously reported. Although our participants were relatively satiated with smoking when they completed the CPT, these findings suggest that smokers' withdrawal experience was positively associated with their demand for cigarettes.

In contrast, we did not find alcohol demand indices and latent factors were correlated with alcohol-dependence measures except for the SAWS scores. Several studies have reported positive correlations, such as drinks per week (21, 38, 39), monthly binge drinking days (39), and AUDIT scores (38, 40). Although the exact reasons for this discrepancy are unclear, we speculate that two factors may be relevant. The first is that the APT used in our study is different from other studies in terms of its instruction about framing the hypothetical drinking context, which will be discussed more in the study limitations later. Briefly, our generic description of the drinking situations may be insufficient to allow participants to imagine their typical drinking scenarios (e.g., bar) thus that they could not accurately report their alcohol demand. The other possible reason might be differences between study populations. Unlike previous studies (21, 22), our participants were treatment seeking, and thus their motivation of quitting/reducing drinking and smoking may have changed how they responded in these purchase tasks. Besides the difference of motivations, our participants were more dependent on alcohol than the undergraduate samples tested previously (40)—the average AUDIT score in our sample was almost twice that of theirs. Similarly, all of our participants had a diagnosis of AUD, while only about 50% who were dependent or abusing alcohol in the study by Amlung et al. (21). Additionally, our participants were also heavy smokers and importantly, several studies found that smoking resulted in higher demand for alcohol than nonsmoking (13, 21, 22). Thus, smoking may have resulted in a higher and more uniform alcohol use demand, masking a possible linear relationship between dependence and demand. Consistent with this possibility, we did not find any relationships between alcohol demand and alcohol misuse diagnoses. Although this possibility exists, future studies evaluating this population (i.e., treatment-seeking smokers with AUD) will help address whether heavy smoking can indeed mask the relationship between alcohol dependence measures and alcohol demand indices.

The positive correlations between alcohol and cigarette demand indices suggest that those who had higher demand for alcohol tended to have higher demand for cigarettes too. This co-demand pattern is consistent with a recent study (22) which revealed the same positive correlations among a similar sample of heavy drinking smokers (but who were not seeking treatment). Moreover, by conducting hierarchical multiple regression analyses, their study found that smoking had a positive impact on the alcohol demand, but not the other way around (22). Their finding may help explain the relative higher demand for alcohol than for cigarettes among treatment-seeking smokers with AUD in the present study, because our participants were more dependent on nicotine (FTND = 5.6, CPD = 18.3) than those nontreatment seeking heavy drinking smokers (FTND = 4.4, CPD = 14.0) in their study (22)—the relatively higher level of smoking in our sample may have resulted in greater alcohol demand in an asymmetric fashion.

An important study factor that should be taken into account is the differential alcohol and smoking satiation statuses among the participants. Although our participants were instructed to complete the hypothetical purchase tasks in a general context, we cannot rule out the possibility that the reported demand patterns may have been influenced by their alcohol and smoking statuses. Previously, we speculated that the special characteristics (e.g., heavy alcohol use) may have caused the null correlations between alcohol demand and alcohol-related measures. Unlike other alcohol-related measures, alcohol withdrawal scores were correlated with alcohol demand metrics, which support the possibility that alcohol deprivation status may have indeed increased the reported demand for alcohol among our participants who experienced more alcohol withdrawal, consistent with a previous study which showed the increased cigarette demand among nicotine-deprived smokers (41). In the current study, we also found that cigarette demand metrics were positively correlated with smoking withdrawal, which suggests an increased demand for cigarettes due to smoking deprivation. However, the exact effects of alcohol deprivation on alcohol demand are more speculative with the current study design (e.g., all participants were deprived of alcohol), which can be examined in future studies that contrast the alcohol demand metrics between deprived and satiated patients with AUD.

The study has the following limitations. First, the APT and CPT were administered separately, with each having no assumption of allocating limited resources to the other. Although our findings suggested that alcohol had higher demand than cigarettes using the single-commodity tasks (i.e., APT and CPT), we do not have direct evidence that alcohol is preferred if both drugs are considered in the same context. Such relative preference between two co-used drugs can be best captured by a cross-commodity task wherein the consumption patterns for both drugs are examined simultaneously. Using the cross-commodity paradigm, researchers have found a complex interplay between cannabis and alcohol use with nontrivial proportions of the study sample (i.e., adult past-month cannabis and alcohol users) showing patterns of complementarity, substitution, and independence (42). However, in a different cross-commodity study involving marijuana and tobacco cigarettes, researchers found an independent demand pattern between these two drugs (43). These studies suggest the manipulation robustness of using the cross-commodity paradigm in substance use research to simultaneously study co-use of drugs. More importantly, this paradigm provides a better ecological validity by placing participants in a more realistic context with their access to both drugs while having limited shared resources. Future studies should consider using this cross-commodity paradigm to better capture the demand for alcohol and cigarettes among smokers with AUD, which may shed light on developing personalized treatments based on relative demand patterns between alcohol and cigarettes.

Second, to make the participants have similar contexts for the APT and CPT, the APT's instruction used the same contextual description as the CPT's, and differences in the current APT's instructions from previous studies (31) may have affected participants' ability to report their alcohol demand with ecological validity. Previous studies have generally assessed alcohol demand under contexts in which alcohol is likely to be consumed (e.g., at a bar during peak drinking times). Similarly, time parameters such as duration of access (31) and weekend vs. weekday (44) have been shown to impact alcohol demand.

Third, per protocol requirements, participants were abstinent from alcohol to have proper cognitive functionality to complete the visits, but they could smoke *ad libitum*. Thus, differences in alcohol deprivation and smoking satiation may have affected the demand for alcohol and cigarettes.

Alcohol appeared to have higher relative reinforcing efficacy than cigarettes among adult smokers with alcohol use disorder, as evidenced by their greater demand for alcohol than for cigarettes, although it is possible that acute substance status may play a role in modulating the demand for alcohol and cigarettes. A two-factor structure was identified for both alcohol and cigarette demand curves, and the differential loadings of demand indices in the current population of heavy drinking smokers and other less dependent younger samples assessed previously suggest a distinct demand pattern for smokers with AUD. As an important future direction of the present study, hierarchical multiple regressions analyses of multiple purchase tasks (21, 22) should be conducted to provide a deeper understanding of cross-substance demand for alcohol and cigarettes among treatment-seeking smokers with AUD.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Texas MD Anderson Cancer Center Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JR designed the current study and wrote the protocol. NA-D, RA, and PC designed the parent clinical study and developed its protocol. MK-H provided medical oversight for the entire study. JY provided expertise on implementing, analyzing, and interpreting the behavioral economics tasks. YC, PL, and JR wrote the first draft of the manuscript. All other authors edited the manuscript and approved the final manuscript.

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OPINION
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Imagining the Future to Reshape the Past: A Path to Combine Cue Extinction and Memory Reconsolidation With Episodic Foresight for Addiction Treatment

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INTRODUCTION

Continuous maladaptive drug-related memories that are resistant to extinction and cause drug-seeking behaviors to be triggered are known to be one of the hallmarks of drug addiction (1). These drug-related memories are salient, strong, and persistent due to chronic maladaptive consolidation processes. Due to the salient content of drug-related memories formed during drug-taking behaviors, certain stimuli (e.g., peers, locations, paraphernalia) become encoded with reward contingencies associated with drugs. As a result of this learning processing, drug-paired stimuli acquire incentive motivational properties that change them into salient cues (2). According to Pavlovian conditioning, consequent exposure to these stimuli (*Henceforth called* drug cues) activates the original memories and evokes craving. This enhanced retrieval co-occurs with the activation of limbic cortico-striatal pathways involved in reward processing (3). A serious question in addiction neuroscience is whether these memories could be actively erased/reshaped in favor of the recovery process. Different research groups suggested various treatment strategies during the last decade to modulate these memories. Here in this short opinion paper, we propose a novel framework titled "Cue-induced Retrieval and Reconsolidation with Episodic Foresight" (CIREF) that aims to combine three different cognitive interventions, i.e., cue-exposure, memory reconsolidation, and episodic future thinking, to reshape these maladaptive drug-related memories toward more adaptive memories to support addiction recovery.

MEMORY RECONSOLIDATION AND CUE EXPOSURE

Several studies revealed that when old consolidated memories are reactivated, they may become transiently liable to change their content and salient features (4, 5). This reconsolidation stage that lasts between 1 and 6 h, followed by memory reactivation (6), provides a critical time window to reduce memories' motivational and emotional salience. This "destabilization process" necessitates a subsequent period of restabilization, or *memory reconsolidation,* during which the reactivated memory could be updated, strengthened, modified, disrupted, or erased (7, 8). Some addiction researchers and clinicians hope that renewal of the drug-related memories and alteration of their

related motivational and emotional salience via memory reconsolidation could reduce the risk of relapse (9).

To begin the drug-related memory reconsolidation process, patients could be presented with drug cues that make them mentally travel back in time and retrieve the emotional experiences for further elaboration. Previously conducted trials that implemented behavioral memory reconsolidation interventions were often supplemented by extinction-enhancing pharmacological treatments such as D-cycloserine (10–12) or β-adrenergic antagonists like Propranolol (13, 14) and have shown to be impactful in terms of drug cue reactivity extinction (15–17). Positive results in the extinction of drug cue reactivity are suggested to be highly dependent on the efficiency of reactivating maladaptive drug memories (18, 19), and that comes as no surprise that drug cue-exposure seems like a promising strategy for aiding retrieval and reactivation of such memories.

In the experimental context of addiction research, *drug cue-exposure,* in which the drug-related cues are repeatedly presented in the absence of reinforcement (20), is supposed to reduce drug saliency cues. In the clinical context, Cue-Exposure Therapies (CET) for addiction recovery have been developed to extinguish the conditioned craving-provoking effects of drug cues using extinction procedures (21).

At the same time, despite the promising findings of experimental trials that utilized CET and memory reconsolidation paradigms for addiction treatment, mixed results have been obtained regarding the efficacy of these approaches in terms of craving, relapse rate, and the number of abstinent days in the actual treatment setting (22–24). More recently, skeptical arguments have questioned the efficacy as well as the assumption underlying CET trials—which is drug cue extinction in the lab settings could be translated to a reduction of cue-reactivity in real-life settings, leading to lessened problematic drug use—questioning the efficacy and the ecological validity of CET for drug addiction (25). Moreover, a guided approach that leads to opting for healthier "alternatives" is lacking through learning to react to drug-cues in a neutral way (i.e., CET's ideal outcome) and modifying persistent maladaptive drug-related memories (i.e., memory reconsolidation's ideal outcome). Therefore, this shortcoming raises the need for a rigorous, multi-faceted add-on to these approaches to target not only the past and present-oriented aspects of cognitive processing of drug-related memories but also implement a tool for choosing healthier alternatives in response to drug-cues and the reactivation of drug-related memories. Similarly, given the key contribution of future decision-making in four main phases of addiction (*initiation*, *progression*, *treatment-seeking*, and *recovery*), interventions that effectively target aberrant decision-making and ultimately effectuate foreseeing the steps leading to recovery are crucial additions to reshape those aspects of cognitive processing modified in aid of CET and memory reconsolidation prospectively (26).

In this opinion paper and for the first time, we propose a new framework as a cognitive intervention termed Cue-induced Retrieval and Reconsolidation with Episodic Foresight (CIREF) for utilizing a combination of episodic future thinking with cue-induced memory reconsolidation to confer greater benefits by adding a future-oriented cognitive training modality.

EPISODIC FUTURE THINKING: HOW COULD IT PUT EXTINCTION INTO PRACTICE?

Despite the widely conceived notion about memory and its retrospective nature over decades ago, cognitive psychologists and neuroscientists' attention has been recently drawn to the future-oriented aspect of memory. This heed was majorly inspired by Tulving's conception of episodic memory and mental time travel, highlighting the prospective facet of human memory (27, 28). Future thinking or prospection (29) has four primary steps: *simulation*, *prediction*, *intention,* and *planning*; 28), which provide the capacity to imagine and project oneself forward in time and to pre-experience personal events that might happen in the future (30–32).

EFT has become a focus of growing interest among neuroscientists and psychologists, most probably owing to its vast contributions to various cognitive functions and adaptive behaviors, such as decision-making, planning, self-control, goal-attainment, goal-directed behavior, and psychological well-being in general (33–36). Moreover, EFT has considerable implications in "implementation intentions" as a deliberate self-regulatory strategy. Pre-deciding how to implement one's goals, simulating the mental representations of probable future events related to a specific goal, and specifying the fully detailed steps leading to goal attainment take place with the aid of EFT (30, 37). Hence, the ability to elaborately simulate possible future events stands as an essential factor in the treatment of mental health issues such as addictive behaviors, given their associations with impaired value-based decision-making and goal-directed behaviors.

EFT has been recently utilized as an intervention in both clinical and non-clinical populations (38). This dynamism mainly results from evidence showing the adaptive function of the EFT, allowing individuals to simulate distant outcomes and desires (39). In other words, the ability to envision future events may result in more accurate predictions of future behaviors and outcomes by allowing one to mentally "try" various potential ways to react to upcoming situations without engaging in actual behaviors (40). Across different populations, EFT has been shown to enhance the prospective memory—remembering to do something in the future at a specific time, which comprises planning, coordinating, and executing one's intention in an appropriate time in the future; for instance, remembering to take a medicine at a specific time of the day (e.g., tomorrow at 10 a.m.) (41–45). Studies suggest that individuals with drug use or other addictive behaviors experience difficulties with prospective memory that could reduce their ability to form a memory-dependent strategy, such as forming the intention and plans to quit drug use. Hence, cognitive training interventions that target prospective memory in the context of drug addiction could be effectively implemented by rehearsing the simulation and planning self-initiated strategies within probable risky

situations to achieve intention completion and control drug-seeking behavior in these populations (46).

Another cognitive mechanism that EFT has effectively targeted in several cognitive enhancement studies in samples with addictive behaviors is intertemporal value-based decision-making—choosing between options associated with rewarding outcomes at different time points in the future (47). Numerous theories have proposed that the discounting of delayed rewards with a preference for immediate payoffs compared to greater but delayed ones (i.e., delay discounting) is impaired decision-making that contributes to the development of addictive behaviors [e.g., (48–51)]. Peters and Büchel were the first to show that engaging in EFT reduces delay discounting rates by modulating decision-making and EFT neural networks (including the anterior cingulate cortex, hippocampus, and amygdala). They further showed that these networks enable future-minded choices allowing one to opt for options that maximize future payoffs (52). Moreover, these critical insights contributed to the formation of Reinforcer Pathology Theory (RPT) (53, 54).

Simply put, RPT states that reinforcers are integrated over a temporal window, measured by delay discounting. The length of that window in part determines the relative reinforcing value of substances vs. the other positive pro-social events. Importantly, this perspective recognizes the important temporal features of these different reinforcers. Drugs are brief, immediate, intense, and reliable. At the same time, pro-social reinforcers are less intense, variable in their outcome (e.g., good, bad, or neutral day at work), and that value accrues over time and investment. When the temporal window is short, brief, intense, reliable reinforcers would have greater value. In contrast, a longer temporal window will decrease substance valuation and increase the valuation of pro-social reinforcers.

In light of these advances and seminal findings, several experimental studies and clinical trials investigated the therapeutic effects of EFT on reducing delay discounting and consequent maladaptive behaviors and reported positive health-related outcomes as a result of engaging in EFT in people with alcohol use disorder, overweight, obese and prediabetic individuals, cigarette smokers, cannabis users, and people with cocaine use disorder (55–61). Moreover, EFT training for individuals with addictive behaviors is suggested to improve the efficiency of other psychosocial interventions aiming to attain emotional reappraisal and correction (62). Lastly, the repeated regeneration of episodic future thinking events has been shown to progressively increase the temporal window in those with alcohol use disorder (63). Since addictive behaviors are primarily associated with the pervasive preference of smaller immediate rewards in lieu of larger delayed ones (i.e., steep discounting), and this preference often leads to impulsive maladaptive behaviors such as drug-seeking and drug use (64), the therapeutic effects of EFT potentially arise from its ability to reduce discounting rates. The studies that implemented EFT as an intervention suggested that pre-experiencing future actions broadens one's temporal window by simulating the value of the reward and therefore facilitating the evaluation of behavior's long-term outcomes (e.g., becoming overweight resulting from excessive calorie intake, developing lung cancer resulting from smoking) (65). These findings indicate that EFT has therapeutic effects on addictive behaviors by changing the excessive discounting of the future while promoting healthy and adaptive decisions resulting in positive behavior change. Considering the aforementioned positive effects, the current paper proposes a new framework for integrating EFT with cue-induced memory reconsolidation in the context of addiction treatment.

EPISODIC FUTURE THINKING IN CUE EXPOSURE CONTEXT

As we discussed before, drug-related memories could be retrieved and reactivated as a result of drug cue-exposure. During this context, patients could be asked to imagine themselves in a hypothetical drug-related situation associated with the presented cue (e.g., being offered to use drugs, passing by a group of drug-users in a park, etc.) taking place in the future and elaborate on it in episodic details. The five stages of the CIREF intervention take place in the same order as the EFT stages and subsequent to the cue-exposure as follows:

1) **Activating Past Memories With Cue Exposure:** Patients initially become exposed to drug-related stimuli using formerly validated pictorial cues (66). This drug cue-exposure process leads to reactivation of maladaptive drug-related memories that happened in the past, which causes the patients to retrieve the drug-related memories and possibly re-experience the emotional arousal associated with them. Past memories become unstable during the reactivation stage and become ready to undergo potential modifications throughout the next stages.
2) **Simulating Future Cue Exposures:** Patients are prompted to vividly simulate a novel future event that may happen in response to drug-cue encounter in as much detail as possible and verbally describe who they are with, what they are doing (and thinking), where they exactly are, and how they feel (*Simulation* phase of EFT). Imagining the probable future events in the proposed manner would improve the ecological validity of the intervention.
3) **Predicting Response to Cue Exposure and Its Outcomes:** Subsequently, patients are asked to predict their associated emotions and behaviors in the simulated event (*Prediction* phase of EFT). As the patients verbally express their predictions, different options of how to deal with the potential drug-related situation should be predicted and vividly imagined. During this stage, patients expect both positive and negative scenarios that may happen due to being exposed to drug-related situations. The probable future behaviors and emotions (both positive and negative) undergo a *pre-appraisal* stage by the patient based on the predicted outcomes.
4) **Making Intentions in the Context of Cue Exposure:** Upon prediction of their reactions, patients are guided to replace immediate rewards that may be chosen impulsively with later self-controlled reward choices (*Intention* phase of EFT). The intention formation phase in this framework is similar to the

"goal-setting" exercises taking place in psychotherapy settings and implementation of intentions (37) in which the patient specifies the *when, where, and how* of responses leading to goal attainment.

5) **Developing Executive Plan for Adaptive Response:** Finally, the unstable retrieved drug-related memory, therefore, will be updated with memory reconsolidation strategies that are not limited to modification of the retrospective memory *per se* but also supplemented with the reconstruction of the prospective memory leading to optimal planning for the future and behaving upon it (*Planning* phase of EFT). During the planning phase, patients are guided to plan the organization of steps needed to arrive at a specific autobiographical future outcome (67).

To put it differently, while the patients undergo the CIREF cognitive intervention (multiple sessions of individual or group-based therapy meetings), the maladaptive drug-related memories become triggered by a stepwise exposure using a large database of drug-related stimuli. After exposure to each individually validated drug cue set, the patients are asked to imagine themselves in a hypothetical cue-associated drug-related situation that could be happening in the future and elaborate on it

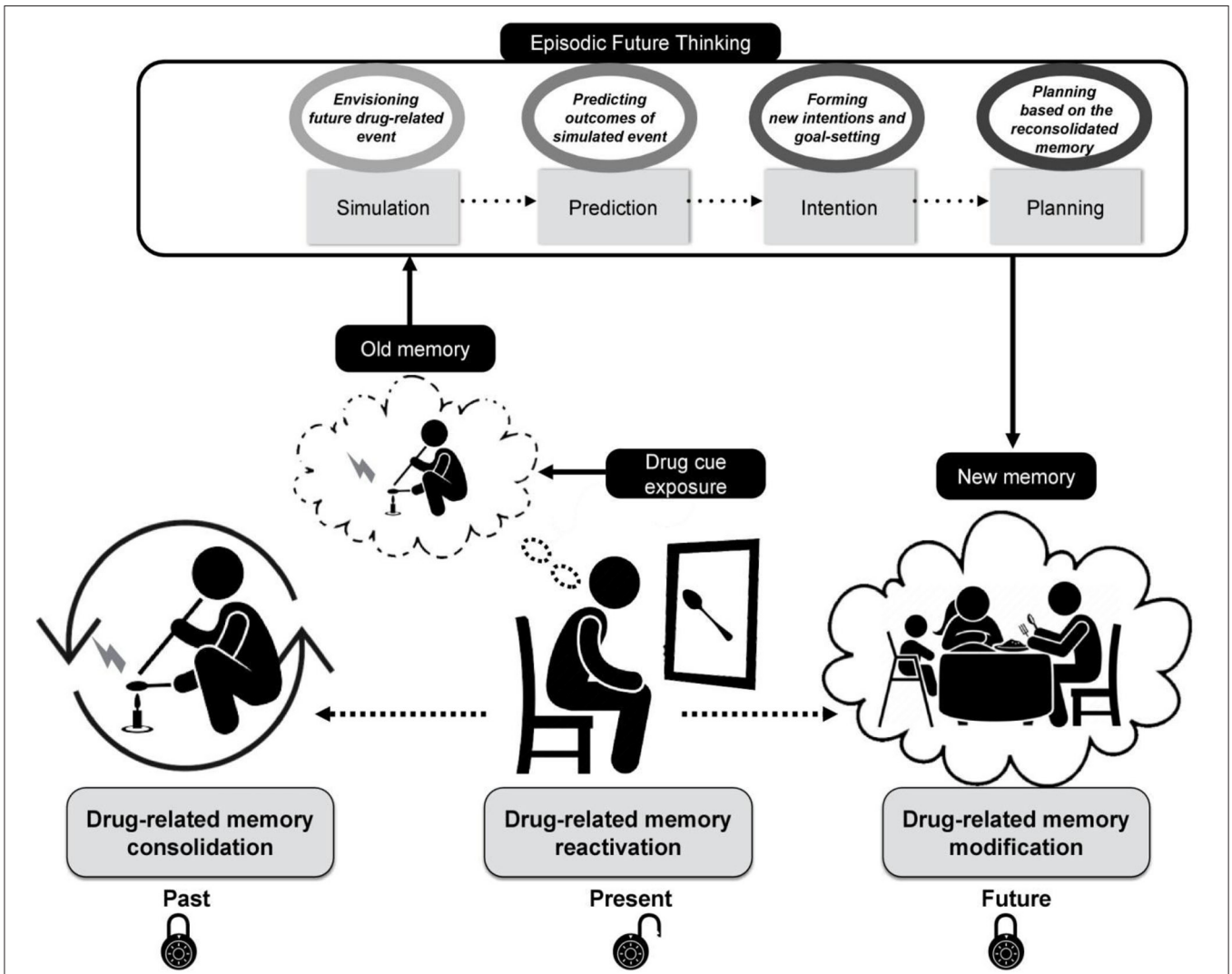

FIGURE 1 | A schematic diagram illustrating the cognitive processes underlying "Cue-induced Retrieval and Reconsolidation with Episodic Foresight (CIREF)," which applies episodic future thinking to cue-induced memory reconsolidation. The maladaptive drug-related memory that has been consolidated and stored in the past (Left) becomes reactivated as a result of drug cue exposure (Middle). The reactivated memory becomes transiently labile and prone to modification. The extinction process of maladaptive drug-related memories takes place as a result of repetitive exposure to relevant drug cues. Implementing episodic future thinking during this stage engages the person in (1) simulation of a future drug-related event, (2) prediction of emotions and reactions related to it, (3) intention of modifying the drug-seeking behavior triggered by cue exposure, and (4) planning for future actions in response to drug cue exposure maintaining healthy behavior (Top). The boxes in oval shapes depict processes underlying each stage. The reconsolidated memory is therefore updated and re-encoded in aid of episodic future thinking, and the drug cue has undergone extinction as a result of cue exposure therapy (Right).

in episodic details, mentally predicting and "trying out" different options and their outcomes and planning their future actions upon them. Then, the planned activities based on reconsolidated memories become stored as a new prospective memory guiding the patients to recall their planned intentions at some future point in time. **Figure 1** illustrates the conceptual process of the proposed framework and the implications of each stage of this approach in real-life settings.

CIREF benefits from EFT enhancement as a translatable approach in clinical settings (68) that is also necessitated by pieces of evidence showing that individuals with addictive behaviors have difficulties imagining future events and implementing intentions based on them (69–72). Moreover, the suggested framework could fill in the gaps of CET and memory reconsolidation interventions by taking a step further from classical conditioning and updating past drug-related memories by implementing goal-based strategies. Individuals struggling with addiction could develop their "future sightedness" and increase the length of their temporal window trained via EFT within this framework and consequently make healthier decisions, possibly by viewing future events as more connected to their present (73).

FUTURE DIRECTIONS AND CONCLUSION

Theoretically, two sets of clinical outcomes are expected to be accomplished at both neural and behavioral levels after individuals with addictive behaviors undergo the CIREF intervention. The first set of which are short-term outcomes comprising cue reactivity—the physiological and subjective reactions while being exposed to drug-related stimuli—and drug craving (i.e., feeling the urge to use drugs or be engaged with addictive behavior). These outcomes are expected to be immediate changes in patients' behavior after completion of the CIREF intervention and could be measured with self-report measures (e.g., craving scales and questionnaires), as well as brain imaging techniques (e.g., cue reactivity fMRI task) (74). Ideally, we are expecting that the CIREF approach would lead to some long-term outcomes as well. The long-term clinical outcomes include changes in abstinence measures, such as duration of abstinence (usually measured by biochemical validation methods like urine drug tests in the context of substance use disorders), type of abstinence (i.e., point prevalence, continuous, or prolonged), and relapse rates (75). Therefore, the clinical outcomes of the CIREF approach could be validated at multiple levels using measurements of the neural and cognitive targets (as mediators) and ultimate behavioral outcomes in future studies.

There are potential limitations to the CIREF approach. For instance, the person who is guiding the intervention (i.e., the therapist) has to be conscious of the cue-induced craving levels and ensure that the patients' cue-reactivity and craving that are triggered by the drug cue encounter and simulation (step 1 and 2 of the CIREF intervention) will be managed and mitigated effectively before the patient starts to form intentions and plan for healthier outcomes (step 4 and 5 of the CIREF intervention). A self-report assessment of craving before and after each session of the intervention and ending the session with common psychological craving management strategies (76) could potentially address this limitation as it helps the therapist to gain more control over patients' cue-elicited craving.

Furthermore, there is a thorough and in-depth protocol paper in preparation by our team of authors elaborating on each stage of the CIREF framework that provides the detailed considerations that should be taken into account while implementing each stage of this multicomponent intervention and its translational limitations.

In sum, addiction is a complex disorder that may persist due to a lack of proper integration of past memories and new learning. We propose a novel cognitive interventional framework for drug addiction titled "Cue-Induced Retrieval and Reconsolidation with Episodic Foresight (CIREF)," aiming to supplement cue-induced memory reconsolidation strategies focused on retrieval-extinction procedures with episodic future thinking for optimal results. Episodic future thinking guides patients with addictive behaviors to simulate future events that trigger cue-induced drug craving and mentally rehearse coping strategies that lead to addiction recovery. CIREF provides a multi-faceted approach for addiction treatment in light of targeting both past and future-oriented cognition affected by addiction. Further research is needed to bridge the gap between fundamental laboratory research and applied research to translate the presented framework's basic idea into an actual manualized or computerized intervention for future clinical investigations.

AUTHOR CONTRIBUTIONS

PR, TR, and HE conceived the conceptual framework of the paper. PR and TR wrote the first draft of the manuscript. HE and WB edited the manuscript and gave conceptual advice. All authors discussed the implications and commented on the final manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

GLOSSARY

Cue-exposure therapy	A behavior therapy technique in which a patient is exposed to stimuli that induce cravings for specific substances of use (e.g., alcohol) while the therapist uses other techniques to reduce or eliminate the craving and prevent their habitual response (i.e., drug use) (77, 78).
Memory reconsolidation	The active process of restabilizng a reactivated memory that has been formerly stored in long-term memory, while new information is incorporated during reconsolidation into an updated memory (8, 79).
Episodic future thinking	The mental capacity to imagine or simulate events or experiences that might occur in one's personal future to pre-experience a probable event (30, 31).
Reinforcer pathology theory	The Reinforcer Pathology theory proposes conditions that result in an excessive valuation of addictive substances/behaviors as observed in addictive disorders (e.g., drug addiction, overeating). This approach identifies and measures a process that is well-correlated with a disorder or disease, followed by interventions designed to change that disease-correlated process and assess its effects on other aspects of the disorder (53, 80).
Incentive salience theory	The Incentive Salience Theory of addiction suggests that addiction is caused primarily by drug-induced sensitization in the brain mesocorticolimbic pathways that attribute incentive salience to reward-associated stimuli. This theory proposes that sensitization of the neural systems responsible for incentive salience (drug wanting) can occur independently of changes in neural systems that mediate the subjective pleasurable effects of drugs (drug "liking") (81, 82).
Delay discounting	The decrease in the present subjective value of a reward as the delay to its receipt increases. Delay discounting is a commonly used behavioral measure of impulsive decision making (83, 84).
Implementation intentions	Implementation intentions are if-then plans specifying when, where, and how the person will set their actions into motion that spell out in advance how one wants to reach a goal (85).

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ORIGINAL RESEARCH
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An Effective and Safe Novel Treatment of Opioid Use Disorder: Unilateral Transcranial Photobiomodulation

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Background: The opioid epidemic is a global tragedy even with current treatments, and a novel, safe, and effective treatment would be welcomed. We report here our findings from our second randomized controlled trial to evaluate unilateral transcranial photobiomodulation as a treatment for opioid use disorder.

Methods: We enrolled 39 participants with active opioid cravings at 2 sites, 19 received the active treatment which consisted of a 4-min twice weekly (every 3 or 4 days) application of a light-emitting diode at 810 nm with an irradiance of 250 mW/cm^2 and a fluence of 60 J/cm^2 to the forehead over either the left or right dorsolateral prefrontal cortex with a fluence to the brain of 2.1 J/cm^2. Twenty participants received a sham treatment with the same device with foil over the bulb. The side of the treatment was based on Dual-Brain Psychology, which posits that one hemisphere is more affected by past maltreatments and is more prone to anxiety and drug cravings that the other hemisphere. We treated the hemisphere with the more positive hemispheric emotional valence (HEV) by 2 tests for HEV.

Results: Our primary outcome was changes in pre-treatment opioid craving scale (OCS) minus baseline, and we found using a mixed model that the active group had a highly significant treatment * time benefit over the sham group, $p < 0.0001$, effect size at the last follow-up of 1.5. The active treatment benefited those not on buprenorphine as well as those not on it. The TimeLine Follow Back measure of opioid use was significantly better in the actively treated group, $p = 0.0001$, with an effect size of 0.45. We observed no adverse effects.

Conclusion: Active unilateral transcranial photobiomodulation to the brain hemisphere with the better HEV was better than sham in the reduction of opioid cravings and opioid use to a very significant degree in a RCT of 39 participants at 2 independent sites. In the active group those on buprenorphine and those not on it both had improvements in cravings over the study. No adverse responses were reported in either group. ClinicalTrials.gov Identifier: NCT04340622.

Keywords: opioid use disorder, opioid cravings, opioid use, hemispheric laterality, photobiomodulation

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INTRODUCTION

Opioid use disorder (OUD) is causing profound suffering, death, and destruction to individuals, families, and societies on a global scale. According to the National Institute on Drug Abuse (1), "The combined healthcare, crime-related, and productivity costs of tobacco, alcohol, and illicit drugs exceed $700 billion a year, but dollars only poorly approximate the devastating human cost of substance use disorders." According to the CDC, opioids were involved in 42,249 deaths in 2016, a 28% increase over 2015 and 5-fold increase since 1999 (2). The mental suffering of drug abused patients and their families, the physical health complications, the loss of productivity, and the increase in criminality are all catastrophically injurious. Current treatments are obviously not stemming the tide of this disaster and there is a pressing need for additional stand-alone or add-on treatments that are safe and efficacious.

