COGNITIVE CONTROL AND REWARD PROCESSING IN ADDICTION

EDITED BY: Qi Li, Arne Møller and Xingchao Wang

PUBLISHED IN: Frontiers in Psychiatry

frontiers Research Topics

frontiers

ISSN 1664-8714
ISBN 978-2-88974-893-8
DOI 10.3389/978-2-88974-893-8

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: frontiersin.org/about/contact

COGNITIVE CONTROL AND REWARD PROCESSING IN ADDICTION

Topic Editors:
Qi Li, University of Chinese Academy of Sciences, China
Arne Møller, Aarhus University Hospital, Denmark
Xingchao Wang, Shanxi University, China

Citation: Li, Q., Møller, A., Wang, X., eds. (2022). Cognitive Control and Reward Processing in Addiction. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-88974-893-8

Table of Contents

frontiers in Psychiatry

BRIEF RESEARCH REPORT
published: 27 November 2020
doi: 10.3389/fpsyt.2020.599256

Does Chronic Cannabis Use Impact Risky Decision-Making: An Examination of fMRI Activation and Effective Connectivity?

David R. Raymond[1], *Adrian Paneto*[2], *Karmen K. Yoder*[3], *Brian F. O'Donnell*[1,4], *Joshua W. Brown*[1,4], *William P. Hetrick*[1,4] *and Sharlene D. Newman*[1,4,5]*

[1] Department of Psychological and Brain Sciences, Indiana University Bloomington, Bloomington, IN, United States, [2] Department of Counseling Psychology, Indiana University Bloomington, Bloomington, IN, United States, [3] Department of Radiology, Indiana University Medical School, Indianapolis, IN, United States, [4] Program in Neuroscience, Indiana University Bloomington, Bloomington, IN, United States, [5] Department of Psychology, Alabama Life Research Institute, University of Alabama Tuscaloosa, Tuscaloosa, AL, United States

OPEN ACCESS

Edited by:
Qi Li,
University of Chinese Academy of Sciences, China

Reviewed by:
Ruben David Baler,
National Institutes of Health (NIH), United States
Liangsuo Ma,
University of Texas Health Science Center at Houston, United States

***Correspondence:**
Sharlene D. Newman
sdnewman@ua.edu

Specialty section:
This article was submitted to Addictive Disorders, a section of the journal Frontiers in Psychiatry

Received: 26 August 2020
Accepted: 03 November 2020
Published: 27 November 2020

Citation:
Raymond DR, Paneto A, Yoder KK, O'Donnell BF, Brown JW, Hetrick WP and Newman SD (2020) Does Chronic Cannabis Use Impact Risky Decision-Making: An Examination of fMRI Activation and Effective Connectivity? Front. Psychiatry 11:599256. doi: 10.3389/fpsyt.2020.599256

With the increase in use of cannabis and its shifting legal status in the United States, cannabis use has become an important research focus. While studies of other drug populations have shown marked increases in risky decision-making, the literature on cannabis users is not as clear. The current study examined the performance of 17 cannabis users and 14 non-users on the Balloon Analog Risk Task (BART) using behavioral, fMRI and effective connectivity methods. Significant attenuation was found in a functional pathway projecting from the dorsal anterior cingulate cortex (dACC) to the nucleus accumbens (NAc) in cannabis users compared to non-using controls as well as decreases in risk-taking behaviors. These findings suggest that cannabis users may process and evaluate risks and rewards differently than non-users.

Keywords: cannabis, decision-making, effective connectivity, fMRI, reward, risk

INTRODUCTION

Cannabis (CB) use has been on the rise in recent years, in part due to the drug's increased acceptance and shifting status from an illegal to a legal drug in some US states. Cannabis is the most used illicit drug in the United States and thus is an important area of study. Delta-9-tetrahydrocannabinol (THC) is the psychoactive component of CB and has been linked to depression (1) and psychotic disorders, including schizophrenia (2–4). Heavy CB use has also been linked to poorer neurocognitive functioning (5–8).

While the chronic use of alcohol and other drugs of addiction have been associated with increased risk-taking behaviors and poor inhibitory control (9), CB use has not consistently been found to be linked to increased risk-taking (10, 11). For example, Gilman et al. (12) found that increased risk-taking behavior in CB users depended on stimulus type with greater risk-taking observed when the rewards were social, health/safety, and ethical factors but not when the rewards were monetary. A study by Vivas et al. (11) found that CB use actually enhanced inhibitory control compared to non-users. Another study used transcranial direct current stimulation (tDCS) to stimulate the left and right dorsal lateral prefrontal cortex (DLPFC) in chronic cannabis users and controls and found that chronic cannabis users made more conservative decisions than controls during sham stimulation (placebo) but during active stimulation of the right DLPFC, controls made

more conservative decisions while activations of both right and left DLPFC in cannabis users led to increased risk-taking (13). Additionally, Wesley et al. (14) found that cannabis users performed worse on a version of the Iowa Gambling Task than controls and that during that cannabis users showed significantly less activation in response to loss during the strategy planning phase of the task, namely in the anterior cingulate cortex (ACC), medial frontal cortex, precuneus, superior parietal lobe, occipital lobe and cerebellum. These results suggest various disturbances in regions of executive function, as well as in certain properties like reward salience, in chronic cannabis users which do not paint a clear picture of what these differences could mean.

Task-based activation and resting state functional MRI studies have shown altered activity and connectivity between key regions associated with risky decision-making in CB users; however, there are inconsistencies regarding how the connectivity varies across studies. The primary regions involved in risky decision making include those related to affective processing of stimuli (anterior insula and ventral striatum, including the nucleus accumbens) and integrating cognitive and affective information (medial prefrontal cortex, including the anterior cingulate) (15–17). Cousijn et al. (16) found that the amount of weekly CB use was positively related to activation in the right anterior insula, right ventral striatum and ventrolateral prefrontal cortex during an Iowa Gambling Task. Additionally, Lichenstein et al. (18) reported attenuated functional connectivity (FC) between the nucleus accumbens (NAc) and the medial prefrontal cortex (mPFC) in CB users. Fischer et al. (19) found a similar result, such that there was reduced resting state functional connectivity (rsFC) between the NAc and PFC in patients with CB use disorder and schizophrenia. However, Filbey et al. (20) found increased FC between the NAc and the ACC when CB users were viewing CB use cues. While previous studies do show activation and connectivity differences between CB users and non-users there are still a limited number of studies and there is still some inconsistency with regard to the directionality of connectivity differences.

The current study uses the Balloon Analog Risk Task (BART) to examine risk-taking behavior in CB users. The BART is a gambling task designed as a behavioral measure of risk taking which requires participants to inflate a balloon more and more for money while risking the balloon exploding and losing their money. The BART has been used to investigate the relationship between risk-taking and decision-making in various drug use groups. Researchers have found that number of balloon inflations (more inflations is equivalent to higher levels of risk-taking) is increased in nicotine smokers relative to non-smokers (21) and is positively correlated with severity of polysubstance use (22). Alternatively, number of balloon inflations was found to be negatively correlated with long-term alcohol use in a 2013 study by Campbell et al. (23) While the BART has been used to study risk-taking and reward processing in different substance users, few studies have investigated differences in BART performance in CB users and those that have found no differences in BART performances between CB users and non-users, but did find negative correlations between Cannabis Use Disorder symptoms and CB use severity with performance in other risk-taking paradigms, namely the IGT (24, 25). The current study uses a modified version of the BART which utilizes parametric modulation to generate more precise representations of risk-taking in hopes of clarifying the disparity in results.

The current study also uses effective connectivity analysis to examine the connectivity differences within the reward network between CB users and non-users. Effective connectivity tests an *a priori* defined model containing directed connections (26). Here a model that included a connection from the dorsal ACC (dACC) to the NAc, the anterior insula to the NAc, and the anterior insula to the dACC was tested. This model was based on previous studies that show a directed glutamatergic connection between the dACC and NAc which plays an important role in modulating the addicted brain's response to rewards (27). A number of studies have proposed a connection between the ACC and insula (28, 29), with White and colleagues finding that the activation of the insula precedes that of the ACC suggesting a potential directed connection from the insula to the ACC. Finally, previous work using effective connectivity during cue-elicited incentive anticipation, a component of reward processing which is shown to be maladaptive in people who are addicted to drugs (30), has also suggested a directed connection from the insula to the NAc (15). It was predicted that this reward network would be disrupted in CB users while performing a risky decision task.

METHODS

Participants

A total of 40 participants took part in the study. Subjects were recruited by local advertisements. After detailed description of the study, written and verbal informed consent was obtained from each participant. All subjects were required to be 18 years or older. Subjects were asked to refrain from alcohol or CB use the day prior to the MRI scan. The research protocol was approved by Indiana University's Institutional Review Board for the protection of human subjects.

Inclusion/Exclusion Criteria

All participants had to be free of psychological disorders (with the exception of cannabis use disorder for the CB group), free of any neurological disorder, head trauma with loss of consciousness > 10 min, learning disability, contraindication to MRI, be between the ages of 18 and 30 years, not a user of illicit drugs (other than CB), and have abstained from CB and alcohol use for at least 12 h prior to the scan. Participants completed a battery of assessments including the Structured Clinical Interview for DSM-IV-TR (SCID-IV-TR), Research Version (31); a written drug use questionnaire; the short Michigan alcohol screening test (SMAST); the Cannabis Use Disorder Identification Test (CUDIT). The control subjects had no history of substance dependence, and no use of CB in the past 3 months. The CB group were not required to have a diagnosis of CUD. The group characteristics include: [1] an average age of CB initiation of 16.5 $\pm$ 1.9 years; [2] used an average of 5.2 $\pm$ 2.1 days/week; [3] used an average of 11.4 $\pm$ 7.4 joints/bowls/week; and 4) of the 13 who have used wax, 11 had used in the past 6 months. Eight were

TABLE 1 | Demographics.

	Controls	CB Users	2-tailed *t*-test *p*-value
n	14	17	
#Males	6	8	
Age	23.5 ± 4	21.2 ± 3	0.093
Average days since last CB use (prior to scan)		1.3 ± 1 days	
Average days since last alcohol use (prior to scan)	6.4 ± 5.5	3.6 ± 2.8	0.42
CUDIT	0.15 ± 0.4	13.4 ± 4.8	<0.0001
SMAST	0.5 ± 1	0.29 ± 0.7	0.58

lost to existing mood disorders (depression and/or anxiety) and an additional one was lost to excessive subject motion during scanning. This left 14 control non-users (6 males, age 23.5 ± 4) and 17 CB users (8 males, age 21.2 ± 3). Groups did not significantly differ in age, sex, days since last alcohol use at the time of screening or SMAST score ($p > 0.1$) (see **Table 1**).

Procedure

Potential participants were contacted via telephone and underwent a preliminary screening process. If the potential participant qualified for the study, they were scheduled for a testing day. On this day, participants arrived at the laboratory space and after signing a consent form, completed a variety of surveys and batteries about demographics and drug and alcohol use. After completing these surveys, researchers examined the results to ensure the participants still qualified for the MRI scans. If the participants qualified, a 2nd day was scheduled in which participants underwent the MRI tests while completing the BART. After the MRI scan, participation was complete and participants were compensated for their time and their performance at the BART.

BART Task

The BART design used in this study was modeled from previous imaging design (32) and was administered in two, 8-min blocks during fMRI data collection. As participants continued to inflate in pursuit of greater reward, the probability of an explosion increased parametrically. Participants were informed that higher winnings during the task would yield in bonus monetary reward for participation in the study in order to incentivize participation and mimic real-world risk-reward decision making.

Each block began and ended with a 30 s, white fixation cross ("+") on a black background in order to establish a baseline for activity. At the beginning of each trial, the screen displayed the image of a purple balloon above a small, green rectangle which indicated that the participant should make a decision. This rectangle was above the participant's current wager amount for that balloon and the participant's total winnings earned for that block at that point in time (**Figure 1**). At this point, the participant had unlimited time to choose inflation or to "win" and add the current wager to their total winnings. After this decision was made, there was a delay between 0 and 6 s before the outcome (balloon explosion, successful inflation, or "You Win!") was displayed. The winning display was present for 1 s. If the inflation was successful, then the decision rectangle would be red for either 1.5, 2, or 2.5 s, indicating that a decision could not be made. Once the rectangle became green again, the participant could make a decision. If the inflation was unsuccessful, an exploded balloon was presented for 0.5 s followed by the text "You Lose!," which was present for 1 s. After either a win or a loss, the screen was blank for 2, 3, or 4 s until a new trial display was presented.

Along with the baseline monetary compensation for time and participation in this study, participants were rewarded with additional funds based on their performance on the BART (and additional 50% of total earnings over two trials of the BART).

MRI Acquisition and Analysis

Image acquisition was performed on a 3T Siemens Prisma MRI scanner and using a 64-channel head coil. Foam pads were used to minimize head motion for all participants. High-resolution T1-weighted anatomical images were acquired in the sagittal plane using an MP-RAGE sequence [TR = 2.4 s; TE = 2.36 ms; inversion time = 1.0 s; flip angle 8°; imaging matrix = 320 × 320; 256 slices; voxel size = 0.7 × 0.7 × 0.7 mm^3]. Functional BOLD data for each participant was collected in two blocks using a gradient echo T2-weighted echo planar imaging sequence [TR = 2.0 s; TE = 0.25 s; flip angle 70°; imaging matrix = 64x220; 35 slices; voxel size = 3.4 × 3.4 × 3.8 mm^3; 0-mm gap; 240 volumes].

MRI data were processed and analyzed using SPM5 [University College London; (33)]. The preprocessing steps that were applied to the functional MRI data included: slice timing correction, motion correction using a rigid body realignment algorithm, co-registration, spatial normalization using the MNI template and each person's T1 scan, and smoothing with the Gaussian kernel filter of 8 mm. The final voxel size after normalization was 2 × 2 × 2 mm^3. The amount of head motion was closely examined and no subject showed excessive movements > 1 mm.

Event-related responses were analyzed using a general linear model (GLM) with 9 experimental condition regressors, 2 constants, and 6 motion regressors. Five of experimental condition conditions included: the choice to inflate the balloon (ChooseInflate); the choice to stop inflating the balloon (ChooseWin); the losing/balloon explosion outcome (ExplodeOutcome); the successful inflation outcome (Successful Inflate); and the winning outcome (WinOutcome). The remaining conditions were four parametric modulators to identify brain regions where activation was positively or negatively correlated with the probability of explosion: ChooseInflate*P(explode), ChooseWin*P(explode), WinOutcome*P(explode), and ExplodeOutcome*P(explode). The ChooseInflate*P(explode) is referred to here is the risk-taking condition that was examined in this analysis. Activation threshold was set at $p < 0.001$ with an extent of 150 voxels to correct for multiple corrections.

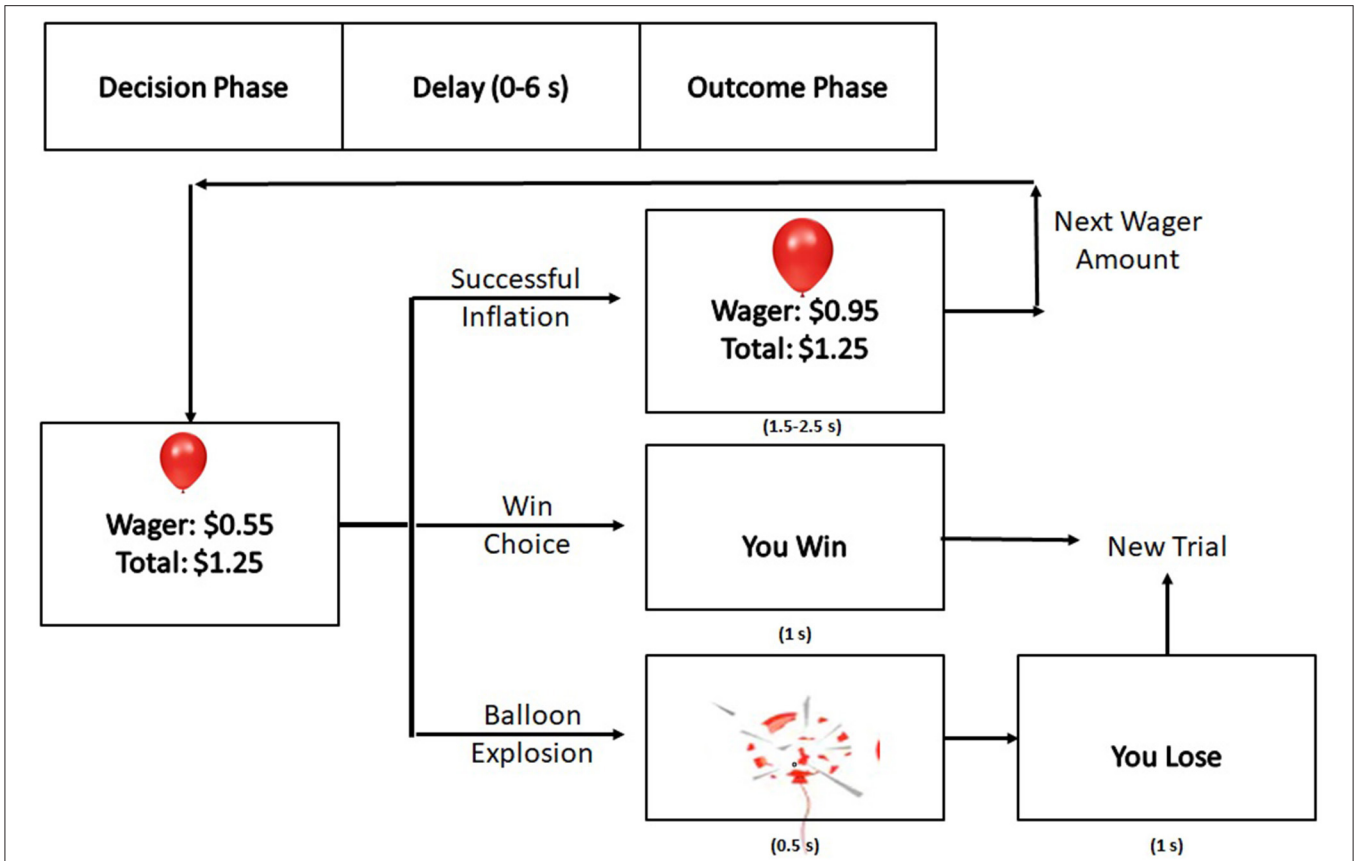

FIGURE 1 | A Depiction of the typical trial in the BART task.

TABLE 2 | Behavioral results.

	CB users	Non-users	2-tailed *t*-test *p*-value
Winnings	20.7 ± 5.6	25.9 ± 7.3	0.03
Trials completed	34.5 ± 4.5	33.9 ± 5.9	0.8
Inflations	167.5 ± 23	171.9 ± 14.2	0.5
Wins	21.1 ± 5.7	21.6 ± 7.5	0.8
Explosions	13.4 ± 5.2	12.3 ± 3.3	0.5

Effective Connectivity Modeling and Analysis

Effective connectivity analyses, or the average change in BOLD activity in one ROI as influenced by a different ROI, was conducted using Structural Equation Modeling (SEM) and performed using SPSS (25, IBM Corporation) and AMOS (25, IBM Corporation). ROIs and the directionality of their connections were determined a priori and as described in the introduction. The ROIs and the network constructed were determined by the wealth of evidence which associate and incorporate the dACC, NAc, and insula with reward and decision-making processes (15, 34). The beta weights from the GLM fMRI analysis for the risk-taking condition were extracted for each ROI. ROIs were determined using the group analysis (collapsed across CB user and non-user groups). Those beta weights were used as input into the predesigned model. A multi-group path analysis was performed in AMOS using critical ratios for differences between parameters to test pair-wise coefficient differences. Coefficients for each path within the network were generated using multi-group path analysis.

RESULTS

Behavioral Results

When examining the performance differences between groups, the control group won more money than did the CB user group, see **Table 2**. No other measures were found to be significantly different.

fMRI Results

The current study focused on activation related to risk-taking. Risk-taking was examined by parametrically modulating the decision to inflate with the probability of balloon explosion. An analysis of activation related to risk taking behaviors collapsed across both groups showed significant activation in regions typically associated with risky decision making and

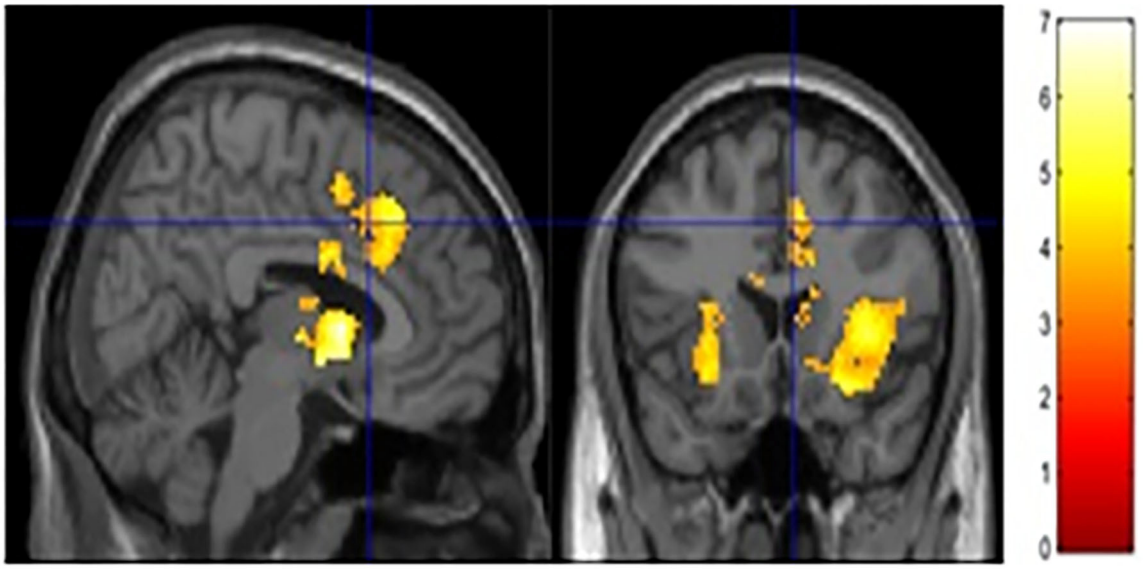

FIGURE 2 | Risk activity collapsed across groups. Significant activity was observed in the ACC, NAc and bilateral insula.

TABLE 3 | fMRI activation.

Region	BA	*k*	*z*	*x, y, z*
R. Ventral striatum		2,191	5.33	6, 8, 4
R. insula	13		5.09	36, 22, 4
Anterior Cingulate	32	456	4.75	8, 28, 42
R. Ventral striatum		307	4.53	14, −14, 20
R. Insula	13	256	4.38	34, −36, 24
L. Insula	13	434	4.27	−28, 22, 0
L. Insula	13	177	4.16	−28, −34, 38
R. Precentral	4	182	4.13	26, −16, 42

TABLE 4 | Effective connectivity parameter estimates.

			Estimate	S.E.	C.R.	*p*
CB users						
dACC	<---	Insula	0.219	0.176	1.248	0.212
NAC	<---	Insula	0.518	0.228	2.271	0.023
NAC	<---	dACC	0.531	0.311	1.708	0.088
Non-users						
dACC	<---	Insula	0.277	0.234	1.186	0.236
NAC	<---	Insula	0.45	0.175	2.579	0.01
NAC	<---	dACC	−0.616	0.196	−3.14	0.002

reward seeking, such as the dACC, NAc, and insula (see **Figure 2** and **Table 3**). However, no significant group differences were observed after correcting for multiple comparisons (see **Supplementary Material** for other analyses).

Effective Connectivity

A network analysis was performed. The unconstrained model had a good fit ($\chi^2 = 0.64$, $p = 0.42$, CFI = 1.000, IFI = 1.019). Both groups showed a significant connection from the insula to NAc (see **Table 4** and **Figure 3**). Neither group showed a significant connection from the insula to the dACC. The connection from the dACC to the NAc was found to be significant for the non-user group but not the CB user group. When directly comparing the parameter estimates, the connection from the dACC to the NAc was found to be significantly different between groups [z-score = −3.121, $p < 0.05$]. Additionally, the connectivity from the dACC to the NAc was negative in the non-user group, suggesting that the dACC has an inhibitory effect on the NAc in non-CB users but not CB users.

DISCUSSION

The primary goal of the current study was to explore the hypothesis that CB interacts with the brain network responsible for risky decision making. The results show that in the group of high functioning chronic CB users the effect is minimal in that there were no fMRI-measured brain activation differences compared to non-using controls when performing the BART task. While there were no brain activation differences between groups, effective connectivity analysis revealed significantly attenuated connectivity between the dACC to the NAc in CB users compared to controls. The results may also suggest that CB users may be more risk *averse* than non-using controls.

Previous studies have found that drug users tend to be more impulsive and risk-taking (9). However, the results reported in the current study suggest that CB users may actually be more risk averse than the non-user group. The users won significantly less money even though they had a similar number of explosions and

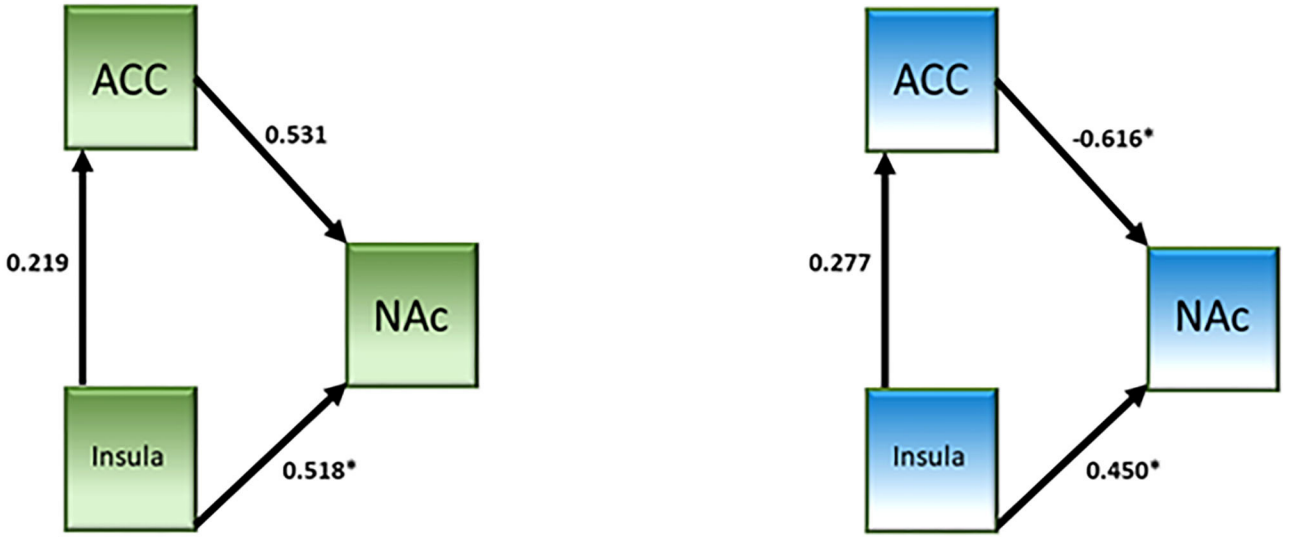

FIGURE 3 | Effective connectivity network analysis results from the cannabis use group (left, green) and the control group (right, blue).

win trials. The reason for the decreased winnings is likely due to prematurely stopping inflations. These findings are contrary to previous studies of drug users. A potential explanation is that CB users may be engaging in more deliberative, as opposed to impulsive, risk-taking behavior. Whiteside and Lynam (35) identified distinct factors of impulsive-like behavior - urgency, (lack of) premeditation, (lack of) perseverance, and sensation seeking. It has also been argued risky decision-making can be conducted using deliberative procedures as well. These different factors of impulsive decision-making elicit different patterns of brain activation [e.g., (36)] with the medial prefrontal cortex, including the dACC, being involved to monitor or inhibit impulsive decisions. Given that the connectivity between the dACC and NAc is lesser in CB users compared to non-users, this may suggest that this pathway either does not operate efficiently or that a more deliberative strategy is preferred by these high functioning CB users. While speculative, some support for this hypothesis can be found by an increased involvement of the right lateral prefrontal cortex for CB users compared to non-users at a lower threshold (see **Supplementary Material**) which has been linked to more deliberative processing (37). Other support can be found in the research on drug use and driving (38, 39). For example, MacDonald et al. (38) found that cannabis users were more cautious when driving under the influence or refrained from driving altogether which was the opposite finding for cocaine users. Another potential explanation for the behavioral finding of potential risk aversion may be related to the use of monetary reward. Gilman et al. (12) failed to observe differences between CB users and non-users during a financial risk-taking task but did observe differences when using social stimuli. It may be that the decreased salience of the monetary reward used in the current study is disincentivizing the CB users to take more risks (i.e., inflate more), or put another way, the monetary reward does not lead to the use of the impulsive strategy but the deliberative one. These effects could be caused by the chronic use of cannabis which makes cannabis a more salient reward than money.

The connectivity from the dACC to the NAc was attenuated in CB users; this attenuation was linked to risky decision-making processes as it was observed for the risk parametric modulator. In addition the connectivity was inhibitory in non-users but not in CB users. A study by Lichentstein et al. (18) showed increased functional connectivity between the NAc and dACC in CB users in response to cannabis-related cues relative to neutral cues. The differences between the Lichentstein et al. study and the current study may account for the differences in results, namely the task and the stimuli (money vs. cannabis). However, both studies show that the connectivity between the dACC and NAc are impacted by chronic CB use. The core of the NAc has been shown to be anatomically connected to the dACC (40). Phasic dopamine release in the core, but not the shell, has been observed following reward-predictive cues (41) and that dopamine release is related to the subjective reward value of the cue (42–44). This suggests that the subjective value of the reward plays a role in how individuals make decisions regarding said rewards, which may account for group differences observed in the current study as well as previous studies showing differences in reward processing as a function of the reward in CB users. Additionally, it may be salience of loss that drives the behavior of CB users, like was seen in Wesley et al. (14). It will be important in future studies to assess the subjective reward value in participants in order to more fully understand risky decision-making and reward processing.

Limitations

There are some limitations of the current study. First, number of participants is small ($N = 31$) and therefore limits the conclusions that can be drawn. The limited sample size may explain the lack of significance in the between group analysis of fMRI activation. Another potential limitation is that we were

unable to examine sex differences due to the small sample size. Previous studies have shown sex differences in neurochemistry when examining chronic CB users; therefore, it is important to further explore those differences when examining risky decision-making. Additionally, some have complained that the BART as well as similar tasks do not effectively engage risk-like behavior due to its repetitive nature; participants "figuring out" the task and how to maximize winnings and then the task no longer assesses risk. Finally, in an attempt to ensure that participants were not intoxicated during the scan they were asked to abstain prior to the session. A recent study suggests that cognitive deficits observed in the abstention period used (<72 h) could be due to either withdrawal or residual effects of acute use (45).