The current evidence-based standard for the treatment for OUD is medication management using buprenorphine (typically in combination with naloxone to prevent misuse) or methadone in relatively low doses to reduce opioid cravings and withdrawal symptoms. Buprenorphine and methadone are substantially more effective than placebo in retaining people in treatment and suppressing illicit opioid use (3, 4). However, there is considerable reluctance to use this approach in some quarters, often from an inaccurate concern that one is substituting one kind of addiction for another. Knudsen et al. (5) estimated that <50% of privately funded substance use disorder treatment programs offer medication management and only about a third of patients with opioid dependence at these programs actually receive it. Further, the dropout rate is high, with estimates that up to 40–50% of patients will discontinue medication management prematurely, frequently within the first month (6–8). Hence, there is a need for effective stand-alone treatments that would be acceptable to individuals and programs that eschew medication management and add-on treatments that can enhance the retention rates and abstinence rates of medication management.

Medication management makes sense pharmacologically but it does not address the underlying psychological and neurobiological factors that place individuals at risk. A complementary or alternative strategy emerges from the work of Schiffer on "Dual-Brain Psychology" (9–12). Based on his clinical experience and on the split-brain studies (13, 14), Schiffer has theorized that, in adulthood, maltreatments, and traumas, especially from childhood, become associated as a persistent trait with one brain hemisphere, either left or right, making the mind of that side immature and prone to seeing the world through the eyes of a traumatized child, affecting the person's affects, thoughts, and behaviors, generally in a negative manner. The other hemisphere has a mental perspective that is more mature and healthier. In his clinical practice, Schiffer uses lateral visual field stimulation to bring forth these different personalities. This is easily accomplished by restricting his patients' vision with taped goggles, their hands, or a letter size envelope to either the left hemifield of the left eye or the right hemifield of the right eye, which is accompanied by enhanced activation throughout the contralateral hemisphere (15). The method and its consequences are best described in his book, Of Two Minds (9), which using transcripts from patient sessions, demonstrated that looking out of one visual field vs. the other led to remarkable changes in personality, in many of his patients, such that he could have conversations with different personalities in the same person, depending on which visual field they were looking out of. Out of one visual field the patient might see Schiffer as harsh and critical as his father had been. He might tend to be critical of himself and if he had a history of drug abuse, he would likely develop drug craving looking out of that lateral visual field, while out of the opposite lateral visual field the patient would generally see Schiffer as supportive and see himself in a positive light. His drug craving would generally be greatly diminished or eliminated. Looking out the first visual field again would usually return the patient to his negative perceptions, thoughts, and actions. Schiffer could have different lengthy conversations with each side, and he would teach the patient to try to encourage the positive side to become more dominate and to recruit that side as a co-therapist in helping the more troubled side. Other than the fact that the lateral visual fields are neurologically connected to the contralateral hemisphere, he does not have a good explanation for his observations, why simple lateral visual stimulation can within seconds alter most patients' psychological state. This effect of lateral visual field stimulation was first reported by Wittling and Schweiger (16) and Wittling and Roschmann (17).

These observations were rigorously tested and well-supported with experiments at our laboratory at McLean Hospital with fMRI (15), near infrared spectroscopy (18), rapid Transcranial Magnetic (rTMS) electroencephalograms (19), evoked potentials (20), and psychometrics (11, 12, 19). Interestingly, while hemispheric valence theories delineate the right hemisphere as the more emotional and/or the more negative (21), Schiffer et al. (18) found that in about 45% of individuals that the more immature personality was actually associated with the left hemisphere. Schiffer proposed that difference in laterality would substantially affect the efficacy of lateralized treatments for depression with rTMS, and confirmed this in two studies (22, 23).

Schiffer then proposed that selectively stimulating the hemisphere associated with the more mature personality would be beneficial in alleviating symptoms of depression, anxiety or drug craving and explored this possibility using transcranial photobiomodulation (tPBM) (24).

Photobiomodulation, formerly called low-level light/laser therapy, is a burgeoning field, which has about 1,500 PubMed citations, most in recent years (25–27). Over decades, these therapies have been used mostly to treat wound healing, musculoskeletal disorder, and gastrointestinal disorders. In 2009 Schiffer and Hamblin and associates (24) performed the first use of transcranial photobiomodulation (tPBM) for the treatment of anxiety and depression. tPBM has been shown to activate mitochondria through near infrared absorption by cytochrome-C (28, 29), increase blood flow (24), integrate and segregate brain networks (30–32), and inhibit the default mode (33). tPBM (29, 34, 35) is a newer part of the burgeoning field of photobiomodulation. tPBM has been used for cognitive enhancement (36–38), sexual disorders (39), traumatic brain injury (31, 40, 41), depression and anxiety disorders (29, 42, 43)

and is being explored for other neurological brain disorders (44–46). Zomorrodi and associates found that in volunteer participants tPBM at 810 nm induced significant EEG changes increasing the power of alpha, beta and gamma and decreasing lower frequencies in a blinded RCT. They also found evidence for improvements in neural connectivity. El Khoury reported (33) that tPBM, by MRI, inhibited the default network, and Figueiro Longo et al. (31) and associates treated patients with traumatic brain injury and found in serial DTI studies that the active group but not sham had marked improvements at 3-months in their fiber pathways, through re-myelinization. Recent work suggests that a membrane opsin, TRPV1 (47) and extracellular TGF-beta1 (48) appear to be involved in the anti-inflammatory effects of photobiomodulation.

We chose F3 or F4 in our initial study in 2009 (24) and a subsequent study (49) because we hypothesized that the dorsolateral prefrontal cortex in each hemisphere might activate a broader area of the irradiated hemisphere and evoke an experiential change. Our primary aim was to activate the hemisphere with the more positive HEV as we did with our lateral visual field test (9, 11, 12, 15, 18, 19, 22, 23). Our strong clinical results (24, 49, 50) suggest that we might have chosen well. We have not tested fp1 or fp2, which we believe might be inhibitory.

Schiffer decided to explore whether using tPBM on the forehead over the more mature hemisphere might lead to improvements in opioid use disorder patients in his private practice. His very positive findings (51) led him to lead the design and performance of an initial double-blinded randomized control trial (RCT) (49), which reported statistically significant positive results with an effect size of 0.73, showing decreased opioid cravings in a within subject design in which 17 participants received an active or a sham treatment at week 1 and the opposite treatment at week 2.

The aim of the present study was to assess in a two-center RCT whether there would be a greater reduction in opioid craving over 4-weeks of twice weekly treatments with active vs. sham tPBM, and to compare the degree of efficacy in participants receiving or not receiving medication management. The primary outcome measure selected *a priori* were ratings on the opioid craving scale and the expectation was that there would be a reduction in opioid cravings of at least 60% in the active group vs. about a 20% decrease in the sham treatment group. We decided to examine opioid use during the study, even though active use was not a requirement for enrollment.

MATERIALS AND METHODS

Setting and Enrollment

This two site RCT took place at MindLight, LLC and in the Developmental Biopsychiatry Research Program at McLean Hospital, Harvard Medical School. The study was approved by the New England Regional IRB (now WCG IRB) and registered at clinicaltrials.gov, Identifier: NCT04340622. All participants provided informed written consent, The main inclusion criteria were a current or recent active opioid use disorder (OUD) diagnosis and current craving for opioids with ratings of at least 4 on the 10-point opioid craving scale (52) and age between 18 and 70 years. Exclusion criteria included past history of a psychotic disorder, violent behavior, past suicide gesture or attempt, current suicidal ideation, neurological disorders, pregnancy, or an inability to understand the consent process. Participants were screened, recruited and assessed independently at the two sites.

Treatment

Each participant was given twice weekly 4-min treatments with either the active unilateral tPBM or its sham. For the active treatment we used a light-emitting diode (LED) at 810 nm with a HWFH of 40 nm (Marubeni America Corporation, 3945 Freedom Circle, Suite 1000, Santa Clara, CA 95054) which when applied to the skin had an irradiance of 250 mW/cm^2. Our device is a prototype for which a Pre-submission has been submitted to the FDA. It can be replicated by an engineer using the Marubeni 810 nm LED and heat sink, a computer fan, and power supply. We are working with Vivonics, Inc., Bedford, MA to design and develop a commercially available device based on our prototype as discussed in the conflicts of interest section.

The treatment consisted of exposure to the light for 4-min at one of 2 sites on the forehead that correspond to the 10–20 EEG sites, F3, and F4, with a fluence of 60 J/cm^2. Based on a penetration of 3.7% of the light to the dura (53), we applied 2.1 J/cm^2 (with an irradiance of about 9 mW/cm^2) to the treated area of the brain. Our level of light exposure is well below the ANSI RP-27 standard of 0.32 W/cm^2. Barolet et al. (54) wrote, "Fluences in the range of tens of J/cm^2 are likely to be protective and overall beneficial to the skin, while fluences in the range of hundreds of J/cm^2 are likely to be damaging and overall deleterious to the skin. The same would apply for irradiance parameters." The delivered fluence of our device to the skin is about 25% less than the device that was used in the study of 1,410 stroke patients without any observed side-effects. A safety study in rats showed that exposure to higher intensities (e.g., 10 X optimal) resulted in no discernible neurological deficits or evidence of histopathological damage at light or electron microscopy levels (55).

The sham treatment was identical to the active treatment except that the LED was covered with aluminum foil to prevent near infrared photons, but not warmth, from reaching the brain. The devices were cooled with a heat sink and a computer fan. The treating clinician applied the light to the participant in a manner that did not allow either the recording research assistant or the participant to see if the device was active or sham.

Measures

The primary outcome measure was ratings of craving on the opioid craving scale (OCS) (52). The scale consists of three questions scored from 0 to 9 and averaged to provide a composite score. The Timeline Followback (56, 57) calendar method was used to determine the days, type, and amount of drug use during the preceding week. Drug use was also assessed by urine drug screen (CLIA Waived Inc. Instant Drug Test Cup II) at each visit. Ratings of depression and anxiety were assessed each week using the Hamilton Depression Rating Scale and

TABLE 1 | Demographic information for participants.

	N	Gender	Ethnicity	Age	Handedness	Grade	ACE	Employment	Buprenorphine
MindLight									
Active	13	2 f, 11 m	5 b, 8 w	44 ± 8.7	4 l, 9 r	12 ± 3.0	4.8 ± 2.6	3 y, 10 n	7 n, 6 y
Sham	11	1 f, 10 m	6 b, 5 w	46 ± 12.0	2 l, 9 r	18 ± 15.1	4.7 ± 3.2	4 y, 7 n	10 n, 1 y
McLean									
Active	7	1 f, 6 m	3 b, 4 w	47 ± 13.8	1 l, 6 r	14 ± 1.9	4.0 ± 2.0	1 y, 6 n	5 n, 2 y
Sham	8	4 f, 4 m	2 b, 6 w	44 ± 14.8	1 l, 7 r	13 ± 2.1	4.8 ± 2.3	4 y, 4 n	3 n, 5 y

The groups were formed by randomization at the 2 sites and are not exactly matched, but by mixed model analysis none of these demographic parameters were significant enough to be included as predictors in the model. Age, Grade, and ACE scores are mean ± SD. f, female; m, male; b, black; w, white.

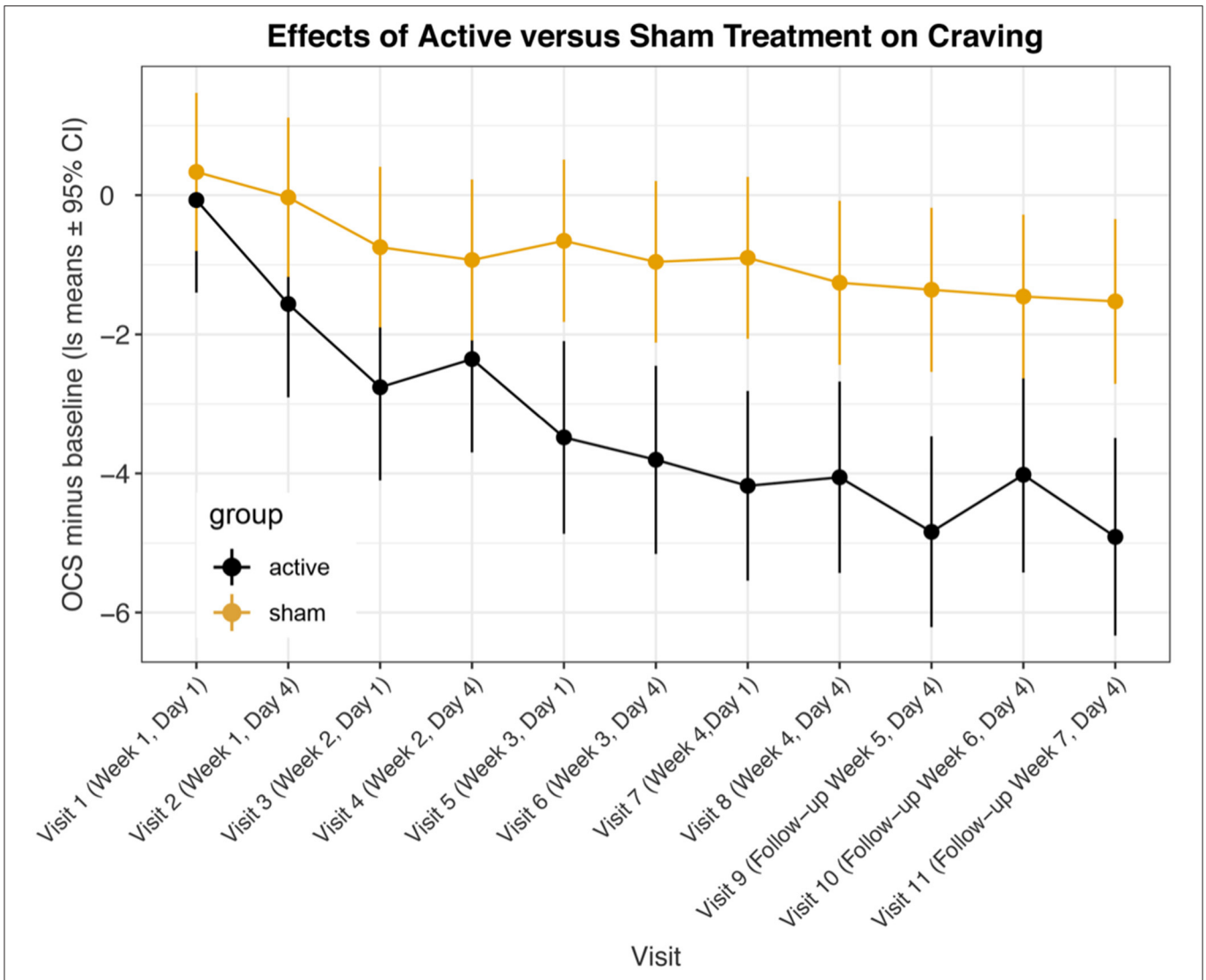

FIGURE 1 | Least square means for opioid craving scores minus baseline from mixed model comparing active vs. sham treatments across visits. Data are means ± 95% confidence intervals.

the Hamilton Anxiety Scale (58, 59). An abbreviated Positive and Negative Affect Scale (PANAS) (60) and a Wellness and Distress 10-point scale, of our design, were also used to provide affect and well-being measures before and after each treatment. Two tests were used to determine which hemisphere had the more positive affect. The first was a lateral visual field test in

which participants partially blocked their vision so that they could see out of only their right lateral or left lateral hemi visual field at a time while viewing photographs of an angry man and rating their levels of anxiety and opioid craving. This test takes 1 min. The second test was a 2.5 min computer test for hemispheric emotional valence (CTHEV), which presented images of angry men to one visual field and then the other while participants rated their emotional response. The hemisphere contralateral to the visual field with the lowest ratings of anxiety and cravings was designated as the more positive hemisphere, and this is the hemisphere to which the active or sham tPBM was applied.

Sequence of Events

Participants were phone screened for eligibility. Those who appeared eligible were invited to the laboratory, had the study fully described, signed an informed consent agreement, participated in an assessment of their psychiatric, medical and drug use history and were then randomize to active or sham treatment groups.

Each participant then moved into the 4-week treatment phase in which they received two treatments each week spaced 3 or 4 days apart. The visit began with a urine drug screen for all participants and a pregnancy test for females. This was followed by pre-treatment assessments consisting of drug use determination via Timeline Followback, Hamilton Depression and Anxiety ratings, the OCS, PANAS, Wellbeing/Distress Scale, the Lateral Visual Field Test and the CTHEV. Participants then received 4-min of active or sham tPBM directed into the more positive hemisphere at frontal positions F3 or F4. This was then followed by an immediate post-treatment evaluation phase during which time the OCS, PANAS, Wellbeing/Distress Scale, Lateral Visual Field Test and the CTHEV were repeated.

Three post-treatment visits spaced 1 week apart then followed the treatment phase. Each visit consisted of a urine drug screen, Timeline Followback, Hamilton Depression and Anxiety ratings, OCS, PANAS, Wellbeing/Distress Scale, Lateral Visual Field Test and CTHEV.

Statistical Approaches

The statistical analyses were conducted using JMP 15.2.1 (61) or R 4.0.3 (62). Our primary measure of craving was the OCS score minus the baseline score. This was chosen because the raw OCS scores were not normally distributed and when transformed by subtracting the baseline, the distributions became normal. Secondly, we felt that the OCS minus the baseline score directly measured the change in OCS that was due to the treatments. For these measures we used mixed models with OCS-baseline as the dependent variable and for the repeated measures correlations we used either a first order autoregressive (AR1) or first or second order autoregressive moving average (ARMA1, ARMA2) covariance structures. We included random intercepts and slope for treatment, site and participants. For fixed effects we first entered a full factorial model that included treatment, time, study site and buprenorphine. We also included covariates for gender, ethnicity, employment, ACE trauma score and handedness following the European guideline on adjustment for baseline covariates in clinical trials (63). We selected the best-fitting parsimonious model by sequentially removing factors that had a $p > 0.05$ and whose removal did not significantly worsen overall fit. From the final model we had a least square mean for Treatment (active vs. sham) and for Treatment * Time. We found that for all of our other outcome measures the raw data were not normally distributed, but the transformed data, by subtracting the baseline, was, and so in all of our mixed model analyses we used the same procedures as with our OCS analyses.

RESULTS

Participants

All participants who passed the phone screen and came in for the initial interview were accepted and gave written informed consent. Most participants at MindLight were recruited from an advertisement on Craigslist, but 4 came from referrals from drug clinics. At McLean, 5 participants came from Craigslist, 4 from drug clinic referrals, 3 from Partners Rally recruitment site, and 3 through friends of participants.

TABLE 2 | Least square mean differences between participants receiving active vs. sham treatment across visits by mixed model.

Visit	Contrast	Difference	Std. error	*t* ratio	*p*-value	Lower 95%	Upper 95%	Feingold d
1	Active-sham	−0.404	0.863	−0.467	0.6406	−0.4	0.86	−0.18
2	Active-sham	−1.532	0.87	−1.76	0.0793	−1.53	0.87	−0.67
3	Active-sham	−2.012	0.873	−2.305	0.0218	−2.01	0.87	−0.88
4	Active-sham	−1.424	0.875	−1.627	0.1048	−1.42	0.88	−0.62
5	Active-sham	−2.827	0.893	−3.164	0.0017	−2.83	0.89	−1.24
6	Active-sham	−2.845	0.88	−3.234	0.0013	−2.84	0.88	−1.24
7	Active-sham	−3.278	0.885	−3.703	0.0003	−3.28	0.89	−1.43
8	Active-sham	−2.797	0.895	−3.124	0.0019	−2.8	0.90	−1.22
9	Active-sham	−3.48	0.893	−3.896	0.0001	−3.48	0.89	−1.52
10	Active-sham	−2.563	0.905	−2.831	0.0049	−2.56	0.91	−1.12
11	Active-sham	−3.384	0.913	−3.709	0.0002	−3.38	0.91	−1.48

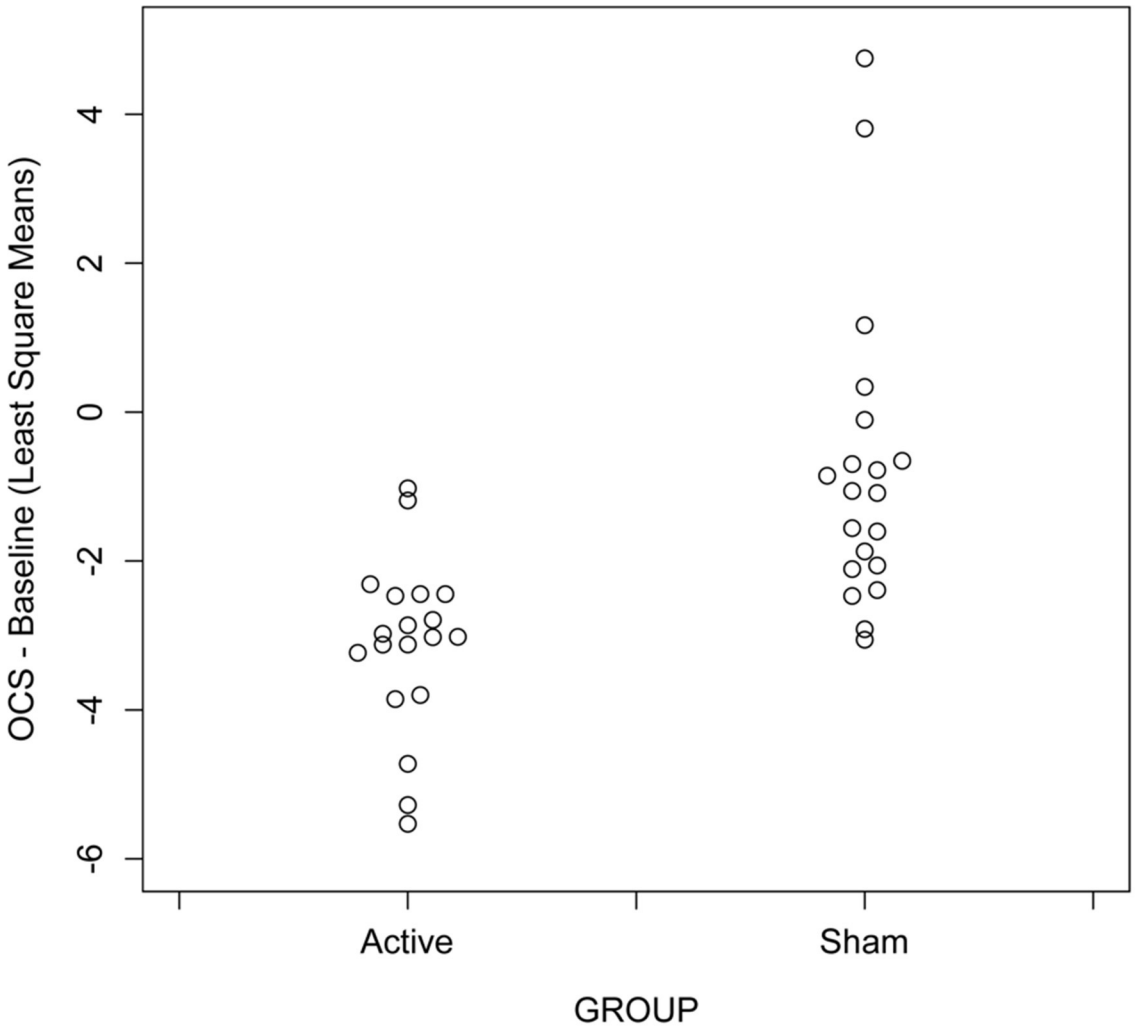

FIGURE 2 | Scatter plots showing differences across visit in opioid craving scores in participants receiving active vs. sham treatment with unilateral transcranial photobiomodulation from mixed model analysis, $N = 39$ with 20 actives.

The participants' demographic information is presented in **Table 1**.

The groups were formed on a first come basis by randomization (by random numbers) at the 2 sites and are not exactly matched, but by mixed model analysis none of these demographic parameters were significant enough to be included as predictors in the model.

Cravings

Our primary outcome was the response of participants to the Active and Sham treatments as measured by the OCS, a 10-point, 0–9 scale.

We recorded the OCS both before and after each treatment visit. We felt that the initial OCS scores before each treatment offered the best indication of the lasting effects of the treatment and we used this as our primary outcome. **Figure 1** and **Table 2** show the mixed model results for the initial OCS score minus baseline for "treatment * time," which show that from visit 5 through visit 11 there were highly significant differences with large effect sizes for each of these visits between the active and sham groups. **Figure 2** shows that by a mixed model analysis the overall treatment effect on initial OCS score was significantly better for the active vs. sham treatment, $p = 0.0004$, effect sized = 0.77, 19 active and 20 sham. **Table 3** shows the percent improvement in cravings by a mixed model analysis. The active group had a 71% improvement in cravings form the 1st visit to the 3rd follow-up at visit 11, and the sham group had a 35% improvement. Overall, there was a 35% greater decrease in OCS scores in participants receiving active vs. sham treatment ($p = 0.005$).

In a previous randomized controlled study (49), we found that greater improvement occurred a week after treatment than immediately after, and in the present Phase I study, we found that the improvements 3 or 4 days after treatment were greater than those immediately after treatment. **Figure 3** shows a comparison of OCS—baseline ratings at MindLight $N = 24$ and McLean

TABLE 3 | Percent decrease in opioid craving score from visit 1 to 11 by mixed model analysis.

Treatment	Estimate	Std. error	DF	Lower 95%	Upper 95%
LEAST SQUARE MEANS ESTIMATES					
Active	71.30%	10.19	156	50.69%	92.0%
Sham	35.39%	8.18	160	18.26%	52.5%
Treatment	**Difference**	**Std. error**	***t* ratio**	**Prob>|t|**	**Lower 95%**	**Upper 95%**
STUDENT's t PAIRWISE DIFFERENCES						
Active-sham	35.02%	12.9	2.72	0.005	9.71%	60.3%

$N = 15$, by mixed model analysis. Including treatment site as a main and interactive effect did not improve the fit (LR Test = 13.10, 0.931) and differences between sites could have easily occurred by chance. **Figure 4** shows the results of a mixed model comparing Active v. Sham, on and off buprenorphine. As expected, in participants off buprenorphine there was a significant Treatment x Visit interaction [$F_{(11,197} = 2.14$, p = 0.019] in the mixed model. This was also true for participants on buprenorphine [$F_{(11,102)} = 1.99$, $p = 0.037$], even though only 14 participants were receiving buprenorphine, 8 Active and 6 Sham. Among the 15 active participants who completed the 3rd follow-up, the percent improvement from baseline for those ($N = 7$) on buprenorphine was 63% ± SD 0.24, and for those ($N = 8$) not on buprenorphine it was 79% ± SD 0.21, $p = 0.0001$ by 2-sided Wilcoxon test.

The full mixed models and data set are presented in the **Supplementary Materials**.

Opioid Used During the Study

Our primary measure of opioid use was the TimeLine FollowBack calendar method in which patients recalled their days and amounts of use. There were significant effects of treatment:visit [$F_{(10,292)} = 7.15$, $p < 0.0001$], visit:site [$F_{(10,292)} = 7.38$, $p < 0.0001$] and treatment:visit:site [$F_{(10,292)} = 5.28$, $p < 0.0001$]. As seen in **Figure 5** there was a substantial reduction in degree of use at the McLean site but not at MindLight. This was likely a consequence of a greater percent of participants using at baseline at McLean vs. MindLight (33 vs. 21%). Overall, there was significantly less use in the active group even though only 10 participants used opioids in the days prior to treatment, $p < 0.0001$. Feingold's d, effect size = 0.45. The second measure of Opioid Use was the days of use minus the baseline and in the active group there was an improvement from baseline of −81 days but a worsening in the sham group of +8. The statistical analysis of this parameter by a 2-sided Wilcoxon Rank Sum Test had a $p = 0.009$. The third measure of Opioid Use is the number of positive twice weekly urine screens. The active group had 8 that were positive, and the sham had 20, which by a 2-sided Wilcoxon Sign Rank Test for the positive urine screens had a $p = 0.025$.

The fourth measure of Opioid Use is retention. In both the active and sham groups at both sites the retention was very high. In the active group one patient dropped out because of a parole violation unrelated to the study. Another active participant completed 7 visits and was 2.33 at baseline and 7 at visit 2, then went to 0 cravings for 5 visits. He reported that he dropped out because of "family problems." One sham patient came for one visit and did not return. The majority of the participants enjoyed coming to the study and most of the participants in the sham group reported at the end of the study that they thought they had received the active treatment.

Symptom Ratings

Mixed model analysis of the HDRS indicated that there was a significant triple interaction between visit:treatment:suboxone [$F_{(22,292)} = 1.59$, $p = 0.049$]. As seen in **Figure 6**, two of the six sham participants on buprenorphine had extremely positive HDRS improvements. Among those not on buprenorphine there was a significant treatment:visit interaction [$F_{(11,194} = 2.06$, $p = 0.025$]. Mixed model analysis of the HARS indicated that there were no significant main or interactive effects of Site or suboxone and the visit:treatment interaction fell short of significance [$F_{(11,314)} = 1.69$, $p = 0.075$].

PANAS Scores

Ratings of positive affect on the PANAS minus baseline did not vary by visit and there was no significant main effect of treatment [$F_{(1,35)} = 2.11$, $p = 0.16$]. Similarly, ratings of negative affect on the PANAS did not vary by visit or treatment. The significant predictors were baseline score [$F_{(1,332)} = 44.10$, $p < 0.0001$] and ethnicity [$F_{(1,35)} = 6.17$, $p = 0.018$].

Wellness and Distress Scales

Ratings of Wellness minus baseline did not vary by visit or site and there was no main or interactive effect of treatment (LR test = 0.57, $p = 0.45$). On the other hand, there was a significant visit:treatment interaction on ratings of Distress minus baseline [$F_{(11,332)} = 2.61$, $p = 0.0034$] in favor of the active treatment.

DISCUSSION

The results reported here offer evidence that unilateral tPBM reduces opioid cravings and use and appears effective in our study in participants both on and off buprenorphine. These finding are consistent with our earlier RCT of unilateral tPBM for opioid cravings (49) and with its off-label use in a clinical practice (51) of OUD. We observed no side-effects, and none were reported as is usual in the literature (28, 29, 64), with one exception, in which a statistically significant, but not clinically significant, 6-point ± SD = 7 increase in diastolic blood pressure was observed over the course of an 8-week tPBM study with an N of 9 in the active group (65), compared with a decrease of 6 points ± 7 in their sham group $N = 9$.

The primary milestone was that active treatment would be associated with a 60% decrease in OCS ratings vs. a 20% decrease in the sham group. Mixed model test results (active = 71.3% ± SE 10.2% vs. sham 35.4 ± 8.2%) exceed the milestones by 11% for the active group and underestimated the response for the sham group by 15 percentage points. Still the difference in improvements in cravings for the active group over sham was highly significant

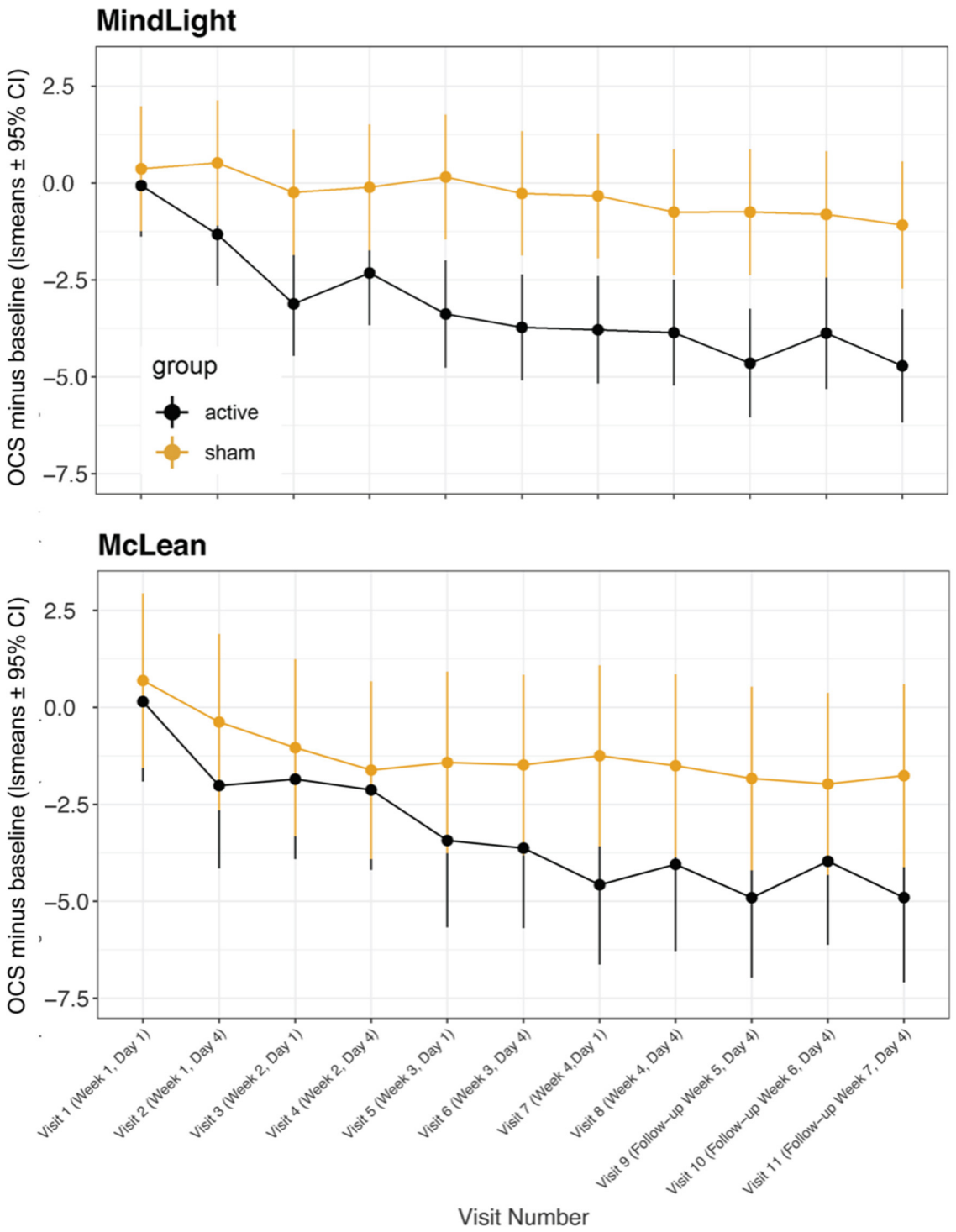

FIGURE 3 | Least square means for opioid craving scores minus baseline from mixed model comparing active vs. sham treatments across visits at MindLight site vs. McLean site. Data are means ± 95% confidence intervals. Overall, there were no significant differences between sites or significant site by visit or treatment interactions.

and had a high effect size for treatment groups by visits. The overall difference between the active and sham groups was also highly significant.

Fudala and associates (66) reported a 4-week treatment study of buprenorphine vs. placebo and from their graph it appears that there was a 40% decrease in cravings at week

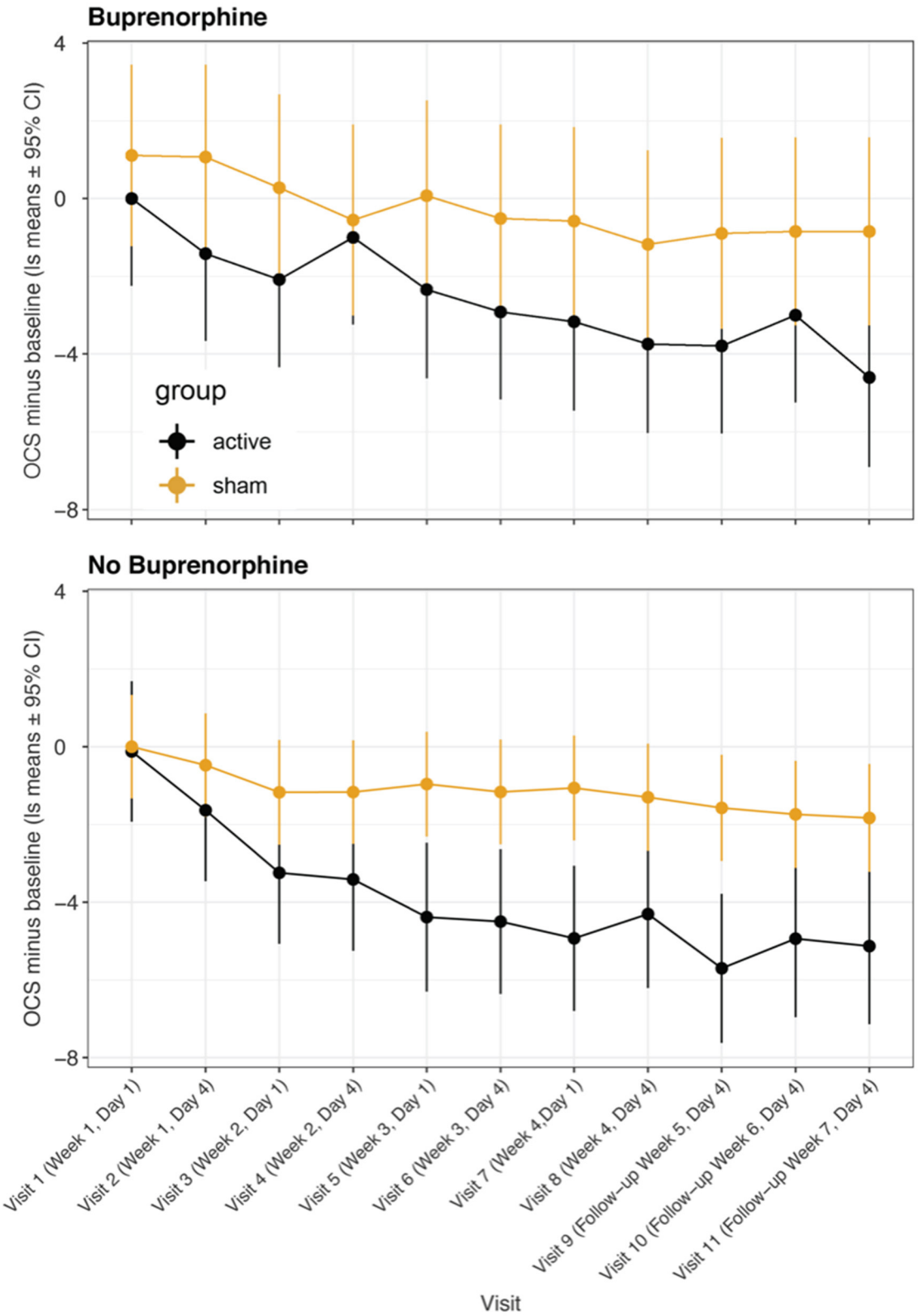

FIGURE 4 | Least square means for opioid craving scores minus baseline from mixed model comparing participants receiving buprenorphine/suboxone vs. participants not receiving medication management. Data are means ± 95% confidence intervals. A significant treatment:visit interaction was present in both groups of participants.

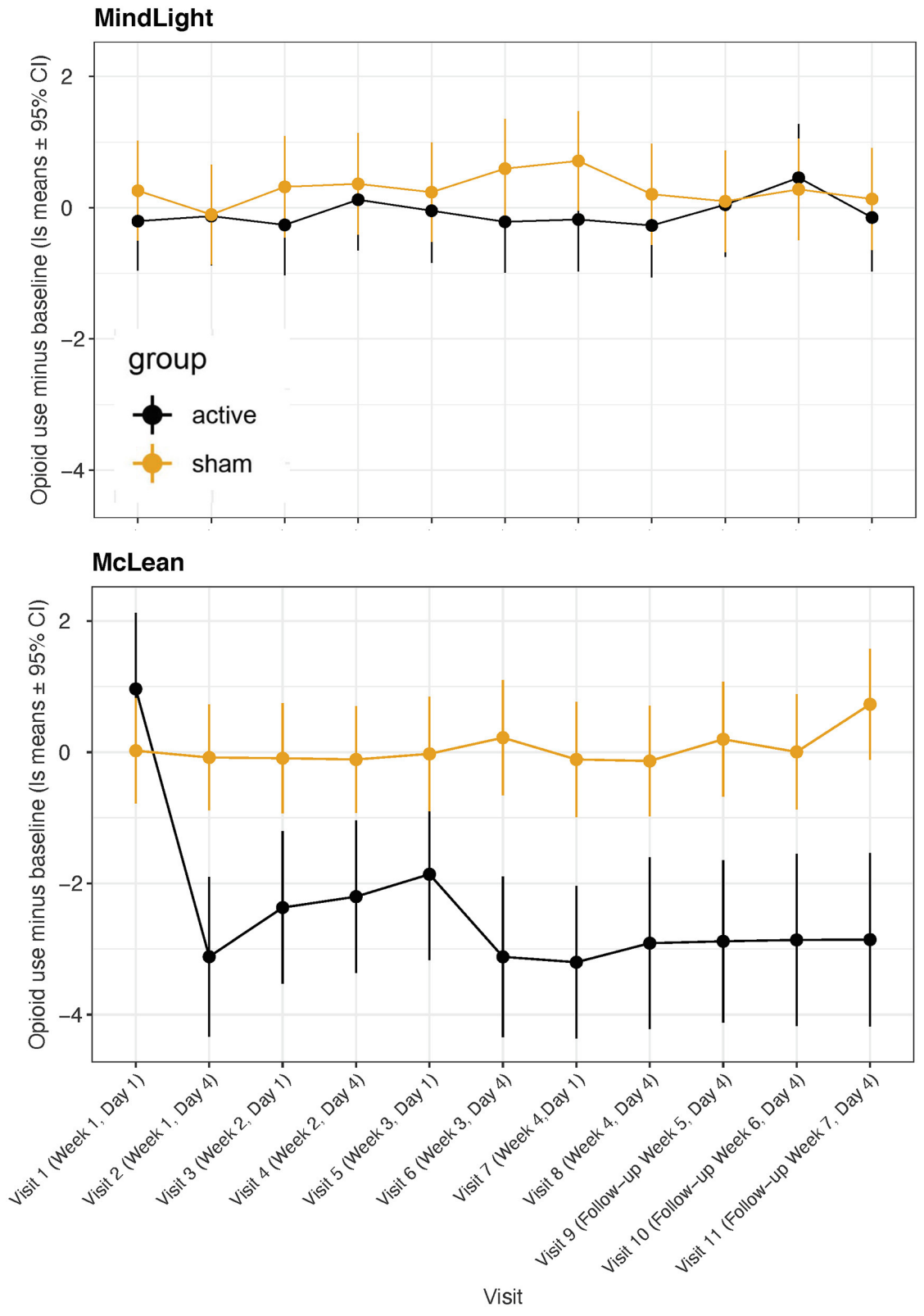

FIGURE 5 | Least square means for Opioid Use (days * amount) minus baseline from TimeLine FollowBack across visits for active vs. sham treatment at MindLight and McLean sites.

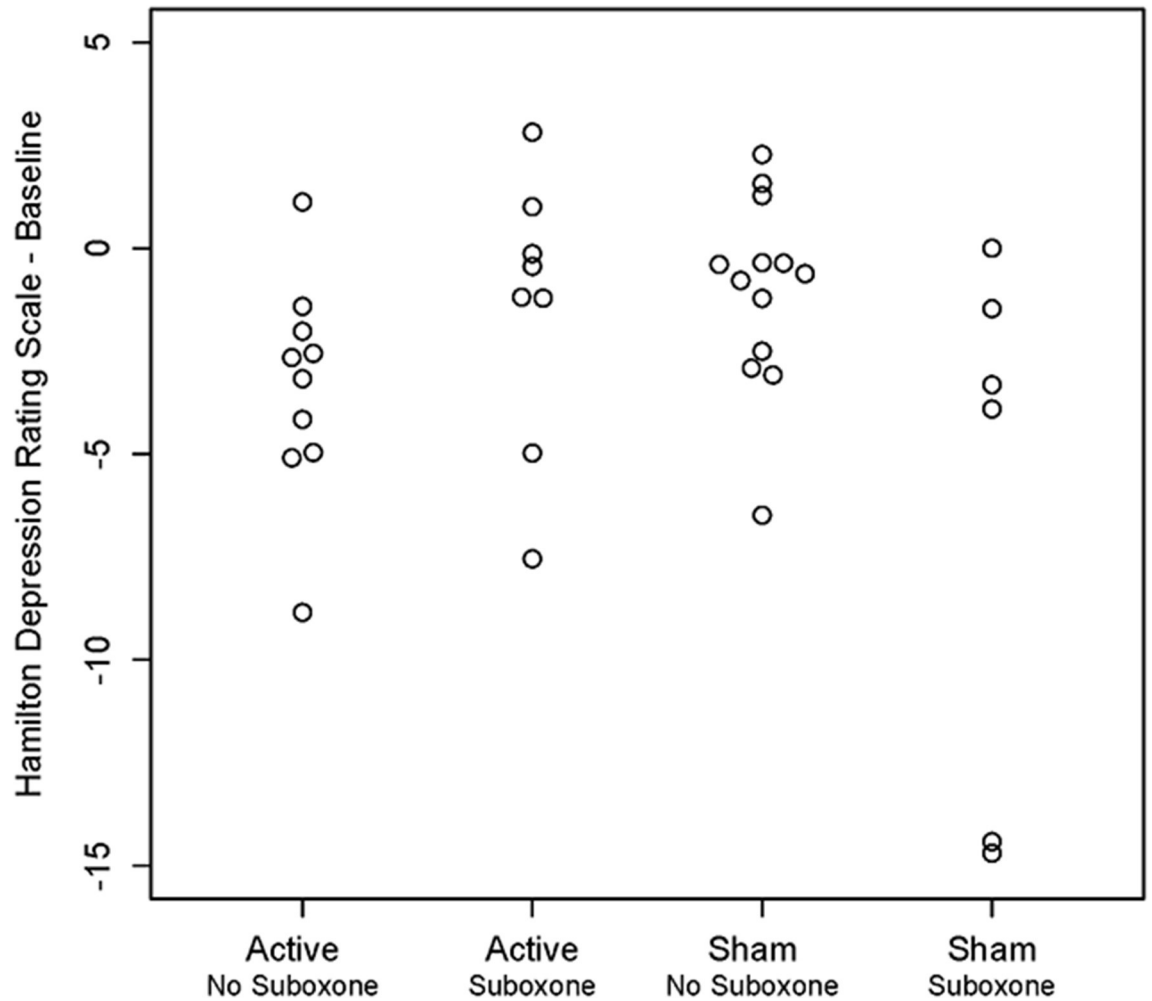

FIGURE 6 | Scatter plot showing individual results for participants on and not on medication management with buprenorphine/suboxone following active vs. sham treatment with unilateral transcranial photobiomodulation. Note unexpected reduction in Hamilton Depression Rating Scale scores in two participants on buprenorphine who received sham treatment.

4 in the active group. In the present study we found a 64% ± SD 26% decrease in cravings in our active group, pre-treatment at the second session in week 4. Their study involved 326 participants and they did not provide exact numbers nor standard deviations, so a statistical comparison between the two studies is not possible, but our results seem at least comparable to theirs. Orman et al. (67) and Hew et al. (68) in a more recent reviews of buprenorphine cite Fudala's study.

In our Aims we did not consider the impact of buprenorphine but *post-hoc* we brought up the question of whether tPBM was a stand-alone treatment or an add-on, and whether tPBM was needed because we already have a treatment for OUD, buprenorphine. Although our inclusion criteria required that the participant have 4/10 craving to be enrolled, participants were allowed to be in treatment with buprenorphine, but not required to. We found that in the active group that there was a steady decrease in cravings over the treatment period in both participants not receivieng buprenorphine ($N = 11$) and these in treatment on buprenorphine ($N = 8$), which did not differ statistically. That is our results showed that participants treated with unilateral tPBM who were on buprenorphine had a steady further reduction in cravings, down an additional 65% over the course of the study and the treatment:visit interaction was significant. Thus, unilateral tPBM appeared to reduced cravings both in those on and those not on buprenorphine. None of these patients received any psychotherapy or other intervention during the study. In private practice, Schiffer (51), reported that combining unilateral tPBM with buprenorphine and integrated with his in-depth psychotherapy was extremely effective in treating patients with OUD.

Unilateral tPBM has advantages over buprenorphine. It is a non-drug treatment and therefore has no drug side-effects or interactions, no drug withdraws, no precipitated opioid withdraws, and no diversion risk. As a non-drug treatment, it may have broader acceptance.

Our second milestone was that active tPBM would reduce opioid use by 40% more than sham treatment. Least square means for days of use were reduced from baseline by 34 and 40%. Eighty-two and ninety-two percent on visits 8–11 in the active treatment group vs. 19, 14, 13, and 1% in the sham treated group. Those in the active group not on suboxone had a significant decrease on this measure of use ($N = 11$, $p = 0.008$), but there was no improvement among those ($N = 8$, $p = 0.96$) on buprenorphine. This was probably a floor effect as only two of the eight participants on suboxone were using opioids at baseline. However, Marcovitz and associates (69) reported that about 50% of patients on buprenorphine relapse over 1 year, and it seems that buprenorphine works well when patients are taking it, but 50% drop out and likely use. Ninety percent relapse after a medical taper (69).

Our other measures for use, days of use and positive urine screens, also showed a large advantage for the actively treated unilateral tPBM patients over sham.

Psychiatric Rating Scales

Among the psychiatric rating scales there was a significant reduction in HDRS for participants not on buprenorphine and there was a treatment:visit interaction on the HARS that fell short of significance. In 2 earlier clinical trial participants showed strong positive responses on the HDRS and HARS (24, 49). There were no significant treatment:visit effects on ratings of positive or negative affect or wellness, but for distress there was a significant treatment:visit effect favoring the active treatment.

Dual-Brain Psychology

Dual-brain psychology was described briefly earlier. This theory was the basis for our using unilateral tPBM to the hemisphere with the more positive HEV, and although this work has not been widely appreciated by clinicians and the academy, this report and the many others cited earlier strongly support its premises. The theory is so different from prior neuroscience and psychological theories that focused on small integrated brain areas relating to psychological function, and more similar to current models that focus on extensive networks. However, it goes much further by suggesting that the entire hemisphere is associated with mental properties, that is a mind or a personality, that is more affected by past maltreatments and traumas while the other hemisphere becomes associated with a healthier personality. The idea that we can have two minds each associated with one hemisphere, left or right (and not having all negative attributes associated with the right hemisphere) is not within our personal experiences, but requires an in-depth psychotherapy aided by hemispheric stimulation to be made apparent. Taking this view seriously requires reassessing our entire thinking about the brain and its relation to psychological states. This study and those that preceded it including, an fMRI study (15) showing that looking out each visual field robustly activates the contralateral hemisphere are strongly supportive of the hypothesis. Another 2 studies showed that the side on which a person feels more depressed by looking out of one visual field and then another, robustly predicted subsequent outcomes to a 2-week course of rTMS at 2 sites (22, 23). A report from a private practice (51) showed that unilateral tPBM was superior to bilateral tPBM, and a sub-study within an RCT (49) showed that cravings were significantly reduced more immediately after active treatment to the positive hemisphere than the negative, but no difference was found after sham treatments. So, we feel that Dual-brain psychology was not only the basis for the conception and design of this study, but it was also affirmed by the study.

Why or how photobiomodulation or lateral visual field stimulation induces in many patients a distinct change in personality is not yet understood, except that in both treatments we seem to be stimulating one brain hemisphere (15, 19, 22, 23) and with that inducing subjective experiences that are associated with it. We consider this an important discovery which we hope will lead to studies into the processes involved. Schiffer has speculated that tPBM might affect the brain biophoton information and thereby impact subjective experiences (70, 71), but this hypothesis is just speculative and will require creative testing.

CONCLUSION

Active unilateral transcranial photobiomodulation to the brain hemisphere with the better HEV was superior to sham for the reduction of opioid cravings and opioid use to a highly significant degree in a RCT of 39 participants at 2 independent sites. In the active group those on buprenorphine and those not on it both had improvements in cravings over the course of the study. No adverse responses were reported in either treatment group.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by WCG IRB and Partners/McLean IRB (ceded). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FS and MT contributed to the design of the study. FS, MT, and WS contributed to the writing of the manuscript. EF, EB, and AK contributed to the data acquisition. All authors contributed to the article and approved the submitted version.

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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.2021.713686/full#supplementary-material

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Conflict of Interest: FS is the Founder of MindLight, LLC, which intends further research and commercialization of the methods and device described in the paper. The author has been issued 2 US patents which cover the method of unilateral tPBM to a positive hemisphere as described in this study: U.S. Patent No. 8303636, Methods for treating psychiatric disorders using light energy. Issued 11/06/2012, and U.S. Patent No. 8574279, Methods for treating psychiatric disorders using light energy. Issued 11/05/2013. He has filed on December 5, 2019 a US patent application, #16/703,937, Method and Apparatus for Determining Hemispheric Emotional Valence, and on August 3, 2020, he filed a US provisional patent application #63060177, Enhanced Treatment of Brain Disorders Utilizing Coordinated Negative Suppressive Stimulation and Related Devices Designed to Achieve Treatment.

EF and WS were employed by MindLight, LLC.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REVIEW
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The Relationship Between Alexithymia and Mobile Phone Addiction Among Mainland Chinese Students: A Meta-Analysis

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Alexithymia and mobile phone addiction are common phenomena in daily life. Many studies have explored the internal relationship between them based on different theoretical perspectives, but the extent of the exact correlation is still controversial. To address this controversy and clarify the reasons for the divergence, a meta-analysis of 26 articles comprising 23,387 Chinese students was conducted. The results show that alexithymia was highly positively correlated with mobile phone addiction ($r = 0.41$, 95% CI = [0.37, 0.45]). Furthermore, the relationship was moderated by mobile phone addiction measurement tool and year of publication, with studies using the Mobile Phone Addiction Tendency Scale (MPATS) having higher correlation coefficients than those using the Mobile Phone Addiction Index (MPAI) or other measurement tools. Studies published in 2020–2021 yielded higher correlations than those published in 2014–2016 and 2017–2019. However, the relationship was not moderated by gender, region, or measures of alexithymia. Therefore, our meta-analysis of available published data indicated that alexithymia and mobile phone addiction in Chinese students are not only highly positively correlated but also affected by mobile phone addiction measurement tools and publication year. Longitudinal studies or experimental studies should be strengthened in the future to further establish the direction(s) of causality for the relation between alexithymia and mobile phone addiction.

Keywords: alexithymia, mobile phone addiction, mainland Chinese students, meta- analysis, review

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INTRODUCTION

Globally, mobile phones have become an indispensable part of daily life. Smartphones can perform a variety of functions, such as internet surfing, e-mail management, online games and social networking (1, 2). Over the past decade, smartphone ownership has soared, especially among young people in Europe and Asia. According to the "The 47th China Statistical Report on Internet Development," as of December 2020, the number of mobile internet users of teenagers aged 10–19 has reached 136 million, accounting for 13.5% of the total number of internet users. In different occupational compositions, the proportion of students is the highest, at 21.0% (3).

Although smartphones can help teenagers with online communication, shopping, entertainment, learning and other activities and bring great convenience to their study and life, it should be noted that an increasing number of teenagers are finding it difficult to eliminate the use of mobile phones, which leads to the emergence of mobile phone addiction (MPA) (4, 5).

MPA, also known as mobile phone dependence and problematic mobile phone use, refers to the psychological dependence caused by the excessive use of smartphones, which leads to the loss of control over the use of smartphones and related services, resulting in the interference of daily life and psychological or behavioral problems (6, 7). Studies have shown that MPA can lead to headaches, earaches, changes in brain structure (8), reduced life satisfaction (9), blurred self-concept (10), reduced academic achievement (9) and other mental health problems, such as anxiety and depression (11). Unfortunately, it was reported that students were more vulnerable to MPA (12). A survey of Chinese students' MPA shows that compared to older social groups, Chinese students are usually mentally immature and have less self-regulatory ability (13). Therefore, they are more likely to use mobile phones excessively. The prevalence of MPA among students was 21.3% in China (12); for comparison, the prevalence was 20% in Spain (14), 18.5% in India (15), 10% in British (16). In addition, a recent survey of Chinese students showed that Chinese students' MPA was weakly to moderately positively correlated with anxiety, depression, impulse and sleep quality (17). Therefore, this paper takes students in mainland China as the research object to discuss the problems related to MPA, which is of great significance to the physical and mental health of students in mainland China.

Previous researchers have investigated whether self-esteem (18), loneliness (19) or lifestyle (20) are linked to MPA. As a special personality trait, the relationship between alexithymia and Chinese students' MPA has also been widely investigated (21–23). Used for the first time by Sifneos to describe certain clinical characteristics observed among psychosomatic patients, the term alexithymia refers to a multidimensional personality construct, defined by a set of four characteristics: 1) difficulty in identifying feelings and in distinguishing feelings from bodily sensations of emotional arousal, 2) difficulty in describing and in communicating feelings to others, 3) lack of fantasy and imagination, and 4) an externally oriented style of thinking (24, 25). Studies have found that alexithymia is closely related to the occurrence of negative emotions. First, adolescents with different alexithymia levels showed significant differences in depressive symptoms, with adolescents showing more depressive emotions as alexithymia symptoms increased (26). Second, alexithymia is an important predictor of anxiety, and a reduction in alexithymia can alleviate anxiety symptoms (27). In addition, there was also a significant positive correlation between alexithymia and stress. The alexithymia stress hypothesis posits that individuals with alexithymia characteristics make negative and exaggerated assessments of their environment due to inappropriate descriptions of their emotions, thus affecting their assessment of challenges and threats and ultimately putting themselves in a stressful state (28). Further studies have shown that alexithymia is a risk factor for increasing anxiety, depression and stress, which can eventually lead to mental illness (29). and even suicide risk (30, 31). The self-medication model of drug use disorder suggests that adolescents with negative emotions may improve their emotional status by using the internet or sending text messages, because it is considered to be less harmful than illegal drugs and easier to obtain (32). Finally, alexithymia plays an essential role in the etiopathogenesis of addictive disorders. For example, alexithymia has a significant positive correlation with the severity of alcohol addiction (33), eating disorders (34) and pathological gambling (35). Stratified regression analysis showed that alexithymia was an important predictor of Internet addiction (36). Another study showed that the alexithymia score of potential mobile phone addicts was significantly higher than that of the control group, and it was difficult for potential mobile phone addicts to control their mobile phone use (37). Therefore, alexithymia may not only directly affect MPA but also indirectly affect MPA in mainland Chinese students through mediating factors such as anxiety and depression.

Currently, the screening instruments for MPA mainly include the Mobile Phone Addiction Index (MPAI) (38), the Mobile Phone Addiction Tendency Scale for College Students (MPATS) (39), the Smartphone Addiction Inventory (SPAI) and its Brazilian version (SPAI-BR) (40) and the Smartphone Addiction Scale (SAS) and its short version (SAS-SV) (41). In China, the most commonly used scales for MPA are the MPAI and MPATS. The MPAI consists of 17 items and is rated on a Likert-type scale ranging from 1 ("almost none") to 5 ("always"), including four dimensions of loss of control, abstinence, avoidance and inefficiency. Higher scores indicate a more severe phone addiction. The MPATS mainly includes four dimensions: withdrawal symptoms, prominent behavior, social comfort and emotional change. The scale has 16 items and adopts a Likert 4-point system. A higher score indicates a more severe level of MPA. Similarly, the most commonly used questionnaires for alexithymia in China are the Toronto Alexithymia Scale-20 (TAS-20) (42) Alexithymia Questionnaire of College Students (AQCS) (43). The TAS-20 consists of 20 items with three factors: difficulty in identifying feelings, difficulty in describing feelings and externally oriented thinking. It was rated on a five-point scale, ranging from 1 (strongly disagree) to 5 (strongly agree), with a total score ranging from 20 to 100. All items were summed to create a composite score for each participant, with higher scores indicating higher levels of alexithymia. In traditional TAS-20 cutoffs, a total score >60 indicated that the participant had alexithymia (42). The AQCS consists of 23 questions across 4 dimensions: difficulty identifying feelings, difficulty describing feelings, difficulty analyzing feelings and difficulty experiencing feelings. This tool is rated on a 5-point rating scale with "1: very inconsistent, 5: very consistent." Higher scores indicate higher levels of alexithymia.

Evidence thus far has shown that alexithymia is associated with MPA in Chinese students. However, the strength of identified associations has varied considerably thus far, ranging from small ($r = 0.23$) (22) to large ($r = 0.57$) (21). One of the reasons for this debate is the small sample size of individual studies. Meta-analysis can compile all past studies for a much larger effective sample size to determine an overall relation between alexithymia and MPA. Noting the lack of systemic meta-analyses examining these quantitative studies on the relationship between alexithymia and MPA among Chinese students. The current study was conducted to explore the relationship between alexithymia and MPA among Chinese

students to provide evidence on the strength of the correlation between the two factors.

Moreover, the mixed results might stem from differences in the measures [of alexithymia or MPA (44)] or from demographic differences across the studies' participants (45). As most past studies did not account for moderators, this study also examines whether the relation between alexithymia and MPA differs across (a) the choice of alexithymia measure; (b) the choice of MPA measure; and (c) the demographic profile of the sample (age, gender, region).

Purpose of This Study

This study aims to synthesize the results of previous studies concerning the relation between alexithymia and MPA among Chinese students and to identify some factors that influence this relationship. Specifically, this study (a) calculates an overall effect size for the relation between alexithymia and MPA and (b) tests whether the choice of measures or demographic variables moderates this relation. These objectives were addressed using a meta-analysis, which helps to identify the source of interstudy variability and can uncover interesting associations between studies.

METHODS

The study was designed and written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (46, 47).

Literature Research

Six databases were searched for studies on the relationship between alexithymia and MPA: PubMed, Embase, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang data and Chongqing VIP Information Co., Ltd. (VIP). The retrieval time was from the establishment of the database to May 15, 2021. For English databases, the key words were ("Cell phone* OR Cellular phone* OR Cellular telephone*OR Mobile devices OR Mobile phone OR Smart phone OR Smartphone") AND ("Addiction OR Dependence OR Dependency OR Abuse OR Addicted to OR Overuse OR Problem use OR Compensatory use") OR ("Problematic smartphone use OR Problematic smartphone use OR Problematic mobile phone use OR Problematic cell phone use OR Nomophobia") AND ("Alexithymia OR Affective Symptom OR Symptom, Affective OR Symptoms, Affective OR Alexithymia OR Alexithymia OR Emotional Disturbances OR Disturbance, Emotional OR Disturbances, Emotional OR Emotional Disturbance"). For Chinese databases, the key words all Chinese, namely ("Alexithymia") AND ("Mobile phone addiction OR Problematic smartphone use"). A detailed search strategy is available in **Supplementary Material 1**. In addition, a gray literature search was performed using Google Scholar and CNKI to capture dissertations, theses that met the inclusion criteria. Publication languages were limited to English and Chinese. The reference lists of the retrieved articles were also manually checked to identify additional relevant papers.

Study Selection Criteria

All literature records were independently screened against the following selection criteria by two reviewers for potentially eligible articles: (1) cross-sectional studies offering Pearson's correlation coefficients for the associations between MPA and alexithymia; (2) the article reports sample size; (3) the sample is mainly from Chinese mainland student, excluding prisoners or sick individuals; (4) when multiple publications use the same dataset, the dataset published in the academic journal is used, but if the journal article does not use the complete dataset, the original paper analyzing the complete dataset is used; (5) conference abstracts and review articles were excluded. The selection process included reading the title, abstract and full text of the article, and 26 articles ultimately met the inclusion criteria.

Data Extraction

Data were independently extracted by two authors using a purpose-designed form. The following information was extracted: first author, year of publication, geographic location, literature type, sample size, instruments used to measure the degree of MPA, instruments used to measure alexithymia, and Pearson's correlation coefficients between MPA and alexithymia. Any disagreements were first discussed between these two authors and further disagreements were arbitrated by a third author.

Quality Assessment

The methodological quality of the included cross-sectional studies was assessed using an 11-item checklist that was recommended by the Agency for Health care Research and Quality (AHRQ) (48). The 11 evaluation items are as follows: 1) define the source of information (survey, record review); 2) list inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications; 3) indicate time period used for identifying patients; 4) indicate whether or not subjects were consecutive if not population-based; 5) indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants; 6) describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements); 7) explain any patient exclusions from analysis; 8)describe how confounding was assessed and/or controlled; 9) if applicable, explain how missing data were handled in the analysis; 10) summarize patient response rates and completeness of data collection; 11)clarify what follow-up, was expected and percentage of patients for which incomplete data or follow-up was obtained. The answer to each item was "no," "unclear," and "yes," respectively. Study quality was defined as follows: low quality (0–3 yes), moderate quality (4–7 yes), and high quality (8–11 yes). The methodological quality of all studies included was independently assessed by two researchers. A third author was consulted to resolve any differences.