Conclusions

This preliminary study examining risky decision-making suggests, while minimal, that CB use is associated with functional connectivity from the dACC to the NAc. The decrease in connectivity and the switch between inhibitory to excitatory connectivity may suggest the use of different strategies, or differences in the subjective value of the reward between groups. Further research is necessary to disentangle these possibilities and to replicate the current findings.

DATA AVAILABILITY STATEMENT

The data discussed in this article are available upon request. Please send inquiries to the corresponding author.

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

DR collected and analyzed data and prepared the manuscript. AP designed the study and collected and analyzed data. KY designed the study and prepared the manuscript. BO'D designed the study and recruited subjects for data collection. JB designed the study and prepared the manuscript. WH designed the study. SN designed and managed the study, analyzed the data, and prepared the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by the Indiana Clinical and Translational Sciences Institute, funded in part by grant # UL1TR002529 from the National Institutes of Health, National Center for Advancing Translational Sciences, Clinical and Translational Sciences Award, and the National Institute on Drug Abuse (NIDA) Grant #5R21DA035493 (BFO/SDN). Any opinion, findings, and conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of the NIDA.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.599256/full#supplementary-material

REFERENCES

1. Wright NE, Scerpella D, Lisdahl KM. Marijuana use is associated with behavioral approach and depressive symptoms in adolescents and emerging adults. *PLoS ONE.* (2016) 11:e0166005. doi: 10.1371/journal.pone.0166005
2. Andréasson S, Engström A, Allebeck P, Rydberg U. Cannabis and schizophrenia A longitudinal study of Swedish conscripts. *Lancet.* (1987) 330:1483–6. doi: 10.1016/S0140-6736(87)92620-1
3. Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt TE. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *BMJ.* (2002) 325:1212–3. doi: 10.1136/bmj.325.7374.1212
4. Van Os J, Bak M, Hanssen M, Bijl RV, De Graaf R, Verdoux H. Cannabis use and psychosis: a longitudinal population-based study. *Am J Epidemiol.* (2002) 156:319–27. doi: 10.1093/aje/kwf043
5. Crean RD, Crane NA, Mason BJ. An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions. *J Addict Med.* (2011) 5:1. doi: 10.1097/ADM.0b013e31820c23fa
6. Doss MK, Weafer J, Gallo DA, de Wit H. Δ9-tetrahydrocannabinol at retrieval drives false recollection of neutral and emotional memories. *Biol Psychiatr.* (2018) 84:743–50. doi: 10.1016/j.biopsych.2018.04.020
7. Meier MH, Caspi A, Ambler A, Harrington H, Houts R, Keefe RS, et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proc Natl Acad Sci USA.* (2012) 109:E2657–64. doi: 10.1073/pnas.1206820109
8. Ranganathan M, Radhakrishnan R, Addy PH, Schnakenberg-Martin AM, Williams AH, Carbuto M, et al. Tetrahydrocannabinol (THC) impairs encoding but not retrieval of verbal information. *Prog Neuro-Psychopharmacol Biol Psychiatr.* (2017) 79:176–83. doi: 10.1016/j.pnpbp.2017.06.019
9. Stephan RA, Alhassoon OM, Allen KE, Wollman SC, Hall M, Thomas WJ, et al. Meta-analyses of clinical neuropsychological tests of executive dysfunction and impulsivity in alcohol use disorder. *Am J Drug Alcohol Abuse.* (2017) 43:24–43. doi: 10.1080/00952990.2016.1206113
10. Broyd SJ, van Hell HH, Beale C, Yuecel M, Solowij N. Acute and chronic effects of cannabinoids on human cognition—a systematic review. *Biol Psychiatr.* (2016) 79:557–67. doi: 10.1016/j.biopsych.2015.12.002
11. Vivas AB, Estevez AF, Moreno M, Panagis G, Flores P. Use of cannabis enhances attentional inhibition. *Clin Experi.* (2012) 27:464–9. doi: 10.1002/hup.2248
12. Gilman JM, Calderon V, Curran MT, Evins AE. Young adult cannabis users report greater propensity for risk-taking only in non-monetary domains. *Drug Alcohol Depen.* (2015) 147:26–31. doi: 10.1016/j.drugalcdep.2014.12.020
13. Boggio PS, Zaghi S, Villani AB, Fecteau S, Pascual-Leone A, Fregni F. Modulation of risk-taking in marijuana users by transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC). *Drug Alcohol Depen.* (2010) 112:220–5. doi: 10.1016/j.drugalcdep.2010.06.019
14. Wesley MJ, Hanlon CA, Porrino LJ. Poor decision-making by chronic marijuana users is associated with decreased functional

responsiveness to negative consequences. *Psychiatr Res.* (2011) 191:51–9. doi: 10.1016/j.pscychresns.2010.10.002
15. Cho YT, Fromm S, Guyer AE, Detloff A, Pine DS, Fudge JL, et al. Nucleus accumbens, thalamus and insula connectivity during incentive anticipation in typical adults and adolescents. *Neuroimage.* (2013) 66:508–21. doi: 10.1016/j.neuroimage.2012.10.013
16. Cousijn J, Wiers RW, Ridderinkhof KR, van den Brink W, Veltman DJ, Porrino LJ, et al. Individual differences in decision making and reward processing predict changes in cannabis use: a prospective functional magnetic resonance imaging study. *Addict Biol.* (2013) 18:1013–23. doi: 10.1111/j.1369-1600.2012.00498.x
17. Li X, Lu ZL, D'Argembeau A, Ng M, Bechara A. The Iowa gambling task in fMRI images. *Human Brain Mapp.* (2010) 31:410–23. doi: 10.1002/hbm.20875
18. Lichenstein SD, Musselman S, Shaw DS, Sitnick S, Forbes EE. Nucleus accumbens functional connectivity at age 20 is associated with trajectory of adolescent cannabis use and predicts psychosocial functioning in young adulthood. *Addiction.* (2017) 112:1961–70. doi: 10.1111/add.13882
19. Fischer AS, Whitfield-Gabrieli S, Roth RM, Brunette MF, Green AI. Impaired functional connectivity of brain reward circuitry in patients with schizophrenia and cannabis use disorder: effects of cannabis and THC. *Schizophrenia Res.* (2014) 158:176–82. doi: 10.1016/j.schres.2014.04.033
20. Filbey FM, Dunlop J. Differential reward network functional connectivity in cannabis dependent and non-dependent users. *Drug Alcohol Depend.* (2014) 140:101–11. doi: 10.1016/j.drugalcdep.2014.04.002
21. Lejuez CW, Aklin WM, Zvolensky MJ, Pedulla CM. Evaluation of the Balloon Analogue Risk Task (BART) as a predictor of adolescent real-world risk-taking behaviours. *J Adolescen.* (2003) 26:475–9. doi: 10.1016/S0140-1971(03)00036-8
22. Hopko DR, Lejuez CW, Daughters SB, Aklin WM, Osborne A, Simmons BL, et al. Construct validity of the balloon analogue risk task (BART): relationship with MDMA use by inner-city drug users in residential treatment. *J Psychopathol Behav Assessment.* (2006) 28:95–101. doi: 10.1007/s10862-006-7487-5
23. Campbell JA, Samartgis JR, Crowe SF. Impaired decision making on the balloon analogue risk task as a result of long-term alcohol use. *J Clin Experi Neuropsychol.* (2013) 10:1071–81. doi: 10.1080/13803395.2013.856382
24. Gonzalez R, Schuster RM, Mermelstein RJ, Vassileva J, Martin EM, Diviak KR. Performance of young adult cannabis users on neurocognitive measures of impulsive behavior and their relationship to symptoms of cannabis use disorders. *J Clin Experi Neuropsychol.* (2012) 34:962–76. doi: 10.1080/13803395.2012.703642
25. Crane NA, Schuster RM, Gonzalez R. Preliminary evidence for a sex-specific relationship between amount of cannabis use and neurocognitive performance in young adult cannabis users. *J Int Neuropsychol Soc.* (2013) 19:1009. doi: 10.1017/S135561771300088X
26. Lindquist MA. The statistical analysis of fMRI data. *Statist Sci.* (2008) 23:439–64. doi: 10.1214/09-STS282
27. Kalivas PW, Volkow ND. New medications for drug addiction hiding in glutamatergic neuroplasticity. *Mol Psychiatr.* (2011) 16:974. doi: 10.1038/mp.2011.46
28. Klumpp H, Angstadt M, Phan KL. Insula reactivity and connectivity to anterior cingulate cortex when processing threat in generalized social anxiety disorder. *Biol Psychol.* (2012) 89:273–6. doi: 10.1016/j.biopsycho.2011.10.010
29. White TP, Joseph V, Francis ST, Liddle PF. Aberrant salience network (bilateral insula and anterior cingulate cortex) connectivity during information processing in schizophrenia. *Schizophrenia Res.* (2010) 123:105–15. doi: 10.1016/j.schres.2010.07.020
30. Zilverstand A, Huang AS, Alia-Klein N, Goldstein RZ. Neuroimaging impaired response inhibition and salience attribution in human drug addiction: a systematic review. *Neuron.* (2018) 98:886–903. doi: 10.1016/j.neuron.2018.03.048
31. First MB, Spitzer RL, Gibbon M, Williams JB. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition*. New York, NY: SCID-I/P (2002).
32. Fukunaga R, Brown JW, Bogg T. Decision making in the Balloon Analogue Risk Task (BART): anterior cingulate cortex signals loss aversion but not the infrequency of risky choices. *Cognit Affect Behav Neurosci.* (2012) 12:479–90. doi: 10.3758/s13415-012-0102-1
33. Ashburner J, Friston KJ. Unified segmentation. *Neuroimage.* (2005) 26:839–51. doi: 10.1016/j.neuroimage.2005.02.018
34. Liu X, Hairston J, Schrier M, Fan J. Common and distinct networks underlying reward valence and processing stages: a meta-analysis of functional neuroimaging studies. *Neurosci Biobehav Rev.* (2011) 35:1219–36. doi: 10.1016/j.neubiorev.2010.12.012
35. Whiteside SP, Lynam DR. The five factor model and impulsivity: Using a structural model of personality to understand impulsivity. *Personal Individ Differ.* (2001) 30:669–89. doi: 10.1016/S0191-8869(00)00064-7
36. Wilbertz T, Deserno L, Horstmann A, Neumann J, Villringer A, Heinze HJ, et al. Response inhibition and its relation to multidimensional impulsivity. *Neuroimage.* (2014) 103:241–8. doi: 10.1016/j.neuroimage.2014.09.021
37. Domenech P, Koechlin E. Executive control and decision-making in the prefrontal cortex. *Curr Opin Behav Sci.* (2015) 1:101–6. doi: 10.1016/j.cobeha.2014.10.007
38. MacDonald S, Mann R, Chipman M, Pakula B, Erickson P, Hathaway A, et al. Driving behavior under the influence of cannabis or cocaine. *Traffic Injury Preven.* (2008) 9:190–4. doi: 10.1080/15389580802040295
39. Smiley A. Marijuana: on-road and driving-simulator studies. In: Kalant H, Corrigall W, Hall W, Smart R, editors. *The Health Effects of Cannabis Addiction Research Foundation.* Toronto, ON: Centre for Addiction and Mental Health (1999). p. 173–91. Available online at: https://komornlaw.com/wp-content/uploads/2018/03/the-health-effects-of-cannabis-9780888683250.pdf
40. Kalivas PW, Volkow ND. The neural basis of addiction: a pathology of motivation and choice. *Am J Psychiatry.* (2005) 162:1403–13. doi: 10.1176/appi.ajp.162.8.1403
41. Sunsay C, Rebec GV. Real-time dopamine efflux in the nucleus accumbens core during Pavlovian conditioning. *Behav Neurosci.* (2008) 122:358. doi: 10.1037/0735-7044.122.2.358
42. Day JJ, Jones JL, Wightman RM, Carelli RM. Phasic nucleus accumbens dopamine release encodes effort-and delay-related costs. *Biol Psychiatr.* (2010) 68:306–9. doi: 10.1016/j.biopsych.2010.03.026
43. Sugam JA, Day JJ, Wightman RM, Carelli RM. Phasic nucleus accumbens dopamine encodes risk-based decision-making behavior. *Biol Psychiatr.* (2012) 71:199–205. doi: 10.1016/j.biopsych.2011.09.029
44. Saddoris MP, Cacciapaglia F, Wightman RM, Carelli RM. Differential dopamine release dynamics in the nucleus accumbens core and shell reveal complementary signals for error prediction and incentive motivation. *J Neurosci.* (2015) 35:11572–82. doi: 10.1523/JNEUROSCI.2344-15.2015
45. Scott JC, Slomiak ST, Jones JD, Rosen AF, Moore TM, Gur RC. Association of cannabis with cognitive functioning in adolescents and young adults: a systematic review and meta-analysis. *JAMA Psychiatr.* (2018) 75:585–95. doi: 10.1001/jamapsychiatry.2018.0335

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.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 03 December 2020
doi: 10.3389/fpsyt.2020.604684

Two-Hour Tobacco Abstinence Has No Effect on Cognitive Control in Male Patients With Nicotine Dependence: An ERP Study

Yanling Xue[1†], *Hongliang Zhou*[2†], *Chenguang Jiang*[1], *Xiaohong Liu*[1], *Zhenhe Zhou*[1*] and *Jun Wang*[1*]

[1] Department of Psychiatry, The Affiliated Wuxi Mental Health Center of Nanjing Medical University, Nanjing, China, [2] Nanjing Brain Hospital Affiliated to Nanjing Medical University, Nanjing, China

The average nicotine half-life in body tissues is 2 h. Understanding the influence of pure nicotine abstinence on cognitive control may be helpful in eliminating nicotine dependence (ND) and preventing smoking relapse. This study was to investigate the effects of 2-h tobacco abstinence on cognitive control in patients with ND. Twenty-five patients with ND completed event-related potential (ERP) P300 measurements at the normality state and the abstinence state. Twenty-five healthy controls (HCs) were measured with P300 twice with a 2-h time interval. HAMD and HAMA were used to assess the emotional state. Results showed that there were significant differences in Carbon monoxide (CO) levels between the abstinence state and the normality state in the ND group. There were no significant differences in HAMD and HAMA scores for the abstinence state in the ND group or the normality state in the ND group and the HC group. For P3a, P3b amplitude, and P3a latency, the main effect for ND group was significant. For P3a, P3b amplitude, and latency, the interaction effect for group × time point was not significant, and the main effect for time point was not significant. It concluded that patients with ND present cognitive control deficits, and 2-h tobacco abstinence has no effect on cognitive control deficits in male patients with ND. Our findings may be helpful in eliminating nicotine dependence and preventing smoking relapse.

Keywords: nicotine dependence, event-related potential P300, P3a, P3b, tobacco abstinence

OPEN ACCESS

Edited by:
Qi Li,
University of Chinese Academy of Sciences, China

Reviewed by:
Joelle Choueiry,
University of Ottawa, Canada
Alessio Simonetti,
Baylor College of Medicine, United States

***Correspondence:**
Zhenhe Zhou
zhouzh@njmu.edu.cn
Jun Wang
woodfish2@126.com

[†] *These authors share first authorship*

Specialty section:
This article was submitted to Addictive Disorders, a section of the journal Frontiers in Psychiatry

Received: *10 September 2020*
Accepted: *11 November 2020*
Published: *03 December 2020*

Citation:
Xue Y, Zhou H, Jiang C, Liu X, Zhou Z and Wang J (2020) Two-Hour Tobacco Abstinence Has No Effect on Cognitive Control in Male Patients With Nicotine Dependence: An ERP Study. Front. Psychiatry 11:604684. doi: 10.3389/fpsyt.2020.604684

INTRODUCTION

Tobacco smoking causes nicotine dependence (ND), which leads to over 6 million deaths worldwide per year, and the World Health Organization predicts that this number will rise to 8 million per year by 2030 (1). As a stimulant that expresses its rewarding effects through the release of dopamine and other neurotransmitters in the brain, nicotine is the primary addictive component in tobacco (2).

Cognition is the ability to perform the mental actions or processes of understanding through all kinds of cerebral cortex activities, such as thought, experience, and the senses (3, 4). Executive function is a critical neurocognitive function and can be measured with neuropsychological tests. For example, the Wisconsin Card Sorting Test is a neuropsychological test of the ability to exhibit flexibility in the face of changing schedules of reinforcement (5, 6). Cognitive control belongs to an

important executive function. The event-related potential (ERP) is a technique that can provide an analysis of neural activity with high temporal resolution. Moreover, it is used to measure behavioral alterations in schizophrenia, affective disorders, and addiction (7–9). To assess cognitive function at a deeper level, the ERP P300, which is a positive deflection of electric potential generated ∼300–500 ms after an infrequent stimulus related to a specific event, may provide the possible neural correlates of cognitive processing.

Cognitive impairments (especially cognitive control deficits) are related to the maintenance of nicotine dependence, nicotine abstinence and the target of pharmacotherapy (10). Many previous studies have reported that patients with nicotine dependence (ND) display cognitive dysfunctions (11, 12), especially executive dysfunctions related to nicotine dependence and craving. For example, a previous study investigated the impact of executive functions, including updating, inhibition and shifting processes, on nicotine dependence and craving; the results indicated a prefrontal cortex (PFC) dysfunction affecting the inhibitory capacities of patients with ND (13). A study investigated the effects of smoking on PFC-mediated cognitive flexibility and subjective states in low- and high-nicotine-dependent individuals and found that the PFC-mediated cognitive effect of smoking as well as subjective reports vary according to the degree of nicotine dependence; smoking selectively impairs cognitive flexibility in high-nicotine-dependent individuals (14). Another study employed a reinforcement-learning task to examine the effects of smoking status on monitoring errors and conflict and found that monitoring errors and conflict are influenced by smoking status (15).

The P3 family of ERP components is a marker of cognitive control processes (16). The P300, which is evoked by family of ERP a three-stimulus oddball task, includes P3a and P3b. P3a is evoked by novel stimuli and considered a psychophysiological index of the orienting response, namely, it reflects involuntary attentional switching and attentional reorienting (17, 18). P3b represents correct responses to correct responses to target tones and P3b is associated with the identification of task-relevant target stimuli (19). There were different findings for the effect of acute nicotine on P300 (P3a or P3b) in healthy non-smokers. For example, previous studies showed that acute nicotine did not alter the P3a amplitudes and latencies in healthy non-smokers (20–22); however, a study reported that acute nicotine attenuated P3a amplitudes (23). Studies which involved the influence of nicotine on P300 (P3a or P3b) in chronic smokers indicated that the decreased P300 amplitude was associated with cigarette smoking (24, 25).

Studies using P300 also indicated that patients with ND present cognitive control deficits. A recent study investigated how the age at tobacco smoking onset affects neurophysiological measures of smoking cue reactivity and reported craving in adult smokers using an oddball paradigm P300 (26). The findings revealed that P300 amplitudes at the Cz electrode site were greater in early-onset nicotine-dependent individuals and associated with greater craving at baseline. A previous study explored the effects of nicotine deprivation (12-h nicotine deprivation) on P3a and P3b amplitudes and examined self-reported trait cognitive control as a moderator of nicotine deprivation-induced reductions in P3a and P3b amplitudes (19). This research finding showed that nicotine deprivation reduced P3b amplitude during a three-stimulus oddball task independent of trait cognitive control. However, nicotine deprivation reduced P3a only in subjects who scored lower on measures of trait cognitive control. Another study using an oddball paradigm reported that chronic nicotine-dependent patients present reduced P300 amplitudes compared to individuals who never smoked or those who had terminated smoking (27). Additionally, a previous study indicated persistent P300 amplitude reduction in nicotine-dependent patients using an auditory oddball paradigm (25).

Many studies indicated that nicotine abstinence causes physiological, psychological and cognitive symptoms (28–31). Furthermore, nicotine abstinence may produce depressive symptoms or precipitate a major depressive episode (32). Whether nicotine abstinence may impair cognition or not has been debated. Many studies have indicated that nicotine abstinence exhibits impairments in working memory during smoking abstinence in patients with ND (33–36). However, previous studies reported that smoking abstinence attenuates attentional bias toward positive stimuli (37, 38).

The psychological symptoms produced by nicotine abstinence, such as anxiety and depression, can also lead to cognitive dysfunctions. Nicotine abstinence is associated with cognitive control deficits, and these cognitive control deficits are a hallmark of nicotine abstinence that could be targeted for success in quitting smoking (10). Thus, the early withdrawal period is a vulnerable time for patients with ND and represents a critical window in which to appraise the outcome of refraining from smoking. A better understanding of the influence of pure nicotine abstinence on cognitive control function may be helpful to improve smoking cessation programmes.

Because nicotine entry into circulation is through the pulmonary system, tobacco smoking is a highly addictive form of systemic drug administration. Studies have confirmed that nicotine can reach the brain in 10–20 s, and brain nicotine concentrations increase after smoking each cigarette and then decline over 20–30 min as nicotine redistributes to other organs or tissues; the average nicotine half-life in body tissues is 2 h (39). Previous studies that investigated nicotine abstinence on cognitive control function focused on nicotine deprivation for more than 12 h (11, 19, 31, 40, 41) but could not avoid confounding the cognitive control impairment induced by pure nicotine abstinence and the psychological symptoms produced by nicotine abstinence.

In summary, cognitive control deficits, which can be measured with neuropsychological tests, are related to the maintenance of nicotine dependence, nicotine abstinence and the target of pharmacotherapy. An ERP P300 study may provide a more definitive answer regarding the effects of nicotine deprivation on P3a- or P3b-related neural activity. Additionally, nicotine withdrawal-induced cognitive performance deficits are typically not discovered within 2 h of tobacco deprivation (42, 43). Understanding the influence of pure nicotine abstinence on

cognitive control function may be helpful in eliminating nicotine dependence and preventing smoking relapse. However, to date, the influence of pure nicotine abstinence on cognitive control function is still unclear.

In this study, male patients with ND were selected as subjects. The cognitive control deficits of nicotine deprivation were measured with P300, including P3a and P3b components, which is evoked by a three-stimulus oddball task. To guarantee the influence of pure nicotine abstinence on cognitive control function, cognitive performances were collected at baseline and after 2 h of tobacco deprivation. The hypothesis of this study is that male patients with ND present abnormal P300 components and 2-h tobacco abstinence has no effect on cognitive control deficits. The purpose of this study was to investigate the effects of 2-h tobacco abstinence on cognitive control deficits in patients with ND.

METHOD

Time and Setting

This study was conducted in the Department of Psychiatry, The Affiliated Wuxi Mental Health Center of Nanjing Medical University, Wuxi, People's Republic of China, from January 01, 2018, to March 31, 2020.

Diagnostic Approaches and Participants

This study included patients in the ND group and a healthy control (HC) group. The criteria for inclusion in the ND group included (a) meeting the Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-5) criteria for current nicotine dependence; (b) age range from 18 to 60 years old; (c) had not previously quit smoking and reported smoking more than 10 cigarettes per day in the last 6 months; (d) no smoking cessation in the past 12 months; and (e) no neurological illness or psychiatric disorders as determined by clinical evaluations and medical records or alcohol/other substance dependence. The criteria for inclusion in the HC group included (a) not meeting the criteria for any DSM-5 axis I disorder or personality disorders, as assessed by the Structured Clinical Interview for DSM-5 (SCID-5, Chinese version); (b) age range from 18 to 60 years old; (c) no history of any kind of mental disorder; and (d) no physical illness.

In the present study, 25 patients with nicotine dependence were recruited as the ND group. Patients with ND were recruited from the Smoking Cessation Clinic of Psychiatry Department, The Affiliated Wuxi Mental Health Center of Nanjing Medical University, Wuxi, People's Republic of China. Patients with ND only smoked cigarettes, not electronic or other tobacco products. Twenty-five healthy persons were recruited as the HC group. HCs were recruited from a group of citizens who lived in Wuxi City, China, through local advertisements. All of the participants were Chinese.

Experimental Procedures

All participants were prohibited from drinking any soft drinks, such as coffee, tea, or other recreational drugs, at least 12 h prior to the experiment. That was confirmed verbally before the test day. On the day of the ERP recording, two psychiatric resident physicians collected patient medication information, demographic data, and clinical characteristics and confirmed/excluded a diagnosis of current nicotine dependence. The Annett handedness scale was used for the assessment of handedness (44). Nicotine dependence levels were measured with the Fagerstrom Test of nicotine dependence (FTND) (45). Both patients with ND and HCs were hearing evaluated previous to inclusion in study, and all participants' hearings were in the normal level.

Before starting the experiment, all participants were instructed to try their best to complete the task as quickly and accurately as possible. The authenticity of the 2-h nicotine abstinence was determined by expiratory carbon monoxide levels measured using the QT-200PLUS portable detector of carbon monoxide (CO) (Shenzhen Wellcome Technology Co., Ltd., China). The CO levels of patients with ND were measured 10 min before the experiment. The CO level in the expired air was verified as no more than 6 parts per million (ppm) during the abstinence state, which showed a distinct reduction for each patient compared to that measured during the normal smoking state (more than 10 ppm). The CO levels of HCs also were measured 10 min before the experiment, and the CO levels of all HCs in the expired air were verified as no more than 3 ppm.

All patients with ND were measured with ERP P300 at the normality state (time 1, i.e., just after the last cigarette smoked) and abstinence (time 2, i.e., just at 2 h after the last cigarette smoked). During the 2 h abstinence phase, all participants were arranged to stay in a comfortable room, and all participants skimmed through a newspaper or sat in the room peacefully depending on their own desire. To avoid the practice effect, the HCs were measured with ERP twice with a 2-h time interval (corresponding to time 1 and time 2). The anxiety and depression of all participants were assessed with the Hamilton Anxiety Scale (HAMA) and Hamilton Depression Scale (HAMD, 17-item edition).

All experimental procedures were approved by the Ethics Committee on Human Studies, the Affiliated Wuxi Mental Health Center of Nanjing Medical University, Wuxi, China, and were conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent to participate, and all participants were compensated 300.00 Chinese Yuan (CNY) plus travel costs.

Event-Related Potential Measurement

The event-related potential measurement was obtained from a recent study (46). The BioSemi Active Two system (BioSemi Inc., Amsterdam, Netherlands) was employed for the continuous electroencephalogram recording. The digitization rate was 512 Hz; the bandpass was DC-104 Hertz (Hz), and a common mode sensor served as the reference (PO2 site) using a 64-channel electrode cap. Electrooculogram electrodes were placed below and at the outer canthi of the left eye. A three-stimulus (novelty) auditory oddball paradigm was employed to evoke ERP P3a and P3b. There were 400 binaural, 80 decibel (dB) tones of 50 millisecond (ms) duration stimuli presented to the participants through foam insert earphones. Twelve percent of

the stimuli were target tones (1,500 Hz), 12% were infrequent "novel" sounds (a bird call or a water drop), and 76% were standard tones (1,000 Hz), with an inter-stimulus interval varying between 1.8 and 2.2 s. Stimuli presentation was randomized. The electrical impedance was monitored. The duration of the whole P300 paradigm is 8 min. Participants were in a sound attenuated chamber. All subjects were instructed to press the computer mouse in response to target tones only. Clicking that occurred between 100 and 900 ms after the tone was confirmed as a correct response. Before the formal trial, there was a practice block to make sure participants understood the task.

Event-Related Potential Data Analysis

ERP data were analyzed using BrainVision Analyzer 2.0 (Brain Products GmbH, Munich, Germany). According to a previous study, P3a was analyzed at the Cz electrode site because it is the largest in the frontal regions, and P3b was analyzed at the Pz electrode site because it is the largest in the parietal regions (46–48). An average of the mastoids was reference and bandpass filtered between 0.01 and 20 Hz using a zero phase shift Butterworth filter. Data were segmented by stimulus marker from −100 to 1000 ms, responses to novel sounds (a bird call or a water drop) were employed for P3a, and correct responses to target tones were employed for P3b. Segments were baseline corrected using −100–0 ms pre-stimulus time and eye-blink corrected using established measures (46). Artifact rejection for individual channels was performed, and a given segment was rejected if the voltage gradient exceeded 50 μV/ms, the amplitude was ±100 μV, or the signal was flat (<0.5 μV for more than 100 ms). Segments were averaged across stimulus markers, the P3a amplitude peak was chosen to be 250–450 ms, and the P3b amplitude peak was chosen to be 280–650 ms.

Data Analysis

Statistical Program for Social Sciences software version 19.0 (SPSS, IBM Corporation, Armonk, NY, USA) was employed for the data analysis. Mean age and education were compared between the ND group and the HC group using two-tailed *t* tests, and handedness was compared using the Pearson chi-square test. CO levels were compared in the ND group using paired-samples *t* tests. HAMD scores, HAMA scores, behavioral data [i.e., reaction time (RT), rate of correct responses (Hit rate), and rate of incorrect responses (Error rate) for target stimuli] and the mean amplitudes and the mean latencies of P3a and P3b were compared between the ND group and the HC group using a 2 (ND group vs. HC group) × 2 (time 1 vs. time 2) repeated-measures analysis of variance (ANOVA). The degrees of freedom of the *F* ratio were corrected according to the Greenhouse–Geisser method. Least square difference tests were performed as *post-hoc* analyses if indicated. Correlation analysis between HAMD scores, HAMA scores and measures of P3a and P3b in ND and HC groups separately at time 1 and time 2 were conducted by Pearson's *r*. Alpha values of 0.05 were considered significant.

RESULTS

Demographic Characteristics of Participants

The demographic characteristics of all participants are shown in **Table 1**. There were no significant differences in mean age, mean education years, or handedness between the ND group and the HC group.

Comparisons of CO Levels in the ND Group

Based on the paired-samples *t* test, there were significant differences in CO levels between the abstinence state (mean 5.6 ppm; SD: 1.2) and the normality state (mean 12.1 ppm; SD: 1.0) in the ND group ($t = 3.465$, $p = 0.000$), and CO levels in the abstinence state were less than that in the normality state.

Comparisons of HAMD and HAMA Between the ND Group and the HC Group

As shown in **Table 2**, using HAMD and HAMA scores as dependent variables, a 2 × 2 repeated measures ANOVA with group (ND group vs. HC group) as a between-subjects factor and time point (time 1 vs. time 2) as a within-subjects factor revealed that the interaction effect for group × time point was not significant (for HAMD, $F_{1,\ 48}$= 1.894, $p = 0.162$; for HAMA, $F_{1,\ 48} = 1.934$, $p = 0.178$;); the main effect for group and time point was not significant (for HAMD, $F_{1,\ 48}$= 195.320,187.113, $p = 0.235$, 0.265; for HAMA, $F_{1,\ 48}$= 180.240, 179.089, $p = 0.188$, 0.197).