Statistical Analysis

Effect sizes were calculated through the Pearson product-moment correlation coefficient (r). Since the variance depended strongly on the correlation, the r-coefficient was converted to

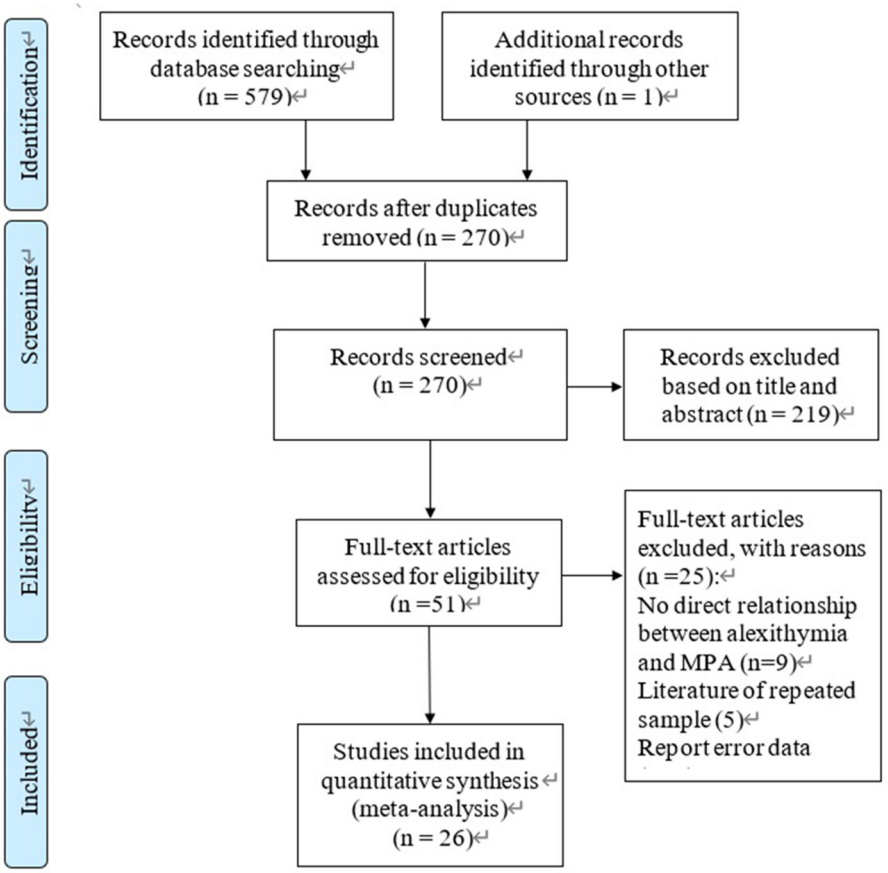

FIGURE 1 | Flow chart of the study selection process.

Fisher's z scale. The transformation from the sample correlation r to Fisher's z is given by formula (1) and the standard error is calculated by formula (2), where n is the sample size. Fisher's z statistic is assumed for normally distributed data, and the 95% confidence interval was computed as formula (3) Finally, an inverse transformation was performed to report the results on the scale of the r-coefficient through formula (4).

(1) $Fisher's\ Z = 0.5\ \chi \ln \frac{1+r}{1-r}$
(2) $S_E = \sqrt{1/(n-3)}$
(3) $95\%CI = Z \pm 1.96(SEz)$
(4) $Summary\ r = \frac{e^{2z}-1}{e^{2z}+1}$ (Z = summary Fisher's Z).

Considering that the heterogeneity of the included studies may affect the results, the random effects model was selected (49). The meta-analysis was performed with the Der-Simonian and Laird's method (50), where the weighting of sample size was introduced into the model as the inverse of variance.

To determine the heterogeneity of the effect sizes, we calculated both the Q statistic and I^2. A Q statistic tests the hypothesis that the observed variance in effect sizes is no greater than that expected by sampling error alone, while I^2 quantifies the dispersion. The I^2 statistic may be interpreted (with caution) as follows: <25, 50, and >75% indicate low, moderate and large heterogeneity, respectively (51). For categorical variables, subgroup analyses were performed to identify potential factors, such as assessment tool, age group and region, which may influence the association between alexithymia and the MPA. Q_B was used to explore the impact of categorical variables on the effect size, and $P < 0.05$ was considered statistically significant. In addition, we also conducted a meta-regression analysis of the female ratio to examine whether gender influences the relationship between MPA and alexithymia in Chinese students. Since the reference standard for the interpretation of the correlation coefficient proposed by Cohen (52) ($r = 0.1$ is low correlation, $r = 0.3$ is medium correlation and $r = 0.5$ is strong correlation) is based on qualitative analysis, it is relatively subjective. Therefore, this paper adopts the suggestions of Gignac and Szodorai (53), and $r = 0.1$, $r = 0.2$ and $r = 0.3$ represent a low correlation, medium correlation and strong correlation respectively.

To evaluate the influence of individual studies on the summary correlation coefficients and test the robustness of the correlations between MPA and alexithymia, sensitivity analyses were conducted by sequentially omitting one study each turn.

TABLE 1 | Characteristics of the 26 studies included in the meta-analysis.

References	Region	Journal	Group	*N*	Female (%)	*r*	MPA scale	Alexithymia scale
Wang (56)	Central	Dissertation	C	751	0.58	0.36	MPAI	TAS-20
Zhang (57)	Central	General	C	4,147	0.69	0.37	SQAPMPU	TAS-20
Zheng (58)	Central	General	M	742	0.43	0.54	MPAI	TAS-20
Li (59)	Central	Dissertation	C	1,105	0.52	0.33	MPAI	TAS-20
Hou et al. (60)	Central	General	C	611	0.37	0.43	MPAI	TAS-20
Chen (61)	Eastern	General	C	346	0.71	0.37	CSMPDQ	TAS-20
Wu (62)	*N*	General	C	220	0.55	0.41	CSMPDQ	TAS-20
Sun et al. (63)	Eastern	General	C	684	0.43	0.26	MPAI	TAS-20
Gao et al. (22)	Eastern	General	C	1,105	0.52	0.23	MPAI	TAS-20
Zhang (64)	Western	General	C	472	0.56	0.40	MPAI	TAS-20
Mei et al. (65)	Central	General	C	1,034	0.91	0.31	MPATS	TAS-20
Hao (66)	Eastern	Dissertation	M	1,447	0.41	0.30	MPAI	TAS-20
Xu (67)	Central	General	M	511	0.43	0.36	MPATS	AQCS
Huang et al. (68)	Central	General	C	479	0.65	0.48	MPAI	TAS-20
Chen and Shao (69)	Eastern	General	C	547	0.30	0.39	MPATS	TAS-20
Lin (70)	Eastern	Dissertation	M	453	0.47	0.56	MPATS	TAS-20
Li (71)	Central	General	M	693	0.46	0.38	MPAI	TAS-20
Hao et al. (23)	Eastern	General	C	847	0.49	0.34	MPAI	TAS-20
ARN (72)	Central	Dissertation	C	519	0.34	0.27	MPAI	TAS-20
Zhu (73)	Central	General	C	491	0.43	0.41	MPATS	AQCS
Huang and Zhao (74)	Central	General	C	1,224	0.44	0.55	MPAI	TAS-20
Yu (75)	Central	General	C	918	0.69	0.55	MPATS	TAS-20
Yuan (76)	Central	Dissertation	C	870	0.77	0.35	TMD	TAS-20
Yu (77)	Eastern	General	C	1,081	0.69	0.57	MPATS	TAS-20
Hou et al. (78)	Eastern	General	C	1,028	0.70	0.55	MPATS	TAS-20
Zhang (79)	Western	General	C	1,062	0.60	0.39	MPATS	TAS-20

C, collegestudent; M, middle school student; MPAI, Mobile phone addiction index; SQAPMPU, Self-rating Questionnaire for Adolescent Problematic Mobile Phone Use; CSMPDQ, College students mobile phone dependence questionnaire; MPATS, Mobile Phone Addiction Tendency Scale; NMP-Q, The Nomophobia Questionnaire; SAS-SV, the Smartphone Addiction Scale—Short Version; TMD, The Test of Mobile Phone Dependence; AQCS, Alexithymia Questionnaire of College Students; TAS-20, Toronto alexithymia scale; N, Not reported.

TABLE 2 | Random-model of the correlation between alexithymia and MPA.

K	*N*	Effect size (r)	95% CI for r	Homogeneity test			Test of null (two tailed)	
				Q (r)	*p*	I^2	*Z*-value	*p*
26	23,687	0.41	[0.37, 0.45]	343.65	0.00	92.7	17.38***	<0.001

****P < 0.001.*

Visual inspection of funnel plots, Egger's linear regression test (54) and the trim-and-fill test (55) were performed to help us assess publication bias. All data were analyzed using Stata 16.0.

RESULTS

Characteristics of Included Studies and Quality Assessment

The flow chart is shown in **Figure 1**. The literature search resulted in 580 studies with one study added after reviewing the gray literature. After eliminating the duplicates, 270 articles remained. There were 219 studies excluded according to titles and abstracts. Finally, the full texts of 51 articles were reviewed. We excluded 25 studies because they were either irrelevant, not correlation studies, unavailable full text, or had apparent data mistakes or reviews. As shown in **Table 1**, 26 studies ultimately met the inclusion criteria, involving a total of 23,387 participants. The sample sizes of the studies ranged from 220 to 4,147. The 11-item checklist recommended by the AHRQ was used to assess the papers. Seven studies were of high quality and 19 studies were of moderate quality (**Supplementary Material 2**).

Homogeneity Tests and Pooled Analyses

As shown in **Table 2**, the homogeneity test for 26 independent samples showed substantial heterogeneity among the selected studies (Q-statistic $= 343.65$; $p < 0.001$; $I^2 = 92.7$)

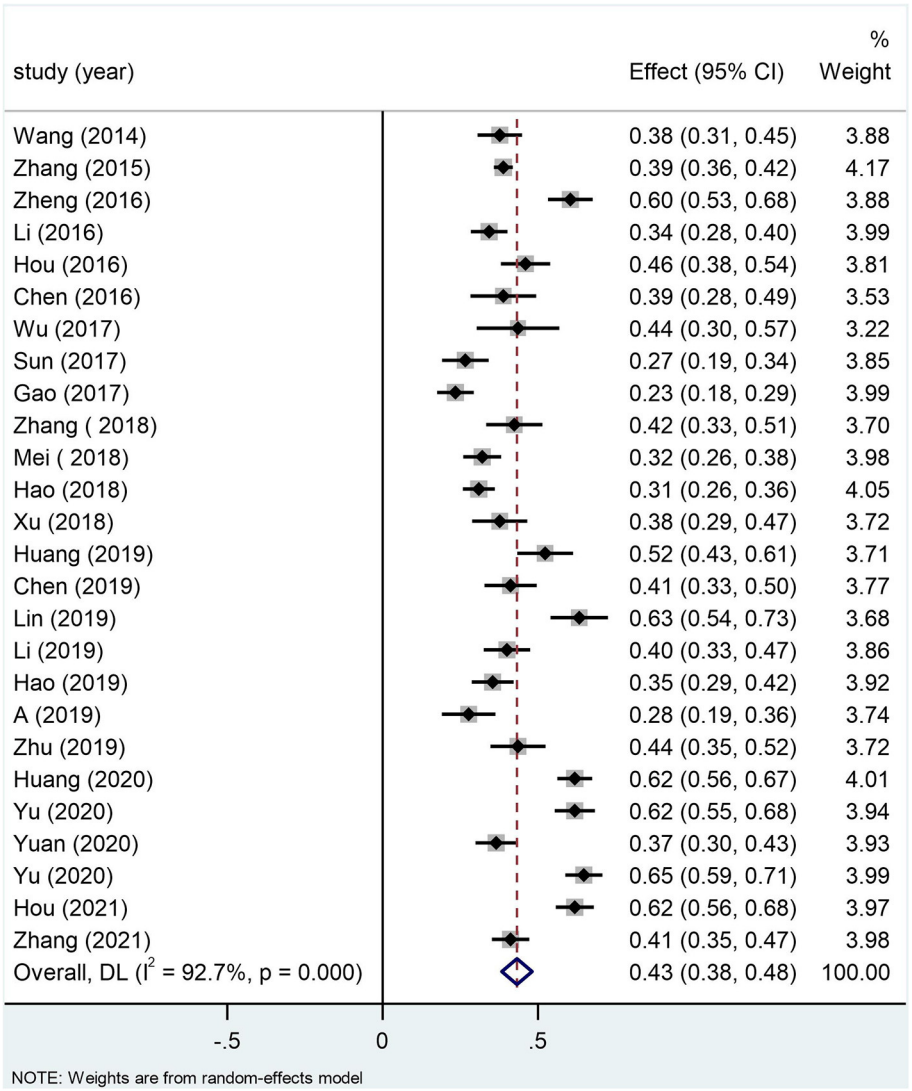

FIGURE 2 | Forest plots for the correlation between alexithymia and mobile phone addiction.

and likely moderation effects. The random effects model showed a significant correlation of 0.41 (95% CI: 0.37–0.45) between alexithymia and MPA. According to the recommendation of Gignac and Szodorai (53), correlations of 0.10, 0.20, and 0.30 are considered relatively small, typical, and relatively large. There was a relatively large positive correlation between alexithymia and MPA among Chinese students. Moreover, the correlation between alexithymia and MPA was stable, as shown by the *Z*-value of 17.38 and $p < 0.001$ (**Figure 2**).

Moderator Analysis

A meta-analysis of variance (ANOVA) test was conducted for the moderating effects of key categorical variables: alexithymia measures, MPA measures, publication year, and regional difference. In addition, meta-regression analysis tests for the moderating effects of a key continuous variables: proportion of females.

Meta-ANOVA

The meta-ANOVA showed that MPA measures, and publication year significantly moderated the relationship between alexithymia and MPA (**Table 3**).

MPA measures significantly moderated the relation between alexithymia and MPA in Chinese students (Q = 11.56, df = 2, $p < 0.05$; **Figure 3**). This positive correlation coefficient was the largest when using the MPATS (r = 0.47, 95% CI = [0.41, 0.52]), but it was relatively small when MPA was measured with the MPAI (r = 0.36, 95% CI = [0.31, 0.42]) or others (r = 0.37, 95% CI = [0.35, 0.39]).

Publication year significantly moderated the relation between alexithymia and MPA (Q = 8.66, df = 2, $p < 0.05$; **Figure 4**).

TABLE 3 | Alexithymia and MPA: univariate analysis of variance for moderator variables.

	Q_{BET}	k	*N*	r	95% CI for r	SE	Q_W	I^2
Alexithymia measures	0.48							
TAS-20		24	22,385	0.41	[0.36, 0.45]	0.27	342.37**	93.3%
ACQS		2	1,002	0.38	[0.33, 0.44]	0.32	0.86**	0.00
MPA measures	11.56*							
MPAI		12	9,991	0.36	[0.31, 0.42]	0.34	117.54**	90.6%
MPATS		10	7,813	0.47	[0.41, 0.52]	0.29	83.36**	89.2%
Others		4	5,583	0.37	[0.35, 0.39]	0.19	0.92**	0.00
Age	0.51							
College student		22	20,052	0.40	[0.35, 0.44]	0.28	280.79**	92.5%
Middle school student		4	3,335	0.45	[0.31, 0.57]	0.59	62.31**	95.2%
Publication year	8.66*							
2014–2016		6	7,702	0.40	[0.34, 0.46]	0.33	37.19**	86.6%
2017–2019		14	9,502	0.36	[0.32, 0.41]	0.30	87.08**	85.1%
2020–2021		6	6,183	0.50	[0.42, 0.57]	0.35	74.75**	93.3%
Region	0.29							
Eastern		9	7,538	0.40	[0.31, 0.49]	0.47	192.37**	95.8%
Central		14	14,095	0.41	[0.36, 0.46]	0.29	150.65**	91.4%
Western		2	1,534	0.39	[0.35, 0.43b]	0.27	0.05	0.00

*$p < 0.05$, **$p < 0.001$.

The correlation is the strongest in 2020–2021 (r = 0.50, 95% CI = [0.42, 0.57]) and smallest in 2017–2019 (r = 0.36, 95% CI = [0.32, 0.41]).

Alexithymia measures (**Figure 5**), age of the participant group (**Figure 6**) and region (**Figure 7**) all did not moderate the correlation between alexithymia and MPA.

Meta-Regression Analysis

As shown in **Table 4**, a meta-regression analysis was used to examine whether sex moderated the correlation between alexithymia and MPA among Chinese students. The results show that the link between alexithymia and MPA was not moderated by gender.

Sensitivity Analyses

To evaluate the robustness of our findings, sensitivity analyses were performed by sequentially removing one individual study each turn and then recalculating the summary correlation coefficients. Sensitivity analyses for summary correlation coefficients between MPA and alexithymia revealed minor changes, indicating that our results were stable (**Figure 8**).

Publication Bias

Judging subjectively, it was difficult to determine whether the funnel plots for the summary correlation coefficients between MPA and alexithymia were symmetric (**Figure 9**). Egger's regression showed no significant bias ($t_{26} = 0.56$, $p = 0.58$) (**Figure 10**). The trim-and-fill analysis also revealed no trimming performed and the data did not change (see **Supplementary Material 3**), indicating that no significant publication bias was detected.

DISCUSSION

To the best of our knowledge, this was the first meta-analysis exploring the pooled correlation coefficients of MPA with alexithymia among Chinese students. Our aim is to expand the existing knowledge about the relationship between MPA and alexithymia among Chinese students to provide a basis for formulating strategies to promote the physical and mental health development of Chinese students.

Relation Between Alexithymia and MPA

The meta-analysis results showed that alexithymia had a large positive correlation with MPA among Chinese students (r = 0.41). The cognitive-behavioral theory of pathological internet use holds that psychopathological status and maladjustment are important factors affecting MPA (80). In the process of real interpersonal communication, students with alexithymia often have some problems, such as low sensitivity to understand emotional changes and lack of verbal expression ability, which have a negative impact on their normal interpersonal communication (81). Smartphones have the advantages of easy access and versatility. They can not only help individuals carry out online social communication and establish virtual social relationships to meet their needs of belonging but also help individuals carry out online entertainment and recreation so that the body can become excited and temporarily relieve their inner helplessness and loneliness (82). When they choose to communicate through mobile phones, they can hide their true feelings and avoid getting along with others face to face. In this way, people with alexithymia can show a more comfortable mental state to alleviate discomfort in real communication (36, 81). This also explains that the impact of alexithymia on

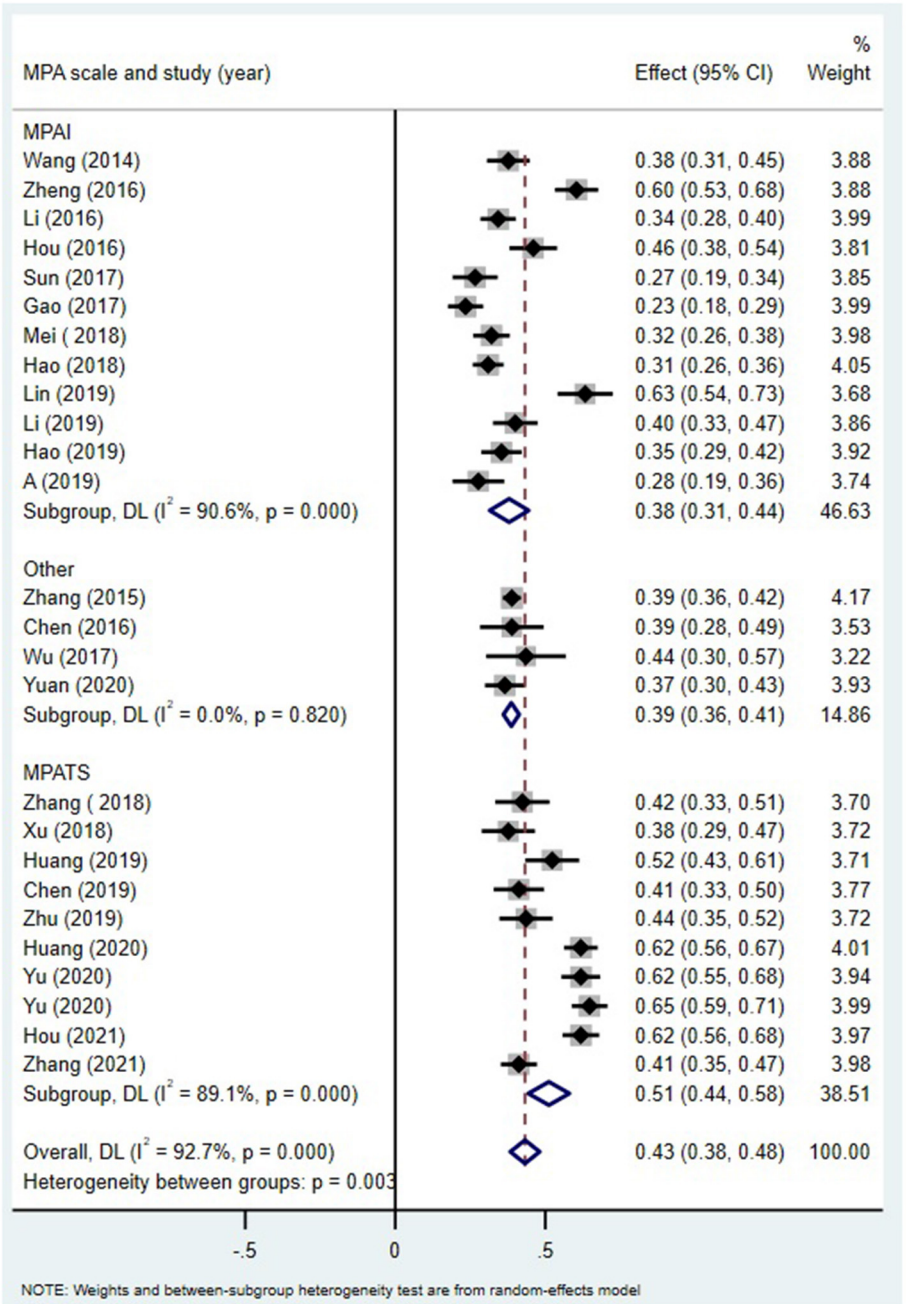

FIGURE 3 | MPA and alexithymia: an analysis of the moderating effects of the MPA measurement tool.

mobile phone dependence plays a role by making individuals pay too much attention to maintaining social relations and social comfort, because individuals with alexithymia prefer to obtain social support and comfort through mobile phones, and it is easier to regard mobile phones as the best choice instead of face-to-face communication (74). In addition, in a study with Chinese students as samples, researchers found that alexithymia not only has a direct positive impact on MPA but also has an indirect impact on MPA through depression, anxiety or stress (22). The same result was found by Lyvers et al. (83). The reason may be that alexithymia patients have defects in emotional cognitive processing and empathy (84), bad coping styles (85) and social support in understanding (86), which usually cannot deal with stress situations well, aggravating negative emotions, such as depression and anxiety. Another study on Chinese students' MPA and alexithymia also found that alexithymia can also affect MPA through self-esteem (69). Self-esteem is an individual's evaluation of self and an important

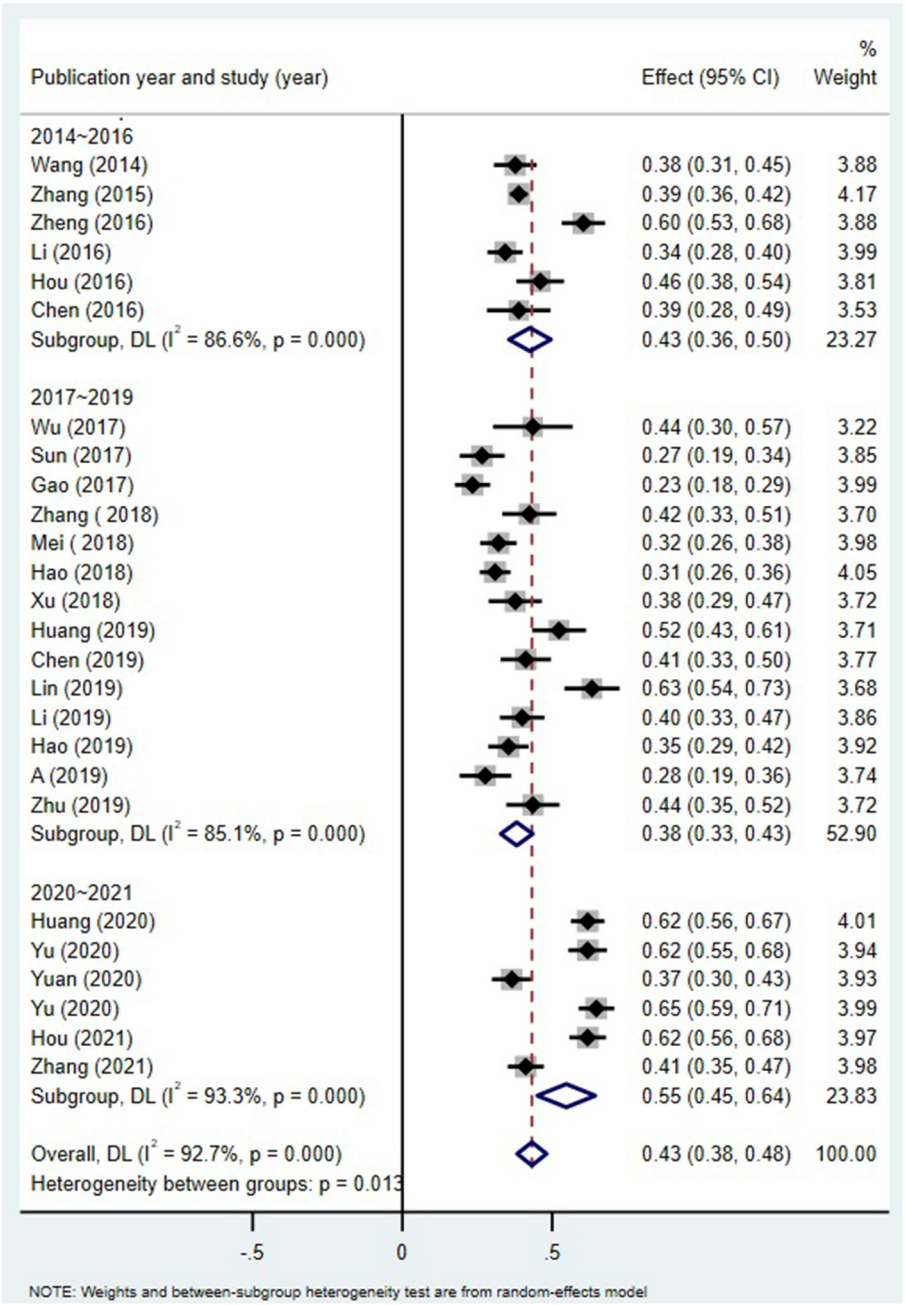

FIGURE 4 | MPA and alexithymia: an analysis of the moderating effects of publication year.

psychological resource in the structure of self-system (87). Alexithymia leads to inconsistency between individual implicit self-esteem and explicit self-esteem, prevents individual emotions from being moderated and adjusted, and induces individual MPA behavior (88).

On the other hand, MPA may also affect the level of alexithymia. According to cognitive-behavioral theory, individuals' cognitions and emotions could not only affect their behaviors but also be influenced by their own behaviors (89). Students with a high degree of MPA tend to neglect offline social communication, which reduces the time and opportunities for offline communication with friends and family and has a negative impact on the establishment of a social emotional support system. When students transfer from the internet world to the real world, they may feel more social alienation, resulting in social isolation and unwillingness to

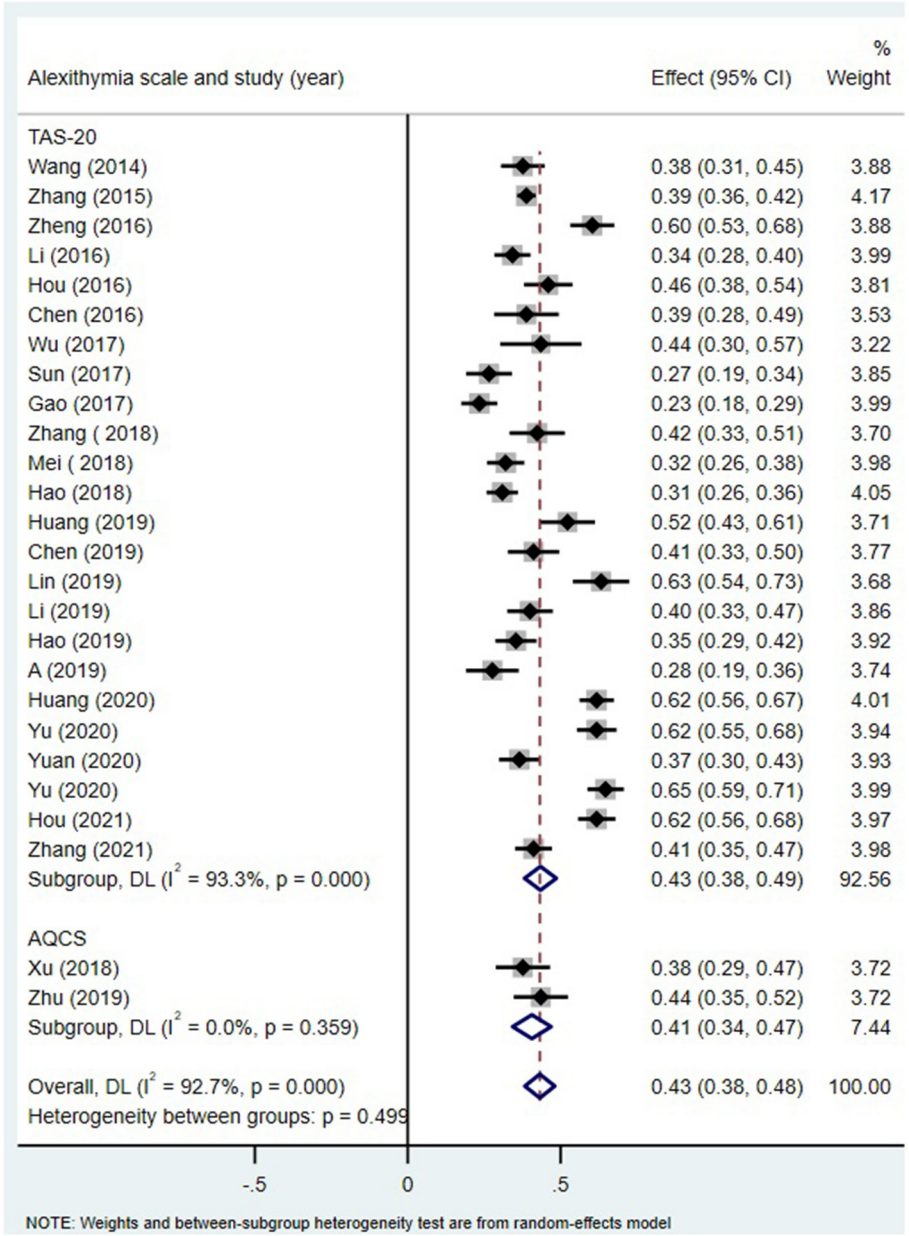

FIGURE 5 | MPA and alexithymia: an analysis of the moderating effects of the alexithymia measurement tool.

communicate with society (43, 90). Therefore, the level of alexithymia may increase.

Moderation Effects

Moderating Role of Alexithymia Measures

The analysis showed that although the research using the TAS-20 had a higher correlation between alexithymia and MPA than those using the AQCS, the difference was not significant ($Q = 0.48$, $p = 0.49$). This indicates that alexithymia measures did not moderate the correlation between alexithymia and MPA among Chinese students. On the one hand, this may be due to the stability of the correlation between alexithymia and MPA across measures, and on the other hand, it may be related to the lack of studies that used the AQCS (only two studies). Therefore, the results of this study cannot fully reflect the relationship between alexithymia and MPA under different alexithymia measurement tools. The results of this study still need to be confirmed by further studies.

Moderating Role of MPA Measures

The measure of MPA moderates the large positive correlation between alexithymia and MPA. This positive correlation is smaller when MPA is measured with MPAI and other ($r = 0.37, 0.36$) than with MAPTS measures (0.47).

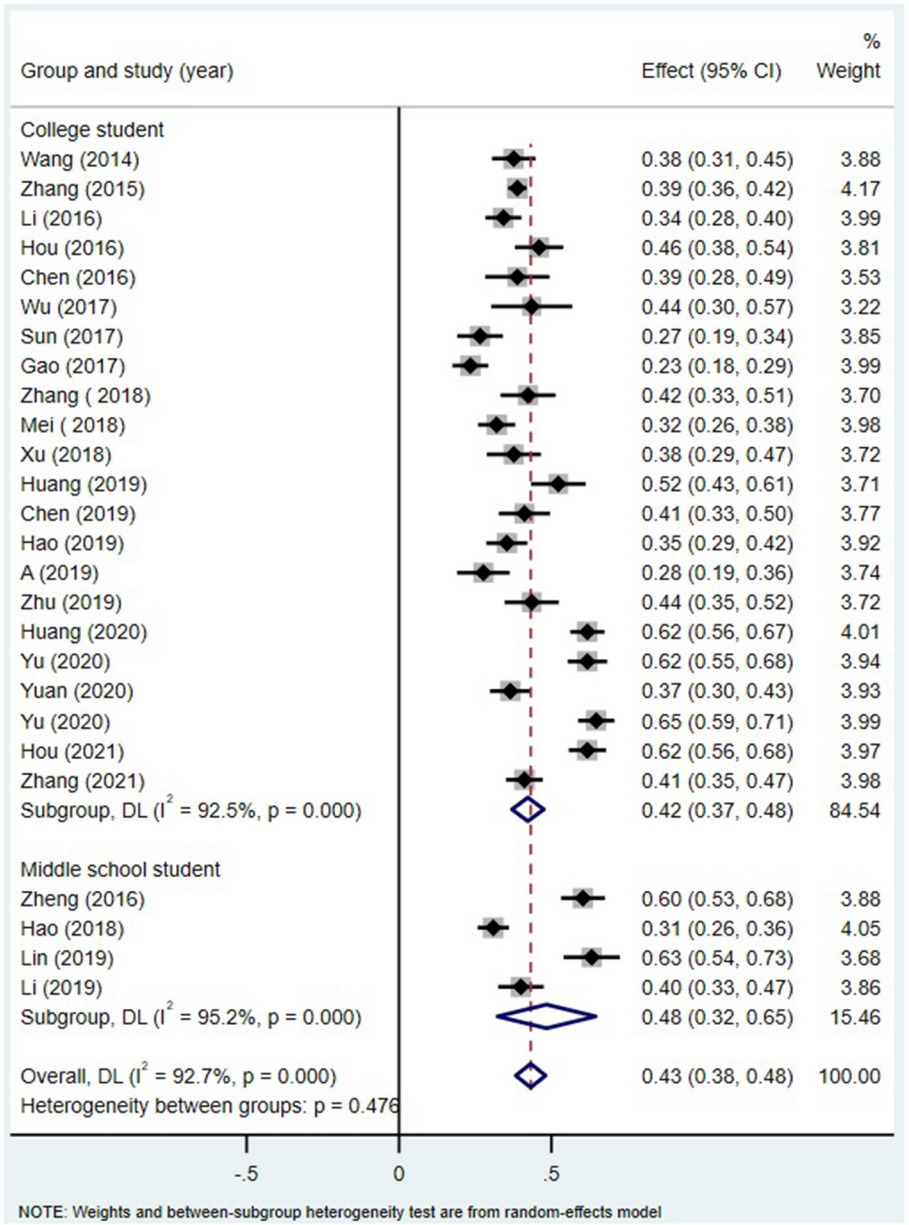

FIGURE 6 | MPA and alexithymia: an analysis of the moderating effects of age group.

Similar results were also reported in a meta-analysis of the relationship between internet addiction and social support (91). This raises the possibility that a lack of acculturation to the mainland Chinese environment may be responsible for the relatively small positive correlation results. Since MAPTS were developed for the Chinese population, they are unlikely to have this problem. In addition, because the MPA measurement tools except MPAI and MPATS are classified as other measures in this study, whether the relationship between alexithymia and MPA is moderated by other less used MPA measures still needs further exploration.

Moderating Role of Age and Gender

Age did not moderate the positive relation between alexithymia and MPA among Chinese students. On the one hand, this may be because college students and middle school students both live in similar cultural atmospheres and social environments, so external environmental factors have the same influence on them, and there is little difference in social support they have received. On the other hand, the age and psychological development level of college students and middle school students are relatively close (92). During this period, they were far away from their parents and began to face study and life alone. To avoid loneliness, they need to obtain more social support. If they cannot obtain

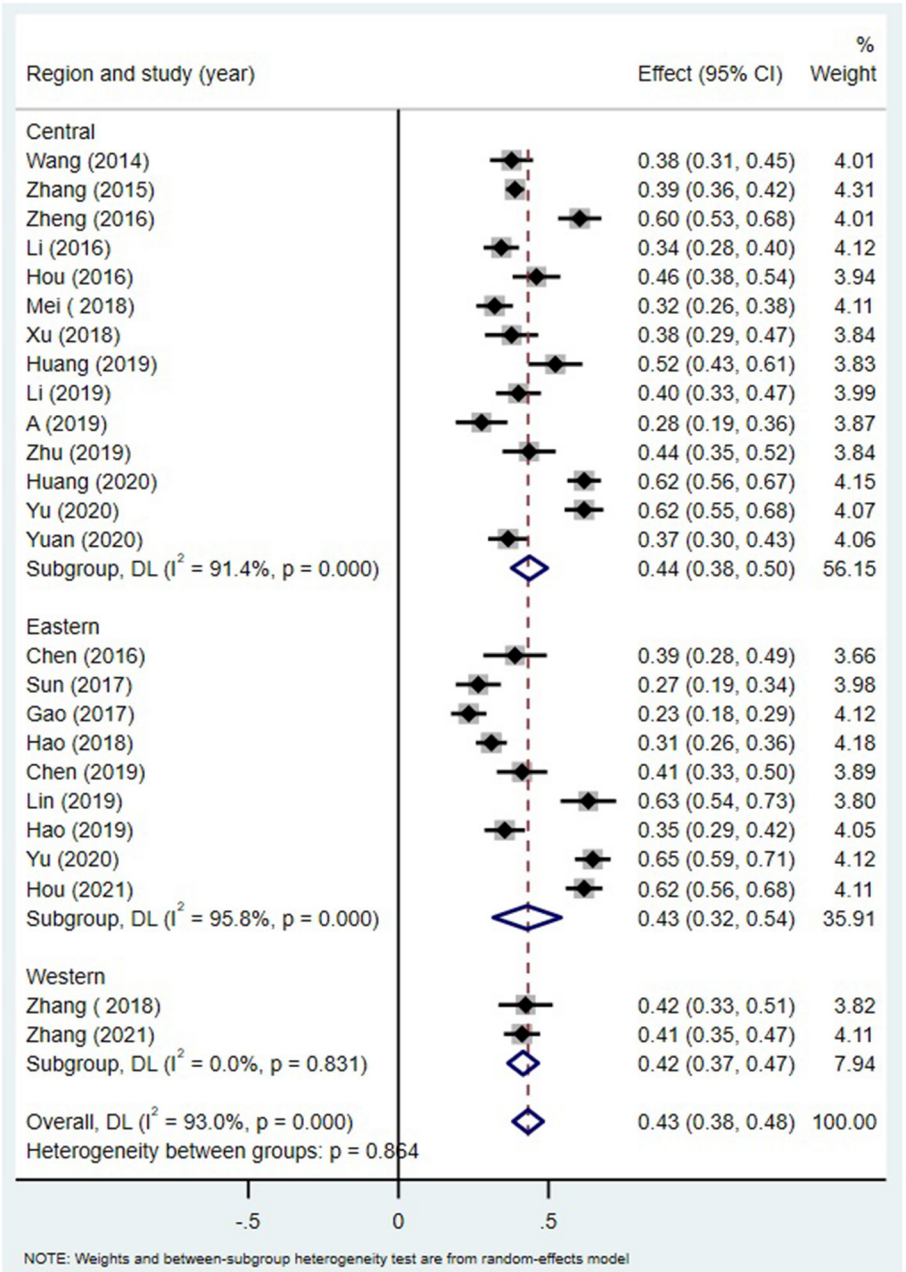

FIGURE 7 | MPA and alexithymia: an analysis of the moderating effects ofregion.

TABLE 4 | Univariate regression analysis of gender (random-effect model).

z	Coef.	SE	*t*	*P* > |t|	95% CI
Female ratio	0.11	0.17	0.62	0.54	−0.25, 0.46
_cons	0.37	0.09	3.89	0.001	0.17, 0.57

satisfaction and emotional vents in real life, they can use mobile phones to meet this demand, which makes them prone to be dependent on mobile phones.

Meta-regression showed that gender had no significant moderating effect on alexithymia and MPA among Chinese students. This suggests that the relationship between alexithymia and MPA may be stable across genders. Although individuals of different genders may have different preferences for the specific content of mobile phone use, boys may prefer gaming apps, while girls may prefer social apps, and there may be no significant gender difference in the overall degree of mobile phone use (93, 94). A meta-analysis similar to this study also found that the relationship between MPA and

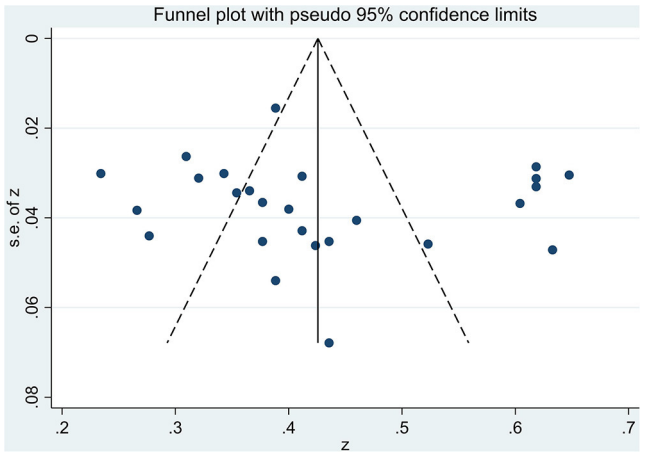

FIGURE 8 | Funnel plot of the 26 studies included in the meta-analysis.

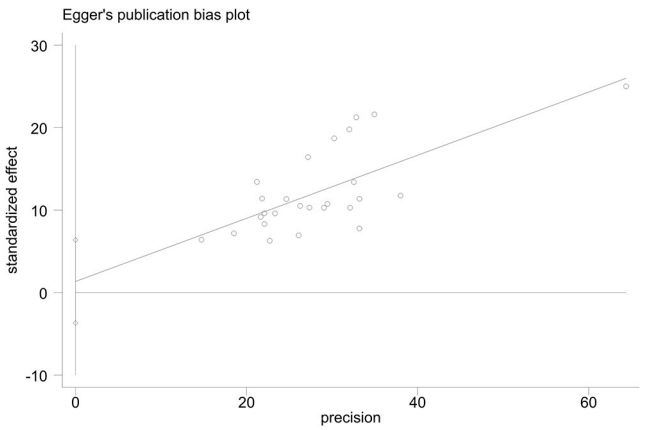

FIGURE 9 | Egger's test of the 26 studies included in the meta-analysis.

anxiety/depression was not moderated by gender (95). This suggests that it may be more common to use a phone to defuse negative feelings when Chinese students' alexithymia cannot be alleviated.

Moderating Role of Regions

The relationship between alexithymia and MPA was not moderated by region. This shows that MPA may be a common problem among students in China, and there is no regional difference. This may be related to the decline in the price of smartphones (96, 97) and the rapid development of mobile internet in China, which has intensified the use of mobile phones among young people. Mobile phones have become an integral part of their lives (98).

In addition, there are only two studies in the western region, which may have a certain impact on the test of moderating variables. Future studies can further expand the number of studies to further test whether the region plays a moderator in the relationship between alexithymia and mobile phone addiction.

Moderating Role of Publication Year

Publication year moderated the positive correlation between alexithymia and MPA, and the results showed that the correlation was generally enhanced with the development of time. This is consistent with the results of a meta-analysis on the relationship between social support and mobile phone dependence of Chinese college students (99). The reason may be that with the popularity of mobile internet, mobile phones play an increasingly important role in Chinese student's lives: they use mobile phones for a longer time, and the frequency of using mobile phones for communication and entertainment is also increasing. Studies have shown that with the popularity of mobile phones and their use years getting longer, the problem of MPA is more likely to occur (56). Additionally, a high level of alexithymia is related to negative social support and maladjustment (100). If individuals have a higher level of alexithymia, MPA is more likely to occur. Therefore, the correlation between alexithymia and MPA is increasing over time. This also reminds us from another point of view that on the one hand, we need to pay attention to the personality traits of teenagers and provide personality quality education for students; on the other hand, we need to constantly improve the social support system of students. However, the studies in this meta-analysis were published in the past 8 years, and the time span is small. Additionally, the number of studies published from 2014–2016 and 2020–2021 is small, which may have s limited the research results.

LIMITATIONS AND PROSPECTS

This study has the following limitations. First, it should be noted that there is no consensus on the concept of MPA at present, so the literature included in this study also includes research on problematic mobile phone use, mobile phone dependence and mobile phone overuse. Second, this study only focuses on the relationship between alexithymia and general mobile phone addiction. Future studies can also analyze the relationship between alexithymia and specific social network addiction or online game addiction. Third, the studies in this study were all cross-sectional studies. In the future, longitudinal research design can be added to further clarify the causal role of alexithymia and mobile phone addiction. Finally, this study only focused on the simple correlation between alexithymia and MPA. Future research can further focus on the psychological variables (e.g., introverted personality, self-disclosure, etc.) that directly affect the relationship between alexithymia and mobile phone addiction in Chinese students, so as to provide a clearer idea for future research on mental health interventions.

CONCLUSION

There was a positive correlation between alexithymia and MPA among Chinese students. Students with higher alexithymia levels are more dependent on mobile phones, and vice versa. Furthermore, the relationship was moderated by mobile phone addiction measurement tool and year of publication, with

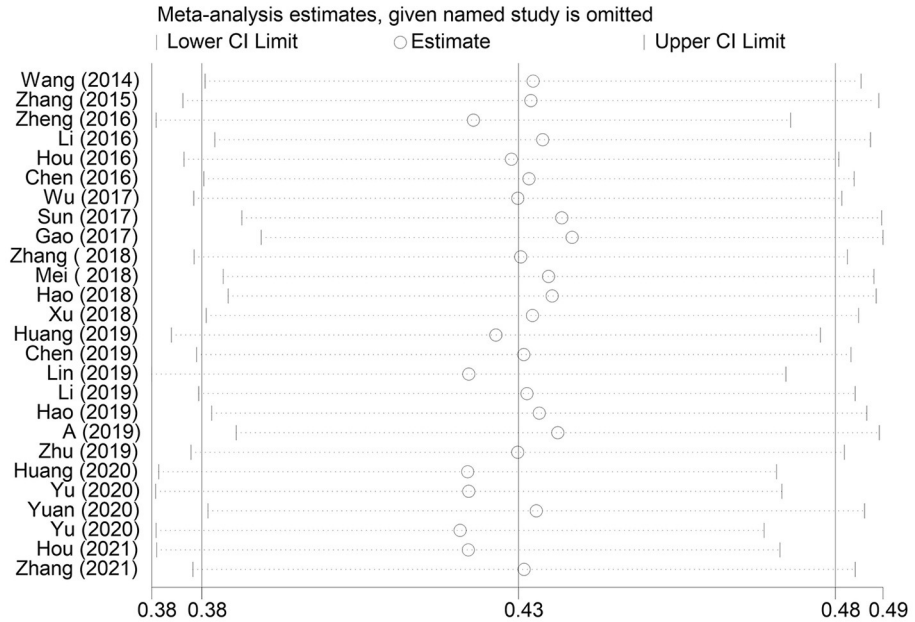

FIGURE 10 | Sensitivity analyses of the 26 studies included in the meta-analysis.

studies using the MPATS having higher correlation coefficients than those using the MPAI or other measurement tools. Studies published in 2020–2021 yielded higher correlations than those published in 2014–2016 and 2017–2019. However, the relationship was not moderated by gender, region, or the measures of alexithymia. Longitudinal studies should be conducted in the future to further reveal the relationship between alexithymia and mobile phone addiction in Chinese students over time.

AUTHOR CONTRIBUTIONS

HH and XW: study design, critical revision of the manuscript, and drafting of the manuscript. GL, YD, CC, and HH: analysis and interpretation of data. All authors approval of the final version for submission.

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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.2022.754542/full#supplementary-material

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Alternations in Dynamic and Static Functional Connectivity Density in Chronic Smokers

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Previous studies have implicated abnormal functional coordination in brain regions of smokers. Neuroimaging studies demonstrated alternations in brain connectivity by using the resting-state functional connectivity (rsFC) method which arbitrarily chooses specific networks or seed regions as priori selections and cannot provide a full picture of the FC changes in chronic smokers. The aim of this study was to investigate the whole-brain functional coordination measured by functional connectivity density (FCD). As the variance of brain activity, dynamic FCD (dFCD) was performed to investigate dynamic changes of whole-brain integration in chronic smokers. In total, 120 chronic smokers and 56 nonsmokers were recruited, and static FCD and dFCD were performed to investigate aberrance of whole-brain functional coordination. Shared aberrance in visual areas has been found in both static and dFCD study in chronic smokers. Furthermore, the results exhibited that both heavy and light smokers demonstrated decreased dFCD in the visual cortex and left precuneus, and also increased dFCD in the right orbitofrontal cortex, left caudate, right putamen, and left thalamus compared with nonsmokers. In addition, alternations of dFCD have been found between heavy and light smokers. Furthermore, the dFCD variations showed significant positive correlation with smoking-related behaviors. The results demonstrated that chronic smokers not only have some initial areas, but also have some regions associated with severity of cigarette smoking. Lastly, dFCD could provide more subtle variations in chronic smokers, and the combination of static and dFCD may deepen our understanding of the brain alternations in chronic smokers.

Keywords: functional connectivity density, static, dynamic, chronic smokers, fMRI, addiction

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INTRODUCTION

Cigarette smoking is considered as the leading cause of preventable disease in the world. It has a negative influence on health, economic and society. Nearly 6 million deaths and over a half trillion dollars in healthcare costs in the world are attributed to smoking (1). In addition, cigarette smoking has also been associated with the higher risk of cognitive decline and dementia (2, 3). According to previous studies, chronic smokers lose at least 10 years of life compared to nonsmokers (4). Although a large number of smokers are willing to quit smoking, only a few people could succeed without the help of medication or other treatment (5). In fact, most of them relapse within only 1 week (6). Therefore, a better understanding of the neural effects of smoking in human brains is important to help chronic smokers quit smoking. There exists an amount of evidence stating that that cigarette smoking has a negative influence on functional alternations in the brain. For instance, substance addiction might alter the sensitivity of brain regions, including motivation and reward (7).

Numerous neuroimaging studies have been conducted to explore alternations of functional coordination in several brain regions and networks of smokers in recent years. Resting-state functional magnetic resonance imaging (fMRI) studies have reported that chronic smokers showed widespread abnormal functional connectivity (FC) in some brain regions. The orbitofrontal cortex (OFC) is thought to integrate and modulate activity from several limbic areas involved in reward processing (8). Activation has been recorded in brain regions including the caudate, OFC, and parahippocampal gyrus during control scanning in response to smoking-related images (9). Compared with nonsmokers, smokers had lower connectivity associated with key network hubs, including the default mode network (DMN) (10). Lower FC has been found between the caudate and OFC in smokers (11). Decreased FC in the left thalamo-precuneus has also been found in relapsing addicts (12). Furthermore, widespread FC attenuation has been observed in the reward circuit of smokers compared with non-smokers (13). In addition, neuroimaging studies have found alternations in brain coordination among different severity of smoking. That is, smokers with greater nicotine dependence severity tend to demonstrate greater engagement of sensorimotor and motor preparation circuits, and Fagerström Test for Nicotine Dependence (FTND) scores were positively associated with increased connectivity between insular and dorsal striatum and early visual processing cortex (14). Therefore, this research attempted to identify the alternations of brain coordination between smokers with different nicotine dependence severity by using a cross-sectional sample. However, all above FC studies required prior assumption and cannot provide a landscape of whole-brain FC changes, which might exist some limitations for exploratory analyses.

Recently, resting-state FC density (FCD) has been performed to measure the number of resting-state functional connections of a given voxel with all other voxels in the whole brain (15). This has been generally used in some psychiatric disorders to investigate the aberrance in brain static FC (16, 17). Unlike the seed-based FC method, FCD is a kind of method that is defined by the functional connections between each voxel in the brain. It does not need previous hypothesis (15). Therefore, FCD might be an approach that could provide more information compared with FC. Higher FCD of a specific voxel indicates that it is functionally connected with a large number of voxels within the brain and that the voxel plays a more important role in information processing compared with others. A previous study has used this method to demonstrate brain coordination in smokers of different states, i.e., abstinence and satiety state (16). Considering the dynamic nature of brain activity (18), the sliding window correlation approach has been widely used in the FC method to demonstrate the collaboration of brain regions by measuring the time-varying covariance of their neural signals during resting-state (19). The aberrance of the variance of FC has been conducted in many other mental diseases such as depression and schizophrenia (20, 21). In addition, the dynamic FCD (dFCD) method has been conducted in some diseases, including generalized anxiety disorder (GAD) and benign epilepsy with centrotemporal spikes (22, 23), despite not yet being performed on smokers in previous research. In the current study, the sliding window correlation approach was combined with FCD to evaluate the variance of brain activity. In conclusion, the static FCD provides a new avenue to illustrate the FC of whole brain, whereas the dFCD was calculated to identify the variance of brain activity by dividing the whole time series into different segmentations. Therefore, exploiting the methods of static and dFCD could help to provide supplementary evidence to uncover the aberrance of brain areas between chronic smokers and nonsmokers.

In the current study, we aimed to identify the aberrance of brain FC caused by cigarette smoking using static and dFCD method in 120 chronic smokers and 56 age- and gender- matched nonsmokers. Based on previous studies, we hypothesized that (1) the static and dFCD method could reveal shared and different brain areas showing functional abnormalities (20), and that (2) there might exist some brain regions that can be associated with the severity of smoking. In addition, the correlation analyses were performed to identify the relationships between FCD measurements and smoking-related behaviors.

MATERIALS AND METHODS

Participants

In total, 120 chronic smokers and 56 nonsmokers were recruited from online advertisement, and all the participants are males. Then, 120 chronic smokers were divided into 61 nonsmokers (cigarette per day>20) and 59 light smokers (cigarette per day <20) (24). Smokers eligible for the study included those that: met the DSM-IV criteria for nicotine dependence, smoked at least 10 cigarettes per day for the past 5 years, had no period of smoking abstinence longer than 3 months in the past years, and whose smokers' nicotine addiction was assessed by the FTND. Nonsmokers were those who smoked <5 cigarettes in his lifetime. The exclusion criteria included physical illnesses, such as brain tumor, obstructive lung disease; a history of neurological and psychiatric diseases; addiction to other substances (except nicotine); and those with contraindications to MRI. This study

aimed to study differences in neural activity between smokers in satiety state and nonsmokers. Smokers were required to smoke a cigarette 30-45 min before examination to prevent withdrawal symptoms. All the participants provided informed consents to the study protocol. The study was reviewed and approved by the Local Medical Ethics Committee of the First Affiliated Hospital of Zhengzhou University.

Data Acquisition

Magnetic resonance imaging data were obtained using a 3.0T German Siemens Magnetom Skyra magnetic resonance imaging equipment with a sixteen-channel prototype quadrature birdcage head coil. Participants were instructed to keep their eyes closed, not to fall asleep, and to maintain their head motionless during scanning. Functional images were obtained using an echo planar imaging sequence with the following parameters: repetition time (TR)/echo time = 2,000/30 ms, matrix size = 64 × 64, flip angle = 80°, field of view = 240 × 240 mm, voxel size = 3 × 3 × 3 mm, slices = 36, slice thickness = 4 mm, no gap, and a total of 180 volumes.

Image Analysis and Preprocessing

The Data Processing and Analysis of Brain Imaging (DPABI v3.0) (http://rfmri.org/DPABI) toolbox was used to preprocess the functional imaging data. Imaging preprocess was performed as follows. The first 5 volumes from each subject were discarded. Then, functional images were slice-timing corrected, realigned (cut off < 2.5 mm or 2.5°), spatially normalized to the Montreal Neurologic Institute space, and re-sampled to 3 × 3 × 3 mm^3. Next, several spurious variances (24 head motion parameters, global signals, ventricular signals, and white matter signals) were regressed using multiple linear regression analysis. For a precise head motion correction, the parameters from scrubbing data were also regressed. Previous researches reported that the global signal regression could improve the accuracy of FC calculation (25). Thus, we regressed the global signal in our study. Framewise displacement (FD) was calculated for each time point (26), and participants with mean FD value exceeding.5 mm were excluded. Subsequently, functional images were trended and temporal band-pass filtered.01 Hz∼0.08 Hz.

Estimation of Static and Dynamic FC Density

In comparison to static FCD, dFCD is a method combining with sliding window correlation approach looking at variation across the time series. To calculate the static FCD, Pearson's linear correlation was used to evaluate the strength of the FC between voxels. Two voxels with a correlation coefficient of R >0.6 were considered significantly connected. This threshold was proposed to be the optimal threshold for calculating resting-state FCD in a previous study (15). The dFCD analysis was performed by using Dynamic Brain Connectome (DynamicBC) toolbox (27) (V2.0 http://restfmri.net/forum/DynamicBC). The window length is a key parameter in sliding window correlation calculation. According to the rule of thumb, the minimum window length should exceed $1/f_{min}$, where f_{min} denoted the minimum frequency of time courses (28). Therefore, we selected 50 TRs as a window wise and a window overlap of 90%. To certify the robustness of the sliding-window analysis, we also examined other window wises that were included in validation analysis. In each sliding window, we obtained a global FCD map in each window by computing Pearson's correlations between the voxels within the whole brain. Two voxels were considered to be connected when the Pearson's correlation coefficient of the two voxels was greater than a given threshold $r = 0.2$ according to the significant level of $p < 0.001$ (uncorrected) in order to eliminate weak correlation which may be caused by noise (29). The temporal variability was calculated by the SD of FCD across sliding windows. Then, the temporal variability map of each subject was normalized into a z-score matrix. Subsequently, all the normalized images were smoothed (6 × 6 × 6 mm full width at half maximum Gaussian kernel).

Statistical Analysis

One-way ANOVA was conducted among the three groups for voxels within the whole brain to explore the alternation of static and dFCD among nonsmokers, light smokers, and heavy smokers. In this step, age, years of education, and mean FD were included as covariates. The threshold of gaussian random field correction (GRF) was performed on the F-value map with voxel $p < 0.005$, cluster $p < 0.01$ (two-tailed).

Then, to investigate the details about the aberrance among these three groups, a two tailed two-sample *t*-test was performed between each pair of groups based on those brain regions having a significant F value alternation among three groups to detect the between-group differences in static and dFCD. Region of interest (ROIs) were defined as spheres with radius of 6 mm centered at the MNI coordinate reported for the brain regions having a significant F value. To examine the association between the abnormalities of FCD measurements and cigarette smoking, correlation analyses were performed between FCD measurements and smoking-related behaviors including pack-years and FTND.

Validation Analyses

Since there is no clear conclusion on the optimal window length for the sliding window method. We validated our results with window lengths of 30 and 80 TRs. The additional window lengths were 30 and 80 TRs. In addition, we have conducted analyses that global signal was not regressed to verify the stability of our results. The corresponding results are shown in the **Supplementary Materials**.

To exclude the effect of head motion on observed results, Pearson correlation was calculated between the dFCD of ROI signals with mean FD among three groups. In addition, the mean FD was compared among three groups and between heavy smokers and light smokers.

RESULTS

Demographics and Clinical Characteristics

In total, there were 61 heavy smokers, 59 light smokers, and 56 nonsmokers included in the current study. No significant difference was found among groups in terms of

TABLE 1 | Demographic and smoking behaviors.

	Heavy smokers	Light smokers	Nonsmokers	*p* value
Sex (male/female)	61/0	59/0	56/0	–
Age (mean±SD)	36.78 ± 7.78	35.40 ± 8.96	36.52 ± 7.48	0.096[a]
Education (mean±SD)	14.23 ± 2.35	14.56 ± 2.51	15.23 ± 3.09	0.084[a]
FTND (mean±SD)	5.39 ± 1.99	2.29 ± 1.57	–	–
Cigarette per day (mean±SD)	26.89 ± 6.88	12.02 ± 4.15	–	–
Peak-year (mean±SD)	26.89 ± 13.33	9.96 ± 7.04	–	–

FTND, Fagerström Test for Nicotine Dependence; Pack-years, (Years of smoking × Cigarettes smoked per day)/20.
[a]One-way ANOVA.

TABLE 2 | Brain regions with changed static and dynamic functional connectivity density (FCD) among the three groups.

Indices	Cluster	Voxels	Brain region	Sphere	Peak intensity	MNI coordinate
Dynamic FCD:	1	1671	Caudate	L	16.79	−18, 18, 12
			ParaHippocampal Gyrus	L	16.53	−30, −18, −24
			Thalamus	L	12.13	9, −12, 9
	2	636	Frontal Gyrus	R	14.32	21, 12, −12
			Pallidum	R	14.25	15, 9, −3
			Orbitofrontal Cortex	R	13.89	30, 27, −12
	3	74	Superior Temporal Gyrus	L	11.43	−69, −21, 6
			Middle Temporal Gyrus	L	11.02	−69, −33, 3
	4	269	Cuneus	R	10.99	3, −72, 21
			Calcarine	R	10.90	15, −63, 9
			Calcarine	L	9.21	−12, −75, 9
	5	60	Thalamus	R	9.512	9, −12, 9
	6	78	Precuneus	L	9.61	−6, −48, 54
Static FCD:	1	380	Occipital Cortex	L	12.19	−27, −75, 18
			Calcarine	L	11.47	−12, −75, 12
	2	72	Calcarine	R	10.36	9, −72, 18
			Cuneus	R	6.68	12, −87, 15

GRF corrected, voxel $p < 0.005$, cluster $p < 0.01$; L, left; R, right.

sociodemographic characteristics, such as age and year of education. The detailed demographic information and smoking behaviors were shown in **Table 1**.

Static FCD Between Chronic Smokers and Nonsmokers

The three groups presented significantly static FCD of brain regions in the visual cortex, including the bilateral calcarine and right cuneus (GRF corrected $p < 0.005$, $F = 6.20$, **Table 2**, **Figure 1**).

The *post-hoc* results demonstrated that both heavy and light smokers showed decreased static FCD in the bilateral calcarine, and heavy smokers showed significantly lower static FCD in the right calcarine compared with light smokers. As for right cuneus, only heavy smokers showed significantly decreased static FCD in comparison to nonsmokers.

Dynamic FCD Differences Between Chronic Smokers and Nonsmokers

The three groups presented significantly different dFCD of brain regions in the right OFC, dorsal striatum (left caudate and right putamen), visual cortex (bilateral calcarine and right cuneus), DMN [left parahippocampal gyrus, left precuneus and middle temporal gyrus (MTG)], and bilateral thalamus ($p < 0.005$, GRF corrected, $F = 6.20$, **Table 2, Figure 1**).

The *post-hoc* results demonstrated that both light and heavy smokers showed decreased dFCD in the brain areas of visual cortex (including bilateral calcarine and right cuneus) and left precuneus, and also showed increased dFCD in right OFC, dorsal striatum (left caudate and right putamen), and left thalamus compared with nonsmokers (**Figure 2**). In addition, heavy smokers showed an increased dFCD in the right thalamus, while light smokers showed decreased dFCD in MTG in comparison to nonsmokers. Moreover, heavy smokers showed increased dFCD in left MTG and right thalamus, and decreased dFCD in left parahippocampal gyrus compared with light smokers (**Figure 3**). The details were showed in **Supplementary Table S1**.

Correlation Analyses

The results showed that the temporal variability in dFCD in the left MTG was positively correlated with pack-years and FTND ($r = 0.292$, $p = 0.001$, Bonferroni corrected). Temporal variability

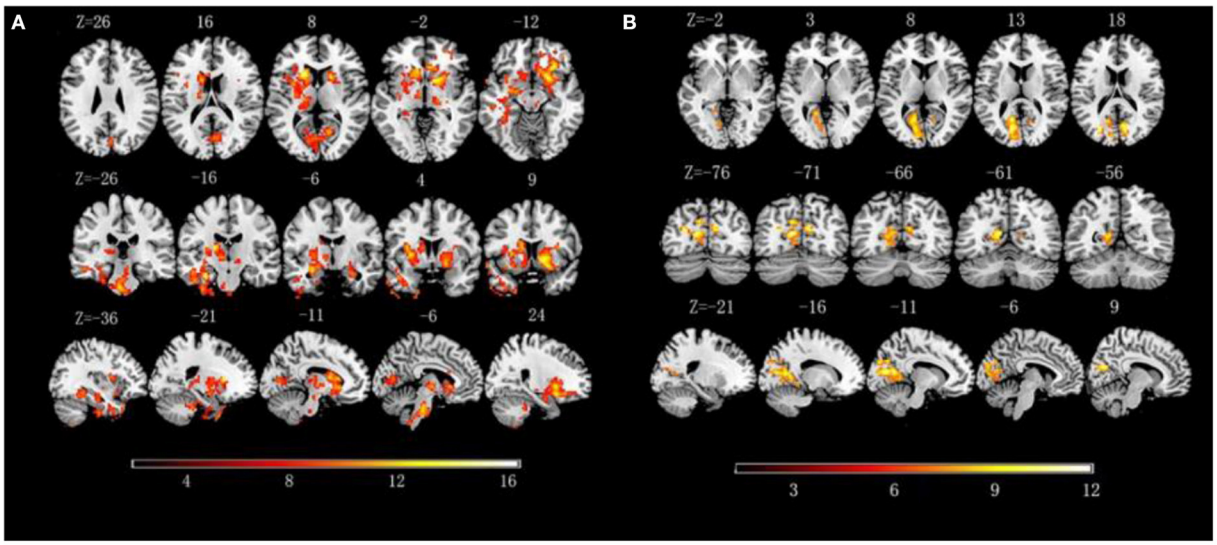

FIGURE 1 | (A) Significant alternations of dynamic functional connectivity density (dFCD) among three groups; **(B)** Significant alternations of static functional connectivity density (FCD) among three groups.