Behavioral Data Analysis

As shown in **Table 2**, using RT, Hit rate and Error rate as dependent variables, a 2 × 2 repeated measures ANOVA with group (ND group vs. HC group) as a between-subjects factor and time point (time 1 vs. time 2) as a within-subjects factor revealed that the interaction effect for group × time point was not significant (for RT, $F_{1,\ 48} = 2.043$, $p = 0.177$; for Hit rate, $F_{1,\ 48} = 1.986$, $p = 0.180$; for Error rate, $F_{1,\ 48} = 2.123$, $p = 0.216$), and the main effect for time point was not significant (for RT, $F_{1,\ 48} = 0.749$, $p = 0.270$; for Hit rate, $F_{1,\ 48} = 0.912$, $p = 0.294$; for Error rate, $F_{1,\ 48} = 0.883$, $p = 0.293$); however, the main effect for group was significant (for RT, $F_{1,\ 48} = 7.840$, $p = 0.027$; for Hit rate, $F_{1,\ 48} = 6.542$, $p = 0.019$; for Error rate, $F_{1,\ 48} = 6.380$, $p = 0.021$). RT in ND group were longer than that in HC group; Hit rate in ND group were lower than that in HC group; Error rate in ND group were higher than that in HC group.

ERP Data Analysis

All ERP data are shown in **Table 2**. Using P3a and P3b as dependent variables, a 2 × 2 repeated-measures ANOVA was performed on mean amplitudes and mean latencies, respectively, with the group (ND group vs. HC group) as the between-subjects factor and time point (time 1 vs. time 2) as the within-subjects factor.

P3a Component

As shown in **Figure 1** and **Table 3**, for amplitude, the interaction effect for group × time point was not significant ($F_{1,\ 48} = 2.147$, $p = 0.149$), and the main effect for time point was not significant

TABLE 1 | Demographic data of participants.

Variable	ND ($n = 25$)	HC ($n = 25$)	Test statistic
Mean age (SD)	32.0 (10.3)	30.9 (6.9)	$t = 0.421$, $p = 0.676$
Age range	22–59	23–58	–
Education (SD)	14.2 (2.3)	15.0 (2.1)	$t = -0.150$, $p = 0.256$
FTND (SD)	7.5 (1.3)	–	–
Handedness (R/M/L)	9/7/9	10/7/8	$\chi^2 = 0.176$, $p = 0.890$
The number of cigarettes smoked per day (SD)	17.5 (1.5)	–	–

ND, Nicotine dependence; HC, Healthy control; SD, Standard deviation; R, Right; M, Mixed; L, Left; FTND, Fagerstrom Test of Nicotine Dependence.

TABLE 2 | HAMD scores, HAMA scores and behavioral data [mean (SD)] in the ND group ($n = 25$) and HC group ($n = 25$).

Variable	ND					HC				
	HAMD	HAMA	RT (ms)	Hit rate	Error rate	HAMD	HAMA	RT (ms)	Hit rate	Error rate
Time 1	13.8 (2.5)	10.3 (2.4)	395.1 (25.2)	0.825 (0.040)	0.208 (0.050)	13.4 (1.9)	10.5 (2.0)	382.1 (19.8)	0.915 (0.038)	0.102 (0.0113)
Time 2	13.6 (2.2)	10.1 (2.8)	394.3 (22.0)	0.826 (0.397)	0.207 (0.488)	13.3 (2.1)	10.2 (2.6)	385.4 (20.3)	0.920 (0.029)	0.101 (0.012)

ND, Nicotine dependence; HC, Healthy control; SD, Standard deviation; RT, reaction time; Hit rate, rate of correct responses for target stimuli; Error rate, rate of incorrect responses for target stimuli.

($F_{1, 48} = 0.262$, $p = 0.611$); however, the main effect for group was significant ($F_{1, 48} = 28.336$, $p = 0.000$). P3a amplitudes in ND group were lower than that in HC group. For latency, the interaction effect for group × time point was not significant ($F_{1, 48} = 1.942$, $p = 0.17$), and the main effect for time point was not significant ($F_{1, 48} = 0.089$, $p = 0.767$); however, the main effect for group was significant ($F_{1, 48} = 5.354$, $p = 0.025$). P3a latencies in ND group were longer than that in HC group.

P3b Component

As shown in **Figure 2** and **Table 3**, for amplitude, the interaction effect for group × time point was not significant ($F_{1, 48} = 0.277$, $p = 0.601$), and the main effect for time point was not significant ($F_{1, 48} = 0.121$, $p = 0.730$); however, the main effect for group was significant ($F_{1, 48} = 5.425$, $p = 0.024$). P3a amplitudes in ND group were lower than that in HC group. For latency, the interaction effect for group × time point was not significant ($F_{1, 48} = 0.043$, $p = 0.836$), and the main effect for time point was not significant ($F_{1, 48} = 1.432$, $p = 0.237$); the main effect for group was not significant ($F_{1, 48} = 1.705$, $p = 0.198$).

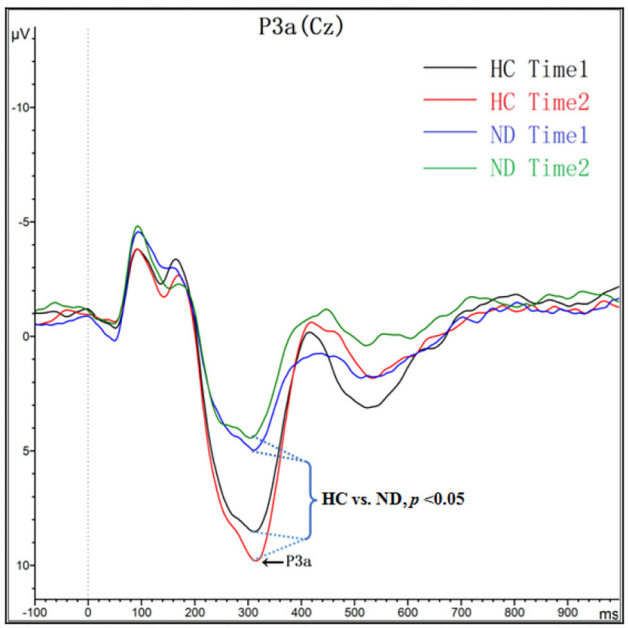

FIGURE 1 | Grand averaged ERP P3a was elicited by a three-stimulus (novelty) auditory oddball paradigm for the ND group (purple lines and green lines) and the HC group (black lines and red lines) at time 1 and time 2. The P3a components were presented within a 250–450 ms latency window at the Cz electrode site.

Correlation Analysis Between HAMD Scores, HAMA Scores, and Amplitudes and Latencies of P3a and P3b in ND and HC Group

HAMD scores were not correlated with amplitudes and latencies of P3a and P3b in ND and HC group at time 1 and time 2 (for amplitudes and latencies of P3a in ND group: $r = 0.135, 0.236$, $p = 0.325, 0.420$; for amplitudes and latencies of P3a in HC group: $r = 0.192, 0.208$, $p = 0.294, 0.383$. for amplitudes and latencies of P3b in ND group: $r = 0.367, 0.330$, $p = 0.221, 0.329$; for amplitudes and latencies of P3b in HC group: $r = 0.204, 0.217$, $p = 0.270, 0.293$.).

HAMA scores were not correlated with amplitudes and latencies of P3a and P3b in ND and HC group at time 1 and time 2 (for amplitudes and latencies of P3a in ND group: $r = 0.241$, 0.196, $p = 0.228, 0.310$; for amplitudes and latencies of P3a in HC group: $r = 0.239, 0.211$, $p = 0.296, 0.285$; for amplitudes and

TABLE 3 | ERP data [mean (SD)] in the ND group ($n = 25$) and HC group ($n = 25$).

Variable	ND (time 1)		ND (time 2)		HC (time 1)		HC (time 2)	
	A (uV)	L (ms)	A (uV)	L (ms)	A (uV)	L (ms)	A (uV)	L (ms)
P3a	5.9 (3.4)	310.8 (25.5)	5.4 (2.9)	306.2 (26.2)	10.8 (4.8)	288.6 (31.4)	11.7 (4.8)	295.7 (32.3)
P3b	4.6 (2.9)	389.5 (74.1)	4.5 (3.0)	397.7 (78.1)	6.4 (3.7)	362.6 (72.1)	6.8 (3.4)	374.2 (71.9)

ND, Nicotine dependence; HC, Healthy control; SD, Standard deviation; A, Amplitudes; L, Latencies.

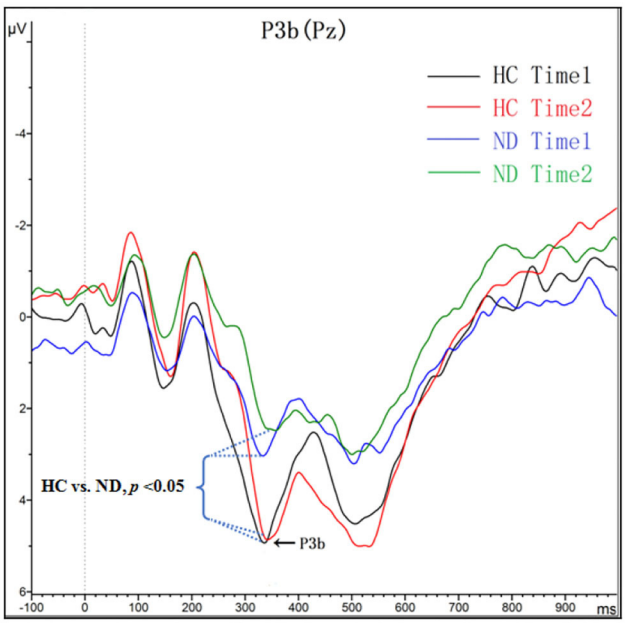

FIGURE 2 | Grand averaged ERP P3b was elicited by a three-stimulus (novelty) auditory oddball paradigm for the ND group (purple lines and green lines) and the HC group (black lines and red lines) at time 1 and time 2. The P3b components were presented within a 280–650 ms latency window at the Pz electrode site.

latencies of P3b in ND group: $r = 0.372, 0.345$, $p = 0.193, 0.256$; for amplitudes and latencies of P3b in HC group: $r = 0.215, 0.229$, $p = 0.264, 0.280$).

DISCUSSION

This study is the first to clarify the effects of 2-h tobacco abstinence on cognitive control deficits in male patients with ND using ERP P300 measurement, including P3a and P3b components, which is evoked by a three-stimulus oddball task. Our results showed that patients with ND elicited a reduction in P3a and P3b amplitude as well as a prolonged P3a latency, and P3a and P3b amplitudes and latencies did not change after 2-h tobacco abstinence. Additionally, patients with ND showed a prolonged RT, a reduced Hit rate as well as an increased Error rate for the target stimuli; HAMD and HAMA scores were not correlated with amplitudes and latencies of P3a and P3b in ND group at just after the last cigarette smoked and abstinence. We verified the hypothesis, i.e., male patients with ND present abnormal P300 components and 2-h tobacco abstinence has no effect on cognitive control deficits.

P3a mainly involves a broad network of cortical regions, including the prefrontal cortex, cingulate gyrus, and hippocampus (49). P3a reflects evidence that transient activation in the neural network is involved in a variety of cognitive tasks that demand continual updating of task-set information for the selection of goal-directed actions (50). Additionally, P3a reflects the initial unhitching of the focus of attention from current information with the aim of preparing to switch attention (50). Previous studies reported that acute nicotine administration may alleviate cognitive dysfunction with increased amplitudes of P3a or P3b, and these effects are relative to information processing task difficulty, amount smoked and nicotine level (51–54). Consistent with previous studies (19, 25), our results showed a reduction in P3a amplitude and a prolonged P3a latency in the patient group, which deduces that nicotine dependence might lead to cognitive control dysfunctions, i.e., the dysfunction of an involuntary switch of attention.

P3b represents correct responses to target tones, and P3b is associated with the identification of task-relevant target stimuli (19). It has been confirmed that P3b is both a trait and state biomarker (46). Because this study was a cross-sectional study, we found a reduction in P3b amplitude compared with normal controls, which may not indicates that cognitive control deficits in patients with ND are trait dependent or state dependent.

According to a previous study, the average nicotine half-life in body tissues is 2 h (39). Our results showed no occurrence of withdrawal symptoms, such as anxiety and depression. More than 12 h of nicotine abstinence may produce many psychological symptoms. Many studies have proven that psychological symptoms, such as anxiety and depression, can lead to cognitive impairments. Previous studies have focused on nicotine abstinence for more than 12 h (11, 19, 31, 40, 41) and found a reduction in both P3a and P3b amplitudes, which indicated that 12-h nicotine abstinence may cause neurocognitive impairments (19). However, in this study, ERP P300 was measured after 2 h of tobacco abstinence, which prevented cognitive status from being induced by psychological symptoms. Our results showed that, compared with the normal smoking state, 2-h tobacco abstinence did not improve or deteriorate P3a and P3b amplitude and latency in patients with ND, which indicates that 2-h tobacco abstinence has no effect on cognitive control deficits.

In conclusion, patients with ND present cognitive control deficits, and after 2 h of tobacco deprivation, the cognitive control deficits do not improve. Specifically, 2-h tobacco abstinence has no effect on cognitive control deficits in male patients with ND. The implication of the findings is that understanding the influence of pure nicotine abstinence on cognitive control may contribute new insights into the neural mechanism of nicotine abstinence in male patients with ND. Furthermore, our results may be helpful in focusing on therapeutic target for eliminating nicotine dependence and preventing smoking relapse.

There are some limitations of this study. First, the results must be considered preliminary due to the small sample size. Future studies with larger sample sizes and the same ERP parameters are needed to confirm the results of this study. Second, in this study, no measures of blood cotinine levels were used to determine the primary metabolite of nicotine precisely. Third, no withdrawal questionnaire was used to assess the withdrawal level for ND patients. Fourth, this study excludes female smokers, hence its applicability to the general population may be limited, further examination of this effect on female smokers is necessary in the future study. Finally, because of the deficient spatial resolution of ERPs, further studies with functional magnetic resonance imaging (fMRI), positron emission tomography (PET) or magnetoencephalography (MEG) should be conducted to determine the influence of 2-h nicotine abstinence on cognitive control deficits.

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 Ethics Committee on Human Studies, the Affiliated Wuxi Mental Health Center of Nanjing Medical University, Wuxi, China. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YX, HZ, JW, and ZZ designed the study. YX, HZ, CJ, XL, JW, and ZZ contributed to the acquisition of the data, analyzed the data, interpreted the results, and drafted the manuscript. ZZ wrote the paper. All the authors critically reviewed the content and approved the final version for publication.

FUNDING

This study was supported by the National Natural Science Foundation, China (No. 81471354) and Key Talents Project Foundation for Medical and Health Services, Jiangsu Province (No. ZDRCC2016019).

REFERENCES

1. World Health Organization. *WHO Report on the Global Tobacco Epidemic, 2013: Enforcing Bans on Tobacco Advertising, Promotion and Sponsorship*. Geneva: World Health Organization (2013).
2. Allenby CE, Boylan KA, Lerman C, Falcone M. Precision medicine for tobacco dependence: development and validation of the nicotine metabolite ratio. *J Neuroimmune Pharmacol.* (2016) 11:471–83. doi: 10.1007/s11481-016-9656-y
3. Zhou HL, Hua LL, Jiang HT, Dai ZP, Han YL, Lin PH, et al. Autonomic nervous system is related to inhibitory and control function through functional inter-region connectivities of OFC in major depression. *Neuropsychiatr Dis Treat.* (2020) 16:235–47. doi: 10.2147/NDT.S238044
4. Zhou HL, Dai ZP, Hua LL, Jiang HT, Tian S, Han YL, et al. Decreased task-related HRV is associated with inhibitory dysfunction through functional interRegion connectivity of PFC in major depressive disorder. *Front Psychiatry.* (2020) 10:989. doi: 10.3389/fpsyt.2019.00989
5. Zhou ZH, Zhou HL, Zhu HM. Working memory, executive function and impulsivity in internet-addictive disorders: a comparison with pathological gambling. *Acta Neuropsychiatr.* (2016) 28:92–100. doi: 10.1017/neu.2015.54
6. Zhou Z, Zhu H, Li C, Wang J. Internet addictive individuals share impulsivity and executive dysfunction with alcohol-dependent patients. *Front Behav Neurosci.* (2014) 8:288. doi: 10.3389/fnbeh.2014.00288
7. Luck SJ, Mathalon DH, O'Donnell BF, Hämäläinen MS, Spencer KM, Javitt DC, et al. A roadmap for the development and validation of event-related potential biomarkers in schizophrenia research. *Biol Psychiatry.* (2011) 70:28–34. doi: 10.1016/j.biopsych.2010.09.021
8. Simonetti A, Lijffijt M, Kahlon RS, Gandy K, Arvind RP, Amin P. Early and late cortical reactivity to passively viewed emotional faces in pediatric bipolar disorder. *J Affect Disord.* (2019) 253:240–7. doi: 10.1016/j.jad.2019.04.076
9. Kreusch F, Quertemon E, Vilenne A, Hansenne M. Alcohol abuse and ERP components in Go/No-go tasks using alcohol-related stimuli: impact of alcohol avoidance. *Int J Psychophysiol.* (2014) 94:92–9. doi: 10.1016/j.ijpsycho.2014.08.001
10. Ashare RL, Schmidt HD. Optimizing treatments for nicotine dependence by increasing cognitive performance during withdrawal. *Expert Opin Drug Discov.* (2014) 9:579–94. doi: 10.1517/17460441.2014.908180
11. Heishman SJ, Kleykamp BA, Singleton EG. Meta-analysis of the acute effects of nicotine and smoking on human performance. *Psychopharmacology (Berl).* (2010) 210:453–69. doi: 10.1007/s00213-010-1848-1
12. Butler K, Le Foll B. Impact of substance use disorder pharmacotherapy on executive function: a narrative review. *Front Psychiatry.* (2019) 10:98. doi: 10.3389/fpsyt.2019.00098
13. Flaudias V, Picot MC, Lopez-Castroman J, Llorca PM, Schmitt A, Perriot J, et al. Executive functions in tobacco dependence: importance of Inhibitory capacities. *PLoS ONE.* (2016) 11: e0150940. doi: 10.1371/journal.pone.0150940
14. Nesic J, Rusted J, Duka T, Jackson A. Degree of dependence influences the effect of smoking on cognitive flexibility. *Pharmacol Biochem Behav.* (2011) 98:376–84. doi: 10.1016/j.pbb.2011.01.015
15. Butler K, Rusted J, Gard P, Jackson A. Performance monitoring in nicotine dependence: considering integration of recent reinforcement history. *Pharmacol Biochem Behav.* (2017) 156:63–70. doi: 10.1016/j.pbb.2017.04.004
16. Polich J. Updating P300: an integrative theory of P3a and P3b. *Clin Neurophysiol.* (2007) 118:2128–48. doi: 10.1016/j.clinph.2007.04.019
17. Escera C, Alho K, Schröger E, Winkler I. Involuntary attention and distractibility as evaluated with event-related brain potentials. *Audiol Neurootol.* (2000) 5:151–66. doi: 10.1159/000013877
18. Friedman D, Cycowicz YM, Gaeta H. The novelty P3: an event-related brain potential (ERP) sign of the brain's evaluation of novelty. *Neurosci Biobehav Rev.* (2001) 25:355–73. doi: 10.1016/s0149-7634(01)00019-7
19. Evans DE, Maxfield ND, Van Rensburg KJ, Oliver JA, Jentink KG, Drobes DJ. Nicotine deprivation influences P300 markers of cognitive control. *Neuropsychopharmacology.* (2013) 38:2525–31. doi: 10.1038/npp.2013.159

20. Knott VJ, Bolton K, Heenan A, Shah D, Fisher DJ, Villeneuve C. Effects of acute nicotine on event-related potential and performance indices of auditory distraction in nonsmokers. *Nicotine Tob Res.* (2009) 11:519–30. doi: 10.1093/ntr/ntp044
21. Knott VJ, Scherling CS, Blais CM, Camarda J, Fisher DJ, Millar A, et al. Acute nicotine fails to alter event-related potential or behavioral performance indices of auditory distraction in cigarette smokers. *Nicotine Tob Res.* (2006) 8:263–73. doi: 10.1080/14622200600576669
22. Knott V, Heenan A, Shah D, Bolton K, Fisher D, Villeneuve C. Electrophysiological evidence of nicotine's distracter-filtering properties in non-smokers. *J Psychopharmacol.* (2011) 25:239–48. doi: 10.1177/0269881109348158
23. Müller BW, Specka M, Steinchen N, Zerbin D, Lodemann E, Finkbeiner T, et al. Auditory target processing in methadone substituted opiate addicts: the effect of nicotine in controls. *BMC Psychiatry.* (2007) 7:63. doi: 10.1186/1471-244X-7-63
24. Hedges D, Bennett DP. Cigarette smoking and P300 amplitude in adults: a systematic review. *Nicotine Tob Res.* (2014) 16:1157–66. doi: 10.1093/ntr/ntu083
25. Neuhaus A, Bajbouj M, Kienast T, Kalus P, Von Haebler D, Winterer G, et al. Persistent dysfunctional frontal lobe activation in former smokers. *Psychopharmacology (Berl).* (2006) 186:191–200. doi: 10.1007/s00213-006-0366-7
26. Mashhoon Y, Betts J, Farmer SL, Lukas SE. Early onset cigarette smokers exhibit greater P300 reactivity to smoking-related stimuli and report greater craving. *Brain Res.* (2018) 1687:173–84. doi: 10.1016/j.brainres.2018.02.037
27. Anokhin AP, Vedeniapin AB, Sirevaag EJ, Bauer LO, O'Connor SJ, Kuperman S, et al. The P300 brain potential is reduced in smokers. *Psychopharmacology (Berl).* (2000)149:409–13. doi: 10.1007/s002130000387
28. Corwin EJ, Klein LC. C-reactive protein and depressed mood in a sub-group of smokers during nicotine abstinence. *Hum Psychopharmacol.* (200)18:329–37. doi: 10.1002/hup.487
29. Shiffman S. Effect of nicotine lozenges on affective smoking withdrawal symptoms: secondary analysis of a randomized, double-blind, placebo-controlled clinical trial. *Clin Ther.* (2008) 30:1461–75. doi: 10.1016/j.clinthera.2008.07.019
30. Saul S, West R, Gilbert D G. Recommendation for the assessment of tobacco craving and withdrawal in smoking cessation trials. *Nicotine Tob Res.* (2004) 6:599–614. doi: 10.1080/14622200410001734067
31. Hughes JR. Effects of abstinence from tobacco: valid symptoms and time course. *Nicotine Tob Res.* (2007) 9:315–27. doi: 10.1080/14622200701188919
32. Hughes JR, Stead LF, Hartmann-Boyce J, Cahill K, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database Syst Rev.* (2014) 1:CD000031. doi: 10.1002/14651858.CD000031.pub4
33. Myers CS, Taylor RC, Moolchan ET, Heishman SJ. Dose-related enhancement of mood and cognition in smokers administered nicotine nasal spray. *Neuropsychopharmacology*. (2008) 33:588–98. doi: 10.1038/sj.npp.1301425
34. Mendrek A, Monterosso J, Simon SL, Jarvik M, Brody A, Olmstead R. Working memory in cigarette smokers: comparison to non-smokers and effects of abstinence. *Addict Behav.* (2006) 31:833–44. doi: 10.1016/j.addbeh.2005.06.009
35. Ashare RL, Falcone M, Lerman C. Cognitive function during nicotine withdrawal: Implications for nicotine dependence treatment. *Neuropharmacology.* (2014) 76:581–91. doi: 10.1016/j.neuropharm.2013.04.034
36. Waters AJ, Carter BL, Robinson JD, Wetter DW, Lam CY, Kerst W, et al. Attentional bias is associated with incentive-related physiological and subjective measures. *Exp Clin Psychopharmacol.* (2009) 17:247–57. doi: 10.1037/a0016658
37. Powell JH, Pickering AD, Dawkins L, West R, Powell JF. Cognitive and psychological correlates of smoking abstinence, and predictors of successful cessation. *Addict Behav.* (2004) 29:1407–26. doi: 10.1016/j.addbeh.2004.06.006
38. Dawkins L, Powell JH, West R, Powell J, Pickering A. A double-blind placebo controlled experimental study of nicotine: I–effects on incentive motivation. *Psychopharmacology (Berl).* (2006) 189:355–67. doi: 10.1007/s00213-006-0588-8
39. Houezec JL. Role of nicotine pharmacokinetics in nicotine addiction and nicotine replacement therapy: a review. *Int J Tuberc Lung Dis.* (2003) 7:811–9. doi: 10.1002/1531-8249(199904)45:43.0.CO;2-H
40. Hughes JR. Effects of abstinence from tobacco: etiology, animal models, epidemiology, and significance: a subjective review. *Nicotine Tob Res.* (2007) 9:329–39. doi: 10.1080/14622200701188927
41. Liu C, Dong F, Li YD, Ren Y, Xie DD, Wang XF, et al. 12h abstinence-induced ERP changes in young smokers: electrophysiological evidence from a Go/NoGo study. *Front Psychol.* (2019) 10:1814. doi: 10.3389/fpsyg.2019.01814
42. Parrott AC, Garnham NJ, Wesnes K, Pincock C. Cigarette smoking and abstinence: comparative effects upon cognitive task performance and mood state over 24 hours. *Hum Psychopharmacol.* (1996) 11:391–400. doi: 10.1002/(SICI)1099-1077(199609)11:5<391::AID-HUP780>3.0.CO;2-Z
43. Hendricks PS, Ditre JW, Drobes DJ, Brandon TH. The early time course of smoking withdrawal effects. *Psychopharmacology (Berl).* (2006) 187:385–96. doi: 10.1007/s00213-006-0429-9
44. Annett M. A classification of hand preference by association analysis. *Br J Psychol.* (1970) 61:303–21. doi: 10.1111/j.2044-8295.1970.tb01248.x
45. Fagerstrom KO, Schneider NG. Measuring nicotine dependence: a review of the Fagerstrom Tolerance Questionnaire. *J Behav Med.* (1989) 12:159–82. doi: 10.1007/BF00846549
46. Monaghan CK, Brickman S, Huynh P, Öngür D, Hall MH. A longitudinal study of event related potentials and correlations with psychosocial functioning and clinical features in first episode psychosis patients. *Int J Psychophysiol.* (2019) 145:48–56. doi: 10.1016/j.ijpsycho.2019.05.007
47. Polich J, Criado JR, Neuropsychology and neuropharmacology of P3a and P3b. *Int J Psychophysiol.* (2006) 60:172–85. doi: 10.1016/j.ijpsycho.2005.12.012
48. Comerchero MD, Polich J. P3a and P3b from typical visual and auditory stimuli. *Clin Neurphysiol.* (1999) 110:24–30. doi: 10.1016/s0168-5597(98)00033-1
49. Correa-Jaraba KS, Lindín M, Díaz F. Increased amplitude of the P3a ERP component as a neurocognitive marker for differentiating amnestic subtypes of mild cognitive impairment. *Front Aging Neurosci.* (2018) 10:19. doi: 10.3389/fnagi.2018.00019
50. Correa-Jaraba KS, Cid-Fernández S, Lindín M, Díaz F. Involuntary capture and voluntary reorienting of attention decline in middle-aged and old participants. *Front Hum Neurosci.* (2016) 10:129. doi: 10.3389/fnhum.2016.00129
51. Houlihan ME, Pritchard WS, Robinson JH. Faster P300 latency after smoking in visual but not auditory oddball tasks. *Psychopharmacology (Berl).* (1996) 123:231–8. doi: 10.1007/BF02246577
52. Ilan AB, Polich J. Tobacco smoking and memory scanning: behavioural and event-related potential effects. *Nicotine Tob Res.* (1999)1:233–40. doi: 10.1080/146222990500 11351
53. Ilan AB, Polich J. Tobacco smoking and event-related brain potentials in a Stroop task. *Int J Psychophysiol.* (2001) 40:109–18. doi: 10.1016/s0167-8760(00)00156-2
54. Domino EF. Effects of tobacco smoking on electroencephalographic, auditory evoked and event-related potentials. *Brain Cogn.* (2003)53:66–74. doi: 10.1016/s0278-2626(03)0204-5

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.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 04 December 2020
doi: 10.3389/fpsyt.2020.599141

Altered Reward Processing System in Internet Gaming Disorder

Syeda Raiha[1,2†], *Guochun Yang*[1,2†], *Lingxiao Wang*[3,4], *Weine Dai*[1,5,6,7], *Haiyan Wu*[8], *Guangteng Meng*[1,2], *Bowei Zhong*[1,2] *and Xun Liu*[1,2*]

[1] Key Laboratory of Behavioral Science, Institute of Psychology, Chinese Academy of Sciences, Beijing, China, [2] Department of Psychology, University of Chinese Academy of Sciences, Beijing, China, [3] Center for Cognition and Brain Disorders, The Affiliated Hospital of Hangzhou Normal University, Hangzhou, China, [4] Zhejiang Key Laboratory for Research in Assessment of Cognitive Impairments, Hangzhou, China, [5] Sino-Danish College, University of Chinese Academy of Sciences, Beijing, China, [6] Sino-Danish Center for Education and Research, Beijing, China, [7] CFIN and Pet Center, Aarhus University, Aarhus, Denmark, [8] Centre for Cognitive and Brain Sciences and Department of Psychology, University of Macau, Taipa, Macau

Converging evidence indicates that addiction involves impairment in reward processing systems. However, the patterns of dysfunction in different stages of reward processing in internet gaming addiction remain unclear. In previous studies, individuals with internet gaming disorder were found to be impulsive and risk taking, but there is no general consensus on the relation between impulsivity and risk-taking tendencies in these individuals. The current study explored behavioral and electrophysiological responses associated with different stages of reward processing among individuals with internet gaming disorders (IGDs) with a delayed discounting task and simple gambling tasks. Compared to the healthy control (HC) group, the IGD group discounted delays more steeply and made more risky choices, irrespective of the outcome. As for the event-related potential (ERP) results, during the reward anticipation stage, IGDs had the same stimulus-preceding negativity (SPN) for both large and small choices, whereas HCs exhibited a higher SPN in large vs. small choices. During the outcome evaluation stage, IGDs exhibited a blunted feedback-related negativity for losses vs. gains. The results indicate impairment across different stages of reward processing among IGDs. Moreover, we found negative correlation between impulsivity indexed by BIS-11 and reward sensitivity indexed by SPN amplitude during anticipation stage only, indicating different neural mechanisms at different stages of reward processing. The current study helps to elucidate the behavioral and neural mechanisms of reward processing in internet gaming addiction.