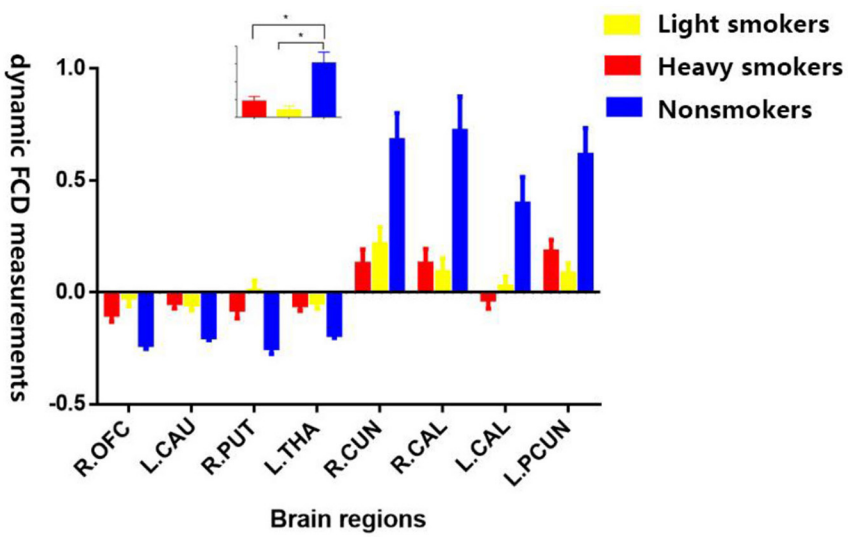

FIGURE 2 | Shared alternations of dFCD measurements of brain regions in both heavy smokers and light smokers compared with nonsmokers. R.OFC, right orbitofrontal cortex; L.CAU, left caudate; R.PUT, right putamen; L.THA, left thalamus; R.CUN, right cuneus; R.CAL, right calcarine; L.CAL, left calcarine; L.PCUN, left precuneus. (The subplot means that both heavy and light smokers have significant alternations of dFCD measurements compared with nonsmokers). * means difference between the two groups has statistical significance.

in the right thalamus was positively correlated with FTND ($r = 0.265$, $p = 0.003$, Bonferroni corrected).

Validation Analyses

Our results reported above could be validated with different window length of 30 and 80 TRs. The corresponding results are shown in the **Supplementary Materials** ($p < 0.01$, **Supplementary Table S2**).

There was no significant difference of mean FD among three groups ($p = 1.45$ for ANOVA). The mean FD in heavy smokers was not significantly different from that in light smokers ($p = 0.096$ for two sample t-test). The correlations between mean FD and ROI signals of brain regions were all not significant ($p > 0.05$).

DISCUSSION

In the current study, we explored altered static and dFCD in chronic smokers compared with nonsmokers. As we assumed, shared abnormalities of dFCD and static FCD both in heavy

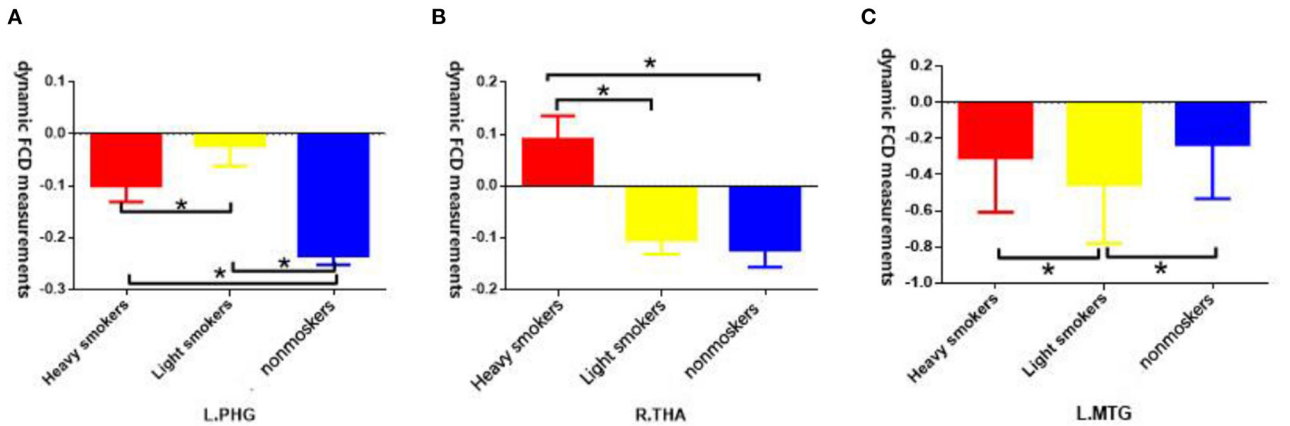

FIGURE 3 | (A) Both heavy smokers and light smokers showed significant alternations of dFCD measurements in left parahippocampal gyrus, significant differences have been found between heavy smokers and light smokers; **(B)** Heavy smokers showed significant alternations of dFCD measurements in right thalamus compared with nonsmokers, significant differences have been found between heavy smokers and light smokers; **(C)** Light smokers showed significant alternations of dFCD measurements in left middle temporal gyrus (MTG) compared with nonsmokers, significant differences have been found between heavy smokers and light smokers. * means difference between the two groups has statistical significance.

and light smokers have been found to be possible inherent abnormalities irrelated with the degree of cigarette smoking. In addition, the aberrance of static FCD and dFCD between heavy and light smokers has been found in certain brain areas. Also, the correlation analyses showed that part of the temporal variability in dFCD of different smoking severity was positively correlated with pack-years and FTND, which was originally thought to be associated with the severity of smoking.

In the dFCD study, heavy smokers exhibited significant increases in the left MTG and right thalamus, and a decrease in the left parahippocampal gyrus in comparison to light smokers. As suggested by previous studies, the MTG and parahippocampal gyrus are core components of DMN. Increased dFCD variability in MTG and decreased dFCD variability in parahippocampal gyrus suggests a disturbed integrity of DMN connectivity in the resting state. The DMN is hypothesized to be correlated with internal mentation (30) and is associated with self-referential mental activity and emotional processing tasks (31). To date, the DMN is reported to be implicated in substance use disorders (32), while the chronic nicotine use is reported to negatively impact FC within the DMN, possibly contributing to the difficulty smokers have in quitting (10). Though it is not typically considered to be part of DMN, strong FC has been proved between thalamus and DMN (33). In addition, the variability of dFCD in the right thalamus and left MTG was positively correlated with smoking behaviors, including pack-years and FTND. Given that the localization of significant correlation was primarily in the DMN, the findings were consistent with the incentive-habit model of addiction (34). In chronic smokers, the degree of nicotine dependence is continually reinforced through positive and negative reinforcement, while greater severity is associated with more reliance on habitual use (14). We may draw a conclusion that with the progression of degree of smoking, smoking-related behaviors may become more habitual. Hence, smokers tend to have more difficulty in quitting smoking. Longitudinally, studies could be applied to examine the alternations of functional coordination in brain regions along with the changes of severity of nicotine dependence.

The dFCD study also revealed shared abnormalities of brain regions in right OFC, dorsal striatum (including left caudate and right putamen), left thalamus, and left precuneus in both heavy and light smokers. The frontal-striatal-thalamic circuits is critical for processing of reward (35, 36). Thereinto, the dorsal striatum is associated with motivation, or the drive for action that leads one to work to obtain rewards (37), which drives to obtain smoking-related reward (38). Smoking addicts who are accompanied with dorsal striatum damage were more likely to discontinue smoking. In addition, the characteristics of this interruption is that smoking can be quitted easily and quickly, without recurrence. Furthermore, the impulse to smoke in these people is reduced compared to those smokers without dorsal striatum damage (39). The thalamus is vulnerable to addictive effects of cigarette smoking due to the high density of acetylcholine receptors (AChRs) (40). It participates in the circuit by relaying striatal inputs to the frontal regions and providing feedback to the striatum. Dysregulation of the OFC is correlated with faulty decision-making and the incapacity to inhibit compulsive and repetitive behaviors (41). Imageology studies indicated that the OFC presented hypoactivity during withdrawal in substance use addiction (42, 43). Consistent with previous studies, in this study, the increased dFCD variability in the frontal-striatal-thalamic circuits suggested that regions involved in reward and impulsive-compulsive behavior exhibited more flexibility in functional regulation with other brain networks in smokers. As for precuneus, it is a crucial component part of DMN, which is thought to be associated with self-referential processing such as monitoring craving or withdrawal symptoms (14). Therefore, we hypothesized that the aberrance of the frontal-striatal-thalamic

circuits and precuneus might be associated with the craving for nicotine and relapse of smoking behaviors. Furthermore, the above alternations were supposed to be inherent abnormalities related to smoking behaviors.

Compared with nonsmokers, both heavy and light smokers also showed alternations of dFCD in bilateral calcarine and right cuneus. Previous studies have demonstrated that calcarine is a component of the visual attention network and plays a major role in visual information integration and attention processing (44). The cortex around the calcarine fissure is the primary visual cortex (45). The bilateral calcarine are components of the occipital cortex, which is considered as low order brain region in the visual cortex (46). The cuneus is functionally connected to a visual network and is considered to be have crucial role in the integration of visual information (47). According to previous studies, smokers display an initial top-down attention bias toward cigarette cues and demonstrate impairment in inhibiting attentional biases (48, 49). Attentional mechanisms of top-down biasing of feature selection in visual cortex have been extensively investigated, indicating that attention exerts its effect by modulating the gain of neural processing in sensory visual areas (50). Therefore, we supposed that the aberrance in visual cortex in chronic smokers might be associated with the impairment of attention biases.

In the current study, static and dFCD methods illustrated brain regions located in the same areas, including the bilateral calcarine and right cuneus. The reduced dFCD variability in visual cortex in chronic smokers might signify the weakness in neural communication between this area and other regions of the brain, which is consistent with the result of static FCD. Alternations in static FCD suggest the functional impairment in visual network. However, in to dFCD, the static index only showed alternations in the more primitive part of visual cortex. The dynamic index tended to show changes in brain regions that associated with emotion and perception. We supposed that dFCD tends to show fluctuation within a short period of time, and it could provide more subtle variations in brain coordination. A combination of static and dynamic FC has been performed in schizophrenia and depression (20, 51). In addition, we used 30 and 80 TRs with 90% overlap to validate our results. The results showed inconsistent results in some brain regions in different parameters. Hence, we may draw the conclusion that longer or shorter sliding window size might weaken the sensitivity of examining the variance of dynamic changes in brain connectivity. In this study, heavy smokers showed significantly decreasing static FCD in right calcarine and right cuneus. The reason might be that smoking behaviors in smokers with higher degree of nicotine dependence tend to become more habitual. Hence, incentive effects will be weaker, suggesting that heavy smokers' attentional and approach biases for smoking cues should be attenuated compared with light smokers (34). From the above results, we may draw the conclusion that static FCD tends to perform more subtle variations in comparison to dFCD. In addition, the aberrance of static FCD represents impairment of brain FC, while the dFCD demonstrated the alternations of the variance within brain coordination over a short time and supply more subtle information.

The current study still exists several limitations. First, all the subjects in our study are male. Hence, the current study fails to analyze intergender differences. Second, the sample size is small in this study. A larger size of subjects needs to be performed in the future to verify our results. Finally, the current studies are cross-sectional. To investigate the alternations of brain coordination, accompanied with the development of severity of cigarette smoking in chronic smokers, and to elucidate the static and dynamic characteristics of whole-brain connectivity, longitudinal studies are needed to be conducted in future research.

CONCLUSION

In conclusion, there exists some brain regions that tend to associate with the severity of nicotine dependence. In addition, chronic smokers showed inherent aberrance which is irrelevant to the severity of nicotine dependence. The dFCD significantly outperforms the static FCD, which could provide more variations. The current findings demonstrated that combing static and dynamic analyses could provide complementary evidence to help people understand the changes of neuroscience in cigarette smokers.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Local Medical Ethics Committee of the First Affiliated Hospital of Zhengzhou University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZY contributed to the experiments, data analysis and writing of the manuscript. MW, YW, and HH contributed to performing the experiments and writing and revising the manuscript. WW, XG, and MZ contributed to the data collection. RZ revised the manuscript. YZ, JC, and SH are the guarantor of this study and had complete access to all data in the study. All authors contributed to the article and approved the submitted version.

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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.2022.843254/full#supplementary-material

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Intermittent Theta Burst Stimulation vs. High-Frequency Repetitive Transcranial Magnetic Stimulation in the Treatment of Methamphetamine Patients

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Background and Aims: In this brief report, we compare the effectiveness and safety of intermittent theta burst stimulation (iTBS) and conventional 10 Hz repetitive transcranial magnetic stimulation (rTMS) in patients with methamphetamine use disorder (MAUD). Our study suggests that iTBS would also reduce drug craving in patients with MAUD just as the 10 Hz; thus, there may be no difference in treatment effects between these two methods.

Methods: In total twenty male methamphetamine (MA) addicts were randomly assigned to iTBS ($n = 10$) or 10 Hz ($n = 10$) groups for 12 treatments. Cue-evoked cravings, anxiety, depression, and withdrawal symptoms were measured at baseline before the first treatment, and post-tests after days 10, 15, and 20.

Results: The results showed that iTBS and 10 Hz treatment had similar effectiveness in reducing cue-induced craving in male addicts for MA. Both 10 Hz and iTBS improved withdrawal symptoms of patients with MAUD.

Conclusions: Intermittent theta burst stimulation may be similar in effectiveness as 10 Hz in treating patients with MAUD. The clinical usefulness of rTMS could be improved substantially because of the increase in its capacity, cost, and accessibility. Importantly, the effectiveness of rTMS in the treatment of patients with MAUD is not yet proven, and should be tested in the large double-blind sham-controlled studies.

Keywords: methamphetamine use disorder, iTBS, rTMS, substance abuse, addiction

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INTRODUCTION

Methamphetamine use disorder (MAUD) can cause serious social problems. It is well-accepted that patients with substance use disorder (SUD) experience high cravings and high-relapse rates. Currently, available treatments for MAUD mainly include an extension application of deep electrical stimulation therapy in the human brains based on animal optogenetic and electrical stimulation, which remain to be proven, because of the invasive nature and high price. In addition, target sites have not yet been identified. One of the most widespread addiction rehabilitation treatments in China is physical isolation, which combines physical rehabilitation and psychological counseling, but lacks targeted brain science techniques; implementation of psychological counseling requires a long period of time and extensive counselor experience. Its promotion is limited under existing conditions in China. Non-invasive brain stimulation techniques, such as repetitive transcranial magnetic stimulation (rTMS), may be a more scientifically sound option. rTMS induces sustained changes in the brain regions through high-intensity, focused pulsed magnetic fields (1, 2). Additional findings have also demonstrated the efficacy and safety of rTMS in the left dorsolateral prefrontal cortex (DLPFC) for the treatment of patients with MAUD. For instance, in patients with MAUD, previous studies found that MA abuse impairs motor cortical plasticity and function (3); rTMS can reduce cravings (4), enhance cognitive function (5), and improve withdrawal symptoms (6). These findings have been shown in women (7) and also in a larger sample of men (8).

Repetitive transcranial magnetic stimulation is approved by the U.S. Food and Drug Administration (FDA) for the treatment of major depression (9), migraine with aura (10), obsessive–compulsive disorder (11, 12), and smoking addiction (13). It is widely used in rehabilitation, psychiatry, and neurology departments in many hospitals worldwide, and has been used to treat SUD in the recent years. The FDA-approved stimulation paradigm for the treatment of depression involves high frequency (10 Hz) and 37.5 min of stimulation time (14). Excessive treatment time limits the number of treatments and increases the cost of treatment. Therefore, it is possible that reducing treatment time could improve the feasibility of rTMS and increase economic benefits. A new form of rTMS has arisen, called "theta burst stimulation" (TBS) (15, 16). Unlike 10 Hz stimulation, TBS mimics endogenous rhythms and can strengthen long-duration-enhanced conduction at synapses (16). Intermittent TBS (iTBS) is capable of delivering 600 pulses in 3 min, showing similar or stronger excitatory effects compared with conventional 10 Hz stimulation (17). Several findings have shown that iTBS is superior to sham treatment for the refractory depression (18–20). One study showed that iTBS has similar effectiveness as 10 Hz for treating patients with refractory depression (21). Several studies have used iTBS in MAUD and other forms of addiction, either alone or in combination with conventional treatments. For example, one study found that iTBS affects cocaine consumption and cocaine craving almost the same as in a 15 Hz group (22). Another study evaluated the tolerability and safety of iTBS, which reduced cocaine use in a non-treatment-seeking cohort (23). However, one study indicated that iTBS in the left DLPFC was feasible and tolerable when modulating craving and mood changes in patients with MAUD (24). Cue-induced craving, however, is often treated with inhibition protocols applied to the medial prefrontal cortex (25), but the results have been inconsistent. For instance, continuous TBS (cTBS) of the ventromedial prefrontal cortex weakened neural reactivity to drug and alcohol cues in frontostriatal circuits, but had no effect on drug-/alcohol-induced cravings (26). Therefore, in this study, we chose excitatory protocols. Our study focused on whether iTBS has similar therapeutic effect as 10 Hz in patients with MAUD. Regarding TMS intervention in patients with MAUD, if 3 min of iTBS has similar therapeutic effect as conventional 10 Hz (at least 10 min of treatment time), this greatly improves the efficiency and economic benefit of TMS use.

The effectiveness of iTBS has been confirmed in psychiatry and neurology (27–30). Meanwhile, iTBS has the advantages of short treatment time, high feasibility, and good economic benefits. Therefore, we would investigate the differences in the efficacy of iTBS and classic high-frequency rTMS protocols in patients with MAUD in this study. Then, we hypothesized that compared to the 10 Hz, iTBS has the similar therapeutic effect in patients with MAUD.

METHODS

Participants

This study was a randomized, parallel-controlled case study. In total, twenty male MA addicts aged 24–53 years were recruited from the Gongchen Addiction Rehabilitation Center in Hangzhou, Zhejiang Province. Inclusion criteria included the use of MA (DSM-V diagnosis, positive urine test upon admission, abstinence thereafter). Exclusion criteria was other drug use, infectious disease, sleep deprivation, history of epilepsy or stroke, history of mental illness, metal implants in the brain, cochlear implants, increased intracranial pressure, traumatic brain injury, brain tumor, encephalitis, cerebrovascular disease, cerebral metabolic disease, pacemakers, history of heart disease, illiteracy, and previous rTMS treatment. Experimental procedures were approved by the Ethics Committee of Nanjing Normal University in accordance with the Declaration of Helsinki and the trial was registered in the Chinese Clinical Trial Registration Center (http://www.chictr.org.cn; no. ChiCTR17013610). All the subjects signed informed consent forms before the experiment and participated voluntarily. The 20 MA participants were randomly assigned to either 10 Hz ($n = 10$) or iTBS ($n = 10$) in a 1:1 ratio using a simple randomization procedure.

The research instruments used in this study included the Visual Analog Scale (VAS), which quantitatively assesses craving in patients with MAUD; the mood scales for assessing subjects' withdrawal symptoms were Self-Rating Anxiety Scale (SAS) (31), Self-Rating Depression Scale (SDS) (32), and Withdrawal Symptom Scale for MA Addicts (6). The aforementioned scales have good reliability and validity. The treatment apparatus used was

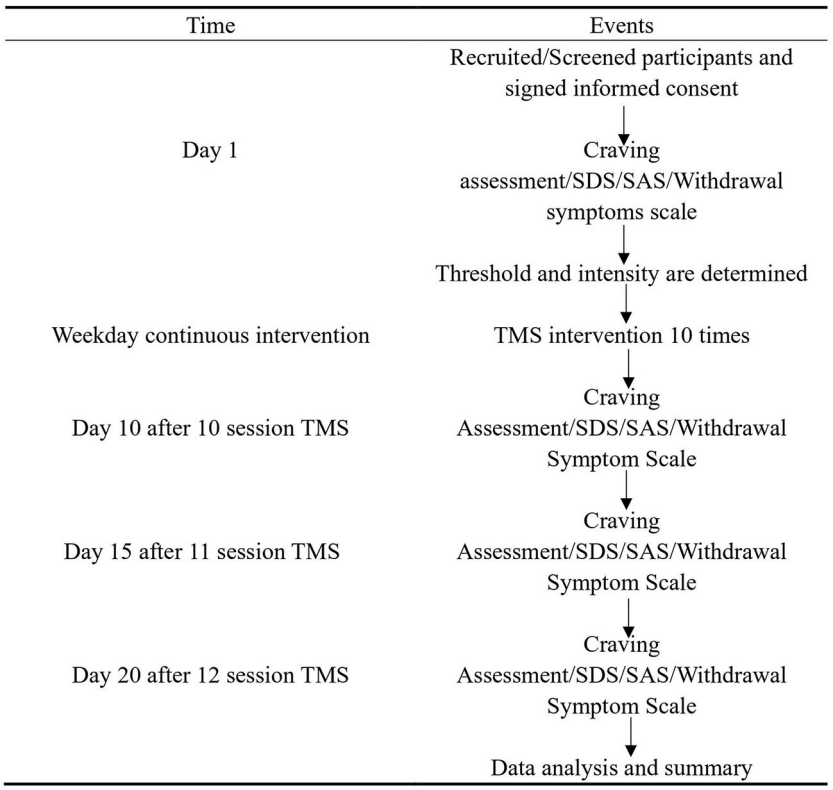

FIGURE 1 | Flowchart of experimental events.

the CCY-IA transcranial magnetic stimulation equipment (Yiruide Co., Wuhan, China). The magnetic stimulus had a biphasic waveform. The maximum stimulator output was 3.0 Tesla.

Craving Score Assessment

Craving score is an important factor in cue-induced addictive behavior and drug relapse. In our study, we asked drug users to watch a 5 min video of MA use in a relaxed state, and then, we assessed cue-induced craving scores using the VAS, with scores ranging from 0 (not at all) to 100 (very much).

rTMS and Experimental Design

In this study, the stimulation protocol was 10 Hz or iTBS, as described in previous studies (15, 33). The parameters for 10 Hz were 5 s on and 10 s off for 10 min, 2,000 pulses. The stimulation intensity was 100% resting motor threshold (RMT). The parameters for iTBS were as follows: 50 Hz of 80% active motor threshold for three pulse trains, repeated at 5 Hz, 2 s on and 8 s off, with a total duration of 190 s, 600 pulses. The participants wore a positioning cap equipped by the Yiruide Company (10–20 EEG system). The circular coil was placed on the subject's left DLPFC at a point 5 cm anterior to the scalp position at which the motor threshold was determined (7); the stimulation was performed for 190 s or 10 min by clicking the start button on the computer screen. The treatment was performed every morning. Side effects were evaluated by asking each question according to the regulations on the instruction record sheet and scoring them (1–10, with 1 representing very mild, 5 being acceptable, and 10 being very severe). The therapist assessed the overall condition of the participant at the end of the 12 sessions. Cue-evoked cravings, anxiety, depression, and withdrawal symptoms were measured at baseline before the first treatment, and posttests after days 10, 15, and 20. The specific experimental process is illustrated in **Figure 1**.

Statistical Analysis

We analyzed the data from this study using IBM Statistical Product and Service Solutions (SPSS 19.0). An independent samples *t*-test was used to compare the differences in demographic variables between the 10 Hz and iTBS groups. This study used a mixed experimental design of 2 (group: 10 Hz and iTBS) × 4 (time: pre-test, post-test, first follow-up, and second follow-up). We used two-way repeated measures ANOVA to compare the changes in craving, SAS, SDS, and MA withdrawal scores over time, between the two groups. The statistical significance threshold was set at $p < 0.05$.

RESULTS

The Demographic Characteristics of the Participants

Table 1 presents the demographic characteristics of the participants, with mean ± standard error. Independent sample

TABLE 1 | Demographic characteristics of patients with MAUD ($M \pm SEM$).

Variable	10 Hz group ($n = 10$)	iTBS group ($n = 10$)	p
Age (years)	38.40 ± 2.25	35.40 ± 2.66	0.37
Years of intake (years)	9.00 ± 1.18	8.50 ± 0.91	0.76
Maximum intake/per intake (g)	0.90 ± 0.19	0.72 ± 0.08	0.29
Monthly intake (g)	15.40 ± 2.79	10.70 ± 2.40	0.05

MAUD, methamphetamine use disorder; iTBS, intermittent theta burst stimulation.

t-tests showed that there were no differences in demographic characteristics such as age [$t_{(18)} = 1.08$, $p > 0.05$], years of MA intake [$t_{(18)} = 0.46$, $p > 0.05$], maximum MA intake [$t_{(18)} = 0.17$, $p > 0.05$], and monthly MA intake [$t_{(18)} = 1.01$, $p > 0.05$] between the 10 Hz and iTBS groups.

Effectiveness of Both 10 Hz and iTBS in Reducing Craving in Patients With MAUD

For craving, repeated measures ANOVA found a significant effect in time [$F_{(3,54)} = 46.944$, $p < 0.001$, $\eta_p^2 = 0.72$]. *Post-hoc* tests showed that 10 Hz reduced craving at day 10 ($M = 27.00$, $SEM = 3.96$), day 15 ($M = 19.00$, $SEM = 3.14$), and day 20 ($M = 21.00$, $SEM = 4.07$) relative to baseline ($M = 57.00$, $SEM = 4.73$). Similarly, iTBS significantly reduced craving among MA addicts on day 10 ($M = 36.00$, $SEM = 7.92$), day 15 ($M = 27.00$, $SEM = 3.96$), and day 20 ($M = 17.00$, $SEM = 1.53$) relative to baseline ($M = 65.00$, $SEM = 5.63$). The group main effect was not significant [$F_{(1,18)} = 1.30$, $p > 0.05$, $\eta_p^2 = 0.07$], and there was no interaction between time and group [$F_{(3,54)} = 1.25$, $p > 0.05$, $\eta_p^2 = 0.07$] (**Figure 2A**).

SAS, SDS, MA Addict Withdrawal Symptoms Scale

For SAS, we used repeated measures ANOVA and found that there was a significant time main effect [$F_{(3,54)} = 12.26$, $p < 0.001$, $\eta_p^2 = 0.41$]. We performed *post-hoc* tests, compared with the baseline ($M = 37.70$, $SEM = 3.50$), and the results showed that 10 Hz did not improve the anxiety of MA addicts on the 10th day ($M = 34.90$, $SEM = 3.27$), but improved the anxiety on the 15th day ($M = 29.90$, $SEM = 3.16$) and day 20 ($M = 27.30$, $SEM = 1.97$) to some extent; however, relative to baseline ($M = 33.20$, $SEM = 1.68$), iTBS did not have this effect on day 10 ($M = 28.40$, $SEM = 1.95$), day 15 ($M = 28.30$, $SEM = 2.63$), and day 20 ($M = 27.30$, $SEM = 2.61$). The group main effect was not significant [$F_{(1,18)} = 0.88$, $p > 0.05$, $\eta_p^2 = 0.05$], and there was no interaction between time and group [$F_{(3,54)} = 2.08$, $p > 0.05$, $\eta_p^2 = 0.10$] (**Figure 2B**).

For SDS, repeated measures ANOVA found that there was a significant time main effect [$F_{(3,54)} = 4.20$, $p < 0.05$, $\eta_p^2 = 0.19$]. In *post-hoc* tests, compared with the baseline ($M = 40.20$, $SEM = 3.17$), the results showed that depression in patients with MAUD was not improved by 10 Hz on the 10th day ($M = 36.80$, $SEM = 4.25$) or the 15th day ($M = 35.40$, $SEM = 3.90$), but improved to a certain extent on the 20th day ($M = 33.10$, $SEM = 2.73$). While relative to baseline ($M = 34.70$, $SEM = 2.72$), iTBS did not have this effect on day 10 ($M = 33.90$, $SEM = 3.60$), day 15 ($M = 31.30$, $SEM = 3.69$) or day 20 ($M = 30.60$, $SEM = 3.82$). The group main effect was not significant [$F_{(1,18)} = 0.68$, $p > 0.05$, $\eta_p^2 = 0.04$], and there was no interaction between time and group [$F_{(3,54)} = 0.32$, $p > 0.05$, $\eta_p^2 = 0.02$] (**Figure 2C**).

In terms of withdrawal scores of patients with MAUD, repeated measures ANOVA found a significant time main effect [$F_{(3,54)} = 9.77$, $p < 0.001$, $\eta_p^2 = 0.35$]. *Post-hoc* tests were performed and compared with baseline ($M = 13.20$, $SEM = 2.63$); the results showed that the withdrawal symptoms of MA addicts at 10 Hz did not improve on day 10 ($M = 10.50$, $SEM = 2.98$) or day 15 ($M = 9.70$, $SEM = 3.02$), whereas at day 20 ($M = 5.90$, $SEM = 1.79$), there was a certain degree of improvement relative to baseline ($M = 11.60$, $SEM = 1.38$). iTBS showed no improvement on day 10 ($M = 9.70$, $SEM = 1.51$) or day 15 ($M = 9.60$, $SEM = 2.38$), but there was some improvement on day 20 ($M = 7.80$, $SEM = 1.48$). The group main effect was not significant [$F_{(1,18)} = 0.00$, $p > 0.05$, $\eta_p^2 = 0.00$], and there was no interaction between time and group [$F_{(3,54)} = 1.06$, $p > 0.05$, $\eta_p^2 = 0.06$] (**Figure 2D**).

In total, three participants (1 in the 10 Hz group, two in the iTBS group) reported mild dizziness or scalp pain after the first two sessions. The symptoms were relieved within 1.5 h. None of the subjects dropped out of the study due to adverse reactions. In general, both 10 Hz and iTBS reduced the cue-induced craving of male addicts for MA. In total 10 Hz or iTBS could improve withdrawal symptoms in patients with MAUD.

DISCUSSION

This study suggests that iTBS is similar in effectiveness as 10 Hz in reducing cravings for MA addiction. Furthermore, there was no difference between the two stimulation forms for treating patients with MAUD. Both forms of rTMS (10 Hz and iTBS) can effectively reduce cue-induced cravings in patients with MAUD, which is consistent with the conclusions of previous studies (4–7, 24). This is of great significance for improving the efficiency and economic benefits of rTMS. rTMS cannot only reduce cue-evoked cravings in patients with MAUD, but also improve anxiety and depression scores to a certain extent, and even has a positive effect on withdrawal symptoms of patients with MAUD. According to our inquiries during the study, there was no significant difference in self-reported adverse events and serious adverse events between the two groups. iTBS had a slightly higher rate of pain but did not lead to a higher dropout rate. These results indicate that 3-min iTBS can be compared with 10-min 10 Hz as an intervention for the treatment of patients with MAUD.

Although this study has certain advantages, it also has several limitations. First, the study did not design a sham group and

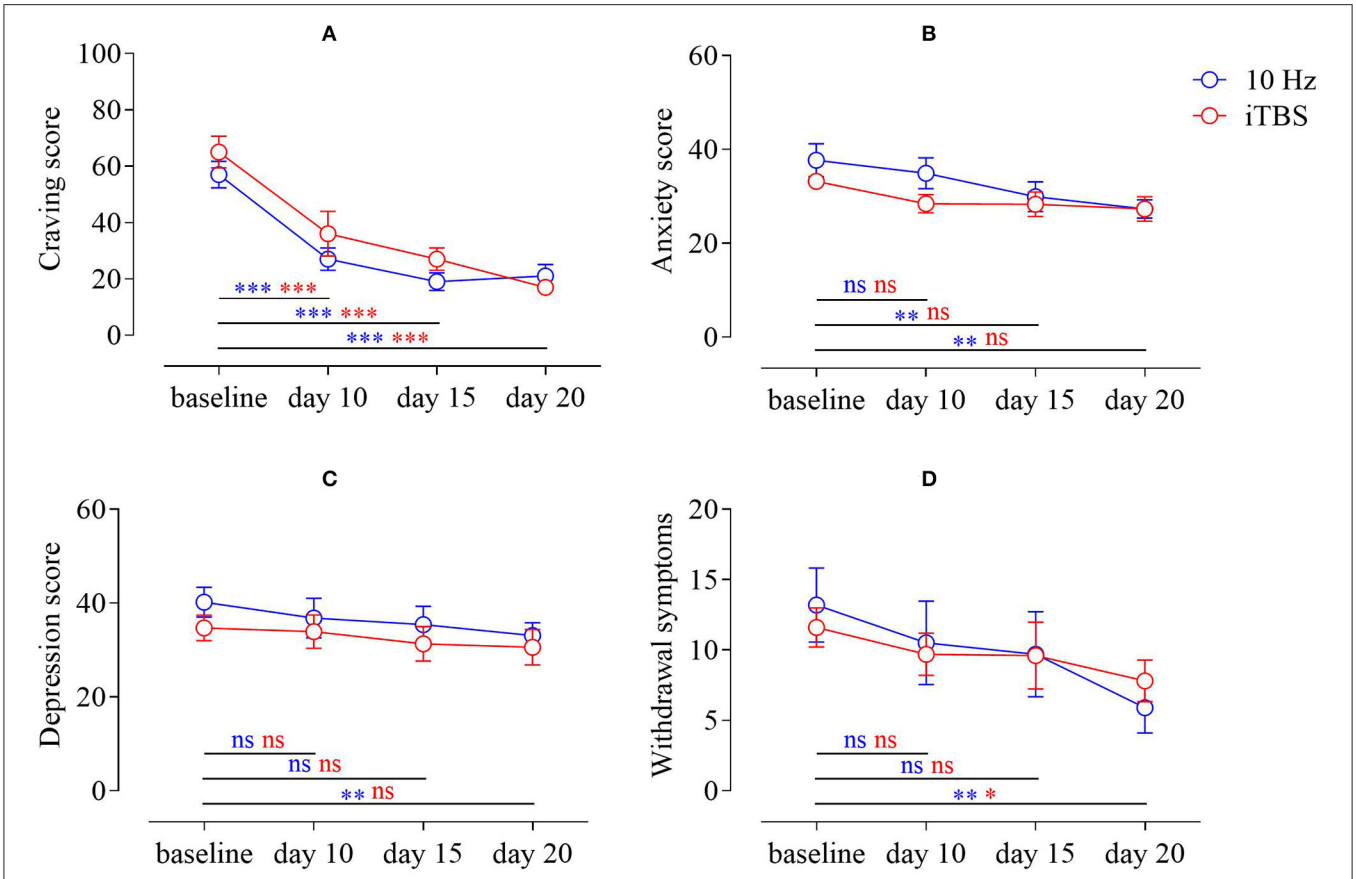

FIGURE 2 | (A) Change in craving scores of MA addicts in the two groups; **(B)** change in anxiety scores of MA addicts in the two groups; **(C)** change in depression scores of MA addicts; **(D)** change in withdrawal symptom scores of MA addicts in both groups (MA–methamphetamine).

could not properly eliminate time or placebo effects. Second, the treatment time for iTBS participants in each session was much shorter than that of the 10 Hz group, which may have led to a specific effect of time with iTBS. Third, we lacked MRI-guided neuronavigation in this study; although this method is not feasible or cost-effective for most studies conducted in addiction rehabilitation centers. As a reference, a previous study showed that in a similar experiment, BeamF3 (a heuristic method based on scalp measurements) could achieve the same stereotactic target as MRI (34). Fourth, since patients with MAUD had been in the rehabilitation center during treatment, there was a lack of urine tests to show whether the improvement in craving led to a reduction in consumption. Finally, due to the current epidemic situation, this study had a small sample size, imposing certain limitations. In future, the sample size should be expanded to further add to the significance of this study.

In conclusion, we found that iTBS may have similar therapeutic effect compared with 10 Hz in patients with MAUD. Typical iTBS treatment (including measuring motion thresholds, etc.) takes 5–10 min, while 10 Hz takes 15–20 min. Therefore, the number of patients with MAUD treated with each iTBS protocol per day can be increased by more than two-fold. In a broader sense, iTBS could have a more positive impact on the effects of enhancing treatment capacity, including improving treatment pathways, and reducing waiting times, thereby helping more patients with MAUD in addiction rehabilitation centers to benefit from the advantages of TMS and help physicians treat more patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by Ethics Committee of Nanjing Normal University (2017-004) and was registered in the Chinese Clinical Trial Registration Center (http://www.chictr.org.cn; no. ChiCTR17013610). The patients/participants

provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

QL: conceptualization. HS: methodology. YH and ZZ: formal analysis. QL, YS, and QW: investigation. QL and YS: data curation. QL and DD: writing, reviewing, and editing. All authors have read and agreed to the published version of the manuscript.

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Preventive Effects of Baclofen but Not Diazepam on Hippocampal Memory and Glucocorticoid Alterations After Prolonged Alcohol Withdrawal in Mice

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Our study aims at comparing in C57/Bl male mice, the impact of repeated injections of baclofen (an agonist of GABAB receptor) or diazepam (a benzodiazepine acting through a positive allosteric modulation of GABAA receptor) administered during the alcohol-withdrawal period on hippocampus-dependent memory impairments and brain regional glucocorticoid dysfunction after a short (1-week) or a long (4-week) abstinence. Hence, mice were submitted to a 6-month alcohol consumption (12%v/v) and were progressively withdrawn to water. Then, after a 1- or 4-weeks abstinence, they were submitted to a contextual memory task followed by measurements of corticosterone concentrations in the dorsal hippocampus (dHPC), the ventral hippocampus (vHPC) and the prefrontal cortex (PFC). Results showed that 1- and 4-week withdrawn mice exhibited a severe memory deficit and a significant abnormal rise of the test-induced increase of corticosterone (TICC) in the dHPC, as compared to water-controls or to mice still under alcohol consumption. Repeated daily systemic administrations of decreasing doses of diazepam (ranged from 0.5 to 0.12 mg/kg) or baclofen (ranged from 1.5 to 0.37 mg/kg) during the last 15 days of the withdrawal period, normalized both memory and TICC scores in the dHPC in 1-week withdrawn animals; in contrast, only baclofen-withdrawn mice showed both normal memory performance and TICC scores in the dHPC after a 4-week withdrawal period. In conclusion, the memory improvement observed in 4-week withdrawn mice administered with baclofen stem from the protracted normalization of glucocorticoid activity in the dHPC, a phenomenon encountered only transitorily in diazepam-treated withdrawn mice.

Keywords: hippocampus, prefrontal cortex, ethanol, glucocorticoids, GABA, memory, alcohol-withdrawal

INTRODUCTION

Evidence in humans and rodents have shown that alcohol-withdrawal (AW) markedly affects memory linked to hippocampal or prefrontal cortex (PFC) functional disorders and the hypothalamic-pituitary-adrenal axis (HPA) activity (1–7). Even if certain alterations induced by alcohol withdrawal on HPA axis dysfunction and fear reactivity may diminish or even disappear with time (8), studies in rodents also evidenced persistent brain regional glucocorticoids (GCs) disturbances after a chronic alcohol consumption in the PFC and the dorsal hippocampus (dHPC), up to 2 months after abstinence (9, 10). Congruently, we recently evidenced persistent working memory deficits associated with exaggerated corticosterone rises in the PFC up to 6-weeks after alcohol withdrawal in mice (11–14).

A way to reduce the HPA axis hyper-activity in abstinent subjects is to act on the GABAergic neurotransmission. Indeed, GABAergic neurons and GCs receptors (GR) have been found to be co-localized in the paraventricular nucleus of the hypothalamus, which demonstrates a critical importance to control the HPA axis activity through the GABAergic mediation (15–18). Baclofen and diazepam have an agonist action on GABAB and GABAA receptors, respectively, and are the main pharmacological treatments delivered to alcoholics during and after abstinence (19–22). These drugs have been found to reduce the HPA axis activity in withdrawn alcoholics (23–27) and to decrease addiction to alcohol both in humans and animals (19, 28–34). However, there are conflicting results on the relative efficacy of both drugs to counteract AW syndrome. In humans, both drugs induced comparable attenuation of the physical symptoms induced by AW, such as withdrawal seizures, anxiety, sweating and tremors over a 10 day withdrawal period (29) whereas a study showed a greater efficacy of the benzodiazepine chlordiazepoxide as compared to baclofen in reducing the physical symptoms of AW (35). In contrast, recent studies did not report different qualitative effects of baclofen and benzodiazepines in severe AW syndrome (36, 37). Overall, a recent review suggests that there is not enough evidence to support the use of baclofen as a first line treatment for AW syndrome (38). Most of these conflicting data have been however drawn after short periods of alcohol abstinence whereas their effects on longer periods of abstinence is lacking. So far, an unresolved issue remains to determine the relative efficacy of baclofen as regard to diazepam on protracted cognitive and GCs dysfunctions after a long period of alcohol abstinence.

As regards this issue, we implemented a mice model of long-lasting AW-induced GCs and cognitive dysfunction (12, 14). We showed that repeated diazepam administration during the withdrawal phase improved working memory and normalized GCs activity in the PFC after a short (1-Week) but not a long (6-Week) abstinence (11); in contrast, we evidenced that a sub-chronic administration of baclofen but not diazepam administered during the withdrawal phase normalized the abnormal HPA axis response to stress and reduced concomitantly the stress-induced alcohol-place preference after a long AW period, demonstrating a persistent preventing effects of baclofen but not diazepam on alcohol-seeking behavior (39).

The present study is a continuation of our previous work and aims to compare the relative efficacy of diazepam and baclofen in counteracting the persistent hippocampal-dependent memory and brain regional GCs disorders observed after AW in mice. To probe this issue, we first investigated the effects of a 1-week, (1-W) or 4-week (4-W) AW periods on memory in a serial contextual memory task known to involve the dHPC activity (40, 41). Additionally, corticosterone concentrations were quantified in the PFC, the dHPC and the ventral HPC (vHPC) of alcohol-withdrawn mice after behavioral testing. According to the data, we further compared the corrective effects of repeated systemic injections of either diazepam or baclofen administered during the withdrawal period on the protracted HPC-dependent memory dysfunction and GCs alterations in 1-W and 4-W-withdrawn animals.

MATERIALS AND METHODS

Animals

This study has been conducted on male C57BL/6 mice (Janvier, France). Mice were 3 months old upon arrival. They were housed by groups of 10 in collective cages (425 × 276 × 153 mm; 820 cm^2), in a temperature-controlled colony room (22 ± 1°C), under a 12:12 light-dark cycle (lights on at 7:00 a.m.). All test procedures were conducted during the light phase of the cycle between 8.00 and 12.00 a.m. During the food deprivation phase, mice (28 to 32 g) were housed individually and were maintained at 85–90% of their *ad libitum* body weight throughout the behavioral study. In both experiments 1 and 2, animals were daily handled 6 min/day during the week preceeding the beginning of the behavioral phase, to reduce the emotional reactivity to he experimenter.

Alcohol Intake and Withdrawal Procedures

The experimental device is depicted in **Figure 1**. At the age of 4 months, mice were given as their sole liquid source, water containing increasing concentrations of ethanol as follows: 4% (v/v) the first week, 8% (v/v) the second week and 12% (v/v) for the 6 consecutive months. After alcohol exposure, alcohol was progressively replaced by water by steps of 4% every 3 days, then water to the end of experiments. Behavioral testing began either after 1-week (1-W-withdrawn) or 4-weeks (4-W-withdrawn) of water supply (see **Figure 1**). The alcohol group was submitted to the same alcohol exposure as withdrawn animals, except that they were still under alcohol intake at the time of experiments. Control animals received permanently water. All procedures were performed between 8:00 and 12:00 a.m.

Apparatus

Memory testing occurred in a four hole-board apparatus (45 × 45 × 30 cm) enclosed with gray Plexiglas walls. On the floor, 4 holes opening on a food cup (3 cm diameter × 2.5 cm in depth) were located 6 cm away from the sidewalls. Photocells located inside each hole quantified automatically the number of head-dips.

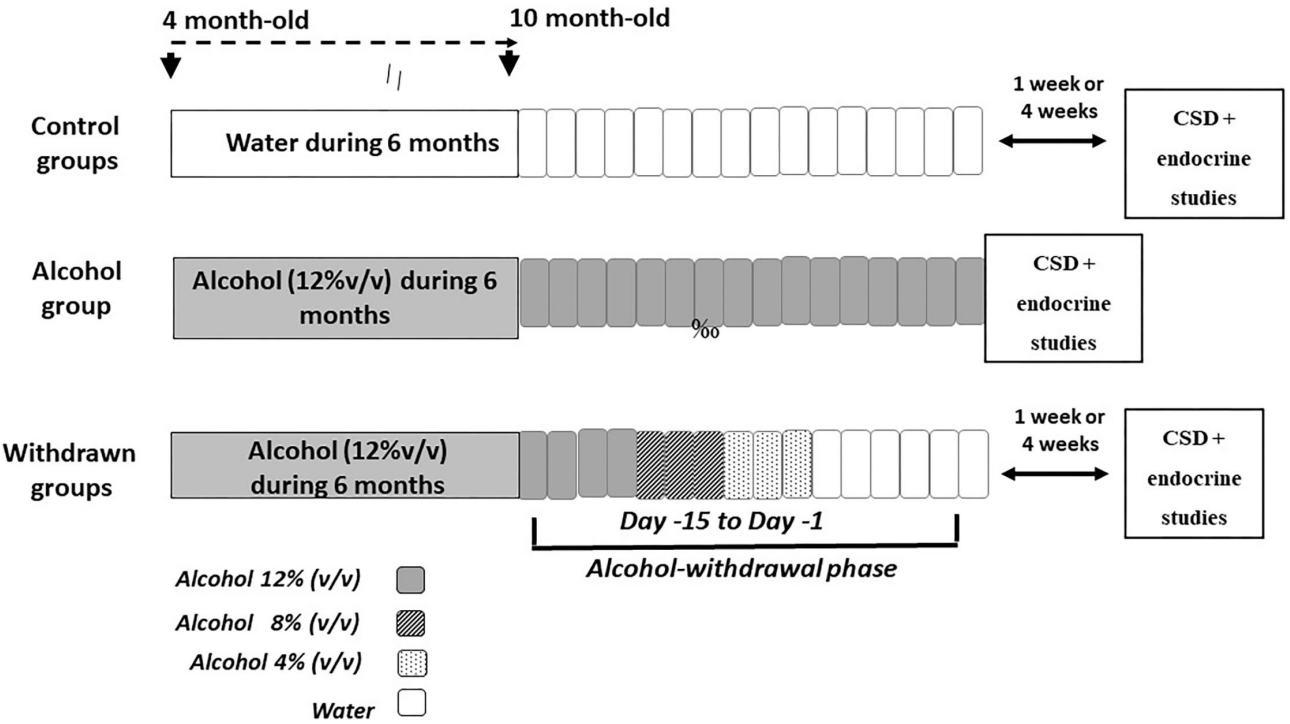

FIGURE 1 | Schematic overview of the alcohol exposure and withdrawal procedures. The withdrawn groups were submitted to a 6-month exposure to alcohol (120% v/v) followed by a withdrawal phase that lasted 15 days (from Day−15 to Day−1), during which alcohol was progressively withdrawn from the solution by steps of 4% (Day−15 to Day−12: alcohol 12%; Day−11 to Day−9: alcohol 8% v/v; Day−8 to Day−6: alcohol 4%; then water for the remaining days). Either 1- or 4-weeks after the end of the withdrawal phase, mice were submitted to memory testing in the CSD task followed by the endocrine study. The alcohol group was exposed to a 6-months alcohol exposure and was still under the alcohol solution at the time of memory testing. Control groups were exposed to the same general schedule except that they received permanently water as the sole source of fluid.

Contextual Serial Discrimination Task

The contextual and serial memory task (CSD) has been described in full in previous papers (40, 42, 43) and in **Figure 2**.

All mice were first food-deprived before being submitted to the behavioral test. The food deprivation procedure is aimed at increasing the motivation for the pellets used as reinforcing agents in the hole-board. To that aim, mice were given a limited quantity of food for 3 consecutive days (3 g the first day, 2 g the second day and finally 1 g the third day) before the beginning of the behavioral experiment. This food regimen induced a progressive weight loss comprised between 10 and 12% of the initial weight (before the food deprivation procedure). During this period, some pellets used in the behavioral test were placed in their cage in order to get them used to eating them.

During the acquisition phase, food-deprived mice learned two successive discriminations (D1 and D2, 6 min each) performed on two different floors differing by the color and texture (white and smooth or black and rough). The floors are alternated from one mouse to another and from one discrimination to another in order to avoid a bias related to their positioning in the series. The two serial discriminations were separated each by a 2-min time interval during which the mouse was placed in its home cage. For D1 and D2, ten 20-mg pellets (Bioserv, France) were available only in a specific hole out of the 4 holes of the device; the baited holes at D1 and D2 of the acquisition phase were changed from one mouse to another but in all cases, the baited holes at D1 and D2 were systematically opposite and symmetrical.

The retention phase occurred 24 h later, mice were replaced for 6 min on the floor used specifically at D1, with no food pellets in the apparatus. We previously showed that the memory of D1 was dependent on the dHPC activity but not on vHPC or PFC ones (40, 41, 43, 44). Two measures were taken: (1) the number of head-dips in the "correct" hole (parameter 1: head-dips into the hole previously baited on the same floor-context); (2) the number of head-dips in the "interfering" hole (parameter 2: head-dips into the hole previously baited on the other floor-context at D2). Parameters 1 and 2 allowed calculus of the "discrimination index" (% correct responses–% interfering responses). A positive difference means that mice explore more often the contextually correct hole as compared to the interfering spatial one, so that the higher the discrimination index, the more accurate is contextual memory (45).

Pharmacological Procedure

Two weeks before the pharmacological treatments, mice were housed in individual cages (331 × 159 × 132 mm; 335 cm^2) with continuous access to alcohol. Diazepam (Valium®, Roche) and baclofen (Baclofen®, Mylan) were diluted in a vehicle solution

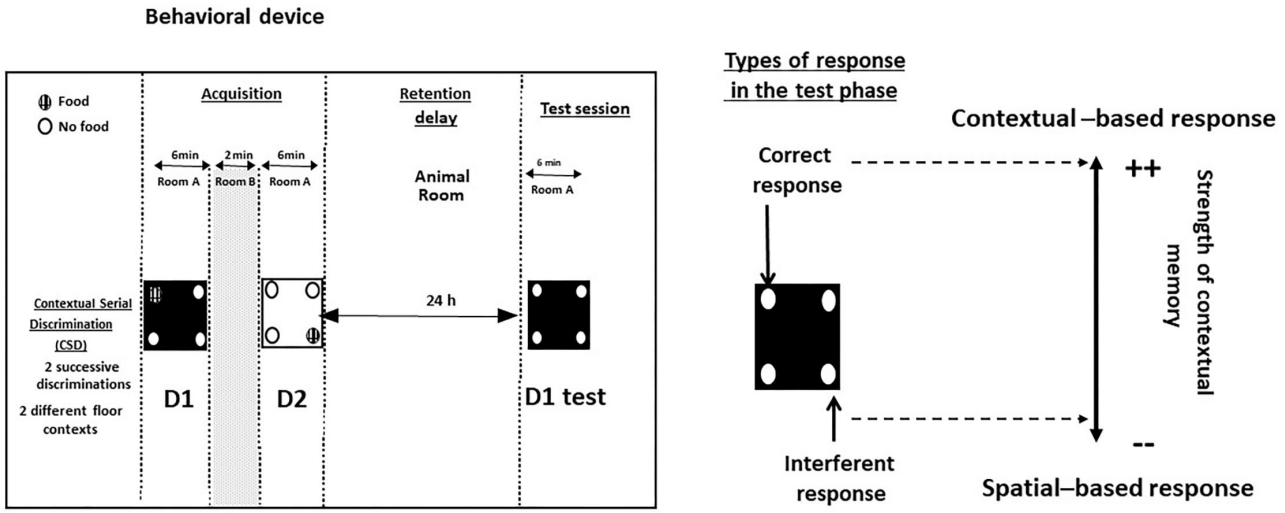

FIGURE 2 | (A) Behavioral device for the study of contextual memory in the CSD task; **(B)** Types of responses during the test phase. Correct responses: head-dips into the hole previously baited at D1 of the acquisition phase; interferent response: head-dips into the hole baited at D2 of the acquisition phase.

(0.9% NaCl) and injected intraperitoneally (10 mL/kg, i.p., 1 injection/day). Drug doses were based on pilot experiments and previous studies (46, 47). In all experiments, drugs were administered over the 15 final days of the withdrawal phase while mice were still under a 12% ethanol (v/v) regimen at the beginning of the pharmacological treatments (**Figure 3**) according to previous studies (11, 39). Doses were progressively decreased from Day-15 to Day-1, to avoid potential negative effects of an abrupt cessation of drug administrations. Behavioral testing began either 1- or 4-weeks after the last injection. Our previous biological analyses showed that, at the time of memory testing, both diazepam and baclofen compounds were no longer detectable in the blood of treated animals and their controls (39).

Corticosterone Assays

As shown in earlier studies, the maximum peak of corticosterone in the hippocampus or the PFC was observed 1 h after the occurrence of behavioral testing or the onset of a stressor (11, 40, 41, 48–50). Thus, in the present study, the brains were collected 1 h after behavioral testing. All mice were replaced in their individual cage in the colony room during the 1-h delay separating the end of behavioral testing and sacrifice. After this delay was elapsed, mice were briefly anesthetized (Isoflurane®) during a brief 30-s inhalation exposure followed by a rapid decapitation. The choice of isoflurane relies on the fact that studies have shown that this anesthetic has little or no effect on plasma corticosterone levels in male rats (51–53); in addition, the very short time between anesthesia and decapitation reduces the risk of interaction with brain corticosterone levels. After decapitation, the brains were quickly extracted according to the stereotaxic atlas of Lehmann for mouse brain (54); prefrontal cortex (from bregma +2.80 mm to +1.80 mm); dorsal hippocampi (from bregma −1.20 to −2.20 mm) and ventral hippocampi (from bregma −2.80 mm to −3.80 mm) and were rapidly dissected on ice using a brain matrix (ASI instruments, USA) to perform serial coronal slices (55); the hippocampus and cortex were snap-frozen on dry ice, then stored at −80°C.

Corticosterone Analyses

Tissues were homogenized with a small Dounce potter in buffer containing 300 µL RIPA Lysis Buffer, 6 µL PMSF and a protease inhibitor cocktail 1:1000 (Euromedex, France). The homogenized tissues were sonicated by ultra sounds on ice-cold (9 pulses it 5 s, amplitude 40) and centrifuged at 1,300 g for 30 min at 4°C. Supernatants were kept and stored at −80°C until quantification. Samples were prepared (dilution 1/3, 15 µL; 50 µL total) for colorimetric evaluation in a spectrophotometer (Victor, France). Corticosterone was measured using a commercial ELISA assay (Corticosterone Immunoassay, Euromedex, France).

Blood Alcohol Concentration Measurement

Samples (20 ul) of blood were proceeded for blood alcohol concentration using an EnzyChrom™ Ethanol Assay Kit (ECET-100, BioAssay Systems, Euromedex) according to the manufacturer's instructions.

Statistical Analyses

Data were expressed as Means ± SEM. Analyses were performed using the Statview 5.0 software (Statistical Analysis System Institute Inc., NC, USA). The data were analyzed using one or two-ways ANOVA to determine main factor effects and their interaction, and followed by appropriate post *hoc* tests (Bonferroni/Dunnett). Correlation analyses were performed by the Spearman's correlation coefficient R. For all tests, $p<0.05$ was considered statistically significant.

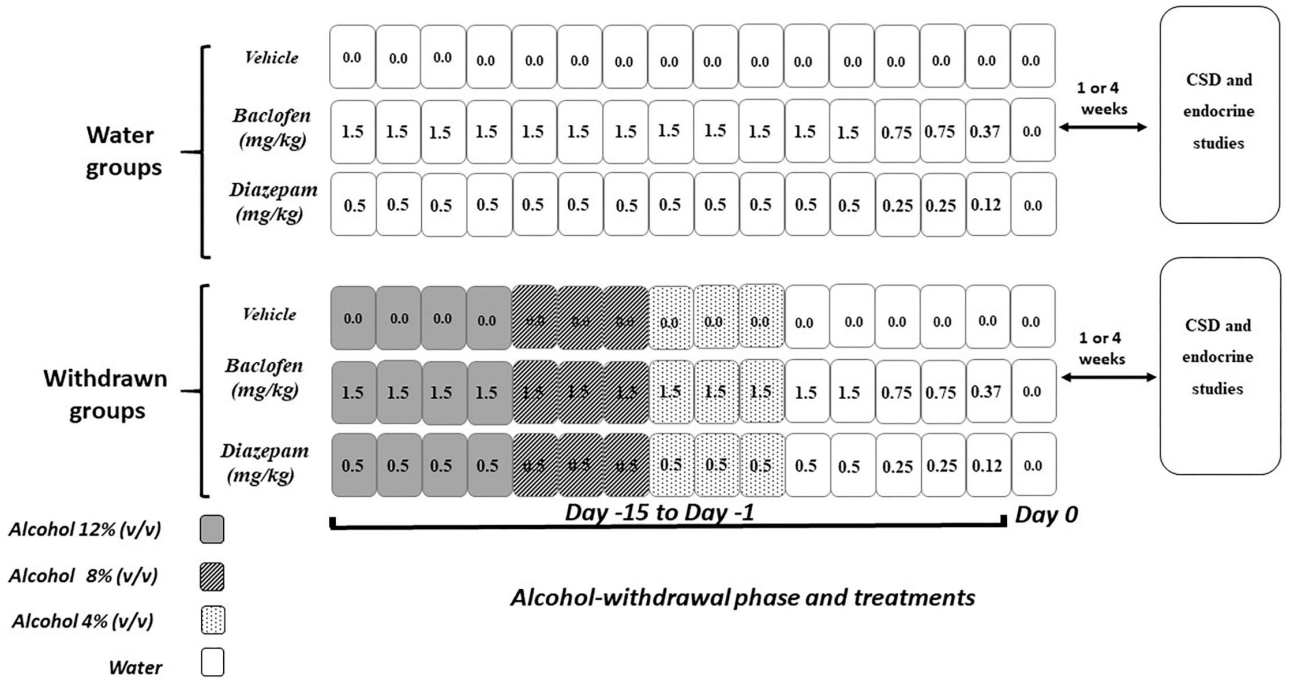

FIGURE 3 | Pharmacological procedure. Diazepam and baclofen were administered by intraperitoneal injection (1/day) both in control (Water groups, upper part) and in withdrawn mice (withdrawn groups, lower part) during 15 consecutive days (Day−15 to Day−1). The pharmacological treatments started when withdrawn mice were still under the alcohol regimen (12% v/v, 4 consecutive days, dark rectangles), then 8% v/v (next 3 consecutive days gray rectangles), and finally 4% v/v (3 remaining consecutive days, light gray rectangles) followed by water (white rectangles). All mice received on the first 12 days of treatment either vehicles or diazepam at 0.5 mg/kg or baclofen at 1.5 mg/kg, followed at Days 3 and 2 by doses being half of the starting dose-−0.25 and 0.75 mg/kg, respectively, for diazepam and baclofen—and finally (Day−1) by 0.12 or 0.37 mg/kg diazepam and baclofen doses, respectively. Control groups receiving water were submitted to the same pharmacological procedures as those used in withdrawn groups. Behavioral testing and endocrinological studies occurred either 1- or 4-weeks after the last injection.

RESULTS

Alcohol Intake and Concentration in Blood

At the end of the feed deprivation period, the weights of the animals ranged from 27.3 ± 0.8 g (minimum) to 31.7 ± 0.6 g (maximum); all mice showed a weight loss of 10% to 12% of their initial weight. Among the withdrawn groups submitted to the CSD tasks, the mean daily alcohol consumption (mL) over the 6-month alcohol exposure was 3.85 ± 0.42 mL/mouse and no significant between-groups difference was observed [$F_{(7,57)} = 1.02$; $p = 0.14$]. Thus, exposure to alcohol was considered as equivalent among the withdrawn groups. In comparison, the mean daily water consumption was measured in two groups of water controls; the mean daily water consumption was 3.1 ± 0.6 mL which did not significantly differ from alcohol-treated groups ($p < 0.09$). The blood concentration of ethanol was quantified with a commercial Elisa kit (Euromedex, France) and was 0.49 ± 0.24 g/L (10.7 ± 5.2 mM or 0.62 ± 0.30%) in mice still under the alcohol regimen in experiment 1 and below the limit of quantification in all withdrawn groups (0 ± 0 g/L) of the study at the time of memory testing.

1st Experiment: AW Induces Long-Lasting Contextual Memory Deficits Associated With Excessive Test-Induced Increase of Corticosterone in the Dorsal Hippocampus

In Experiment 1, independent groups of 1-W and 4-W-withdrawn mice were compared to mice still exposed to alcohol (Alcohol) and to Water-controls. Each group consists of 9 mice.

Memory Task

Acquisition Phase (Data Not Shown)

ANOVA's analyses did not evidence a significant between-groups difference on the total amount of head-dips both on the first [$F_{(3,32)} = 1.02$; $p = 0.11$] and second discriminations [$F_{(3,32)} = 0.98$; $p = 0.17$]. No significant between-group difference was observed on the % number of head-dips in the baited hole of the first and second discrimination ($p > 0.10$ in both analyses).

Test Phase

No significant between-group difference was observed on the total number of head-dips [$F_{(3,32)} = 0.71$; $p = 0.36$; Alcohol: 47.8

± 4.5; Water-controls: 49.3 ± 6.2; 1-W-withdrawn: 51.8 ± 3.1; 4-W-withdrawn: 47.6 ± 5.2].

The discrimination index was significantly different among the groups [$F_{(3,32)} = 23.07$; $p < 0.0001$; **Figure 4A**). Water-control and Alcohol groups exhibited a positive index [+48.09 ± 6.5% and +51.0 ± 5.3%, respectively; $F_{(1,16)} = 0.11$; $p = 0.73$] whereas 1- and 4-W-withdrawn groups showed a negative one (−28.8 ± 8.9% and −26.6 ± 13.8%, respectively; $F_{(1,16)} = 0.019$; $p = 0.89$). Both 1- and 4-W withdrawn mice differed significantly from Alcohol and Water-control groups (all $F > 15$; all ps < 0.0001).

Brain Regional Corticosterone

Naïve Condition

The basal corticosterone concentration was measured in naïve mice from the four cohorts left undisturbed in their home cage during behavioral testing. Corticosterone concentrations are expressed in ng/mL in **Table 1**. No significant between-group differences were observed in the dHPC [$F_{(3,8)} = 0.62$; $p = 0.61$], the vHPC [$F_{(3,8)} = 0.94$; $p = 0.46$] and the PFC [$F_{(3,8)} = 2.15$; $p = 0.17$].

Test Condition

Since no significant difference was observed in basal corticosterone concentrations in the naïve condition, the test-induced increase of corticosterone concentrations (TICC) was expressed for each group as a percent variation of the naïve condition [100 × (Test - Naive)/Naive].

Dorsal Hippocampus

A significant between-group difference was observed [$F_{(3,10)} = 7.72$; $p = 0.0006$] (**Figure 4B**). The Alcohol group exhibited a lower TICC score as compared to Water-controls (+144.9 ± 16.26% vs. +242.6 ± 11.69% respectively; $p = 0.0002$).