Keywords: internet gaming, addiction, reward processing, stimulus-preceding negativity, feedback-related negativity, impulsivity, ERP, gaming addiction

OPEN ACCESS

Edited by:
Xingchao Wang,
Shanxi University, China

Reviewed by:
Guangheng Dong,
Zhejiang Normal University, China
Yuan-Wei Yao,
Freie Universität Berlin, Germany

***Correspondence:**
Xun Liu
liux@psych.ac.cn

[†]These authors have contributed equally to this work

Specialty section:
This article was submitted to Addictive Disorders, a section of the journal Frontiers in Psychiatry

Received: *26 August 2020*
Accepted: *10 November 2020*
Published: *04 December 2020*

Citation:
Raiha S, Yang G, Wang L, Dai W, Wu H, Meng G, Zhong B and Liu X (2020) Altered Reward Processing System in Internet Gaming Disorder. Front. Psychiatry 11:599141. doi: 10.3389/fpsyt.2020.599141

INTRODUCTION

Internet gaming disorder is a rapidly increasing concern in today's world. It is a preoccupation and obsession with internet games that interferes with one's social, personal, or occupational life, with typical symptoms of dependence being tolerance, withdrawal, and failed attempts to quit the habit (1). As one of the most common behavioral addictions, it is an emerging health concern. It has been included as Internet Gaming Disorder in ICD-11 and as a "Condition for Further Study" in DSM-5. Internet gaming disorders (IGDs) often struggle in their day-to-day activities, relationships, and

jobs because of prolonged game play. They are more likely to have poor sleep quality (2), tend to suffer from emotional problems such as depression and anxiety (2, 3), have poor coping skills (4) and are more prone to developing psychopathology or psychopathological symptoms in the long run (5–7). IGDs often use internet games as an escape from negative moods and feelings, such as hopelessness and guilt (1), allowing them to feel relaxed (6) and in control of the situation (8).

Reward processing is an important aspect of human functioning affecting daily life, and has also been regarded as a key neural mechanism involved in behavioral and cognitive processes related to addiction (9, 10). Impairments in reward processing is the core symptom of many kinds of mental and neurological diseases (11, 12), including drug addiction. It can be classified into two stages: reward anticipation and outcome evaluation (13).

Reward anticipation refers to the incentive salience of a reward. Incentive salience is a psychological process that imbues the perception of stimuli with salience and transforms them into incentive stimuli. Previous addiction studies conducted on substance addiction and internet gaming disorder indicated altered reward processing system among the addicts during the reward anticipation stage. They found less activations in ventral stratum and decreased prefrontal cortical sensitivity to monetary rewards (14–17).

Outcome evaluation refers to the hedonic enjoyment received from reward consumption. IGDs have been found to have alterations in the reward processing system (18–20). The addiction studies conducted on substance addiction and behavioral addiction (i.e., internet gaming disorder) have found addicts to be driven toward high rewards and tend to ignore negative consequences, thus resulting in impaired decision making process and risk taking tendencies (21–26).

Monetary rewards are frequently used to study neural mechanisms involved in reward processing among healthy and addicted individuals (27, 28). However, the findings have been inconsistent about whether individuals with addiction have enhanced or blunted responses to monetary rewards.

The inhibitory control dysfunction theory (29) attempts to explain the alterations in the reward processing systems underlying addiction. It proposes impulsivity and reward processing as the underlying factors of addiction that play a role in promoting or limiting drug use at each of the three stages of addiction: (i) initiation of use, (ii) maintenance of use, and (iii) relapse. According to this theory, impulsivity is a personality trait while impairment in reward processing refers to sensitivity to rewards (positive effects of the drug) paired with insensitivity to punishment (negative outcomes of the drug). This theory has often found support from the research studies (30–34) that found addicts to be impulsive and indulge in risky decision making.

Currently, there is no conclusive evidence from previous studies providing a consensus about the neural correlates of the reward processing system at different stages of reward processing. In the current study, we focused on three key ERP components: stimulus-preceding negativity (SPN), feedback-related negativity (FRN), and P300. SPN is a negative-going slow wave. It is considered an electrophysiological index of reward expectation. Previous research has shown that people with substance dependence had larger SPN while anticipating substance related cues than controls (35, 36). The two other ERP components, FRN and P300, play important roles in outcome evaluation. FRN is usually a negative deflection following feedback onset that typically peaks around 250 ms. Previous studies have found that people with substance dependence have a larger FRN peak, indicating impairment in outcome evaluation processes (23, 37). P300 is a positive deflection typically peaking around 300–500 ms after feedback onset. Previous studies have found that people with substance dependence have larger P300 amplitudes than controls, indicating their poor attentional control.

IGDs have been found to have high impulsivity (38) and high sensation seeking (5). These personality traits are associated with inability to delay gratification, leading to steep delay discounting. Delay discounting refers to the subjective devaluation of an outcome with an increase in delay of its attainment (39, 40). Previous studies have found IGDs to be highly impulsive, which is reflected by a dysfunctional prefrontal cortex (41) and decreased frontostriatal connectivity (42), leading to risky decisions.

IGDs have altered risk evaluation, high risk taking tendencies, and tend to indulge in risky decision making (30, 32, 43–45). They were found to have enhanced reward sensitivity and decreased loss sensitivity compared to control counterparts. A similar study conducted on IGD adolescents (46) testing the dual-system model found that individuals with internet gaming addiction have altered reward processing and inhibitory control in a gambling task and a Go/No Go task, respectively. These impairments in reward processing system make it difficult for IGDs to quit playing internet games despite negative effects on their daily life, such as poor grades and deterioration of relationships (5, 7). Their altered reward processing system also makes them prone to developing psychopathology (47, 48).

A few fMRI studies (32, 34, 49) have examined the neural basis of reward processing among IGDs. However, the low temporal resolution made fMRI a less powerful technique to answer the question about different processing stages. Instead, ERP technique has fine-grained temporal resolution, and is uniquely suitable to investigate in detail the time course of reward processing in internet gaming addiction. To our knowledge, no ERP study on internet gaming disorder to date has explored the neural correlates of behavioral addiction across different stages of reward processing. The P300 and FRN components have frequently been studied among IGDs (19, 37). However, the SPN component occurring at the early stages of reward processing often remains a neglected ERP component in these studies. In light of previous work indicating possible abnormal reward system in IGDs, the current study aimed to bridge this gap by exploring alterations in the reward processing system during different stages of reward processing. In the current study, we examined the reward processing systems in IGDs as compared to the HCs while they expected and received rewards during the delayed discounting and a simple gambling task. Behaviorally, we anticipated the IGDs to make more risky choices and discount delays more steeply than the HCs. Neurally, we expected decreased risk sensitivity, indexed by smaller magnitude effect on SPN during the anticipation stage

and reduced FRN magnitude during the outcome-appraisal stage of reward processing. Moreover, based on inhibitory control dysfunction theory, we predicted that larger P300 amplitude would be observed on gain trials than loss trials. We hypothesized that IGDs discount delays more steeply on a delayed discounting task and make more risky decisions, irrespective of whether they were in a gain or loss condition. With a delay discounting task, we further explored and established the relationship between delay gratification and risky decision making among IGDs.

MATERIALS AND METHODS

Participants

Thirty-five male adults (age 22.06 ± 3.65) with internet gaming disorder and another 39 age-matched healthy male adults (age 21.95 ± 3.47) in total were recruited in this study. They had either normal or corrected-to-normal vision and self-reported no history of physical disability, chronic physical illness, or neurological or psychiatric problems. The inclusion criteria for IGDs required minimum scores of 50 on the Internet Addiction Test (IAT) (50), and 5 on the DSM Test for Internet Gaming Disorder (51), while for the control group, the scores on both the tests were required to be lower than these thresholds. The IAT (Cronbach's $\alpha = 0.93$; $r = 0.46$) and DSM Test (Cronbach's $\alpha = 0.91$; $r = 0.44$) were used to screen the IGDs from the control group. These two tests were intended to measure the effect of Internet use on the individual's daily life and the extent of problems caused by it on daily routine, work, social life, sleep routine, and feelings, in accordance with DSM-5 criteria. In addition, the Alcohol Use Disorder Identification Test [AUDIT, (52)], Beck Depression Inventory [BDI-II, (53)], State-Trait Anxiety Inventory-Trait [STAI-T, (54)], and State-Trait Anxiety Inventory-State (STAI-S) were used to exclude those with alcohol use disorder, depression, and anxiety disorders. Moreover, we used the Barratt Impulsiveness Scale-Version 11 [BIS-11, (55)], Behavioral Inhibition System/Behavioral Activation System [BAS/BIS, (56)], and Sensation Seeking Scale (57) to explore impulsivity, reward systems, and sensation seeking in relation to decision making in IGDs. The two groups were counterbalanced on years of education, with high school as the minimum education level (see **Table 1**).

Thirty-three IGDs and 35 HCs completed the delay discounting task, among which 24 IGDs and 26 HCs participated in the ERP study with a simple gambling task. In the gambling task analysis, five subjects (one IGD and four HCs) were excluded from further analysis because they mostly chose one option (high or low, over 90%). With this, we sought to ensure participants' conscious attention on the trials, while employing the excluding criteria comparable to that reported by Dewitt et al. (58). In the ERP analysis, another three subjects (two IGDs and one HC) were excluded from the SPN analysis, and four subjects (two IGDs and two HCs) were excluded from the FRN and P300 analysis, respectively, because too few effective epochs were left after removing artifacts.

The research was approved by the Institutional Review Board of the Institute of Psychology, Chinese Academy of Science before the commencement of the experiments. All participants signed a consent form before participating in the experiment.

TABLE 1 | Sample characteristics.

	HCs	IGDs	*p*-value
Sample size	39	35	
Age (years)	22.06 ± 3.65	21.95 ± 3.47	0.896
Education	15.04 ± 0.56	14.75 ± 0.59	0.520
IAT	22.56 ± 2.04	65.25 ± 2.17	0.000***
AUDIT	0.31 ± 0.73	0.19 ± 0.29	0.504
DSM	0.30 ± 0.22	6.83 ± 0.24	0.000***
BDI	4.11 ± 5.75	11.25 ± 8.76	0.013*
STAI-S	33.96 ± 9.05	42.83 ± 10.43	0.005**
STAI-T	32.37 ± 9.16	37.63 ± 11.58	0.218
BIS-11			
Motor	28.71 ± 2.15	35.52 ± 2.36	0.013*
Attention	26.98 ± 11.08	29.38 ± 9.84	0.397
Non-Planning	25.95 ± 16.48	35.83 ± 14.02	0.029*
BAS/BIS			
BAS	42.07 ± 4.92	43.75 ± 5.19	0.167
BASD	12.97 ± 2.46	13.29 ± 2.40	0.809
BASF	15.07 ± 2.13	16.25 ± 2.38	0.019*
BASR	14.03 ± 1.73	14.21 ± 1.47	0.569
BIS	15.63 ± 2.38	15.92 ± 2.65	0.528
SSS			
Boredom susceptibility	1.83 ± 1.47	2.81 ± 1.88	0.143
Disinhibition seeking	3.59 ± 0.33	3.65 ± 0.34	0.812
Experience seeking	3.92 ± 2.08	4.07 ± 1.60	0.642
Thrill and adventure seeking	4.88 ± 2.52	6.48 ± 2.23	0.039*

*IAT, internet addiction test; AUDIT, the alcohol use disorder identification test; DSM, DSM test for internet gaming; BDI, beck depression inventory; STAI-S, state trait anxiety inventory-state; STAI-T, state trait anxiety inventory-trait; BIS-11, barratt impulsiveness scale, version 11; BIS/BAS, behavioral inhibition system/behavioral activation system; BASD, behavioral activation system-drive; BASF, behavioral activation system-fun-seeking; BASR, behavioral activation system-reward; BIS, behavioral inhibition system; SSS-V, sensation seeking scale form V. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.*

Procedure

Delayed Discounting Task

In this task, participants were required to choose between a small gain that was available immediately and a fixed larger gain (¥ 1,000) that was delayed by one of five periods of time (1 week, 1 month, 6 months, 3 years, and 15 years). The participants practiced by making choices between 2-week delayed periods and varied amounts available immediately, to familiarize themselves with the procedure before the formal experiment procedures. During the formal experiment blocks, there were seven choices for the immediate gain amount with five delayed periods: 1 week, 1 month, 6 months, 1 year, and 15 years. An algorithm was used to adjust the amount of the immediate gain across the seven to estimate the subjective values of delayed gains. The participants were given the opportunity to restart the procedure after each trial to avoid errors that could lead to inaccurate estimates of their subjective values, in case they wanted to modify or change their choice.

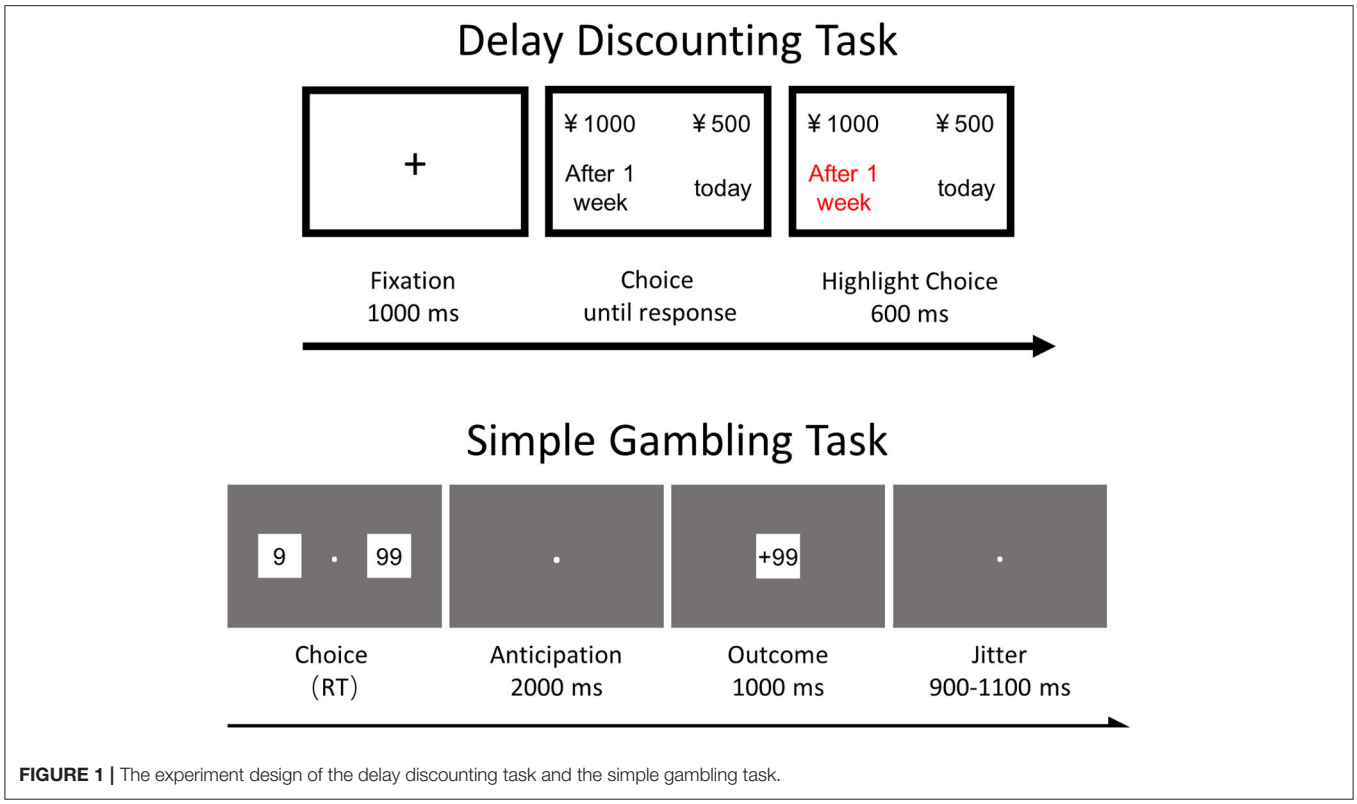

FIGURE 1 | The experiment design of the delay discounting task and the simple gambling task.

Simple Gambling Task

In the simple gambling task, the participants were instructed in the beginning that their remuneration for the experiment would be dependent on the amount they won or lost in this task (see **Figure 1**). The main procedure consisted of one practice block and six main blocks. The practice block consisted of 10 trials, and each main block comprised 80 trials with a short break between two consecutive blocks.

The trial contained two options (9 for low risk and 99 for high risk) appearing on either side of a fixation cross, which disappeared until responses were made. The participants were required to choose one option by pressing "f" (for the left option) or "j" (for the right option). After a response was made, only the fixation cross remained on the screen for 2,000 ms followed by a feedback slide for 1,000 ms. The feedback slide contained points with a "+" or "-" sign to indicate the points they had won or lost for their response.

Electroencephalographic (EEG) Recording and Preprocessing

We used Brain Products System (64 channel amplifier, Brain Vision Recorder Version 2.0; Brain Products, GmbH, Germany) for EEG data recording. The Easy Cap electrode system (EASY-CAP, Herrsching) was used to place electrodes in accordance with the 10–20 system on 64 positions. Vertical eye movements were recorded by placing one electrode below the right eye (VEOG). The channel FCz was set as the reference channel during data recording. Chloride free-electrolyte gel was used to gently abrade the scalp to keep impedances in electrodes below 5 kΩ. EEG data were recorded at a sampling rate of 500 Hz with a pass band of 0.01–100 Hz.

We adopted the analysis approaches from previous studies (26, 59). EEGLAB toolbox (60) running under MATLAB software was used for the raw data analysis. The data were re-referenced to the average of channels TP9 and TP10. The reference channel FCz was then added back to the data. A low-pass filter of 20 Hz was used to determine the SPN for pre-feedback epochs (2,000 ms pre-stimulus, 500 ms post-stimulus), while a band-pass filter of 0.1–20 Hz was applied for FRN and P300 for post-feedback epochs (200 ms pre-stimulus, 800 ms post-stimulus). The independent component analysis ocular correction method was used to remove any artifacts present due to eye movements and eye blinks in the epochs after visual inspection. We set the activity from −200 to 0 ms, and from −2,000 to −1,800 ms as baseline correction for post-feedback components (FRN and P300), and the pre-feedback component (SPN), respectively.

Data Extraction

For the delay discounting task, the area under the discounting curves (AUCs) for each subject were calculated with the method in line with previous studies (61–63). The AUC values were used since they are not affected by the quality of fit of the discounting models, and are usually more normally distributed than other discounting function parameters (e.g., k or h values) (64).

For the gambling task, we calculated the effects of valence (gain or loss) on the basic risky choice proportion and

conditional risky choice proportions (choice following the previous outcome) and reaction times.

At the EEG level, we recorded the peak amplitudes of the four conditions: high gain, low gain, high loss, and low loss on SPN, FRN, and P300 components. The component values for SPN were measured with four electrodes in the left-hemisphere (C3, C5, FC3, and FC5), and four electrodes in the right-hemisphere (C4, C6, FC4, and FC6) electrodes according to the topographic maps and grand average waveforms. The time window for SPN was observed at −200 to 0 ms (before feedback). The FRN was extracted from 250 to 350 ms after the feedback onset at FCz, Fz, and Cz, where it was observed to be maximal. P300 was measured with CPz and Pz from 350 to 450 ms (after the feedback). The channels and time windows for each component were selected according to the activations on the topographic maps and the peak of the waveform, respectively.

Statistical Analysis

Two-sample *t*-tests were applied to the AUC values in the delay-discounting task and the basic choice risk proportion. The basic choice reaction time in the gambling task was analyzed with an analysis of variance (ANOVA) of Group (IA group vs. HC group) × Risk (high risk vs. low risk). The conditional analysis was achieved with a three-way ANOVA of Group (IA group vs. HC group) × Risk (high risk vs. low risk) × Previous Outcome (win vs. loss).

The ERP data for the simple gambling task were analyzed twice, one pre-feedback condition for determining the SPN component and one post-feedback stimuli for FRN and P300 components. Repeated-measure ANOVAs were used for the SPN component with the between-subject factor GROUP (HC group vs. IGD group) and within-subject factor Magnitude (high vs. low) and Hemisphere (right vs. left). Repeated-measure ANOVAs were used for FRN and P300 component, with the between-subjects factor Group (HC group vs. IA group) and within-subject factor Magnitude (high vs. low) and another within-subject factor Valence (gain vs. loss). Greenhouse-Geisser correction was used for two or more factors with major effects. *Post-hoc* analysis was conducted using Bonferroni corrections.

RESULTS

Demographic and Behavioral Data

Table 1 shows the demographic data for the HC and IGD groups. The groups did not differ in age and educational level. As expected, the groups differed significantly on the IAT and DSM Test for Internet Gaming. Moreover, the IGD group scored higher on BDI, STAI, the Motor subscale, Non-Planning in the BIS-11, and the BAS-Fun-Seeking subscale in the BAS/BIS.

Delayed Discounting Task

For the delay discounting task, there was a significant group effect, t (66) = 2.57, $p = 0.012$, indicating that the IGD group discounted delayed outcomes ($M_{AUC} = 0.17$, $SD_{AUC} = 0.02$) more steeply than the HC group ($M_{AUC} = 0.26$, $SD_{AUC} = 0.03$) (see **Figures 2A,B**).

Simple Gambling Task

Reaction Time

For decision making time, there was no significant main effect of group, $F_{(1,43)} = 0.82$, $p = 0.371$, $\eta_p^2 = 0.019$, or condition effect, $F_{(1,43)} = 1.60$, $p = 0.201$, $\eta_p^2 = 0.038$, nor a significant condition × group interaction effect, $F_{(1,43)} = 0.14$, $p = 0.707$, $\eta_p^2 = 0.003$.

Basic Choice

There was a marginally significant group effect, t (43) = 1.82, $p = 0.076$, indicating that a higher proportion (56.5%) of the IGD group preferred risky choices than the HC group (48.2%). Specifically, IGDs tended to make more risky decisions than the chance level (50%), t (22) = 2.020, $p = 0.056$. In contrast, HCs exhibited a risk-neutral pattern, t (21) = −0.563, $p = 0.579$ (see **Figure 2C**).

Risky Choice

Both groups tended to risk larger amounts after facing a loss in the previous trial than when they had a gain in the previous trial, $F_{(1,43)} = 9.59$, $p = 0.003$, $\eta_p^2 = 0.182$, and after making a high-risk choice in the previous trial than when they made a low-risk choice in the previous trial, $F_{(1,43)} = 21.38$, $p = 0.000$, $\eta_p^2 = 0.332$. The IGD group made more risky choices than the HC group, irrespective of the previous outcome, $F_{(1,43)} = 6.12$, $p = 0.017$, $\eta_p^2 = 0.125$ (see **Figure 2D**).

ERP Results

FRN

Figure 3 presents the grand average ERP waveforms at FCz elicited by gains and losses and their differences, and the topographic map for these two groups. Repeated-measures ANOVA revealed a significant magnitude effect on the FRN component, $F_{(1,41)} = 12.33$, $p = 0.001$, $\eta_p^2 = 0.231$, indicating that the FRN amplitude was higher in high-risk than in low-risk outcomes (−2.11 μV vs. −0.67 μV). The interaction between magnitude and group was also statistically significant, $F_{(1,41)} = 5.17$, $p = 0.028$, $\eta_p^2 = 0.112$. Simple effect analysis revealed that the FRN amplitude was greater in high-risk outcomes compared to low-risk outcomes only in the HC group (−2.74 μV vs. −0.36 μV, $p = 0.000$), but not in the IGD group (−1.48 μV vs. −0.97 μV, $p = 0.392$).

P300

Figure 4 presents the grand average ERP waveforms at Pz elicited by gains and losses, and the topographic map for these two groups. Repeated-measures ANOVA revealed significant magnitude effect, $F_{(1,41)} = 74.47$, $p = 0.000$, $\eta_p^2 = 0.645$, indicating that the P300 amplitude was higher in high-risk outcomes than in low-risk outcomes (12.74 μV vs. 7.39 μV); and significant valence effect, $F_{(1,41)} = 7.51$, $p = 0.009$, $\eta_p^2 = 0.155$, indicating that the P300 amplitude was higher in a gain context than in a loss context (10.44 μV vs. 9.70 μV).

SPN

Figure 5 presents the grand average ERP waveforms at C3 and C4 and topographic maps of the SPN (−200 to 0 ms) for these two groups. Repeated-measures ANOVA revealed a significant magnitude effect on the SPN component, $F_{(1,42)} = 5.06$,

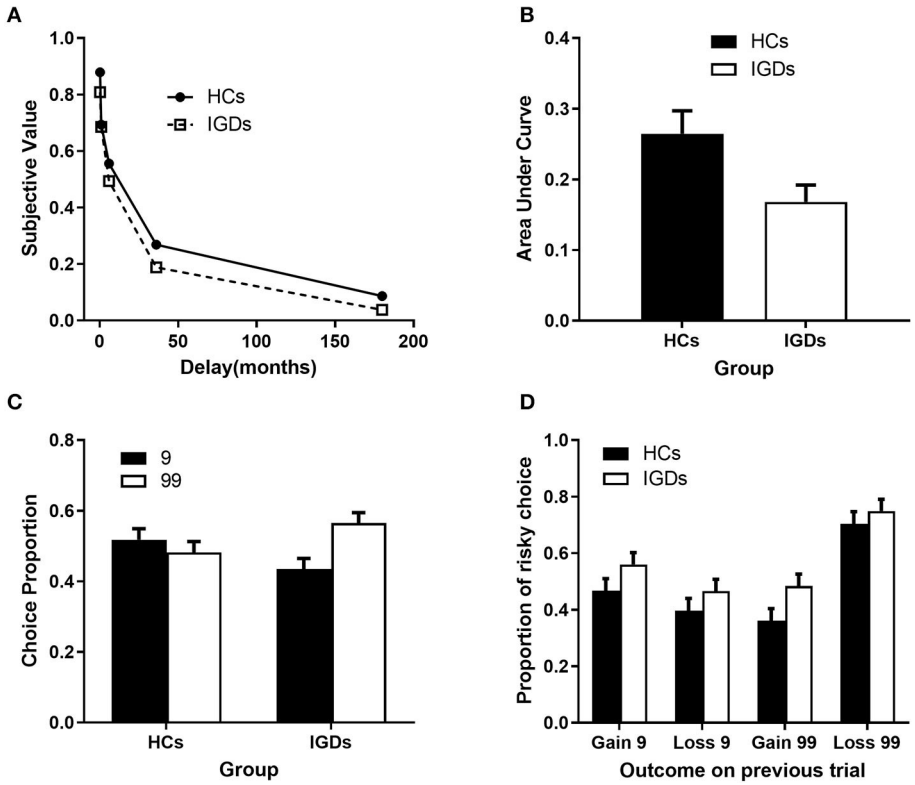

FIGURE 2 | Behavioral Results in delay discounting task and Gambling Task. **(A)** Slope for area under the curve (AUC) and **(B)** the distribution of mean value of area under the curve on Delayed Discounting task. **(C)** Proportion of Basic Choice and Reaction Times on Simple Gambling Task. **(D)** Proportion of Risky Choice on Simple Gambling Task.

$p = 0.030$, $\eta_p{}^2 = 0.108$, indicating that the SPN amplitude was higher for high-risk choices than for low-risk choices (−2.26 μV vs. −1.69 μV). The interaction between magnitude and group was marginally significant, $F_{(1,42)} = 3.03$, $p = 0.089$, $\eta_p{}^2 = 0.067$. Simple effect revealed that the SPN amplitude was greater in high-risk decision making compared to low-risk decision making only in the HC group (−2.41 μV vs. −1.39 μV, $p = 0.006$), but not in the IGD group (−2.12 μV vs. −1.97 μV, $p = 0.727$).

Correlation Results

To examine the potential relationship between impulsivity and risk-taking tendencies at the individual difference level, we calculated the correlation between the impulsivity indices (i.e., AUC and BIS score) and basic choice, risky choice, and three ERP amplitudes within each group independently. Although none of these indices significantly correlated with AUC results, we found significant negative correlation between the BIS score and the SPN amplitude in the left hemisphere when choosing low risk choice, $r = -0.41$, $p = 0.031$, as well as when choosing high risk choice, $r = -0.38$, $p = 0.044$ (see **Figure 6**).

DISCUSSION

In our sample of participants, we found that IGDs had relatively higher impulsivity, higher proneness to risky decision making, reduced ability to delay gratification, reduced ability to evaluate risk, and different outcome expectancies in risky situations. The behavior of IGDs, that is, making more risky choices, is supported by neural patterns indicating higher sensitivity to rewards and lower sensitivity to punishment among IGDs.

Previous research on substance addiction found that people with substance dependence discounted delayed gains more steeply than non-dependent people on a delay discounting task (65–68). This effect has been found to hold true for IGDs, which were shown to be unable to delay gratification, as indicated by their steep pattern of discounting delayed gains on a delayed discounting task (41, 61, 69). The results of the delay discounting task are supported by the high impulsivity scores on the BIS among the IGD group compared to the HC group. The IGD group were more impulsive on the motor impulsiveness and non-planning subscales than the HC group, in accordance with previous studies (70–73). However, there were no differences in attention impulsivity subscale of BIS-11 between the two groups. This may be attributed to the positive effects of online gaming or video gaming on individuals in increasing sustained attention (74, 75). IGDs were revealed to be more thrill and adventure seeking and more sensitive to rewards than HCs. These observations are in line with the findings of previous studies on problematic internet gaming (76–78).

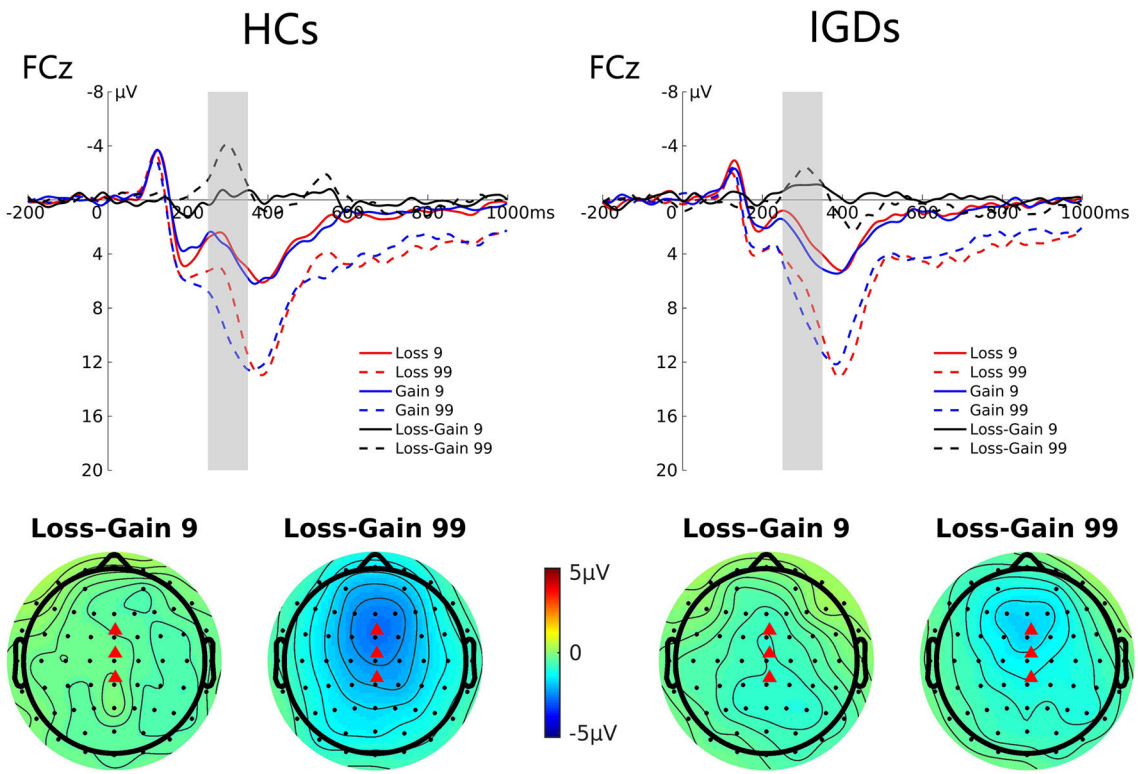

FIGURE 3 | Grand average ERP waveforms following low- and high-risk decisions for HCs and IGDs at FCz. The upper figure shows the ERP waveforms for HCs and IGDs at FCz. FRN is calculated as the difference between loss and gain waveforms after feedback, and the time window was depicted as the shaded areas. The lower figure shows the topographic maps on time window 250–350 ms.