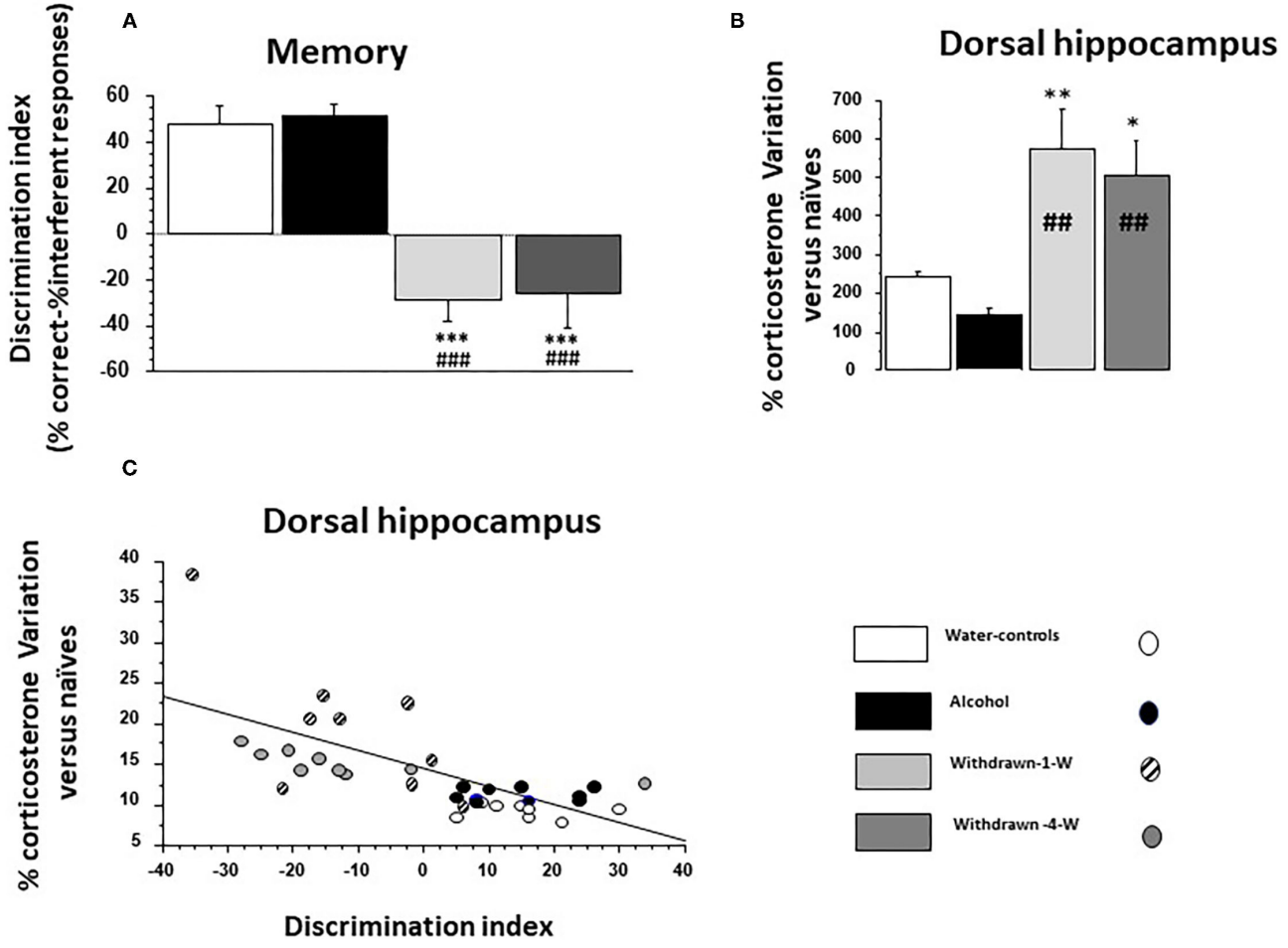

FIGURE 4 | (A) Memory: the discrimination index is significantly lowered in both 1- and 4-W withdrawn groups as compared to both the water-control group (***$p < 0.001$) and the Alcohol group (###$p < 0.001$); **(B)** % test-induced increases of corticosterone concentration (TICC) in the dorsal hippocampus (dHPC) from naïve condition; as can be observed, 1- and 4-W withdrawn mice exhibited a lower TICC score as compared to water-controls (** and *: $p < 0.01$ and $p < 0.05$, respectively) and to Alcohol mice (##$p < 0.01$ in both comparisons); **(C)** Regression analysis between individual TICC score in the dHPC and discrimination index in water-controls (white circle), alcohol (black circles), 1-W (hashed gray circles), and 4-W (hashed dark gray circles) groups. A significant negative correlation was observed, the higher being the TICC score, the lower being the index discrimination.

TABLE 1 | Basal corticosterone concentrations (ng/mL) in naïve condition in the dorsal hippocampus, the ventral hippocampus and the prefrontal cortex.

	Dorsal hippocampus	Ventral hippocampus	Prefrontal cortex
Water-controls	3.88 ± 0.31	4.80 ± 0.50	3.70 ± 0.20
Alcohol	4.91 ± 0.39	3.84 ± 0.61	3.77 ± 0.24
1-W-withdrawn	4.38 ± 0.26	3.96 ± 0.62	3.89 ± 0.34
4-W-withdrawn	3.76 ± 1.0	4.12 ± 0.46	2.87 ± 0.45

No significant between-group difference was observed.

In contrast, TICC scores were significantly increased in 1W-withdrawn (+574.68 ± 103.9 %) and 4W-withdrawn groups (+505.07 ± 90.9%) as compared to Water-controls ($p = 0.009$ and $p = 0.016$, respectively) and to the Alcohol group ($p = 0.0016$ and $p = 0.0022$, respectively).

Ventral Hippocampus

ANOVA analyses evidenced no significant between-group difference [$F_{(3,10)} = 2.31$; $p = 0.09$]. Both the Water-control and Alcohol groups exhibited comparable TICC scores (+239.07 ± 24.6% and +260.4 ± 38.48%, respectively) which were however higher in 1W-withdrawn (+445.5 ± 86.8%) and 4W-withdrawn groups (+396.14 ± 80.5%).

Prefrontal Cortex

No significant between-group difference was observed [$F_{(3,10)} = 2.59$; $p = 0.07$]. Alcohol mice (+295.18 ± 20.91%) exhibited a higher TICC score as compared to Water-controls (+192.5 ± 23.35%) which was increased in 1W- and 4W-withdrawn groups (+421.35 ± 68.21% and +373.78 ± 89.98 %, respectively).

Correlation Analyses

Dorsal Hippocampus

The discrimination index correlated negatively with TICC scores (**Figure 4C**; R = −0.67; $p < 0.0001$). More specifically, Water-control and Alcohol mice exhibited a high discrimination index associated with low TICC scores; in contrast, 1W and 4W-withdrawn groups exhibited a low discrimination index associated with high TICC scores.

Ventral Hippocampus

No significant correlation was observed between the discrimination index and TICC scores (R = 0.14; $p > 0.10$).

Prefrontal Cortex

No significant correlation was observed between the discrimination index and TICC scores (R = 0.21; $p > 0.10$).

Experiment 2. Baclofen but Not Diazepam Reversed the Long-Term Memory Impairments and GCs Alterations in Withdrawn Mice

Experiment 2 was run using 12 groups of mice: 1- and 4-W withdrawn mice receiving either vehicle, diazepam or baclofen ($N = 8$ for all groups except 1-W diazepam: $N = 7$) and their respective water controls ($N = 8$ for all groups except 1-W water control injected with vehicle or baclofen: both $N = 7$).

Memory

Acquisition Phase (Data Not Shown)

No significant between-group differences were observed on the total number of head-dips and the % of head-dips in the baited holes of acquisitions 1 and 2 ($p > 0.10$ in all analyses).

Test Phase

Data are depicted in **Figure 5A**. A two-way ANOVA showed significant effects of groups (withdrawn 1- and 4-W, vehicles 1- and 4-W; $F_{(3,81)} = 56.02$; $p < 0.0001$), drugs (vehicle, baclofen and diazepam; $F_{(2,81)} = 43.53$; $p < 0.001$) and the interaction between groups and drugs was also significant [$F_{(6,81)'} = 28.1$; $p < 0.0001$].

1-W-Withdrawn and Water-Control Groups

A two-way ANOVA showed significant effects of groups (withdrawn-1-W and vehicles-1-W; $F_{(1,40)} = 32.36$; $p < 0.0001$), drugs (vehicle, baclofen and diazepam; $F_{(2,40)} = 9.03$; $p < 0.0006$) and the interaction between groups and drugs was also significant [$F_{(2,40)} = 9.07$; $p < 0.0006$]. Vehicle-withdrawn mice exhibited a lower discrimination index (-16.20 ± 7.3) as compared to vehicle-Water-controls (+46.69 ± 5.9; $p < 0.0001$). Both 1-W-withdrawn diazepam (+29.37 ± 8.86) and 1-W-withdrawn baclofen (+35.04 ± 2.30) groups exhibited higher discrimination indexes as compared to vehicle-withdrawn mice ($p = 0.0005$ and $p < 0.0001$, respectively). In contrast, they did not statistically differ from vehicle-Water-controls ($p = 0.076$ and $p = 0.13$, respectively). In water-controls, diazepam (+46.51 ± 8.93) or baclofen (+46.71 ± 3.38) did not modify the discrimination index as compared to the vehicle-Water-control group ($p = 0.97$ and $p = 0.78$, respectively).

4-W-Withdrawn and Water-Control Groups

A two-way ANOVA showed significant effects of groups [withdrawn-4-W and vehicles-4-W; $F_{(1,41)} = 145.5$; $p < 0.0001$], drugs (vehicle, baclofen and diazepam; $F_{(2,41)} = 57.19$; $p < 0.0001$] and the interaction between groups and drugs was also significant [$F_{(2,41)} = 64.87$; $p < 0.0001$]. Vehicle-withdrawn mice exhibited a lower discrimination index as compared to vehicle-Water-controls (−37.42 ± 6.76 and +52.35 ± 5.35, respectively; $p < 0.0001$). Baclofen-withdrawn mice exhibited a higher discrimination index (+69.08 ± 5.79) as compared to vehicle-withdrawn mice ($p < 0.0001$) which was not observed in diazepam-withdrawn mice (−42.22 ± 4.46; $p = 0.56$ vs. vehicle-withdrawn mice). Baclofen-withdrawn mice did not statistically differ from vehicle-Water-controls ($p = 0.052$) but significantly differed from diazepam-withdrawn mice ($p <$

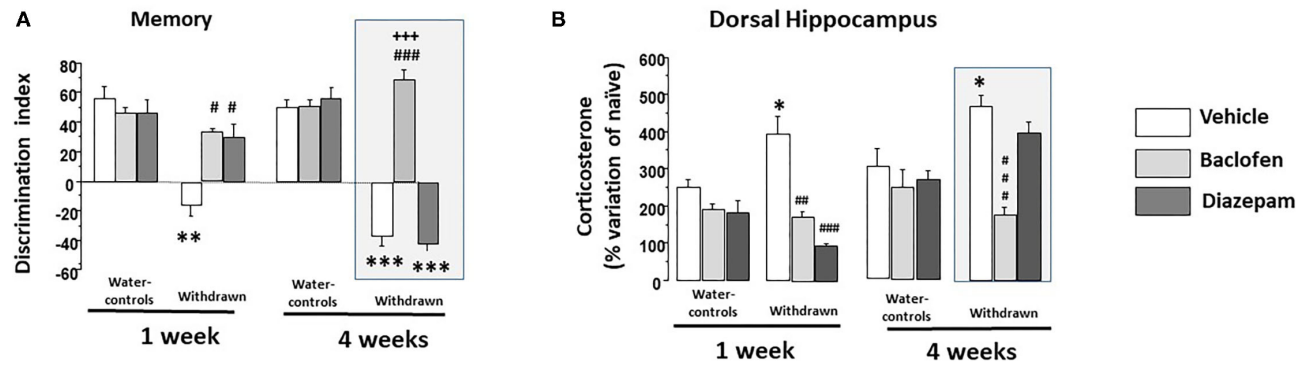

FIGURE 5 | (A) Memory: in 1-W groups (left part), water-controls being injected either with vehicle (white square), diazepam (light gray square) or baclofen (dark gray square) exhibited high and similar discrimination indexes; in contrast, 1-W vehicle-withdrawn mice exhibited a significant negative discrimination index as compared to the vehicle-water group (**$p < 0.01$). 1-W withdrawn groups treated with diazepam or baclofen did not significantly differed from vehicle-water controls ($p > 0.10$ in each comparisons), which were significantly higher than that of the vehicle-withdrawn group (##$p < 0.01$ in both comparisons); in 4-W groups (right part), water-controls treated with vehicle or diazepam or baclofen exhibited high and similar discrimination indexes; in contrast, 4-W vehicle or diazepam-withdrawn mice exhibited significant negative discrimination indexes as compared to the vehicle-water group (***$p < 0.001$ in both comparisons). In contrast, baclofen-withdrawn mice exhibited performance similar to those of vehicle-water controls which were significantly higher than that of the vehicle-withdrawn and diazepam-withdrawn groups (###$p < 0.001$ in both comparisons); **(B)** Test-induced increase of corticosterone concentration (TICC) in the dorsal hippocampus (dHPC) from naïve condition; as can be observed, 1- and 4-W vehicle-withdrawn mice exhibited a higher TICC score as compared to respective vehicle-Water-controls (*$p < 0.05$ in each comparison). Both diazepam and baclofen 1-W-withdrawn mice exhibited a significant attenuation of the TICC score as compared to vehicle -withdrawn 1-W mice (### and ##: $p < 0.001$ and $p < 0.01$, respectively); in contrast however, only baclofen-withdrawn mice still exhibited a significant attenuation of the TICC score in 4-W-withdrawn animals as compared to both vehicle-treated and diazepam-treated withdrawn groups (###$p < 0.001$ in both comparisons). $^{\#}p < 0.05$.

0.0001); in contrast, diazepam-withdrawn mice still exhibited a significant lower discrimination index as compared to vehicle-Water-controls ($p < 0.001$). Diazepam and baclofen Water-control groups (+55.73 ± 7.43 and +50.66 ± 4.30, respectively) did not statistically differ from vehicle ones ($p = 0.71$ and $p = 0.80$, respectively).

Brain Regional Corticosterone Concentrations

Insofar as the correlation between the discrimination index and TICC score was statistically significant only with dHPC corticosterone scores, the endocrinal studies in experiment 2 were performed in the dHPC only.

Naïve Condition

Data are expressed in **Table 2**. No significant between-group difference was evidenced observed [$F_{(11,36)} = 1.24$; $p > 0.10$].

Test Condition

Since no significant difference was observed in basal corticosterone concentration in the naïve condition, the test-induced increase of corticosterone concentrations (TICC) was expressed for each group as a percent variation of the naïve condition [100 × (Test - Naive)/Naive].

Data are depicted in **Figure 5B**. A two-way ANOVA showed significant effects of groups [withdrawn 1- and 4-W, vehicles 1- and 4-W; $F_{(3,81)} = 12.34$; $p < 0.0001$], drugs [vehicle, baclofen and diazepam; $F_{(2,81)} = 27.12$; $p < 0.001$] and the interaction between groups and drugs was also significant [$F_{(6,81)} = 7.73$; $p < 0.0001$].

In the 1-Week groups, a two-way ANOVA showed no significant effects of groups [withdrawn-1-W and vehicles-1-W; $F_{(1,40)} = 0.40$; $p = 0.52$], but a significant effect of drugs [vehicle, baclofen and diazepam; $F_{(2,40)} = 23.89$; $p < 0.0001$] and the interaction between groups and drugs was also significant [$F_{(2,40)} = 9.53$; $p < 0.0004$]. More specifically, vehicle 1-W-withdrawn mice (+394.6 ± 46.6%) exhibited a significant increase of TICC scores as compared to respective Water-control mice (+248.6 ± 24.58%; $p = 0.019$). Diazepam-1-W-withdrawn mice exhibited a significant reduction of TICC scores as compared to vehicle-withdrawn mice (+98.2 ± 6.1%; $p < 0.0001$); a similar reduction of TICC scores was also observed in baclofen-treated withdrawn mice (+173.8 ± 13.2%; $p < 0.0004$ vs. vehicle 1-W-withdrawn mice).

In the 4-week groups, a two-way ANOVA showed significant effects of groups [withdrawn-4-W and vehicles-4-W; $F_{(1,41)} = 6.97$; $p < 0.011$], drugs [vehicle, baclofen and diazepam; $F_{(2,41)} = 13.38$; $p < 0.0001$], and the interaction between groups and drugs was also significant [$F_{(2,41)} = 6.87$; $p < 0.0027$]. More specifically, Vehicle 4-W-withdrawn mice exhibited a significant increase of the TICC scores as compared to respective Water-controls (+468 ± 29.01% and +301.01 ± 50.4%, respectively; $p = 0.012$) which was significantly lowered in baclofen (+175.7 ± 29.01%) but not in diazepam-treated withdrawn groups (+398.37 ± 25.9%; $p < 0.0001$ and $p = 0.09$, respectively, vs. Vehicle-4-W-withdrawn mice). In addition, baclofen-withdrawn mice differed significantly from diazepam-withdrawn ones ($p < 0.0001$).

Correlation Analyses

ANOVA analyses performed in all groups within Experiment 2 showed a significant negative correlation between the

TABLE 2 | Basal corticosterone concentrations (ng/mL) in naïve condition in the in the dorsal hippocampus.

Groups	*N*	Corticosterone in ng/mL
Vehicle Water-controls 1-week	4	4.23 ± 0.30
Baclofen Water-controls 1-week	4	4.26 ± 0.77
Diazepam Water-controls 1-week	4	4.12 ± 0.64
Vehicle 1-week-withdrawn	4	3.97 ± 0.49
Baclofen 1-week-withdrawn	4	4.21 ± 0.58
Diazepam 1-week-withdrawn	4	3.64 ± 0.69
Vehicle Water-controls 4-week	4	3.90 ± 0.40
Baclofen Water-controls 4-week	4	4.08 ± 0.61
Diazepam Water-controls 4-week	4	4.00 ± 0.85
Vehicle 4-week-withdrawn	4	4.20 ± 0.38
Baclofen 4-week-withdrawn	4	3.60 ± 0.52
Diazepam 4-week-withdrawn	4	4.35 ± 0.53

No significant between-group difference was observed.

discrimination index and the TICC score ($R = -055; p < 0.0001$). More specifically, the higher is the discrimination index, the lower is the TICC score.

1-W Groups

The discrimination index correlated negatively with TICC scores ($R = -0.65$; $p < 0.0001$). Interestingly, as shown in **Figure 6** (left), baclofen and diazepam-treated mice exhibited a high discrimination index and a low TICC score similar to vehicle-controls, whereas vehicle-withdrawn mice exhibited an opposite pattern, that is to say a high TICC score and a low discrimination index.

4-W Groups

The discrimination index correlated negatively with TICC scores ($R = -0.57$; $p < 0.0001$). Interestingly, as shown in **Figure 6** (right), baclofen-treated mice exhibited a high discrimination index and a low TICC score similar to vehicle-controls; in contrast to what was observed in 1-W animals however, diazepam-treated mice exhibited an opposite pattern, that is to say a high TICC score and a low discrimination index, therefore similar to that of vehicle-withdrawn mice.

DISCUSSION

Our study aims at comparing the impact of repeated injections of baclofen or diazepam administered during the alcohol-withdrawal period on hippocampus-dependent memory impairments and brain regional GCs dysfunction after a short (1-W) or a long (4-W) abstinence from alcohol. Results showed that both withdrawn groups exhibited contextual memory deficits and significant abnormal rise of the test-induced increase of corticosterone specifically in the dHPC compared to water controls. Interestingly, while both chronic diazepam or baclofen treatment during the withdrawal period rescued contextual memory deficits and prevented the test-induced GCs alterations in 1-W withdrawn animals, only baclofen-treated animals showed memory performance and test-induced rise of corticosterone similar to those of water-controls after a 4-Week withdrawal period.

Alcohol Intake

A prime issue to be addressed rested with assessing whether the memory and endocrine alterations observed in alcohol-withdrawn mice may be caused by differences in diets. Findings evidenced that differences in the daily amount of food consumption may not be held accountable for the deficits since we have already demonstrated that pair-fed animals receiving an isocaloric solution of dextri-maltose during the same duration (6 months period) of alcohol exposure exhibited no memory deficits (56). Moreover, since most mice strains exhibit low appetence for alcohol, they often restrain their daily liquid intake and exhibit signs of dehydration. Such was not the case in our study, since the C57BL/6 strain is an alcohol-preferring strain (57); further, mice submitted to alcohol intake drank a slightly higher daily amount of liquid solution as compared to water controls. Thus, alcohol-withdrawn mice were not dehydrated during alcohol exposure. Finally, the daily alcohol intake during alcohol exposure in the different withdrawn groups was similar: hence, we may legitimately infer that all groups were equally exposed to alcohol, thus allowing for valuable comparisons among the different cohorts.

Moreover, it has been already reported that GABAB and GABAA receptor agonists modulate alcohol drinking (58, 59) and even might have an opposite effect on alcohol drinking as they have for food intake (60).In the present study however, the interaction between alcohol drinking and GABA agonists injections occurred only during the first 10 days of the withdrawal phase, during which the alcohol concentration was progressively decreased to tap water. It is very unlikely that such a short interaction period had any impact on the long-lasting cognitive dysfunction observed in alcohol withdrawn animals.

Alcohol-Withdrawal Produced Long-Lasting Memory Impairments and Brain Regional GCs Dysfunction in the Dorsal Hippocampus

In the present study, we did not directly measure locomotor activity in both the acquisition and test phases of the task. It is known that alcohol consumption and withdrawal may induce side effects such as an alteration of locomotor activity, even though contrasting data are reported according to the duration of the treatments and withdrawal period (see in 60). However, since alterations in locomotor activity can potentially alter the performance in the memory task, one cannot exclude that the lack of measurement of this parameter may be a limitation to the study. Nevertheless, substantial data allow us to rule out this hypothesis. First, we did not observe in the present study a significant difference in the exploration of the total number of head-dips in the baited and unbaited holes among the groups during the acquisition phase: such a finding infers that locomotor activity is similar in all groups. This observation confirmed previous experimental data showing transitory impairments in exploring a 9 hole-board only in

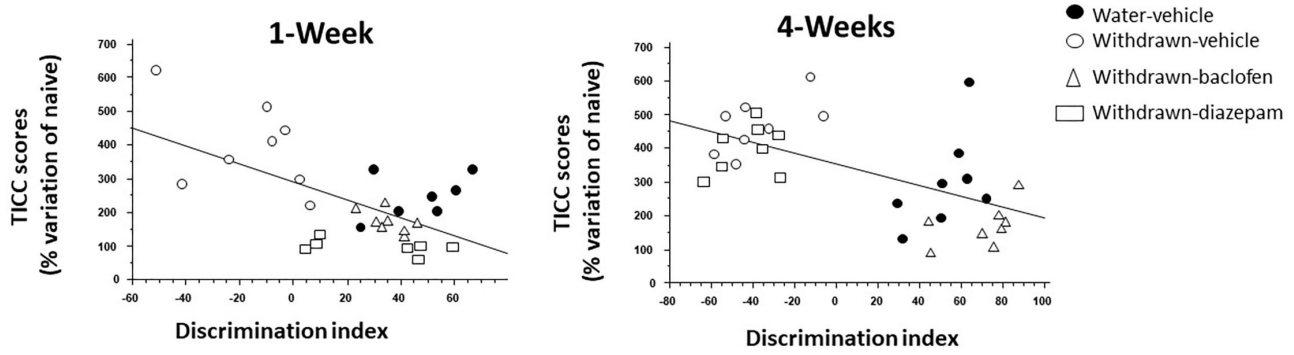

FIGURE 6 | Regression analysis between individual dHPC TICC scores and discrimination indexes in vehicle-Water-controls (hashed squares), withdrawn-vehicle (hashed triangles), diazepam-withdrawn (white circle) and baclofen-withdrawn (black circles) groups. (left): in 1-W groups, a significant negative correlation was observed, the higher being TICC score, the lower being the index discrimination. As can be observed, 1-Week vehicle-withdrawn mice exhibited the lower discrimination index and the higher TICC scores among the 4 groups (right) in 4-Week withdrawn mice, a similar negative correlation was also observed, but in contrast to 1-W withdrawn mice, diazepam-treated withdrawn mice exhibited similar endocrinal and behavioral patterns as vehicle-withdrawn animals.

1-week but not in 6-weeks withdrawn mice, as compared to controls (61). In addition, we previously showed that locomotor activity was spared in withdrawn mice in several other tasks. More specifically, we elicited a normal sequential alternation behavior over 6 successive trials separated by a short intertrial interval, as well as normal choice latencies between arms in a T-maze in 6-weeks alcohol withdrawn mice, as compared to controls (11); we also evidenced that the total number of entries in open and closed arms of an elevated plus-maze was similar in alcohol-withdrawn mice as compared to controls (11) as well as the total number of crossed sections (an index of locomotor activity) in an open-field or in an open area in an odor recognition task in a non-stress condition (39). Thus, in our experimental conditions, an alteration of locomotor activity is unlikely responsible for the cognitive recognition deficits in withdrawn animals.

Our present findings agree with other studies showing that AW produced sustained alterations of memory in alcohol-withdrawn rodents as compared to water-controls or to rodents still under alcohol regimen (7, 13, 43).

From a psychological point of view, exaggerated anxiety levels resulting from alcohol-withdrawal have been considered as a potential key factor of the long-lasting maintenance of cognitive deficits over time. Indeed, human and rodent studies have reported enhanced anxiety-like behaviors in various tests during ethanol withdrawal (62). In our experimental conditions, previous studies evidenced however only a mild increased anxiety-like reactivity in an elevated plus-maze and open-field tasks, and very mild withdrawal symptoms in 1-Week withdrawn animals, which however were not observed in 6-Weeks withdrawn mice (11, 39). In these studies, we showed that circulating and basal brain regional corticosterone levels are not modified by alcohol-withdrawal, as compared to Water-controls. These endocrinal data fit well with the mild anxiety symptoms observed in withdrawn animals. Nevertheless, our findings contrast with other studies showing that withdrawn animals and humans exhibit potentially elevated corticosterone levels during the acute withdrawal phase and that prolonged withdrawal and abstinence are rather characterized by a blunted GC response over time (2). Several factors may, however, account for the discrepancies. Firstly, the withdrawal procedure implemented in our study was not abrupt since the amount of alcohol in the solution was gradually reduced down to water over the 15 days of the withdrawal phase. Such a gradual withdrawal procedure is likely to have induced a reduced emotional reactivity to the withdrawal; secondly, animals in our studies were evaluated for emotional reactivity at least 1-week after withdrawal, rather than in the immediate wake of alcohol intake cessation; such a procedure can attenuate the anxiety-like symptoms often observed after an abrupt alcohol withdrawal. Another factor can also be linked to the strain of mouse used, insofar as C57BL/6 is an alcohol-preferring strain (57) whose HPA axis responses to alcohol and stress differ from other mouse strains (63–65). Given that, an increase of anxiety is unlikely responsible for the contextual memory impairments and GCs dysfunction observed after prolonged alcohol-withdrawal in our experimental conditions.

Endocrine studies in humans (1, 2, 4, 6) and rodents (3, 5, 66) have shown that AW markedly affects the HPA activity. Studies in rodents evidenced persistent brain regional GCs disturbances after a chronic alcohol consumption in the PFC and the dHPC, up to 2 months after abstinence (9, 13). A prime result of this study is to show that the contextual memory impairments observed in alcohol-withdrawn mice are linked with an excessive and significant test-induced corticosterone rise specifically in the dHPC. Indeed, correlation analyses evidenced a significant negative interaction between corticosterone scores in the dHPC and the memory discrimination index, the higher being corticosterone levels, the lower being memory performance. In addition, these findings are in accordance with our previous studies having shown that injections of corticosterone into the dHPC in normal (non-alcoholics) mice induced a severe memory impairment in the CSD task similar to that observed here in alcohol-withdrawn animals (40, 43); moreover, these

studies also showed that blocking the stress-induced increase of corticosterone in the dHPC by a systemic administration of metyrapone (an inhibitor of corticosterone synthesis) prior the onset of a stressor canceled out both the contextual memory deficits and the stress-induced rise of corticosterone in the dHPC (40). Based on these findings, it can be assumed that the abnormal test-induced rise of corticosterone in the dHPC is responsible for the memory impairments observed in 1-W and 4-W withdrawn mice in the CSD task.

Interestingly, the vHPC and the PFC exhibited non-significant enhancements of the TICC scores as compared to water-controls. We previously showed that these brain areas are not recruited in the processes sustaining memory of the first discrimination in the CSD task (41, 43, 44, 67). In contrast, close relationships have been previously observed in 6-week alcohol-withdrawn mice between working memory impairments in a T-maze and TICC scores in the PFC, but not in the dHPC (13). These data suggest that the magnitude of TICC rise within a given brain region may depend on its functional recruitment in the task.

Baclofen but Not Diazepam Cancels Out the Protracted Memory and GCs Alterations Induced by Alcohol-Withdrawal

In the present study, diazepam and baclofen were undetectable in the blood of animals at the time of behavioral testing (39) and therefore, their beneficial impacts cannot be ascribed to an acute effect at the time of memory testing.

We reported here-above that repeated diazepam administrations counteract only transitorily the memory impairment and neuroendocrine disorders in 1-W-withdrawn but not in 4-W-withdrawn mice. We previously evidenced corrective effects of a similar repeated diazepam administration on working memory alterations after a short (1-week) but not a long (6-weeks) withdrawal period (13). The failure of repeated diazepam administration to counteract the persistent cognitive and neurobiological disorders in 4-W-withdrawn mice may stem either from persistent alterations of GABAA receptors (68–70), increased downregulation of the GABAA receptors over repeated diazepam administration (71) or other alcohol-induced functional and structural neuroadaptations that may progressively develop over time after withdrawal, such as alterations of epigenetic mechanisms (12, 72, 73). Indeed, chronic exposure to alcohol produces brain adaptive changes in several neurotransmitter systems, including GABA, glutamate, and norepinephrine pathways (74) in order to compensate for alcohol-induced destabilization and restore neurochemical equilibrium (75). In particular, in different rodent models of alcohol addiction, a reduction in number, function, and sensitivity to GABA of the GABAA receptors have been reported (70, 76–79) as well as alterations of plasticity between synaptic and extrasynaptic receptors (80, 81). These alterations can, in turn, reduce the efficacy of diazepam to counteract the protracted alterations of the HPA axis activity in withdrawn mice.

In sharp contrast, baclofen suppressed the protracted memory impairments and normalized the test-induced increase of corticosterone in the dHPC regardless the withdrawal periods, showing thereby prolonged counteracting effects of baclofen on these impairments. Interestingly, the beneficial effects of baclofen on alcohol addiction and relapse in abstinent subjects as well on HPA axis disorders and protracted cognitive impairments have been well substantiated (14, 39, 82). Thus, Geisel et al. (27) evidenced in abstinent alcoholics increased plasma GC levels, which were decreased in baclofen-treated patients, up to 14-weeks after treatment. In addition, Jacquot et al. (10) showed that the administration of mifepristone (an antagonist of the progesterone and GCs receptors) in mice given at the time of alcohol withdrawal totally suppressed the memory impairments in several recognition tasks up to 2-weeks after alcohol abstinence. According to these authors, the action of mifepristone suggests that GCs during the acute withdrawal phase are important in triggering the subsequent changes in neuronal function responsible for memory deficits during the abstinence period. It is hypothesized that the raised GCs concentrations during the acute withdrawal period are likely to contribute to the above changes in neuronal plasticity seen after withdrawal from chronic alcohol treatment and to the memory deficits. In view of the long-time interval (1- to 2-weeks) between the administration of mifepristone and its protracted effects, it is possible that the drug could have produced its effects by preventing long-lasting changes in the expression of genes that trigger adaptive changes in HPA axis regulation during alcohol withdrawal. More specifically, Huang et al. (83) showed in knock-out mice lacking for the FKBP5 gene (a gene intervening in the negative feedback on HPA axis function) an enhanced sensitivity to alcohol withdrawal.

Since several studies evidenced different HPA axis responses to alcohol consumption and withdrawal in female as compared to male rodents (84, 85), our present findings may indeed be restricted to male mice only. Thus, an extended development to our current study would involve the following stakes, namely, to determine whether similar alcohol-induced endocrine and memory disorders are to be observed in female mice and, further, to assess whether baclofen and diazepam bear similar counteracting effects on such disorders.

CONCLUSION

Overall, the present study provides evidence that acting on the GABAB receptor through repeated baclofen administration during the alcohol-withdrawal phase counteracted the persistent hyper-reactivity of HPA axis to behavioral testing in the dHPC and rescued memory found to be altered up to 4-weeks after the cessation of alcohol intake; in contrast, diazepam, a compound having an agonist action on the GABAA receptor, induced only a transitory beneficial effect on the memory and endocrinal alterations.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The animal study was reviewed and approved by EU Directive 2010/63/EU and by the local Ethical Committee of Bordeaux (#5012089).

AUTHOR CONTRIBUTIONS

HN and MF were equally involved in behavioral and neuroendocrine studies. MN, CP, and BD were involved in data and statistical analyses, the experimental design, and writing of the article. All authors have approved the final article.

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