On the behavioral level, risk-taking tendencies were more pronounced in the IGD group. They were also found to be more prone to make risky choices, irrespective of whether the previous outcome was a win or a loss. These results are in accordance with previous literature that found problematic IGDs to be more focused on and sensitive to wins and less focused on and less sensitive to losses (79, 80). The enhanced reward sensitivity and decreased sensitivity to losses lead them to risky decision making. Previous studies have indicated an association between risky choices and personality factors as impulsivity, sensation seeking, thrill seeking behaviors among addicts. They found that addicts tend to ignore the negative consequences of the situation and focus only on positive rewards (5, 43, 44, 46). Consistently, the IGD group in our current study were also found to have enhanced sensitivity toward rewards as indicated by their higher scores on the BAS/BIS and thrill seeking than the HC group, as well as their less sensitivity to loss, indexed by behavioral choices, SPN and FRN amplitudes in simple gambling task.

At the early stage of reward processing, the SPN was more negative for the larger risk than the smaller risk for the HC group, while no significant differences were found in the IGD group. These results indicated that IGDs expected the same reward outcome whether the risk was high or low, but HCs expected more on a larger risk. Furthermore, the IGDs were less concerned about the outcome, indicating their high risk-taking tendencies. These results are consistent with previous findings that found an altered ability to evaluate risk among IGDs (22, 32, 81).

At the later stages of reward processing, the more prominent FRN amplitude for high-risk choices in comparison with low risk choices was observed in the HC group. However, such results diminished in the IGD group, indicating their increased risk-taking tendencies and decreased sensitivity toward high risk situations. FRN is associated with the binary evaluation of positive vs. negative outcomes (gains vs. losses in our study) based on external feedback that outcome is worse than expected (82). The amplitude of FRN increases when external feedback indicates a negative outcome (i.e., loss). However, the previous studies found that IGDs are less sensitive to negative outcomes. Our results of FRN are consistent with previous studies on individuals with internet gaming disorder (23, 37) that found IGDs to have reduced amplitudes on FRN than healthy controls. Similar to our results of the FRN component, these studies also found a blunted risk effect among IGDs irrespective of the feedback response. Our results on FRN seems to be comparable to the previous studies have found blunted FRN to be associated with unplanned impulsivity and high scores on BIS/BAS system (83, 84). In our sample of participants, the amplitude of the P300 component was significantly larger for the gain than the loss condition indicating their attentional allocation to gains more than the losses. This is

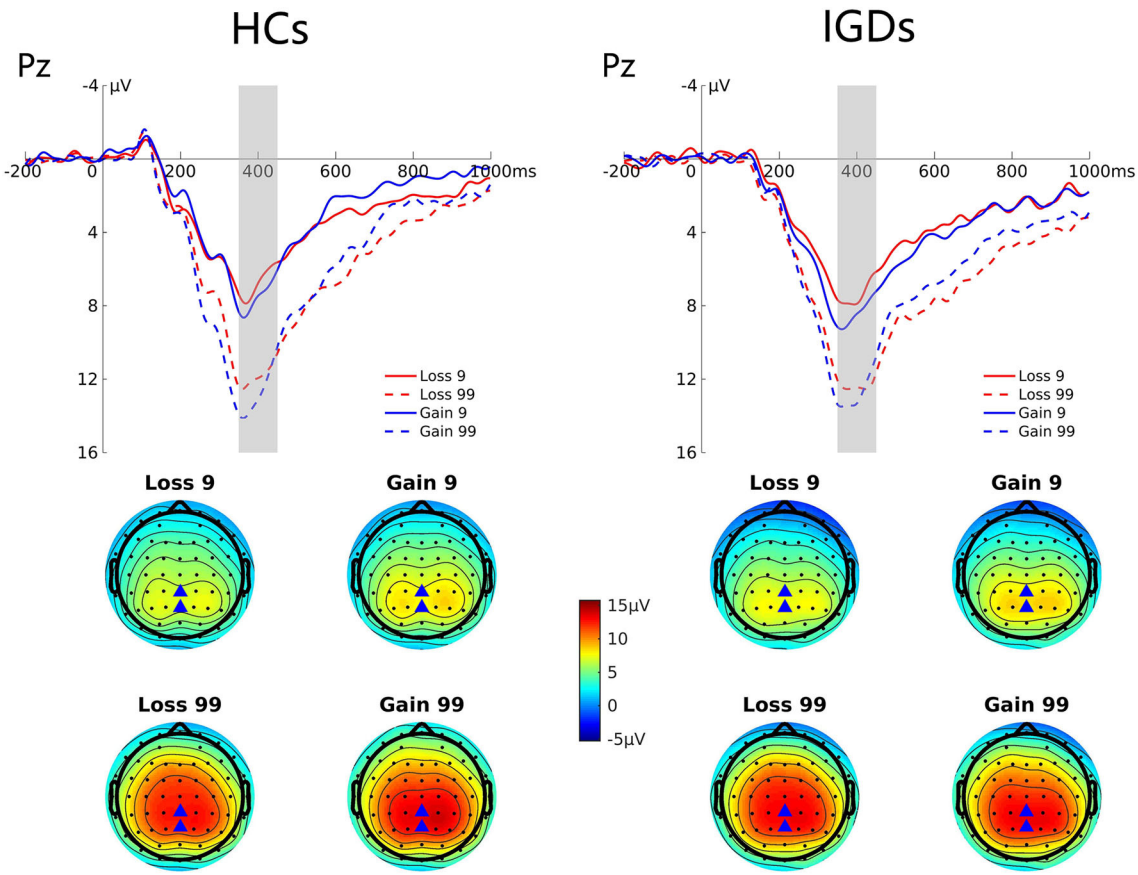

FIGURE 4 | Grand average ERP waveforms following low- and high-risk decisions for HCs and IGDs at Pz. The upper figure shows the ERP waveforms for controls and IGDs at Pz. The time window was depicted as the shaded areas. The lower figure shows the topographic maps on time window 350–450 ms.

consistent with previous studies on decision making and risk-taking (85–87) that found an increase in the amplitudes of the P300 component on gain than loss conditions in a gambling task. The P300 component is often regarded as an index of attentional allocation to task relevant stimuli (88). In contrast to previous studies (37, 89), we did not find a significant group effect on P300 amplitude. A possible explanation for this inconsistency that monetary rewards may not be a strong reinforcer for our IGD group. The enhanced preference toward rewards and less sensitivity toward punishment is indicated but monetary rewards may not be a stronger reinforcer for the IGDs than the HCs, resulting in this inconsistency. Previous studies have also indicated mixed findings while using monetary rewards. In severely addicted individuals, such as cocaine addicts, monetary rewards may not elicit the same sensitivity as using the substance reward they are addicted to (14). This may also be explained considering previous studies (90) that reported an improvement in attentional control as a result of playing computer games.

The results of the current study on IGD are very similar to the previous study conducted on IGD of adolescents (46) that also found IGD to depict high impulsivity on BIS-11, greater tendency to novelty seeking experience on BAS-F subscale of BAS/BIS and significantly greater tendency to indulge in thrill and sensation seeking activities than the non-IGDs. They also found IGD to be more prone to making risky choices but could not find any interaction effect between high risky choices and reaction times, in line with the current study. Although we could not find enhanced FRN for the controls directly, we did find the peak amplitude of the difference between loss and gain to be significantly enhanced on FRN, similar to this study. However, they also only found significant magnitude and valence effect on P300 with no interaction effect between group and the peak amplitude on P300, similar to our study. These similarities give an indication that impairment in reward processing is extended to the adulthood following the same pattern as observed among the adolescents suffering from internet gaming disorder.

We found SPN component and subjective impulsivity, as indicated by BIS-11 scores, to be negatively correlated with each other in the IGD group. It indicates that risk sensitivity during the anticipation stage decreases as the impulsivity level increases among IGDs. This is in line with the addiction studies that found high risk taking tendencies to be associated with high impulsivity (91, 92). However, the similar pattern could not be found in the outcome-appraisal stage, nor any correlation pattern could

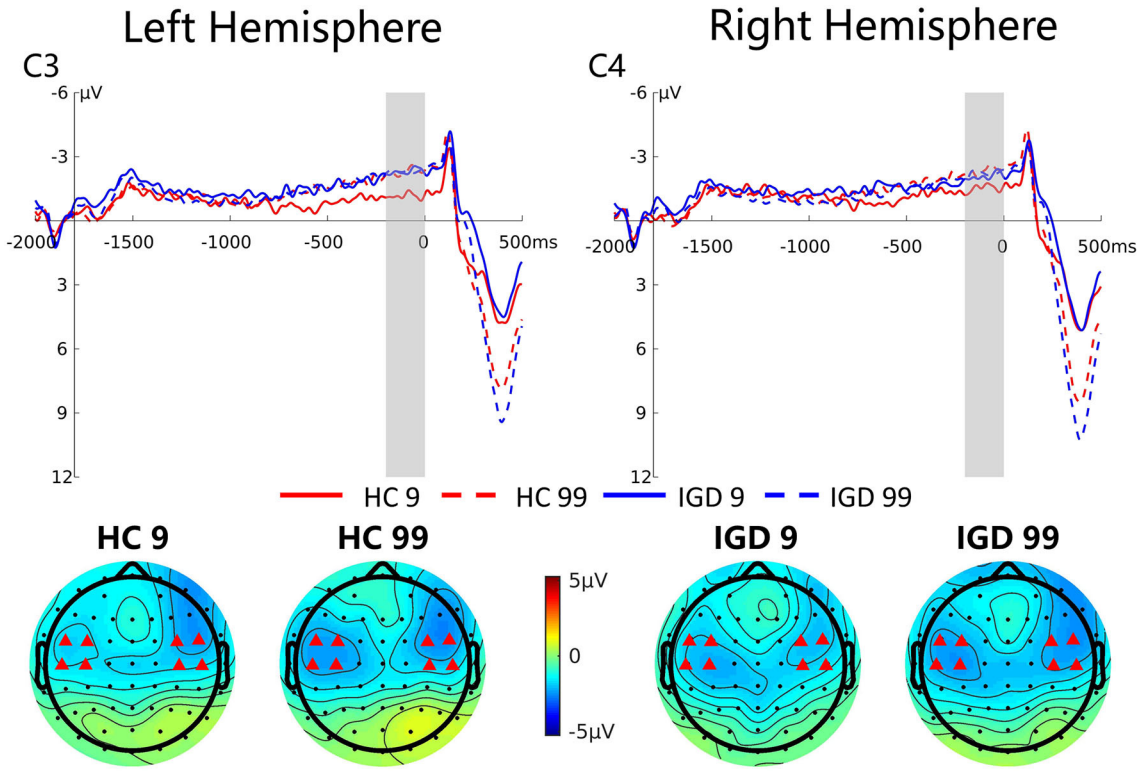

FIGURE 5 | Grand average ERP waveforms following low- and high-risk decisions for HCs and IGDs at C3 and C4. The upper figure shows the ERP waveforms for controls and internet gamer at C3 and C4. The time window was depicted as the shaded areas. The lower figure shows the topographic maps on time window −200 to 0 ms.

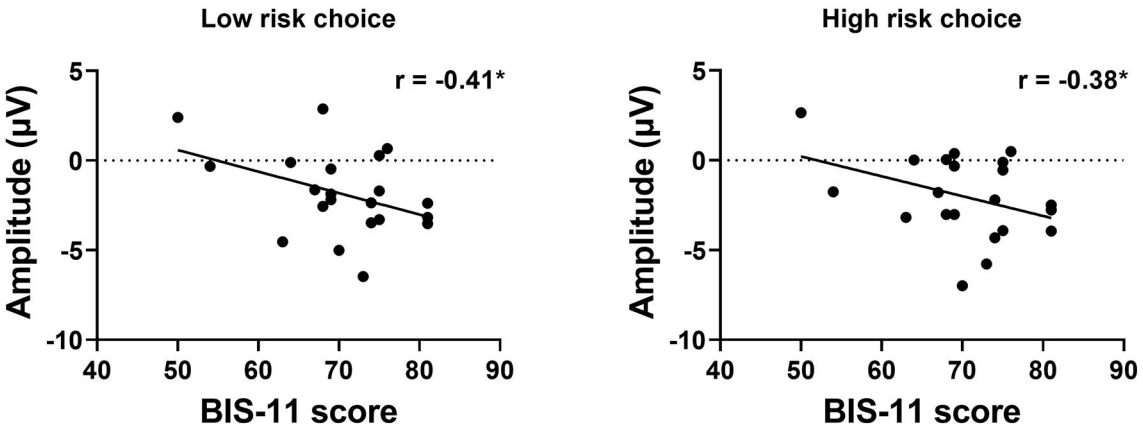

FIGURE 6 | Correlation between BIS score and the SPN amplitude. The left panel shows the result when choosing low risk choices, and the right panel shows the result when choosing high risk choices.

be determined between impulsivity and delayed discounting and risk-taking strategies on the behavioral level. In agreement with studies (93, 94) that indicated that impulsivity and risky decision making are distinct constructs, our results are consistent with the notion that the relation between impulsivity and risk taking is more complex and these personality measures may function as distinct constructs among IGDs (93). The dominant construct in each internet gamer may vary from individual to individual, for example, some IGDs may be impulsive but not risk-taking and vice versa. In a recent study, researchers found impulsivity and risk-taking tendencies to be distinct constructs associated with separate moods. Risky decision making and high-risk behaviors were found to be influenced by the positive emotions while high impulsivity was found to be associated

with negative emotions (94). These results indicate the contrast between anticipation and outcome-appraisal stage, in relation to association between decreased risk sensitivity and impulsivity traits. Future studies may explore the effect of each dominant construct on reward processing among IGDs with different degrees of dependence with larger sample sizes.

This study explored the neural correlates of internet gaming disorder across different stages of reward processing. The results strengthen the notion that IGDs share common patterns of reward processing impairments with people with substance dependence. It also gives an insight into the distinct attentional allocation patterns found among IGDs, owing to their gaming addiction. The common and distinct patterns provide useful behavioral and neurological markers for subsequent prevention and intervention.

Due to the high prevalence of internet gaming addiction among young male adults, we selected only young male adults under 30 years old, which may also be one of the limitations of our study. Another limitation is the relatively small sample size. Although our study has indicated the patterns of impairment across different stages of reward processing, larger sample size studies may be required to confirm this impairment pattern, as well as across different age groups. An additional concern is the possible confounding effect of the relatively higher BDI and STAI-S scores of IGDs than HCs, which may bias the results of this study. Here, we would like to mention that the cognitive effects of internet gaming may be manifold and might also be linked to certain factors affecting the decision of the participants, such as mood, emotion and attention. Nevertheless, the results of the two tasks (delayed discounting task and simple gambling task) provide insight into some behavioral and neural patterns of reward processing among IGDs. Similar to people with substance dependence, the internet addiction group showed high impulsivity, reduced ability to delay gratification, altered ability to evaluate risk, altered outcome expectancies from risky situations and decisions, and risk-taking tendencies. However, IGDs in our sample were found to use an avoidance system in response to punishment, giving us an insight into a distinct pattern of reward processing among IGDs. They were found to be much more focused on larger gains and demonstrated less sensitivity to losses.

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 Review Board of Institute of Psychology, CAS. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SR: data curation, writing—original draft, and writing—editing. GY: data curation, writing—original draft, and writing—editing. LW: writing—review and editing. WD: writing—review and editing. HW: writing—review and editing. GM: writing—review and editing. BZ: writing—review and editing. XL: conceptualization, writing—review and editing, supervision, project administration, and funding acquisition. All authors contributed to the article and approved the submitted version.

FUNDING

This research was supported by the National Key R&D Program of China (2016YFC0800901-Z03), the National Natural Science Foundation of China (Grants 31271194 and 61621136008/DFG TRR-169).

ACKNOWLEDGMENTS

We thank Ya Zheng for providing invaluable comments on the manuscript, Moqian Tian and Zhenghan Li for providing help in data analysis, Honghui Xu, Hao Yu, and Ziwei Chen for helping in data collection.

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)* (2013).
2. Bhandari PM, Neupane D, Rijal S, Thapa K, Mishra SR, Poudyal AK. Sleep quality, internet addiction and depressive symptoms among undergraduate students in Nepal. *BMC Psychiatry.* (2017) 17:106. doi: 10.1186/s12888-017-1275-5
3. Coventry KR. Mood state, arousal, decision making, and persistence at gaming. *Addiction.* (2001) 96:1860–1.
4. Brand M, Laier C, Young KS. Internet addiction: coping styles, expectancies, and treatment implications. *Front. Psychol.* (2014) 5:1256. doi: 10.3389/fpsyg.2014.01256
5. Floros G, Siomos K, Stogiannidou A, Giouzepas I, Garyfallos G. The relationship between personality, defense styles, internet addiction disorder, and psychopathology in college students. *Cyberpsychol. Behav. Soc. Netw.* (2014) 17:672–6. doi: 10.1089/cyber.2014.0182
6. Yan W, Li Y, Sui N. The relationship between recent stressful life events, personality traits, perceived family functioning and internet addiction among college students. *Stress Health.* (2014) 30:3–11. doi: 10.1002/smi.2490
7. Kim E, Yim HW, Jeong H, Jo SJ, Lee HK, Son HJ, et al. The association between aggression and risk of Internet gaming disorder in Korean adolescents: the mediation effect of father-adolescent communication style. *Epidemiol. Health.* (2018) 40:e2018039. doi: 10.4178/epih.e2018039
8. Bailey K, West R, Kuffel J. What would my avatar do? Gaming, pathology, and risky decision making. *Front. Psychol.* (2013) 4:609. doi: 10.3389/fpsyg.2013.00609
9. Trafton JA, Gifford EV. Behavioral reactivity and addiction: the adaptation of behavioral response to reward opportunities. *J. Neuropsychiatry Clin. Neurosci.* (2008) 20:23–35. doi: 10.1176/jnp.2008.20.1.23

10. Flagel SB, Akil H, Robinson TE. Individual differences in the attribution of incentive salience to reward-related cues: implications for addiction. *Neuropharmacology.* (2009) 56(Suppl. 1):139–48. doi: 10.1016/j.neuropharm.2008.06.027
11. Weiss F, Koob GF. Drug addiction: functional neurotoxicity of the brain reward systems. *Neurotoxicol. Res.* (2001) 3:145–56. doi: 10.1007/BF03033235
12. Ahmed SH. Neuroscience. Addiction as compulsive reward prediction. *Science.* (2004) 306:1901–2. doi: 10.1126/science.1107071
13. Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res. Brain Res. Rev.* (1993) 18:247–91. doi: 10.1016/0165-0173(93)90013-P
14. Goldstein RZ, Alia-Klein N, Tomasi D, Zhang L, Cottone LA, Maloney T, et al. Is decreased prefrontal cortical sensitivity to monetary reward associated with impaired motivation and self-control in cocaine addiction? *Am. J. Psychiatry.* (2007) 164:43–51. doi: 10.1176/ajp.2007.164.1.43
15. Beck A, Schlagenhauf F, Wustenberg T, Hein J, Kienast T, Kahnt T, et al. Ventral striatal activation during reward anticipation correlates with impulsivity in alcoholics. *Biol. Psychiatry.* (2009) 66:734–42. doi: 10.1016/j.biopsych.2009.04.035
16. Peters J, Bromberg U, Schneider S, Brassen S, Menz M, Banaschewski T, et al. Lower ventral striatal activation during reward anticipation in adolescent smokers. *Am. J. Psychiatry.* (2011) 168:540–9. doi: 10.1176/appi.ajp.2010.10071024
17. Hahn T, Notebaert KH, Dresler T, Kowarsch L, Reif A, Fallgatter AJ. Linking online gaming and addictive behavior: converging evidence for a general reward deficiency in frequent online gamers. *Front. Behav. Neurosci.* (2014) 8:385. doi: 10.3389/fnbeh.2014.00385
18. Dong G, Lin X, Hu Y, Xie C, Du X. Imbalanced functional link between executive control network and reward network explain the online-game seeking behaviors in Internet gaming disorder. *Sci. Rep.* (2015) 5:9197. doi: 10.1038/srep09197
19. Duven EC, Muller KW, Beutel ME, Wolfling K. Altered reward processing in pathological computer gamers–ERP-results from a semi-natural gaming-design. *Brain Behav.* (2015) 5:13–23. doi: 10.1002/brb3.293
20. Gleich T, Lorenz RC, Gallinat J, Kuhn S. Functional changes in the reward circuit in response to gaming-related cues after training with a commercial video game. *Neuroimage.* (2017) 152:467–75. doi: 10.1016/j.neuroimage.2017.03.032
21. Powell J, Dawkins L, Davis RE. Smoking, reward responsiveness, and response inhibition: tests of an incentive motivational model. *Biol. Psychiatry.* (2002) 51:151–63. doi: 10.1016/S0006-3223(01)01208-2
22. Lin X, Zhou H, Dong G, Du X. Impaired risk evaluation in people with Internet gaming disorder: fMRI evidence from a probability discounting task. *Prog. Neuropsychopharmacol. Biol. Psychiatry.* (2015) 56:142–8. doi: 10.1016/j.pnpbp.2014.08.016
23. Yau YH, Potenza MN, Mayes LC, Crowley MJ. Blunted feedback processing during risk-taking in adolescents with features of problematic Internet use. *Addict. Behav.* (2015) 45:156–63. doi: 10.1016/j.addbeh.2015.01.008
24. Weinstein A, Abu HB, Timor A, Mama Y. Delay discounting, risk-taking, and rejection sensitivity among individuals with internet and video gaming disorders. *J. Behav. Addict.* (2016) 5:674–82. doi: 10.1556/2006.5.2016.081
25. Hing N, Russell AM, Browne M. Risk factors for gambling problems on online electronic gaming machines, race betting and sports betting. *Front. Psychol.* (2017) 8:779. doi: 10.3389/fpsyg.2017.00779
26. Wei S, Zheng Y, Li Q, Dai W, Sun J, Wu H, et al. Enhanced neural responses to monetary rewards in methamphetamine use disordered individuals compared to healthy controls. *Physiol. Behav.* (2018) 195:118–27. doi: 10.1016/j.physbeh.2018.08.003
27. Balodis IM, Potenza MN. Anticipatory reward processing in addicted populations: a focus on the monetary incentive delay task. *Biol. Psychiatry.* (2015) 77:434–44. doi: 10.1016/j.biopsych.2014.08.020
28. Knutson B, Heinz A. Probing psychiatric symptoms with the monetary incentive delay task. *Biol. Psychiatry.* (2015) 77:418–20. doi: 10.1016/j.biopsych.2014.12.022
29. de Wit H, Richards JB. Dual determinants of drug use in humans: reward and impulsivity. In Bevins RA, Bardo MT, editors. *Motivational Factors in the Etiology of Drug Abuse. Vol. 50 of the Nebraska Symposium on Motivation*. University of Nebraska Press. (2004). p. 19–55.
30. Sun DL, Chen ZJ, Ma N, Zhang XC, Fu XM, Zhang DR. Decision-making and prepotent response inhibition functions in excessive internet users. *CNS Spectr.* (2009) 14:75–81. doi: 10.1017/S1092852900000225
31. Seok JW, Lee KH, Sohn S, Sohn JH. Neural substrates of risky decision making in individuals with Internet addiction. *Aust. N. Z. J. Psychiatry.* (2015) 49:923–32. doi: 10.1177/0004867415598009
32. Yao YW, Chen PR, Li S, Wang LJ, Zhang JT, Yip SW, et al. Decision-making for risky gains and losses among college students with Internet gaming disorder. *PLoS ONE.* (2015) 10:e0116471. doi: 10.1371/journal.pone.0116471
33. Yao YW, Wang LJ, Yip SW, Chen PR, Li S, Xu J, et al. Impaired decision-making under risk is associated with gaming-specific inhibition deficits among college students with Internet gaming disorder. *Psychiatry Res.* (2015) 229:302–9. doi: 10.1016/j.psychres.2015.07.004
34. Wang Y, Wu L, Wang L, Zhang Y, Du X, Dong G. Impaired decision-making and impulse control in internet gaming addicts: evidence from the comparison with recreational internet game users. *Addict. Biol.* (2017) 22:1610–21. doi: 10.1111/adb.12458
35. Dean AC, Sugar CA, Hellemann G, London ED. Is all risk bad? Young adult cigarette smokers fail to take adaptive risk in a laboratory decision-making test. *Psychopharmacology.* (2011) 215:801–11. doi: 10.1007/s00213-011-2182-y
36. Briggs Z, O'Connor M, Jollans EK, O'Halloran L, Dymond S, Whelan R. Flexible emotion-based decision-making behavior varies in current and former smokers. *Addict. Behav.* (2015) 45:269–75. doi: 10.1016/j.addbeh.2015.02.011
37. Balconi M, Venturella I, Finocchiaro R. Evidences from rewarding system, FRN and P300 effect in Internet-addiction in young people. *Brain Sci.* (2017) 7:81. doi: 10.3390/brainsci7070081
38. Kim J, Kim H, Kang E. Impaired feedback processing for symbolic reward in individuals with internet game overuse. *Front. Psychiatry.* (2017) 8:195. doi: 10.3389/fpsyt.2017.00195
39. Rachlin H. Diminishing marginal value as delay discounting. *J. Exp. Anal. Behav.* (1992) 57:407–15. doi: 10.1901/jeab.1992.57-407
40. Jones BA, Rachlin H. Delay, probability, and social discounting in a public goods game. *J. Exp. Anal. Behav.* (2009) 91:61–73. doi: 10.1901/jeab.2009.91-61
41. Wang Y, Wu L, Zhou H, Lin X, Zhang Y, Du X, et al. Impaired executive control and reward circuit in Internet gaming addicts under a delay discounting task: independent component analysis. *Eur. Arch. Psychiatry Clin. Neurosci.* (2017) 267:245–55. doi: 10.1007/s00406-016-0721-6
42. Kim JY, Chun JW, Park CH, Cho H, Choi J, Yang S, et al. The correlation between the frontostriatal network and impulsivity in internet gaming disorder. *Sci. Rep.* (2019) 9:1191. doi: 10.1038/s41598-018-37702-4
43. Hills AM, Dickerson M. Emotion, implicit decision making and persistence at gaming. *Addiction.* (2002) 97:598–9. doi: 10.1046/j.1360-0443.2002.t01-4-00134.x
44. Dong G, Wang J, Yang X, Zhou H. Risk personality traits of Internet addiction: a longitudinal study of internet-addicted Chinese university students. *Asia Pac. Psychiatry.* (2013) 5:316–21. doi: 10.1111/j.1758-5872.2012.00185.x
45. Dong G, Potenza MN. Risk-taking and risky decision-making in internet gaming disorder: implications regarding online gaming in the setting of negative consequences. *J. Psychiatr. Res.* (2016) 73:1–8. doi: 10.1016/j.jpsychires.2015.11.011
46. Li Q, Wang Y, Yang Z, Dai W, Zheng Y, Sun Y, et al. Dysfunctional cognitive control and reward processing in adolescents with Internet gaming disorder. *Psychophysiology.* (2020) 57:e13469. doi: 10.1111/psyp.13469
47. Ko CH, Hsiao S, Liu GC, Yen JY, Yang MJ, Yen CF. The characteristics of decision making, potential to take risks, and personality of college students with Internet addiction. *Psychiatry Res.* (2010) 175:121–5. doi: 10.1016/j.psychres.2008.10.004
48. Ding YJ, Lau CH, Sou KL, Abraham AA, Griffiths SM, Kim JH. Association between internet addiction and high-risk sexual attitudes in Chinese university students from Hong Kong and Macau. *Public Health.* (2016) 132:60–3. doi: 10.1016/j.puhe.2015.11.009
49. Starcevic V. Problematic internet use, reward sensitivity and decision making. *Aust. N. Z. J. Psychiatry.* (2015) 49:937–8. doi: 10.1177/0004867415600077

50. Lai CM, Mak KK, Watanabe H, Ang RP, Pang JS, Ho RC. Psychometric properties of the internet addiction test in Chinese adolescents. *J. Pediatr. Psychol.* (2013) 38:794–807. doi: 10.1093/jpepsy/jst022
51. Koo HJ, Han DH, Park SY, Kwon JH. The structured clinical interview for DSM-5 internet gaming disorder: development and validation for diagnosing IGD in Adolescents. *Psychiatry Investig.* (2017) 14:21–9. doi: 10.4306/pi.2017.14.1.21
52. Babor TF, de la Fuente JR, Saunders J, Grant M. *AUDIT - the Alcohol-Use Disorders Identification Test: Guidelines for Use in Primary Health Care*. Geneva: World Health Organization, Division of Mental Health (1989).
53. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of beck depression inventories -IA and -II in psychiatric outpatients. *J. Pers. Assess.* (1996) 67:588–97. doi: 10.1207/s15327752jpa6703_13
54. Shek DT. The Chinese version of the state-trait anxiety inventory: its relationship to different measures of psychological well-being. *J. Clin. Psychol.* (1993) 49:349–58. doi: 10.1002/1097-4679(199305)49:3%3c349::aid-jclp2270490308%3e3.0.co;2-j
55. Li X, Phillips M, Xu D, Zhang Y-l, Yang S, Tong Y, et al. Reliability and validity of an adapted Chinese version of Barratt impulsiveness scale. *Chinese Mental Health.* (2011) 25:610–5.
56. Li YZ, Zhang Y, Jiang Y, Li H. *The Chinese version of the BIS/BAS Scale: Reliability and Validity* (2008).
57. Wang W, Wu YX, Peng ZG, Lu SW, Wang GP, Fu XM, et al. (2000). Test of sensation seeking in a Chinese sample. *Pers. Individ. Dif.* 28:169–79. doi: 10.1016/S0191-8869(99)00092-6
58. Dewitt B, Fischhoff B, Davis AL, Broomell SB, Roberts MS, Hanmer J. Exclusion criteria as measurements I: identifying invalid responses. *Med. Decis. Making.* (2019) 39:693–703. doi: 10.1177/0272989X19856617
59. Zheng Y, Liu X. Blunted neural responses to monetary risk in high sensation seekers. *Neuropsychologia.* (2015) 71:173–80. doi: 10.1016/j.neuropsychologia.2015.04.002
60. Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J. Neurosci. Methods.* (2004) 134:9–21. doi: 10.1016/j.jneumeth.2003.10.009
61. Li Q, Tian M, Taxer J, Zheng Y, Wu H, Sun S, et al. Problematic internet users' discounting behaviors reflect an inability to delay gratification, not risk taking. *Cyberpsychol. Behav. Soc. Netw.* (2016) 19:172–8. doi: 10.1089/cyber.2015.0295
62. Tian M, Tao R, Zheng Y, Zhang H, Yang G, Li Q, et al. Internet gaming disorder in adolescents is linked to delay discounting but not probability discounting. *Comput. Hum. Behav.* (2018) 80:59–66. doi: 10.1016/j.chb.2017.10.018
63. Zheng Y, Tian M, Li Q, Liu X. Greater tolerance to losses in sensation seeking: evidence from probability and delay discounting. *Drug Alcohol. Depend.* (2018) 194:159–65. doi: 10.1016/j.drugalcdep.2018.09.027
64. Myerson J, Green L, Warusawitharana M. Area under the curve as a measure of discounting. *J. Exp. Anal. Behav.* (2001) 76:235–43. doi: 10.1901/jeab.2001.76-235
65. Madden GJ, Bickel WK, Jacobs EA. Discounting of delayed rewards in opioid-dependent outpatients: exponential or hyperbolic discounting functions? *Exp. Clin. Psychopharmacol.* (1999) 7:284–93. doi: 10.1037/1064-1297.7.3.284
66. Dallery J, Raiff BR. Delay discounting predicts cigarette smoking in a laboratory model of abstinence reinforcement. *Psychopharmacology.* (2007) 190:485–96. doi: 10.1007/s00213-006-0627-5
67. Field M, Rush M, Cole J, Goudie A. The smoking stroop and delay discounting in smokers: effects of environmental smoking cues. *J. Psychopharmacol.* (2007) 21:603–10. doi: 10.1177/0269881106070995
68. Andrade LF, Alessi SM, Petry NM. The effects of alcohol problems and smoking on delay discounting in individuals with gambling problems. *J. Psychoactive Drugs.* (2013) 45:241–8. doi: 10.1080/02791072.2013.803645
69. Buono FD, Sprong ME, Lloyd DP, Cutter CJ, Printz DM, Sullivan RM, et al. Delay discounting of video game players: comparison of time duration among gamers. *Cyberpsychol. Behav. Soc. Netw.* (2017) 20:104–8. doi: 10.1089/cyber.2016.0451
70. Skinner MD, Aubin HJ, Berlin I. Impulsivity in smoking, nonsmoking, and ex-smoking alcoholics. *Addict. Behav.* (2004) 29:973–8. doi: 10.1016/j.addbeh.2004.02.045
71. Doran N, McChargue D, Cohen L. Impulsivity and the reinforcing value of cigarette smoking. *Addict. Behav.* (2007) 32:90–8. doi: 10.1016/j.addbeh.2006.03.023
72. VanderVeen JW, Cohen LM, Cukrowicz KC, Trotter DR. The role of impulsivity on smoking maintenance. *Nicotine Tob. Res.* (2008) 10:1397–404. doi: 10.1080/14622200802239330
73. Spillane NS, Smith GT, Kahler CW. Impulsivity-like traits and smoking behavior in college students. *Addict. Behav.* (2010) 35:700–5. doi: 10.1016/j.addbeh.2010.03.008
74. Mishra J, Bavelier D, Gazzaley A. How to assess gaming-induced benefits on attention and working memory. *Games Health J.* (2012) 1:192–8. doi: 10.1089/g4h.2011.0033
75. Trisolini DC, Petilli MA, Daini R. Is action video gaming related to sustained attention of adolescents? *Q. J. Exp. Psychol.* (2018) 71:1033–9. doi: 10.1080/17470218.2017.1310912
76. Hu J, Zhen S, Yu C, Zhang Q, Zhang W. Sensation seeking and online gaming addiction in adolescents: a moderated mediation model of positive affective associations and impulsivity. *Front. Psychol.* (2017) 8:699. doi: 10.3389/fpsyg.2017.00699
77. Yen JY, Liu TL, Wang PW, Chen CS, Yen CF, Ko CH. Association between Internet gaming disorder and adult attention deficit and hyperactivity disorder and their correlates: impulsivity and hostility. *Addict. Behav.* (2017) 64:308–13. doi: 10.1016/j.addbeh.2016.04.024
78. Tian Y, Yu C, Lin S, Lu J, Liu Y, Zhang W. Sensation seeking, deviant peer affiliation, and internet gaming addiction among Chinese adolescents: the moderating effect of parental knowledge. *Front. Psychol.* (2018) 9:2727. doi: 10.3389/fpsyg.2018.02727
79. Dong G, Hu Y, Lin X. Reward/punishment sensitivities among internet addicts: implications for their addictive behaviors. *Prog. Neuropsychopharmacol. Biol. Psychiatry.* (2013) 46:139–45. doi: 10.1016/j.pnpbp.2013.07.007
80. Altbacker A, Plozer E, Darnai G, Perlaki G, Horvath R, Orsi G, et al. Problematic internet use is associated with structural alterations in the brain reward system in females. *Brain Imaging Behav.* (2016) 10:953–9. doi: 10.1007/s11682-015-9454-9
81. Qi X, Du X, Yang Y, Du G, Gao P, Zhang Y, et al. Decreased modulation by the risk level on the brain activation during decision making in adolescents with internet gaming disorder. *Front. Behav. Neurosci.* (2015) 9:296. doi: 10.3389/fnbeh.2015.00296
82. Hajcak G, Moser JS, Holroyd CB, Simons RF. The feedback-related negativity reflects the binary evaluation of good versus bad outcomes. *Biol. Psychol.* (2006) 71:148–54. doi: 10.1016/j.biopsycho.2005.04.001
83. Balconi M, Crivelli D. FRN and P300 ERP effect modulation in response to feedback sensitivity: the contribution of punishment-reward system (BIS/BAS) and behaviour identification of action. *Neurosci. Res.* (2010) 66:162–72. doi: 10.1016/j.neures.2009.10.011
84. Onoda K, Abe S, Yamaguchi S. Feedback-related negativity is correlated with unplanned impulsivity. *Neuroreport.* (2010) 21:736–9. doi: 10.1097/WNR.0b013e32833bfd36
85. Nieuwenhuis S, Aston-Jones G, Cohen JD. Decision making, the P3, and the locus coeruleus-norepinephrine system. *Psychol. Bull.* (2005) 131:510–32. doi: 10.1037/0033-2909.131.4.510
86. Kamarajan C, Pandey AK, Chorlian DB, Manz N, Stimus AT, Bauer LO, et al. Reward processing deficits and impulsivity in high-risk offspring of alcoholics: a study of event-related potentials during a monetary gambling task. *Int. J. Psychophysiol.* (2015) 98(2 Pt 1):182–200. doi: 10.1016/j.ijpsycho.2015.09.005
87. Pornpattananangkul N, Nadig A, Heidinger S, Walden K, Nusslock R. Elevated outcome-anticipation and outcome-evaluation ERPs associated with a greater preference for larger-but-delayed rewards. *Cogn. Affect. Behav. Neurosci.* (2017) 17:625–41. doi: 10.3758/s13415-017-0501-4
88. Kok A. On the utility of P3 amplitude as a measure of processing capacity. *Psychophysiology.* (2001) 38:557–77. doi: 10.1017/S0048577201990559
89. Grose-Fifer J, Migliaccio R, Zottoli TM. Feedback processing in adolescence: an event-related potential study of age and gender differences. *Dev. Neurosci.* (2014) 36:228–38. doi: 10.1159/000358917
90. Colzato LS, van den Wildenberg WP, Zmigrod S, Hommel B. Action video gaming and cognitive control: playing first person shooter games is associated

with improvement in working memory but not action inhibition. *Psychol. Res.* (2013) 77:234–9. doi: 10.1007/s00426-012-0415-2
91. Bakhshani NM. Impulsivity: a predisposition toward risky behaviors. *Int. J. High Risk Behav. Addict.* (2014) 3:e20428. doi: 10.5812/ijhrba.20428
92. Rieser NM, Shaul L, Blankers M, Koeter MWJ, Schippers GM, Goudriaan AE. The predictive value of impulsivity and risk-taking measures for substance use in substance dependent offenders. *Front. Behav. Neurosci.* (2019) 13:192. doi: 10.3389/fnbeh.2019.00192
93. Ryan KK, Mackillop J, Carpenter MJ. The relationship between impulsivity, risk-taking propensity and nicotine dependence among older adolescent smokers. *Addict. Behav.* (2013) 38:1431–4. doi: 10.1016/j.addbeh.2012.08.013
94. Herman AM, Critchley HD, Duka T. Risk-taking and impulsivity: the role of mood states and interoception. *Front. Psychol.* (2018) 9:1625. doi: 10.3389/fpsyg.2018.01625

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.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 08 December 2020
doi: 10.3389/fpsyt.2020.606891

Cognitive Control Deficits in Alcohol Dependence Are a Trait- and State-Dependent Biomarker: An ERP Study

Xiaohong Liu[1†], Hongliang Zhou[2†], Chenguang Jiang[1], Yanling Xue[1], Zhenhe Zhou[3] and Jun Wang[3*]*

[1] Department of Substance Dependence, The Affiliated Wuxi Mental Health Center of Nanjing Medical University, Wuxi, China, [2] Nanjing Brain Hospital Affiliated to Nanjing Medical University, Wuxi, China, [3] Department of Psychiatry, The Affiliated Wuxi Mental Health Center of Nanjing Medical University, Wuxi, China

OPEN ACCESS

Edited by:
Qi Li,
University of Chinese Academy of Sciences, China

Reviewed by:
Kesong Hu,
Lake Superior State University, United States
Alessio Simonetti,
Baylor College of Medicine, United States

***Correspondence:**
Zhenhe Zhou
zhouzh@njmu.edu.cn
Jun Wang
woodfish2@126.com

[†] These authors share first authorship

Specialty section:
This article was submitted to Addictive Disorders, a section of the journal Frontiers in Psychiatry

Received: 15 September 2020
Accepted: 11 November 2020
Published: 08 December 2020

Citation:
Liu X, Zhou H, Jiang C, Xue Y, Zhou Z and Wang J (2020) Cognitive Control Deficits in Alcohol Dependence Are a Trait- and State-Dependent Biomarker: An ERP Study. Front. Psychiatry 11:606891. doi: 10.3389/fpsyt.2020.606891

Alcohol dependence (AD) presents cognitive control deficits. Event-related potential (ERP) P300 reflects cognitive control-related processing. The aim of this study was to investigate whether cognitive control deficits are a trait biomarker or a state biomarker in AD. Participants included 30 AD patients and 30 healthy controls (HCs). All participants were measured with P300 evoked by a three-stimulus auditory oddball paradigm at a normal state (time 1, i.e., just after the last alcohol intake) and abstinence (time 2, i.e., just after a 4-week abstinence). The results showed that for P3a and P3b amplitude, the interaction effect for group × time point was significant, the simple effect for group at time 1 level and time 2 level was significant, and the simple effect for time point at AD group level was significant; however, the simple effect for time point at HC group level was not significant. Above results indicated that compared to HCs, AD patients present reductions of P3a/3b amplitude, and after 4-week alcohol abstinence, although P3a/3b amplitudes were improved, they were still lower than those of HCs. For P3a and P3b latencies, no significant differences were observed. These findings conclude that AD patients present cognitive control deficits that are reflected by P3a/3b and that cognitive control deficits in AD are trait- and state-dependent. The implication of these findings is helpful to understand the psychological and neural processes for AD, and these findings suggest that improving the cognitive control function may impact the treatment effect for AD.

Keywords: alcohol dependence, cognitive control, event-related potential, trait dependent biomarker, state dependent biomarker

INTRODUCTION

Alcohol dependence (AD) is a relapsing disorder and presents a loss of volitional control over consumption, impaired executive functions, a pathological preoccupation with alcohol seeking, and a compulsive drive for harmful drinking, disregarding many serious life consequences, such as deteriorating health, professional responsibilities, and family loss. AD involves not only alcohol-related liver and cerebral cortex diseases but also violence and traffic accidents. Understanding the psychological and neural processes of AD is an important public health issue.

Cognitive control is a sort of cognitive ability that is involved in the adjustment of perceptual selection and action; namely, cognitive control can be regarded as a flexible, goal-directed behavior that is essential for efficient information processing and behavioral response under conditions of uncertainty and underlies a broad range of executive functions (1, 2). AD is associated with cognitive control dysfunctions, and cognitive control is mediated through the interaction between inherent large-scale brain networks involved in externally oriented executive functioning and internally focused thought processing (3). Many previous studies have indicated that AD patients present cognitive control dysfunction; in particular, altered impulse control has been implicated in AD. For example, a study used functional magnetic resonance imaging (fMRI) during a stop signal task to investigate cognitive control function in AD patients, and the results showed that AD patients displayed longer go trial and stop signal reaction times, a higher stop success rate and post-error slowing; AD patients displayed less activity in cortical and subcortical structures, including the putamen, insula, and amygdala, during risk-taking decisions in the stop signal task. These results provided evidence for altered neural processing during impulse control in AD (4). A recent study used fMRI to investigate the relationship between AD severity and delay discounting neural activation and concluded that AD severity tracks with dysregulations in cognitive control and reward evaluation areas during impulsive and delayed decisions (5). Another study also used fMRI to investigate the relationship between AD severity and functional connectivity of fronto-striatal networks during a stop signal task, and the results indicated that patients with more severe AD displayed less frontal connectivity with the striatum, a component of cognitive control networks important for response inhibition (6).

Event-related potential (ERP) is a tool for a functional measure of brain activity that occurs time-locked to external stimuli and reflects successive stages of information processing. The ERP is a technique that can provide an analysis of neural activity with the high temporal resolution and high informative power on neural alterations in several disorders including schizophrenia, affective disorders, and substance abuse disorders (7–9). Previous studies have indicated that ERP P300 (P300) reflects cognitive control-related processing; therefore, P300 is thought to serve as a marker of cognitive control processes (10, 11). P300 includes P3a and P3b. P3b is elicited by target stimuli of the traditional oddball task, whereas P3a is elicited by novel or nontarget stimuli of the traditional oddball task. Substantial evidence exists regarding P300 deficits in AD patients. However, whether P3a/3b deficits are present primarily during AD (i.e., state-dependent) or are an integral part of the disorder (i.e., trait-dependent) is still controversial. Many studies have confirmed that AD patients displayed reduced P3a/3b amplitudes while performing an oddball task (12), suggesting that AD patients exhibited a disability to allocate neural resources for encoding specific stimuli, which could be due to impaired cortical functions. These results support P300 deficit as a trait biomarker in AD. However, a study showed that P300 deficit was not present in treatment-naive alcohol-dependent patients without comorbidities (13), which support the concept that P300 might be a state-dependent biomarker in AD. Clarifying whether a cognitive control deficit, which is reflected by P3a/3b deficits, is a trait biomarker or a state biomarker in AD will be helpful to understand the psychological and neural processes for AD.

Considering that a state characteristic is transient and a trait characteristic is enduring (14), longitudinal research is essential to determine whether P3a/3b deficits are state- or trait-dependent in AD. No longitudinal study to date has investigated whether P3a/3b deficits either are present primarily during AD (i.e., state-dependent) or form an integral part of the disorder (i.e., trait-dependent), or a combination of the two (i.e., state- as well as trait-dependent).

Alcohol-dependent patients' cognitive problem is also an emotion-anxiety problem. Previous studies showed that children of alcohol-dependent patients displayed a higher frequency of psychopathological states, which are known to have a strong effect on depression or anxiety (15), and present altered activations of the amygdala, which is involved in the elicitation and decoding of emotional feeling (16). The State-Trait Anxiety Inventory (STAI) has a sensitivity in detecting anxiety disorders and anxiety-like behaviors (17) and has been employed to capture enduring characteristics and patterns of symptoms (18). However, the assessment of the anxiety level by using STAI depends on the participant's ability to subjectively comment or report on his or her own mental state (18). Therefore, using the measurement of P3a/3b to determine whether cognitive control deficits are trait- and state-dependent can be an advantage of objectivity of the assessment of anxiety level in AD.

The Severity of Alcohol Dependence Questionnaire (SADQ) is usually used for the assessment of the severity of AD (19). A previous study showed that the Chinese version of the Severity of Alcohol Dependence Questionnaire (SADQ-C) consists of four principal components, including withdrawal relief drinking, affective withdrawal signs, physical withdrawal signs, and reinstatement of withdrawal symptoms following abstinence. The internal consistency of SADQ-C was Cronbach's α of 0.92, which confirmed that the SADQ-C is a reliable tool for AD severity assessment and it can be used to administer the treatment outcome in male patients with AD (20).

In the present study, patients with AD were selected as subjects, and cognitive control functions were measured with P3a and P3b, which were elicited by a three-stimulus oddball task; assessments of cognitive control functions were performed at baseline and after a 4-week follow-up. The hypothesis of this study is that cognitive control deficits in AD are both a trait- and state-dependent biomarker, which is reflected by P3a/3b. The aim of this study was to investigate whether a cognitive control deficit, which is reflected by P3a/3b deficits, is a trait biomarker or a state biomarker in AD.

METHODS

Time and Setting

The present study was conducted in the Department of Substance Dependence, The Affiliated Wuxi Mental Health Centre of Nanjing Medical University, China, from March 1, 2018, to April 30, 2020.

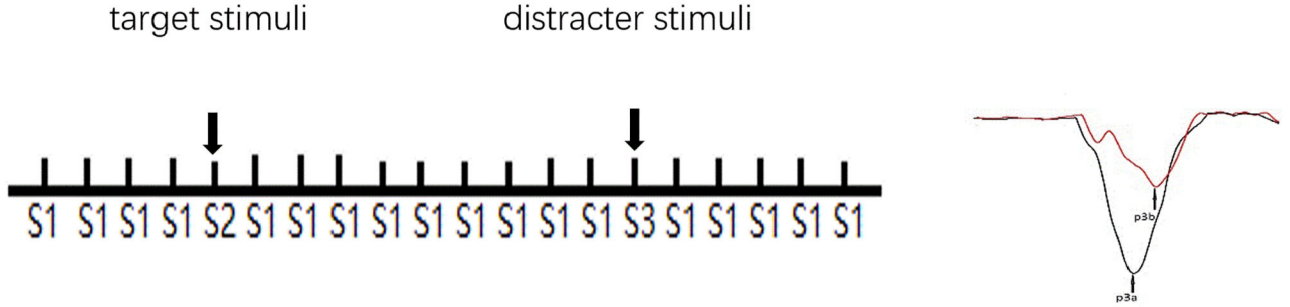

FIGURE 1 | Schematic illustration of the three-stimulus auditory oddball paradigm. S1: standard stimuli. S2: infrequent target stimuli randomly appeared in a background of frequently occurring S1. S3: infrequent distracter stimuli randomly appeared in a background of occurring S1. The subjects were instructed to respond (click the left mouse button) when S2, but not any other stimuli, appeared. S3 elicits a P3a, and S2 elicits a P3b.

TABLE 1 | Demographic and clinical characteristics of participants.

	AD	HC	Test statistic
Sex ratio (M/F)	30/0	30/0	–
Mean age (SD), years	43.2 (7.4)	43.9 (7.6)	$t = 0.110$, $p = 0.912$
Age range	27–57	28–59	–
Education (SD)	8.3 (2.1)	9.4 (2.1)	$t = 1.763$, $p = 0.850$
Years of addiction (SD)	18.9 (10.0)	–	–
Handedness (R/M/L)	10/9/11	11/10/9	$\chi 2 = 0.230$, $p = 0.725$
SADQ (SD)	26.4 (2.5)	–	–
Blood alcohol concentration (mg/100 ml, SD)	75.6 (3.2)	–	–
HAMA (SD)	5.6 (1.3)	3.5 (1.9)	$t = 0.241$, $p = 0.621$
HAMD (SD)	6.4 (2.3)	5.1 (2.5)	$t = 0.107$, $p = 0.735$

AD, alcohol-dependent individual group; HC, normal control group; M, male; F, female; SD, standard deviation; R, right; M, mixed; L, left; SADQ, Severity of Alcohol Dependence Questionnaire; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale.

TABLE 2 | ERP data [mean (SD)] in the AD group ($n = 30$) and HC group ($n = 30$).

Variable	AD (time 1)		AD (time 2)		HC (time 1)		HC (time 2)	
	A (μV)	L (ms)	A (μV)	L (ms)	A (μV)	L (ms)	A (μV)	L (ms)
P3a	6.6 (1.6)	310.7 (18.3)	8.6 (1.0)	308.5 (24.9)	9.9 (0.6)	302.2 (25.7)	9.7 (0.9)	307.0 (29.6)
P3b	4.4 (1.5)	354.7 (29.6)	5.9 (1.5)	351.5 (24.1)	7.2 (1.3)	350.5 (24.2)	7.0 (1.2)	349.3 (24.5)

AD, alcohol dependence; HC, health control; SD, standard deviation; A, amplitude; L, latency; ERP, event-related potential.

Diagnostic Criteria and Participants

The present study included an AD group and a healthy control (HC) group. The criteria for inclusion in the AD group were as follows: (1) met the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), criteria for AD; (2) were in an age range from 18 to 60 years old; (3) did not receive any medication for 2 weeks prior to the study; (4) were not smokers; and (5) had no neurological illness or comorbid psychiatric illness, as determined by medical records, or other substance dependence. The inclusion criteria for the HC group were as follows: (1) did not meet the criteria for any DSM-5 axis I disorder or personality disorders, as assessed by the Structured Clinical Interview for DSM-5 (SCID-5, Chinese version); (2) were in an age range from 18 to 60 years old; and (3) had no history of any kind of mental disorder or any kind of physical illness.

In this study, 30 AD patients were recruited as the AD group. The AD patients were inpatients at the Department of Substance Dependence. Thirty healthy individuals were recruited as the HC group. HCs were recruited from a group of citizens who lived in Wuxi City, Jiangsu Province, China, through local advertising. Both AD patients and HCs were Chinese.

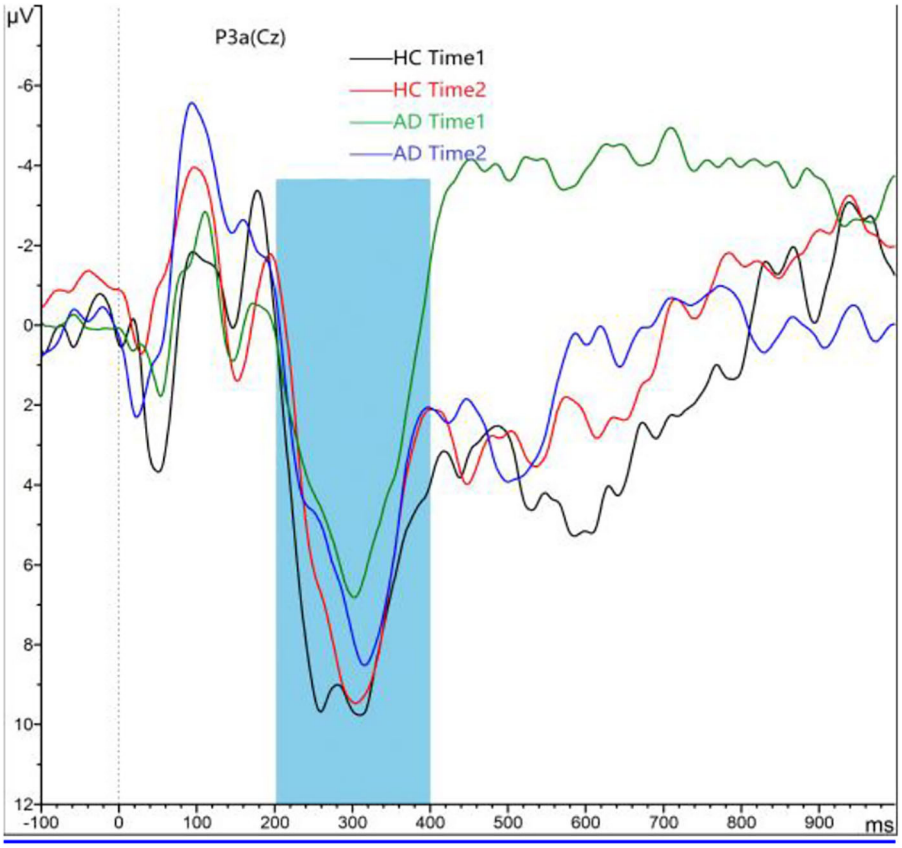

FIGURE 2 | Grand averaged P3a was elicited by a three-stimulus auditory oddball paradigm for the alcohol dependence (AD) group (purple lines and green lines) and the healthy control (HC) group (black lines and red lines) at time 1 and time 2. The P3a was presented within a 250- to 450-ms latency window at the Cz electrode site. The gray area is timeframe.

Event-Related Potential Measurement

ERP measurement was taken from a recent study (21). The BioSemi Active Two system (BioSemi Inc., Amsterdam, Netherlands) was employed continuously for the electroencephalogram (EEG) record. The digitization rate was 512 Hertz (Hz); the bandpass was DC-104 Hz, and the common mode sense served as the reference (PO2 site) using a 64-channel electrode cap. Electro-oculogram electrodes were placed below and at the outer canthi of the left eye. A three-stimulus auditory oddball paradigm was employed to elicit P3a and P3b. A total of 400 binaural, 80-decibel (dB) tones with 50-ms-duration stimuli were presented to the participants through foam insert earphones. Overall, 12% of the stimuli were target tones (1,500 Hz), 12% infrequent "novel" sounds (a bird call or a water drop), and 76% standard tones (1,000 Hz), with an interstimulus interval varying between 1.8 and 2.2 s. Stimuli presentation was randomized. The electrical impedance was monitored. The duration of the whole P300 paradigm is 8 min. Participants were in a sound attenuated chamber. All subjects were told to press the computer mouse button in response to the target tones. Clicking occurrence between 100 and 900 ms after the tone served as a correct response. Before the formal trial, there was a practice block to make sure participants understood the task (see **Figure 1**).

Event-Related Potential Data Analysis

Brain Vision Analyzer 2.0 (Brain Products GmbH, Munich, Germany) was used for ERP data analysis. P3a was analyzed at the Cz site because it is largest in the frontal regions, and P3b was analyzed at the Pz site because it is largest over the parietal regions (21–23). An average of the mastoids was the reference and was bandpass filtered between 0.01 and 20 Hz using a zero-phase shift Butterworth filter. Data were segmented by a stimulus marker from −100 to 1,000 ms, responses to novel sounds were employed for P3a, and correct responses to target tones were employed for P3b. Segments were baseline-corrected using a −100 to 0 ms pre-stimulus time and eye-blink corrected using established measures. Artifact rejection for individual channels was performed, and a given segment was rejected if the voltage gradient exceeded 50 μV/ms, the amplitude was ±100 μV, or the signal was flat (<0.5 μV for more than 100 ms). Segments were averaged across stimulus markers, and the P3a amplitude peak was chosen from 250 to

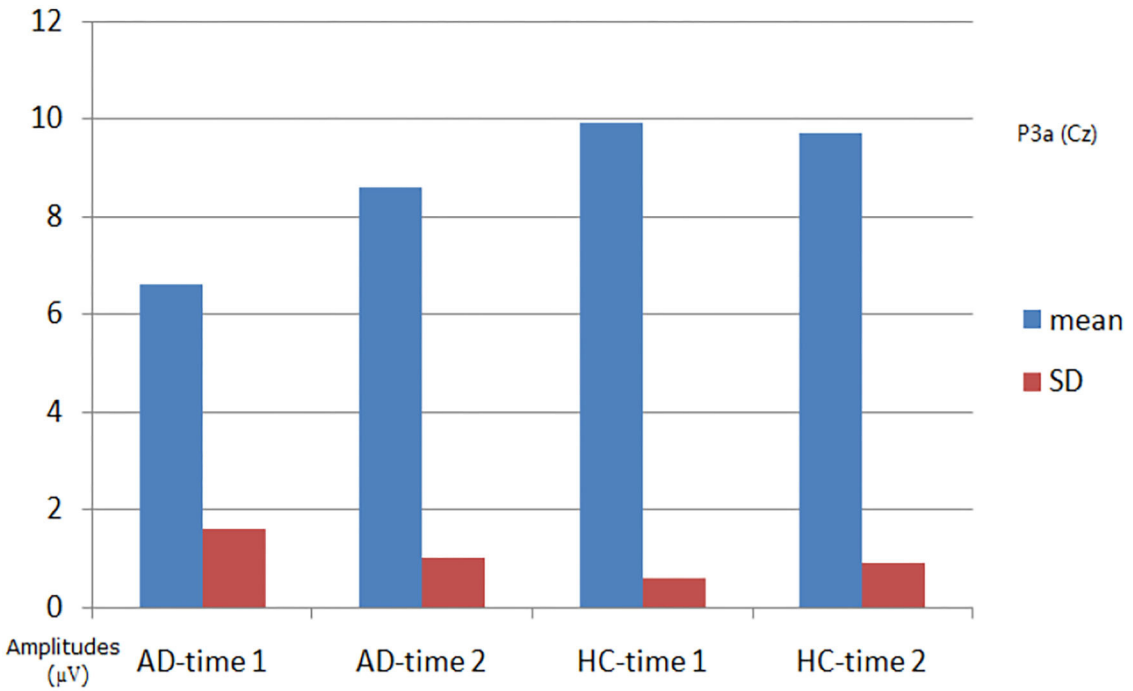

FIGURE 3 | Plot of P3a amplitude analysis. The interaction effect for group × time point was significant; the simple effect for group at time 1 level and time 2 level was significant; the simple effect for time point at the alcohol dependence (AD) group level was significant; the simple effect for time point at the healthy control (HC) group level was not significant.

450 ms, while the P3b amplitude peak was chosen from 280 to 650 ms.

Experiment Procedures

On the day of the ERP recording, two psychiatric resident physicians collected patient demographic data, clinical characteristics, and confirmed/excluded a diagnosis of AD. The Annett handedness scale was used for the assessments of handedness (24). AD levels were measured with the SADQ, and a breath alcohol reading was used to measure blood alcohol concentration in the AD group.

All AD patients were measured with P300 at a normal state (time 1, i.e., just after the last alcohol intake) and abstinence (time 2, i.e., just after a 4-week abstinence). When measuring P300 at time 2, all AD patients had to end any treatment with medication for 2 weeks. To avoid the practice effect, the HCs were measured with P300 twice in a 2-week interval (corresponding to time 1 and time 2). The anxiety and depression of all participants were assessed with the Hamilton Anxiety Scale (HAMA) and the Hamilton Depression Scale (17-item edition, HAMD).

All experimental procedures were approved by the Ethics Committee on Human Studies, the Affiliated Wuxi Mental Health Centre of Nanjing Medical University, Wuxi, Jiangsu Province, China, and they were conducted in accordance with the Declaration of Helsinki. All participants provided their written informed consent to participate, and all were compensated with 600.00 Chinese Yuan plus travel costs.

Data Analysis

Statistical Program for the Social Sciences software version 19.0 (SPSS, IBM Corporation, Armonk, NY, USA) was employed for the data analysis. Mean age and education were compared between the AD group and the HC group using two-tailed *t*-tests, and handedness was compared using the Pearson chi-square test. HAMD and HAMA scores were compared between the AD group and the HC group using paired-samples *t*-tests. The mean amplitudes and the mean latencies of P3a and P3b were compared between the AD group and the HC group using repeated ANOVA. The degrees of freedom of the *F* ratio were corrected according to the Greenhouse–Geisser method. Least square difference tests were performed as *post hoc* analyses if indicated. Alpha values of 0.05 were considered significant.

RESULTS

Demographic Characteristics of Participants

Demographic characteristics of participants are shown in **Table 1**. There were no significant differences between the demographic characteristics of the participants in the AD group

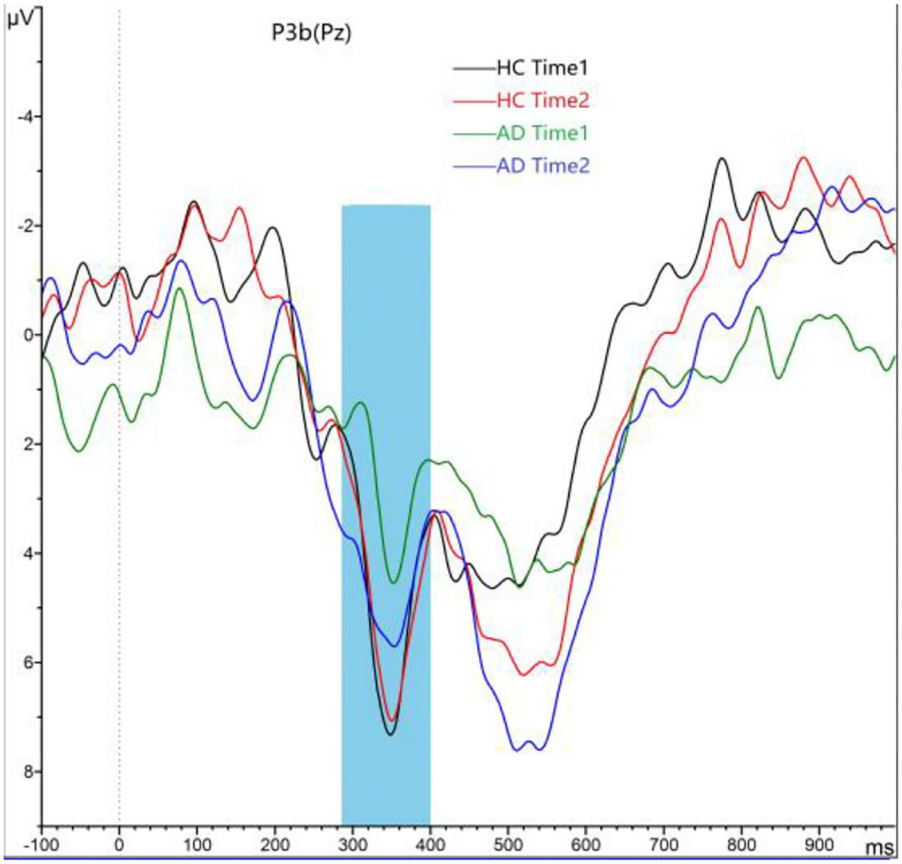

FIGURE 4 | Grand averaged P3b was elicited by a three-stimulus auditory oddball paradigm for the alcohol dependence (AD) group (purple lines and green lines) and the healthy control (HC) group (black lines and red lines) at time 1 and time 2. The P3b was presented within a 280- to 650-ms latency window at the Pz electrode site. The gray area is timeframe.

and those of the people in the HC group. The HAMA and HAMD scores were higher in the AD group than in the HC group; however, no significant differences were observed.

Event-Related Potential Data Analysis

ERP data from the AD group and the HC group are shown in **Table 2**. In this study, using P3a and P3b as dependent variables, a 2 × 2 repeated-measures ANOVA on mean amplitudes and the mean latencies with group (AD group vs. HC group) as a between-subjects factor and time point (time 1 vs. time 2) as a within-subjects factor, was performed.

P3a Component

As shown in **Figures 2**, **3**, for P3a amplitude, the interaction effect for group × time point was significant ($F_{1, 58} = 38.573$, $p < 0.001$). The simple effect for group at time 1 level and time 2 level was significant ($F_{1, 58} = 107.482, 18.006$, all $p < 0.001$). The simple effect for time point at AD group level was significant ($F_{1, 58} = 40.385$, $p < 0.001$). However, the simple effect for time point at HC group level was not significant ($F_{1, 58} = 1.875$, $p = 0.181$). Compared to HCs, AD patients present reductions of P3a amplitude, and after 4-week alcohol abstinence, although P3a amplitudes were improved, they were still lower than those of HCs.

For P3a latency, the interaction effect for group × time point was not significant ($F_{1, 58} = 1.123$, $p = 0.298$), and the main effect for time point was not significant ($F_{1, 58} = 0.238$, $p = 0.630$); the main effect for group was not significant ($F_{1, 58} = 2.150$, $p = 0.153$).

P3b Component

As shown in **Figures 4**, **5**, for P3b amplitude, the interaction effect for group × time point was significant ($F_{1, 58} = 10.968$, $p = 0.002$). The simple effect for group at time 1 level and time 2 level was significant ($F_{1, 58} = 56.161, 8.817$, $p < 0.001$). The simple effect for time point at AD group level was significant ($F_{1, 58} = 16.782$, $p < 0.001$). However, the simple effect for time point at HC group level was not significant ($F_{1, 58} = 0.240$, $p = 0.628$). Compared to HCs, AD patients present reductions of P3b amplitude, and after 4-week alcohol abstinence, although P3b amplitudes were improved, they were still lower than those of HCs.

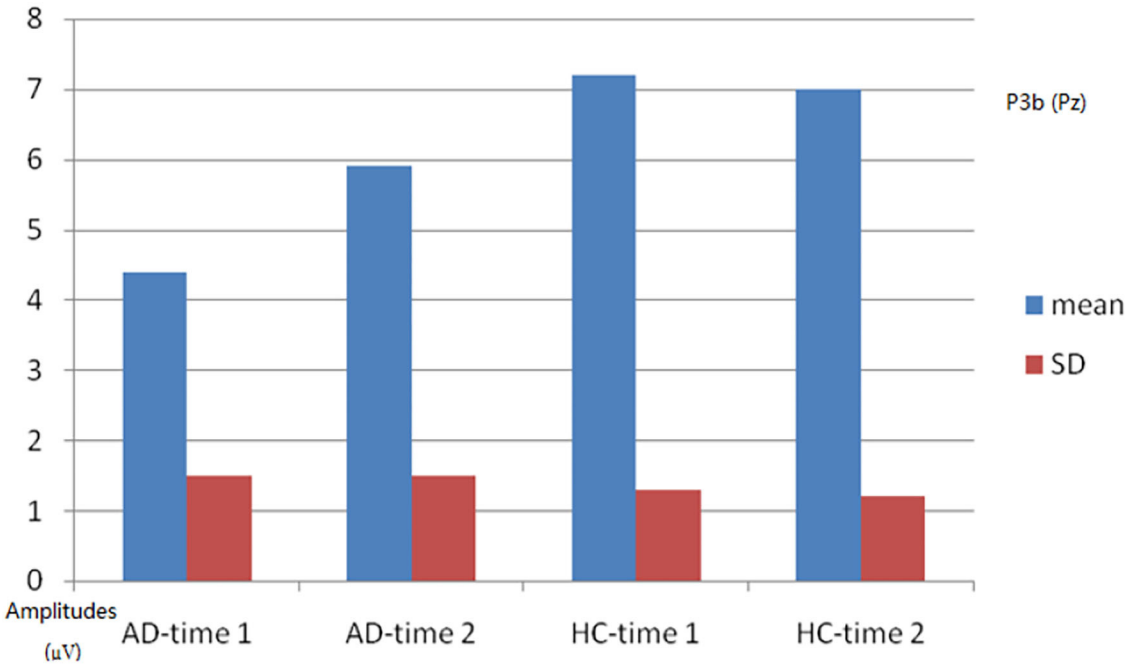

FIGURE 5 | Plot of P3b amplitude analysis. The interaction effect for group × time point was significant; the simple effect for group at time 1 level and time 2 level was significant; the simple effect for time point at the alcohol dependence (AD) group level was significant; the simple effect for time point at the healthy control (HC) group level was not significant.

For P3b latency, the interaction effect for group × time point was not significant ($F_{1, 58} = 0.046$, $p = 0.831$), and the main effect for time point was not significant ($F_{1, 58} = 0.180$, $p = 0.674$); the main effect for group was not significant ($F_{1, 58} = 0.523$, $p = 0.475$).

DISCUSSION

This study investigated whether cognitive control deficits, which are reflected by P3a/3b deficits, in AD are present primarily just after the last alcohol intake (i.e., state-dependent) or are associated with the disorder (i.e., trait-dependent) in a longitudinal study. We compared P3a/3b amplitudes and latencies between AD patients across different stages of illness, i.e., a normal state (just after the last alcohol intake) vs. abstinence (just after 4-week abstinence). Our study results showed that compared to HCs, AD patients present reductions of P3a/3b amplitude, and after 4-week alcohol abstinence, although P3a/3b amplitudes were improved, they were still lower than those of HCs.

Many studies have manifested that the reduced P3a/3b amplitude exists in AD patients (25–29). Additionally, studies have confirmed that P300 amplitude is an endophenotype of AD risk (30, 31). Family-based association analysis shows the ACN9 gene is significantly associated with AD and P300 amplitude variation (32). Consistent with previous study findings, we discovered a relatively reduced P3a/3b amplitude in AD patients compared to HCs at a normal state (just after the last alcohol intake). In addition, this study showed that even in AD patients who appear to be rather stable in the abstinence period (just after the 4-week abstinence), P3a/3b amplitudes are still lower than those in HCs. Our results support a trait-dependent view on cognitive control deficits in AD patients, which suggests that cognitive control deficits may be a useful target for genetic studies in AD.

In support of a more state-dependent view of the illness, this study demonstrated that AD patients who stayed in the abstinence period (just after 4-week abstinence) improved in their P3a/3b amplitudes; however, those amplitudes were still lower than those of HCs. These results are in agreement with those of a previous study showing that the P3b amplitudes were significantly reduced in treatment-naive AD patients but were dramatically smaller than those observed in treated AD patients (33). Other studies have shown that the reduced P3a/3b amplitudes are no longer detectable when an internalized psychiatric comorbidity is taken into account (34). Furthermore, a previous study revealed that P3b amplitude is negatively correlated with a history of externalizing behaviors in patients with substance use disorder (35). Together with the above findings, our results indicate that cognitive control deficits are also state-dependent.

Previous studies showed that some drugs affecting substance abuse, like olanzapine or lithium, might persist in the body for more than 2 weeks and might affect the results found (36, 37). In the present study, we made a survey to all patients with AD,

and they did not receive any medication for 8 weeks prior to the study; therefore, our findings were not affected by other drugs.

In conclusion, AD patients present cognitive control deficits that are reflected by ERP P3a/3b, and cognitive control deficits in AD are trait- and state-dependent. These findings suggest that improving the cognitive control function may impact the treatment effect for AD.

There are some limitations in this study. First, because of the small sample size, the study results must be considered preliminary. Future studies with larger sample sizes and the same ERP parameters are needed to verify the outcome of this study. Second, in the present study, since all participants were male, the results may be influenced by gender bias. In future research, we will consider adding female samples to verify the results of the present study. Third, owing to the deficient spatial resolution of P300, further studies with fMRI or positron emission tomography (PET) should be conducted to investigate whether cognitive control deficits in AD are trait- or state-dependent.

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 Ethics Committee on Human Studies, the Affiliated Wuxi Mental Health Centre of Nanjing Medical University, Wuxi, Jiangsu Province, China. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XL and HZ contributed to data curation, formal analysis, methodology, writing the original draft, and writing, review, and editing. XL, HZ, CJ, YX, ZZ, and JW contributed to data curation, formal analysis, and methodology. ZZ contributed to data curation, formal analysis, methodology, and writing, review, and editing. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by the National Natural Science Foundation, China (No. 81471354) and Key Talents Project Foundation for Medical and Health Services, Jiangsu Province (No. ZDRCC2016019).

ACKNOWLEDGMENTS

We thank the editors and reviewers of this manuscript for many helpful suggestions.

REFERENCES

1. Rouault M, Koechlin E. Prefrontal function and cognitive control: from action to language. *Curr Opin Behav Sci.* (2018) 21:106–11. doi: 10.1016/j.cobeha.2018.03.008
2. Kelley R, Flouty O, Emmons EB, Kim Y, Kingyon J, Wessel JR, et al. A human prefrontal-subthalamic circuit for cognitive control. *Brain.* (2018) 141:205–16. doi: 10.1093/brain/awx300
3. Schmaal L, Goudriaan AE, Joos L, Krüse AM, Dom G, Van Den Brink W, et al. Modafinil modulates resting-state functional network connectivity and cognitive control in alcohol-dependent patients. *Biol Psychiatry.* (2013) 73:789–95. doi: 10.1016/j.biopsych.2012.12.025
4. Li CS, Luo X, Yan P, Bergquist K, Sinha R. Altered impulse control in alcohol dependence: neural measures of stop signal performance. *Alcohol Clin Exp Res.* (2009) 33:740–50. doi: 10.1111/j.1530-0277.2008.00891.x
5. Lim AC, Cservenka A, Ray LA. Effects of alcohol dependence severity on neural correlates of delay discounting. *Alcohol Alcohol.* (2017) 52:506–15. doi: 10.1093/alcalc/agx015
6. Courtney KE, Ghahremani DG, Ray LA. Fronto-striatal functional connectivity during response inhibition in alcohol dependence. *Addict Biol.* (2013) 18:593–604. doi: 10.1111/adb.12013
7. Luck SJ, Mathalon DH, O'donnell BF, Hämäläinen MS, Spencer KM, Javitt DC, et al. A roadmap for the development and validation of event-related potential biomarkers in schizophrenia research. *Biol Psychiatry.* (2011) 70:28–34. doi: 10.1016/j.biopsych.2010.09.021
8. Simonetti A, Lijffijt M, Kahlon RS, Gandy K, Arvind RP, Amin P, et al. Early and late cortical reactivity to passively viewed emotional faces in pediatric bipolar disorder. *J Affect Disord.* (2019) 253:240–7. doi: 10.1016/j.jad.2019.04.076
9. Kreusch F, Quertemont E, Vilenne A, Hansenne M. Alcohol abuse and ERP components in Go/No-go tasks using alcohol-related stimuli: impact of alcohol avoidance. *Int J Psychophysiol.* (2014) 94:92–9. doi: 10.1016/j.ijpsycho.2014.08.001
10. Dien J, Spencer KM, Donchin E. Parsing the late positive complex: mental chronometry and the ERP components that inhabit the neighborhood of the P300. *Psychophysiology.* (2004) 41:665–78. doi: 10.1111/j.1469-8986.2004.00193.x
11. Polich J. Updating P300: an integrative theory of P3a and P3b. *Clin Neurophysiol.* (2007) 118:2128–48. doi: 10.1016/j.clinph.2007.04.019
12. Hamidovic A, Wang Y. The P300 in alcohol use disorder: a meta-analysis and meta- regression. *Prog Neuropsychopharmacol Biol Psychiatry.* (2019) 95:109716. doi: 10.1016/j.pnpbp.2019.109716
13. Cuzen NL, Andrew C, Thomas KG, Stein DJ, Fein G. Absence of P300 reduction in South African treatment-naïve adolescents with alcohol dependence. *Alcohol Clin Exp Res.* (2013) 37:40–48. doi: 10.1111/j.1530-0277.2012.01837.x
14. Chen Y, Norton D, Mcbain R. Trait and state markers of schizophrenia in visual processing. In: Ritsner MS, editor. *The Handbook of Neuropsychiatric Biomarkers, Endophenotypes and Genes: Neuropsychological Endophenotypes and Biomarkers*. Dordrecht: Springer Netherlands (2009). p. 211–20.
15. Sher KJ, Walitzer KS, Wood PK, Brent EE. Characteristics of children of alcoholics: putative risk factors, substance use and abuse, and psychopathology. *J Abnorm Psychol.* (1991) 100:427–48. doi: 10.1037/0021-843X.100.4.427
16. Glahn DC, Lovallo WR, Fox PT. Reduced amygdala activation in young adults at high risk of alcoholism: studies from the Oklahoma family health patterns project. *Biol Psychiatry.* (2007) 61:1306–9. doi: 10.1016/j.biopsych.2006.09.041

17. Donzuso G, Cerasa A, Gioia MC, Caracciolo M, Quattrone A. The neuroanatomical correlates of anxiety in a healthy population: differences between the State-Trait Anxiety Inventory and the Hamilton Anxiety Rating Scale. *Brain Behav.* (2014) 4:504–14. doi: 10.1002/brb3.232
18. Balon R. Rating scales for anxiety/anxiety disorders. *Curr Psychiatry Rep.* (2007) 9:271–7. doi: 10.1007/s11920-007-0032-8
19. Stockwell T, Murphy D, Hodgson R. The severity of alcohol dependence questionnaire: its use, reliability and validity. *Br J Addict.* (1983) 78:145–55. doi: 10.1111/j.1360-0443.1983.tb05502.x
20. Cheng W-J, Huang M, Huang P, Gau Y-F, Chen C-H. The Chinese version of the severity of alcohol dependence questionnaire: reliability and factor structure. *Taiwan J Psychiatry.* (2009) 23:159–66. doi: 10.29478/TJP.200906.0008
21. Monaghan CK, Brickman S, Huynh P, Öngür D, Hall MH. A longitudinal study of event related potentials and correlations with psychosocial functioning and clinical features in first episode psychosis patients. *Int J Psychophysiol.* (2019) 145:48–56. doi: 10.1016/j.ijpsycho.2019.05.007
22. Polich J, Criado JR. Neuropsychology and neuropharmacology of P3a and P3b. *Int J Psychophysiol.* (2006) 60:172–85. doi: 10.1016/j.ijpsycho.2005.12.012
23. Comerchero MD, Polich J. P3a and P3b from typical auditory and visual stimuli. *Clin Neurophysiol.* (1999) 110:24–30. doi: 10.1016/S0168-5597(98)00033-1
24. Annett M. A classification of hand preference by association analysis. *Br J Psychol.* (1970) 61:303–21. doi: 10.1111/j.2044-8295.1970.tb01248.x
25. Carlson SR, Iacono WG, Mcgue M. P300 amplitude in adolescent twins discordant and concordant for alcohol use disorders. *Biol Psychol.* (2002) 61:203–27. doi: 10.1016/S0301-0511(02)00059-5
26. Hill SY, Jones BL, Holmes B, Steinhauer SR, Zezza N, Stiffler S. Cholinergic receptor gene (CHRM2) variation and familial loading for alcohol dependence predict childhood developmental trajectories of P300. *Psychiatry Res.* (2013) 209:504–11. doi: 10.1016/j.psychres.2013.04.027
27. Hesselbrock V, Bauer L, O'connor S, Gillen R. Reduced P300 amplitude in relation to family history of alcoholism and antisocial personality disorder among young men at risk for alcoholism. *Alcohol Alcohol Suppl.* (1993) 2:95–100.
28. Hill SY, Shen S. Neurodevelopmental patterns of visual P3b in association with familial risk for alcohol dependence and childhood diagnosis. *Biol Psychiatry.* (2002) 51:621–31. doi: 10.1016/S0006-3223(01)01301-4
29. Chen ACH, Porjesz B, Rangaswamy M, Kamarajan C, Tang Y, Jones KA, et al. Reduced frontal lobe activity in subjects with high impulsivity and alcoholism. *Alcohol Clin Exp Res.* (2007) 31:156–65. doi: 10.1111/j.1530-0277.2006.00277.x
30. Wright MJ, Luciano M, Hansell NK, Montgomery GW, Geffen GM, Martin NG. QTLs identified for P3 amplitude in a non-clinical sample: importance of neurodevelopmental and neurotransmitter genes. *Biol Psychiatry.* (2008) 63:864–73. doi: 10.1016/j.biopsych.2007.09.002
31. Polich J, Pollock VE, Bloom FE. Meta-analysis of P300 amplitude from males at risk for alcoholism. *Psychol Bull.* (1994) 115:55–73. doi: 10.1037/0033-2909.115.1.55
32. Hill SY, Jones BL, Zezza N, Stiffler S. ACN9 and alcohol dependence: family-based association analysis in multiplex alcohol dependence families. *Am J Med Genet B Neuropsychiatr Genet.* (2015) 168b:179–87. doi: 10.1002/ajmg.b.32295
33. Fein G, Andrew C. Event-related potentials during visual target detection in treatment-naïve active alcoholics. *Alcohol Clin Exp Res.* (2011) 35:1171–9. doi: 10.1111/j.1530-0277.2011.01450.x
34. Hill SY, Locke J, Steinhauer SR. Absence of visual and auditory P300 reduction in nondepressed male and female alcoholics. *Biol Psychiatry.* (1999) 46:982–9. doi: 10.1016/S0006-3223(99)00054-2
35. Bauer LO. CNS recovery from cocaine, cocaine and alcohol, or opioid dependence: a P300 study. *Clin Neurophysiol.* (2001) 112:1508–15. doi: 10.1016/S1388-2457(01)00583-1
36. Sani G, Kotzalidis GD, Vöhringer P, Pucci D, Simonetti A, Manfredi G, et al. Effectiveness of short-term olanzapine in patients with bipolar I disorder, with or without comorbidity with substance use disorder. *J Clin Psychopharmacol.* (2013) 33:231–5. doi: 10.1097/JCP.0b013e318287019c
37. Clark DC, Fawcett J. Does lithium carbonate therapy for alcoholism deter relapse drinking? *Recent Dev Alcohol.* (1989) 7:315–28. doi: 10.1007/978-1-4899-1678-5_16

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.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 28 January 2021
doi: 10.3389/fpsyt.2021.628933

Monetary Reward Discounting, Inhibitory Control, and Trait Impulsivity in Young Adults With Internet Gaming Disorder and Nicotine Dependence

Wan-Sen Yan, Ruo-Ting Chen, Meng-Meng Liu and Dan-Hui Zheng*

Department of Psychology, School of Medical Humanitarians, Guizhou Medical University, Guiyang, China

Internet Gaming Disorder (IGD) has been considered a potential behavioral or non-substance addiction that requires further investigation. Recognition of the commonalities between IGD and Substance Use disorders (SUD) would be of great help to better understand the basic mechanisms of addictive behaviors and excessive Internet gaming. However, little research has targeted a straightforward contrast between IGD and SUD on neuropsychological aspects. The present study thus aimed to explore the associations of reward processing and inhibitory control with IGD and nicotine dependence (ND) in young adults. Fifty-eight IGD and 53 ND individuals, as well as 57 age- and gender-matched healthy controls, were assessed with a series of measurements including the Delay-discounting Test (DDT), Probability Discounting Test (PDT), the Stroop Color-Word Task, a revised Go/No Go Task, and the Barratt Impulsiveness Scale (BIS-11). Multivariate analysis of variance (mANOVA) models revealed that both IGD and ND groups scored higher than healthy controls on the BIS-11 attentional, motor, and non-planning impulsiveness (Cohen's $d = 0.41–1.75$). Higher degrees of delay discounting on the DDT were also found in IGD and ND groups compared to healthy controls (Cohen's $d = 0.53–0.69$). Although IGD group did not differ from healthy controls on the PDT, ND group had a lower degree of probability discounting than healthy controls (Cohen's $d = 0.55$), suggesting a reduction in risk aversion. Furthermore, ND subjects showed a lower correct accuracy in the incongruent trials of the Stroop task than healthy controls (Cohen's $d = 0.61$). On the Go/No Go task, both IGD and ND groups had a lower correct accuracy in the No-Go trials than healthy controls (Cohen's $d = 1.35–1.50$), indicating compromised response inhibition. These findings suggested that IGD was linked to both anomalous reward discounting and dysfunctional inhibitory control, which was comparable with one typical SUD category (i.e., ND). This study might promote a better understanding of the pathogenesis of IGD as a potential addictive disorder similar to SUD.

Keywords: Internet Gaming Disorder, Nicotine Dependence, inhibitory control, reward discounting, impulsivity

OPEN ACCESS

Edited by:
Xingchao Wang,
Shanxi University, China

Reviewed by:
Marco Di Nicola,
Catholic University of the Sacred Heart, Italy
Hollis C. Karoly,
Colorado State University, United States

****Correspondence:***
Wan-Sen Yan
yanwansen@163.com

Specialty section:
This article was submitted to Addictive Disorders, a section of the journal Frontiers in Psychiatry

Received: *13 November 2020*
Accepted: *05 January 2021*
Published: *28 January 2021*

Citation:
Yan W-S, Chen R-T, Liu M-M and Zheng D-H (2021) Monetary Reward Discounting, Inhibitory Control, and Trait Impulsivity in Young Adults With Internet Gaming Disorder and Nicotine Dependence. Front. Psychiatry 12:628933. doi: 10.3389/fpsyt.2021.628933

INTRODUCTION

Internet Gaming Disorder (IGD) has been included as a tentative behavioral or non-substance addiction that warrants further research before it can be accepted as a full disorder in the latest revision of the Diagnostic and Statistical Manual of Mental Disorders (i.e., DSM-5) (1). More recently, IGD was proposed in the list of addictive conditions and was formally recognized as Gaming Disorder in the 11th revision of the International Classification of Diseases (i.e., ICD-11) (2–4). Both in the DSM-5 and ICD-11, IGD is characterized by a pattern of persistent and disordered gaming behavior, which leads to significant clinical impairments within a period of at least 12 months (5, 6). To be diagnosed as IGD in the DSM-5, five of the nine diagnosis criteria (i.e., preoccupation, withdrawal, tolerance, loss of control, loss of interest or giving up other activities, continued overuse, deception, escape of negative feelings, negative consequences) must be endorsed within a 12-month period (1). Prevalence estimates of IGD among general samples have been always below 5% (7, 8), with a low of 0.5% and a high of 10% (9). In recent meta-analysis studies, the global prevalence of IGD was reported to be about 3.05% with significant variability (10), ranging from 0.21 to 57.5% in general populations, 3.2–91.0% in clinical populations, and 50.42–79.25% in populations undergoing intervention (i.e., severe cases) (11).

As a putative non-substance addiction, IGD has led to a large number of issues, concerns, and scientific dialogues from experts in the field (12–16). Although IGD seems to share many clinical manifestations with Substance Use disorders (SUD) in terms of etiology, biology, and treatment (13, 17–19), it remains a highly controversial topic whether IGD should qualify as a new clinical disorder (12, 20, 21), and a wider range of empirical studies are needed to clarify the theoretical underpinnings of IGD (2). In a manner, understanding the biological, psychological, and social processes underlying different forms of addictive behaviors stands to capture the core elements of IGD, such as on the commonalities and distinctions between IGD and SUD (22).

However, little research by now has targeted a straightforward contrast between IGD and other well-identified addictions on neuropsychological aspects. Considering the core features of impulsivity and compulsivity involved in addictive behaviors, one prior study has tried to detect the similarities and differences among male patients with IGD, Gambling Disorder (GD), and Alcohol Use Disorder (AUD) compared to healthy controls with a small sample size (23). It was reported that the IGD and AUD groups had higher impulsivity scores on the Barratt Impulsiveness Scale (BIS-11) and showed decreased proportions of successful stops on the Stop-Signal Test than the healthy controls, while only the GD group made more errors on the compulsivity test (i.e., the Intra-Extra Dimensional Set Shift Test) compared with healthy controls (23). Another latest study assessed trait impulsivity, delay discounting, and decision making between patients with IGD and GD compared to healthy controls, reporting that IGD and GD groups did not differ from healthy controls on the BIS-11, but both groups displayed a steeper delay curve (i.e., a higher discounting degree) on the Delay Discounting Task (DDT) (24). Despite these preliminary evidence, recognition of the commonalities between IGD and SUD/GD would be of great help to better understand the basic mechanisms of IGD from a cross-spectrum view (25).

Relative to other populations, adolescents and young adults have been found to be more susceptible to IGD because of their age-related immaturity of cognitive control as well as their easy access to the Internet during this period (26–31). Analogously, cigarette smoking behavior (or even worse, Nicotine Dependence) as one kind of SUD categories has also been available and increasing in youths from middle schools to universities (32–35), sometimes equally between males and females (36). In many cases, Nicotine Dependence (ND) and IGD tend to co-occur in young men (37, 38), and there is a high co-occurrence of cigarette smoking with IGD in both adults and adolescents (39). Interestingly, although significant correlations of IGD with various forms of SUD including nicotine, alcohol, caffeine, and cannabis use were found in the adult and elder populations (39), cigarette smoking, rather than other substance use, was strongly associated with IGD in the adolescent and younger populations (40). Moreover, cue-induced smoking craving and gaming urge showed similar neurobiological correlates (e.g., higher parahippocampus activation) in young adult subjects comorbid with ND and IGD (37), and young ND and IGD individuals shared decreased resting-state functional connectivity of the dorsolateral prefrontal cortex with the right insula and left inferior frontal gyrus, which are related to craving and impulsive inhibitions (41). Nevertheless, the common and distinct aspects of neuropsychological characteristics between IGD and ND are not well-acknowledged given the scarce evidence with a direct comparison between them.

According to recent neurocognitive models of addiction, the neural substrates implicated in addictive behaviors might include multiple brain systems that govern reward seeking/risk taking, craving and cognitive control (42, 43). Indeed, individuals with IGD are often characterized by heightened reward-seeking, persistent craving, and decreased executive control (44–46). Furthermore, the developmental theories of adolescent brains highlighted the imbalance between a salient reward-seeking system and a hypoactive executive-control system, which is closely associated with various risky behaviors including IGD during adolescence and early adulthood (47, 48). Thus, it is necessary to extend the neurocognitive underpinnings of IGD by evaluating both reward processing and cognitive control among adolescents and young adults with IGD, especially in direct contrast to those with other addictive behaviors (e.g., ND).

The Delay-discounting Test (DDT) (49) is a widely-used reward choice task that assesses the ability of delay of gratification by choosing between immediate and prospective monetary rewards (50). Similarly, the Probability Discounting Test (PDT) (51) evaluates the propensity of taking a risk for gaining more valuable rewards by choosing between one smaller reward delivered "for sure" and another larger but probabilistic reward (52). Previous case-control studies have consistently revealed a higher degree of delay discounting among adolescents and young adults with IGD (53–58), though some data showed no differences between problematic and normal Internet users on the DDT (25). More interestingly, treatment seekers diagnosed

with IGD displayed a similar tendency on discounting long-term rewards faster with those diagnosed with gambling disorder (24). In heavy smokers and nicotine-dependent individuals, greater delay-discounting rates were also found (59–63), and the degree of delay discounting was significantly related to the severity of ND (64, 65). However, regarding probability discounting, limited data have been discrepant. Some studies showed that IGD participants preferred the probabilistic rewards to those delivered "for sure," compared to recreational Internet game users and healthy controls (66–68). Nonetheless, some adolescents and college students with IGD revealed no differences on the PDT compared to healthy controls (53, 54). Analogously, some data revealed that heavy smokers showed a shallower rate of probability discounting than never- smokers (63, 68), while more studies displayed no differences between heavy/habitual smokers and never-smokers on the PDT (60, 69–71), and acute smoking abstinence did not reveal an increase in probability discounting of money or cigarettes (72).

Together with reward processing, cognitive control is believed to play a critical role in the transition from recreational drug use to drug addiction, given the fact that some individuals who use addictive drugs finally develop an addiction while others do not (73–77). Abnormalities in cognitive control have been observed in IGD samples (67, 78, 79), accompanied by neural alterations in the prefrontal regions (18, 80, 81). Although cognitive control consists of a series of cognitive processes that regulate goal-directed actions and adaptive responses to complex situations, such as response inhibition, performance monitoring, and working memory (82), most studies concerning IGD mainly investigated inhibitory control or response inhibition (83, 84). Previous studies revealed that adolescents with IGD committed more errors in the incongruent conditions than healthy controls on the Stroop tasks (85–88). Adolescents and young adults with IGD also made more commission errors in no-go trials on the Go/No-Go tasks, and showed longer stop-signal reaction time (SSRT) on the Stop- Signal tasks (23, 31, 89, 90). Nevertheless, some studies did not reveal differences on the Go/No-Go task between IGD and healthy control groups (91–93). Except for the diverse samples, these inconsistent results might also be due to the mixed processing of both stimulus-driven attentional bias and response inhibition in the Go/No-Go task itself (i.e., novelty from 25% No-Go trials vs. 75% Go trials). A newly modified Go/No-Go task, containing 75% frequent-Go trials, 12.5% infrequent-Go trials, and 12.5% No-Go trials, has been developed to directly detect response inhibition (94). A clear association between inhibitory control taxed by this novel task and smoking relapse vulnerability was revealed in treatment-seeking smokers (95). Nonetheless, deficits in inhibitory control were not consistently found in ND. Some data revealed that inhibitory control performance was negatively correlated with smoking behavior (96, 97), and subjects with ND showed impaired inhibitory control following 12-h abstinence (98). However, heavy smokers and non-smokers displayed no differences on the classical Go/No-Go tasks (99, 100), though smokers committed more errors on the Stroop task (101). Given the mixed tasks used in the literature and no direct comparison between IGD and ND, it remains unclear whether inhibitory control dysfunctions are simultaneously connected to IGD and ND in young adults.

Therefore, the main purpose of this current study was to gather more empirical evidence about the associations of reward processing and inhibitory control with both IGD and ND among young adults, targeting a straightforward contrast between IGD individuals, ND individuals, and healthy controls on the Delay-discounting Test (DDT), the Probability Discounting Test (PDT), the Stroop Color-Word Task, and the revised Go/No Go Task. Besides, we also employed the Barratt Impulsiveness Scale (BIS-11) to test trait impulsivity, considering the inconsistent BIS-11 data between IGD and other addictive disorders (23, 24). We generally hypothesized that as a putative non-substance addiction, IGD might share an aberrant pattern of inhibitory control and reward discounting with ND that is one typical kind of SUD categories.

METHODS

Participants and Procedure

A total of 168 young adult subjects participated in this study, including 58 individuals with Internet Gaming Disorder (IGD; mean age: 20.19 ± 1.42 years; 35 males, 60.3%), 53 individuals with Nicotine Dependence (ND; mean age: 20.64 ± 1.72 years; 33 males, 62.3%), and 57 age- and gender-matched healthy controls (HC; mean age: 20.19 ± 1.41 years; 36 males, 63.2%). All of them were college students recruited during April and September 2019, through advertisement and flier from two local universities in Guiyang City, China. Participants were invited to complete a person-to-person screening interview conducted by an experienced psychiatrist and a well-trained clinical psychologist in the laboratory, and then they finished a battery of questionnaires and cognitive tasks when enrolled according to the clinical interview.

Inclusion criteria for the IGD group included: (1) ≥18 years of age; (2) meeting five or more of the nine criteria for IGD proposed in the DSM-5 (1); (3) having a score of 50 or more on the Internet Addiction Test (IAT) (102), which indicates severe or problematic Internet use (103); and (4) at least 3 h per day spent on playing Internet games (mainly the Multiplayer Online Battle Arena games, such as the League of Legends, the Arena of Valor, and the Game For Peace/Playerunknown's Battlegrounds) over a 12-month period. The exclusion criteria included current/past major psychiatric disorders (e.g., schizophrenia, bipolar disorder), neurological diseases or mental disorders, brain trauma, use of psychoactive drugs (e.g., cocaine, heroin, methamphetamine), alcohol abuse or dependence, and current/past smoking.

Inclusion criteria for the ND group included: (1) ≥18 years of age; (2) endorsing three or more of the seven criteria for Nicotine Dependence in the DSM-IV-TR (104); (3) having a score of 4 or more on the Fagerström Test for Nicotine Dependence (FTND) (105), which is determined as high nicotine dependence (106, 107); and (4) daily smoking with at least 10 cigarettes over a 12-month period. Moreover, the ND group should have no history of regular Internet gaming, with a score of <40 on the IAT indicating normal Internet use (103). The exclusion criteria

were same as those for the IGD group (except for the criterion of current/past smoking).

The healthy controls met the following criteria: (1) ≥18 years of age; (2) a score of <40 on the IAT and no experience of Internet gaming; (3) non-smoking and a score of 0 on the FTND; and (4) no current/past major psychiatric disorders, neurological diseases or mental disorders, brain trauma, use of psychoactive drugs, alcohol abuse or dependence. All subjects were right-handed and had normal or rectified eyesight, without any color vision deficiency. All of them gave written informed consent and were compensated with a gift equal to RMB ¥ 50 for their time. The current study was reviewed and approved by the Human Research Ethics Committee at the Guizhou Medical University. The proposed study design, recruitment process, and our plans to compensate the participants were in accordance with the Declaration of Helsinki.

Monetary Reward Discounting Tasks

We used the Delay-discounting Test (DDT) (49) and Probability Discounting Test (PDT) (51) to assess discounting degrees of rewards in the context of monetary choice. The DDT contains a set of choices between a smaller immediate reward and a larger delayed reward. The degree of delay discounting is calculated by the hyperbolic equation $V = A/(1+kD)$. In this equation, k is a free parameter, with a larger k-value describing a higher degree of delay discounting. An adapted version of DDT among Chinese students (108) was used in this study, as reported in our previous studies (25, 109). Examples of choices on this task are "A: receiving RMB ¥1000 now; B: receiving RMB ¥10000 one year later" and "A: receiving RMB ¥9000 now; B: receiving RMB ¥10000 one year later." The k-value was calculated and log-transformed in keeping with the literature. The PDT consists of three parts (i.e., Part A: $20 vs. $80; Part B: $40 vs. $100; Part C: $40 vs. $60), with 10 choices in each part. Subjects have to choose between a smaller amount of money delivered "for sure" and a larger amount of money delivered probabilistically. Examples of choices are "A: $20 for sure; B: a 1-in-10 chance/10% of winning $80" and "A: $40 for sure; B: a 5-in-10 chance/50% of winning $100." This task has been properly used in our previous study reported elsewhere (109). The degree of probability discounting is calculated by the equation $V = A/(1+h\Theta)$, in which the free parameter h refers to the degree of probability discounting. Lower h indicates that the probabilistic rewards are less steeply discounted, thus suggesting a reduction in risk aversion or a higher level of risk-taking (51). The h scores in each part were calculated and log-transformed to get a normal distribution as suggested before.

Inhibitory Control Tasks

The standard Stroop Color-Word Task (110) was used to measure respond inhibition under cognitive interference condition. In this task, participants are instructed to name the color of the words that are printed in a certain ink. There are two kinds of trials. In congruent trials, the word is printed in a concordant color (e.g., the word RED printed in red ink), while in the incongruent trials, the word-color pairs are always conflicting (e.g., the word RED printed in green ink). In our study, the colored words were presented on the black screen in a 7 × 7 cm size. Each word was presented for 1350ms, with a total interstimulus interval of 2000ms, according to previous studies (111). There were 54 word-color pairs each in the congruent and incongruent trials, and the task lasted for about 6 min. Subjects had 8 trails to check up on the response keys (e.g., "1" for RED, "2" for GREEN) before formal experiments. This task was programmed using the E-prime Version 2.0 (Psychology Software Tools, Inc., Sharpsburg, PA, USA). Response time (RT) and correct accuracy in the congruent and incongruent trials were analyzed.

A modified and validated Go/No Go Task (94, 95) was employed to investigate inhibitory control or response inhibition. This task was designed to separate the processing of infrequent stimuli (e.g., stimulus-driven attention) from inhibitory processes by including three different types of colored circles: frequent-go trials (frequent gray, $n = 388$, about 75%), infrequent-go trials (rare yellow, $n = 65$, about 12.5%), and no-go trials (rare blue, $n = 65$, about 12.5%). The contrast of the no-go trials vs. the infrequent-go trials was expected to detect the process of response inhibition. In this task, a colored circle was presented on the black screen for 400 ms with a 400-ms interstimulus interval over 7 min. Participants were told to press a button as quickly as possible with the right index finger in response to gray and yellow circles, but to withhold a response to blue circles. The frequent-go, infrequent-go, and no-go trials were intermixed in pseudo-random order. Prior to the formal experiments, subjects practiced 30 filler trials (10 gray, 10 yellow, and 10 blue circles). This task was also programmed using the E-prime Version 2.0. Reported no-go accuracy was adjusted, including just those no-go trials with a correct response to the preceding go trial, to control for the effects of attentional lapses (94, 95).

Trait Impulsivity Measurement

The Barratt Impulsiveness Scale-11 (BIS-11) (112) was employed to measure impulsive traits on three dimensions (Motor Impulsiveness, Attentional Impulsiveness, Non-planning Impulsiveness). Each dimension consists of 8 or 11 items that are rated on a 4-point scale (1 = rarely/never, 4 = almost always/always). Scores of each dimension were obtained for analyses, with higher scores indicating higher levels of trait impulsivity. Cronbach's α was 0.69–0.81 for the three dimensions in this study.

Data Analysis

All data were analyzed with the Statistical Package for the Social Sciences for Windows, Version 19.0 (SPSS Inc., Chicago, IL, USA). Categorical data such as gender, ethnicity, and home locality were analyzed with chi-square tests for group comparisons. The 3 (group: IGD, ND, HC) × 2 (gender: male, female) multivariate analysis of variance (mANOVA) models were used to compare task scores. *Post-hoc* tests were conducted using Fisher's least significant differences protected t-tests. Partial correlations were tested between task performance and gaming/smoking variables in IGD and ND groups, controlling for gender, age, ethnicity, and home locality. Statistical significance was set as $p < 0.05$, two-tailed.

RESULTS

Demographic Characteristics and Trait Impulsivity

Table 1 describes the demographic characteristics and BIS-11 scores of the Internet Gaming Disorder (IGD), Nicotine Dependence (ND), and healthy controls (HC) groups. No between-group differences were detected on age [$F_{(2, 165)}$ =1.597, $p = 0.260$], gender ($\chi^2 = 0.101$, $p = 0.951$), ethnicity ($\chi^2 = 0.211$, $p = 0.900$), or home locality ($\chi^2 = 0.090$, $p = 0.956$). IGD group had a higher IAT score than ND and HC groups [$F_{(2, 165)} = 752.96$, $p < 0.001$]. On the BIS-11, the 3 (group: IGD, ND, HC) × 2 (gender: male, female) mANOVA model revealed significant between-group effects on all of the three dimensions, including Motor Impulsiveness [$F_{(2, 162)} = 8.255$, $p < 0.001$, $\eta_p^2 = 0.092$], Attentional Impulsiveness [$F_{(2, 162)} = 44.111$, $p < 0.001$, η_p^2 =0.353], and Non-planning Impulsiveness [$F_{(2, 162)} = 5.867$, $p = 0.003$, $\eta_p^2 = 0.068$]. Pairwise comparisons showed that both IGD and ND groups scored higher than healthy controls on Motor Impulsiveness (Cohen's $d = 0.78$, $p < 0.001$; Cohen's $d = 0.53$, $p = 0.007$, respectively), Attentional Impulsiveness (Cohen's $d = 1.75$, $p < 0.001$; Cohen's $d = 0.92$, $p < 0.001$, respectively), and Non-planning Impulsiveness (Cohen's $d = 0.64$, $p = 0.001$; Cohen's $d = 0.41$, $p = 0.049$, respectively). The IGD and ND groups did not differ from each other on Motor Impulsiveness ($p = 0.253$) or Non-planning Impulsiveness ($p = 0.172$), but IGD group scored higher than ND group on Attentional Impulsiveness (Cohen's $d = 0.83$, $p < 0.001$). Main effects of gender and interaction effects of group × gender were not significant on any of these dimensions ($ps > 0.05$).

Monetary Reward Discounting

The scores on the delay-discounting and probability-discounting tasks of the IGD, ND, and HC groups are displayed in **Table 2**. The mANOVA models showed that group effects were significant on the DDT score (i.e., log-transformed k value) and on the PDT score (i.e., log-transformed h value) of the Part A [$F_{(2, 162)} = 7.505$, $p = 0.001$, $\eta_p^2 = 0.085$; $F_{(2, 162)} = 7.118$, $p = 0.001$, $\eta_p^2 = 0.081$, respectively], but not on the PDT Part B or Part C scores [$F_{(2, 162)} = 2.975$, $p = 0.054$; $F_{(2, 162)} = 2.674$, $p = 0.072$, respectively]. Pairwise comparisons revealed that both IGD and ND groups had a higher degree of delay discounting (i.e., log-transformed k-value) on the DDT than healthy controls (Cohen's $d = 0.53$, $p = 0.002$; Cohen's $d = 0.69$, $p = 0.001$, respectively), but the difference between IGD and ND groups was not significant ($p = 0.253$). By contrast, ND group had a lower probability-discounting degree (i.e., log-transformed h-value) on the PDT (Part A), compared with healthy controls (Cohen's $d = 0.55$, $p = 0.004$) and IGD group (Cohen's $d = 0.79$, $p < 0.001$), but IGD group did not differ from healthy controls ($p = 0.546$). Main effects of gender and interaction effects of group × gender were not significant on any of the DDT and PDT scores ($ps > 0.05$).

Inhibitory Control Performance

The inhibitory control performance on the Stroop Color-Word Task and Go/No Go Task of the IGD, ND, and HC groups are showed in **Table 3**. On the Stroop task, the mANOVA models revealed that the group effects on correct accuracy were significant in the incongruent trials [$F_{(2, 162)} = 6.351$, $p = 0.002$, $\eta_p^2 = 0.073$] but not in the congruent trials [$F_{(2, 162)} = 2.648$, $p = 0.076$], and the group effects on response time were not significant in the congruent or incongruent trials

TABLE 1 | Demographic characteristics and BIS-11 scores for the three groups.

Variables	a. IGD ($n = 58$)	b. ND ($n = 53$)	c. HC ($n = 57$)	F/χ^2	p	*Post-hoc* test ($p < 0.05$)
Age, years ($M \pm SD$)	20.19 ± 1.42	20.64 ± 1.72	20.19 ± 1.41	1.597	0.206	-
Gender, Male *n* (%)	35 (60.3)	33 (62.3)	36 (63.2)	0.101	0.951	-
Ethnicity, Hans *n* (%)	42 (72.4)	37 (69.8)	42 (73.7)	0.211	0.900	-
Home locality, Urban *n* (%)	34 (58.6)	31 (58.5)	32 (56.1)	0.090	0.956	-
IAT score ($M \pm SD$)	67.83 ± 7.67	33.06 ± 3.88	31.88 ± 4.40	752.96***	<0.001	a>b, a>c
Years of regular gaming ($M \pm SD$)	3.91 ± 1.34	-	-	-	-	-
Daily gaming hours ($M \pm SD$)	5.19 ± 1.92	-	-	-	-	-
FTND score ($M \pm SD$)	0.00 ± 0.00	5.83 ± 1.03	0.00 ± 0.00	-	-	-
Years of smoking ($M \pm SD$)	-	4.89 ± 1.63	-	-	-	-
Cigarettes per day ($M \pm SD$)	-	15.08 ± 6.34	-	-	-	-
BIS-11 SCORE ($M \pm SD$)						
Motor impulsiveness	21.88 ± 3.81	20.87 ± 3.36	19.14 ± 3.20	9.134***	<0.001	a>c, b>c
Attentional impulsiveness	20.36 ± 3.32	17.68 ± 3.16	14.86 ± 2.97	43.874***	<0.001	a>b>c
Non-planning impulsiveness	29.86 ± 4.56	28.66 ± 3.43	27.14 ± 3.93	6.625**	0.002	a>c, b>c

IGD, Internet Gaming Disorder; ND, Nicotine Dependence; HC, Healthy Controls; IAT, Internet Addiction Test; FTND, Fagerström Test for Nicotine Dependence; BIS, Barratt Impulsiveness Scale. $^{**}p < 0.01$, $^{***}p < 0.001$.

TABLE 2 | Discounting degrees of the three groups on the DDT and PDT.

Variables	a. IGD ($n = 58$)	b. ND ($n = 53$)	c. HC ($n = 57$)	*F*	*p*	*Post-hoc* test ($p < 0.05$)
DDT score (*M* ± *SD*)						
k value	0.34 ± 0.22	0.35 ± 0.19	0.25 ± 0.22	3.626*	0.029	a>c, b>c
k value (log-transformed)	−0.60 ± 0.41	−0.55 ± 0.32	−0.85 ± 0.53	7.571**	0.001	a>c, b>c
PDT score (*M* ± *SD*)						
Part A ($20 vs. $80):						
h value	5.61 ± 4.39	3.51 ± 4.02	6.26 ± 4.67	5.870**	0.003	a>b, c>b
h value (log-transformed)	0.62 ± 0.35	0.28 ± 0.50	0.57 ± 0.56	8.009***	<0.001	a>b, c>b
Part B ($40 vs. $100):						
h value	3.66 ± 4.53	2.41 ± 3.09	4.12 ± 3.98	2.773	0.065	-
h value (log-transformed)	0.31 ± 0.45	0.14 ± 0.46	0.37 ± 0.52	3.596*	0.030	c>b
Part C ($40 vs. $60):						
h value	3.35 ± 4.99	1.89 ± 3.32	3.06 ± 4.78	1.643	0.197	-
h value (log-transformed)	0.14 ± 0.54	0.06 ± 0.48	0.16 ± 0.48	3.383*	0.036	c>b

IGD, Internet Gaming Disorder; ND, Nicotine Dependence; HC, Healthy Controls; DDT, Delay-discounting Test; PDT, Probability Discounting Test; k represents the delay-discounting degree, h represents the probability-discounting degree.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

TABLE 3 | Inhibitory control performance on the Stroop and Go/No Go tasks *(M ± SD)*.

Variables	a. IGD ($n = 58$)	b. ND ($n = 53$)	c. HC ($n = 57$)	*F*	*p*	*Post-hoc* test ($p < 0.05$)
Stroop color-word task						
Correct accuracy in CC trials (%)	97.53 ± 1.69	96.72 ± 3.05	97.99 ± 2.09	2.780	0.067	-
Correct accuracy in IC trials (%)	92.80 ± 3.39	90.81 ± 4.66	93.50 ± 4.08	6.454**	0.002	a>b, c>b
Response time in CC trials (ms)	557.8 ± 65.6	568.9 ± 56.1	548.4 ± 56.9	1.617	0.202	-
Response time in IC trials (ms)	642.3 ± 94.8	664.0 ± 86.8	653.9 ± 92.6	0.781	0.460	-
Go/No Go task						
Correct accuracy in frequent-go trials (%)	95.20 ± 3.16	94.75 ± 2.44	95.67 ± 2.96	1.413	0.246	-
Correct accuracy in rare-go trials (%)	93.48 ± 4.18	92.71 ± 4.23	93.82 ± 3.67	1.074	0.344	-
Correct accuracy in no-go trials (%)	61.65 ± 6.60	60.55 ± 6.83	69.85 ± 5.47	36.372***	<0.001	c>a, c>b
Response time in frequent-go trials (ms)	165.0 ± 45.7	164.0 ± 55.2	175.1 ± 29.8	1.070	0.345	-
Response time in rare-go trials (ms)	200.1 ± 32.7	198.4 ± 44.0	209.0 ± 32.2	1.351	0.262	-

IGD, Internet Gaming Disorder; ND, Nicotine Dependence; HC, Healthy Controls; CC, Congruent Condition; IC, Incongruent Condition.
**$p < 0.01$, ***$p < 0.001$.

[$F_{(2, 162)} = 1.104$, $p = 0.334$; $F_{(2, 162)} = 0.682$, $p = 0.507$, respectively]. Pairwise comparisons found that ND group had a lower correct accuracy in the incongruent trials compared with healthy controls (Cohen's $d = 0.61$, $p = 0.001$) and IGD group (Cohen's $d = 0.49$, $p = 0.017$), but IGD group did not differ from healthy controls ($p = 0.250$). Main effects of gender and interaction effects of group × gender were not significant on the correct accuracy and response time ($ps > 0.05$). See **Figure 1A** for a clear portrayal of the Stroop performance.

On the Go/No Go task, the mANOVA models revealed significant group effects on correct accuracy in the no-go trials [$F_{(2, 162)} = 38.160, p < 0.001, \eta_p^2 = 0.320$], but not in the frequent-go trials [$F_{(2, 162)} = 1.085$, $p = 0.350$] or the rare-go trials [$F_{(2, 162)} = 0.986$, $p = 0.375$]. Group effects on response time were not significant in the frequent-go or rare-go trials [$F_{(2, 162)} = 0.884$, $p = 0.415$; $F_{(2, 162)} = 0.939$, $p = 0.393$, respectively). Pairwise comparisons found that both IGD and ND groups had a lower correct accuracy in the no-go trials than healthy controls (Cohen's $d = 1.35$, $p < 0.001$; Cohen's $d = 1.50$, $p < 0.001$, respectively), but the accuracy difference between IGD and ND groups was not significant ($p = 0.332$). Main effects of gender and interaction effects of group × gender were not significant on the Go/No Go accuracy and response time ($ps > 0.05$). See **Figure 1B** for a direct description of the Go/No Go performance.

Correlations Between Gaming/Smoking Variables and Task Performance

Partial correlations were tested between Internet gaming variables (i.e., IAT score, years of regular gaming, daily gaming hours), nicotine use variables (i.e., FTND score, years of smoking,

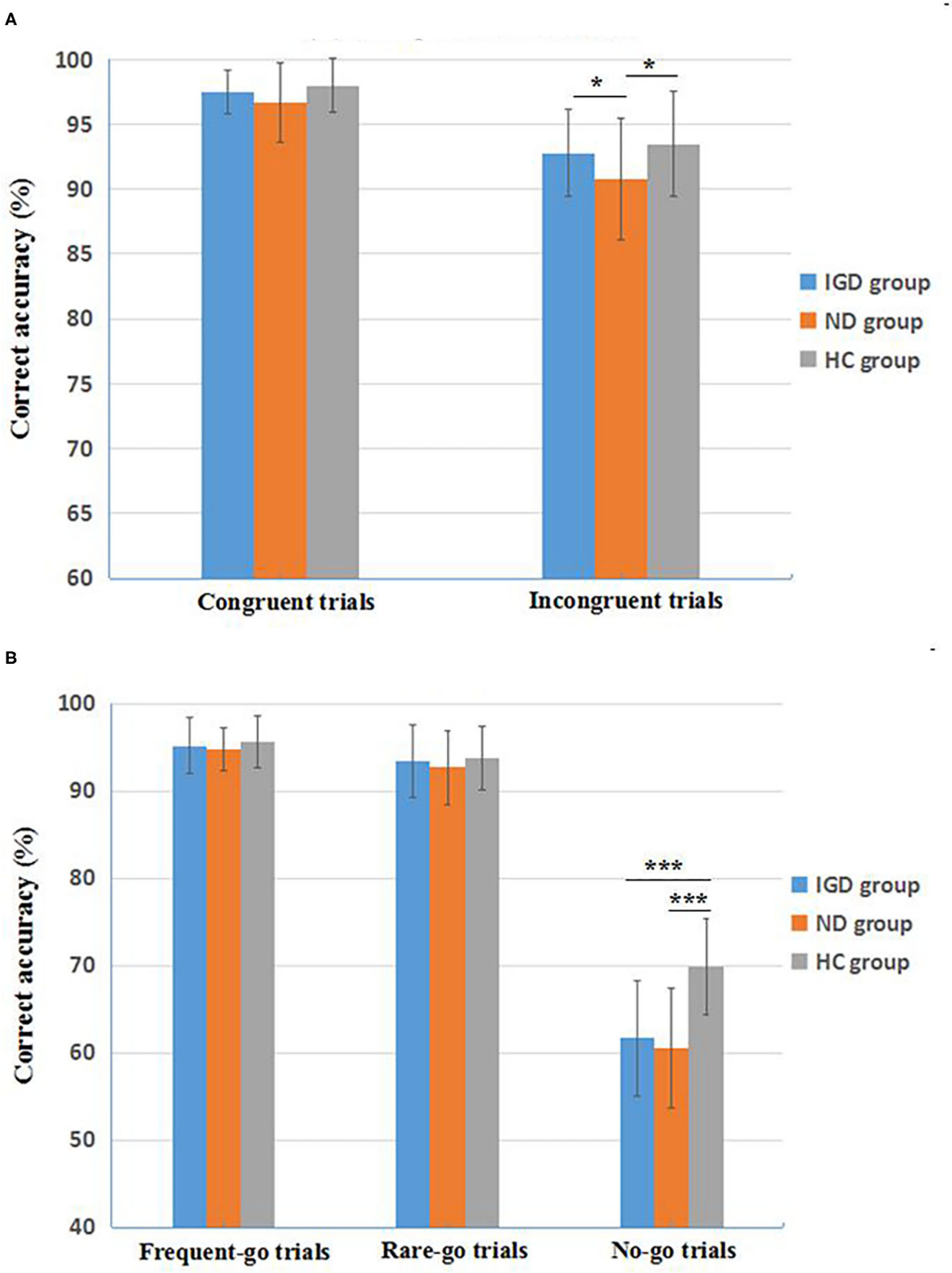

FIGURE 1 | Inhibitory control performance on the Stroop Color-Word Task **(A)** and the revised Go/No Go Task **(B)** of the three groups. IGD, Internet Gaming Disorder; ND, Nicotine Dependence; HC, healthy controls. Data are presented as mean ± standard deviation (*M* ± *SD*). $^{*}p < 0.05$, $^{***}p < 0.001$.

cigarettes per day) and task performance (i.e., BIS-11 scores, DDT and PDT scores, and inhibitory control scores), controlling for gender, age, ethnicity, and home locality. The data showed that most of the correlations were not significant between gaming/smoking variables with trait impulsivity, discounting degrees, and inhibitory control ($ps > 0.05$), except for that of the BIS-11 Non-planning Impulsiveness with FTND score, years of smoking, and cigarettes per day in the ND group ($r_p = 0.267$, $p = 0.05$; $r_p = 0.269$, $p = 0.049$; $r_p = 0.278$, $p = 0.042$, respectively). Please see more details for the partial correlations in the **Supplementary Table 1**.

DISCUSSION

The current study contrasted the characteristics of monetary reward discounting, inhibitory control, and trait impulsivity between Internet Gaming Disorder (IGD) and Nicotine Dependence (ND) individuals, with a well-matched sample of healthy controls as the reference group. To our best knowledge, this is the first study that has targeted a straightforward comparison between IGD and ND on reward processing and cognitive control aspects among young adults. Our data demonstrated that both the IGD and ND groups scored higher on the trait impulsivity (i.e., Motor, Attentional, and Non-planning Impulsiveness) and had higher degrees of delay discounting (i.e., poorer capability of delay gratification) than the healthy controls, while only the ND group showed a lower degree of probability discounting (i.e., lower risk aversion) than healthy controls. Moreover, IGD and ND groups displayed similar impaired inhibitory control on the revised Go/No Go task (i.e., a lower correct accuracy in No-Go trials) compared with healthy controls, but on the Stroop task only the ND subjects showed a lower correct accuracy in the incongruent trials than healthy controls. These findings suggested that IGD was linked to anomalous reward discounting and dysfunctional inhibitory control, comparable with one typical SUD category (i.e., ND) in this study.

In regard to trait impulsivity assessed with the BIS-11, plentiful studies have observed elevated scores among adolescents and young adults with IGD on the three dimensions (i.e., Motor, Attentional, and Non-planning Impulsiveness) (23, 31, 54, 89, 113), despite that some studies revealed no differences on these impulsiveness scores between treatment-seeking patients diagnosed with IGD and healthy controls (24). Our data were consistent with the results of most previous studies, revealing an increased level of trait impulsivity on the BIS model among individuals with IGD. Furthermore, our study detected similar elevated scores of the three dimensions in the Nicotine Dependence (ND) group, in line with the literature of trait impulsivity in cigarette smoking (114). These findings, together with our previous cross-sectional data of trait impulsivity in problematic Internet use and smoking behaviors, indicated that IGD showed a tendency of increased impulsivity traits comparable to ND (25). Interestingly, we further found that the BIS-11 scores were not significantly correlated with the severity of Internet gaming (**Supplementary Table 1**), but more serious nicotine use (e.g., years of smoking) was associated with a higher score on certain impulsivity trait (non-planning impulsiveness), indicating a possible toxic effect of ND on impulsivity. Particularly, nicotine (i.e., the primary component of cigarettes smoking and ND) is a specific agonist of nicotinic acetylcholine receptors (nAChRs), and chronic exposure to nicotine acts as a neuroteratogen by providing excessive cholinergic stimulation in the developing brain (115). Thus, the deleterious effects of ND are mostly connected with nicotine-induced overstimulation that causes overt neurotoxicity and the adaptive desensitization of the nAChRs that causes alterations in cholinergic transmission, which may produce derangements in final neuronal architecture such as the prefrontal cortex, resulting in less prefrontal inhibition and higher levels of impulsive trait (116).

On the monetary reward discounting tasks (i.e., DDT and PDT), our data showed that both IGD and ND groups had a higher delay-discounting degree (log-transformed k value) than the healthy controls, with a medium to large effect size (Cohen's $d = 0.53$–0.69), and no difference was found on the DDT between IGD and ND groups. These data were consistent with previous reports indicating higher degrees of delay discounting among adolescents and young adults with IGD (53–58), as well as among young heavy smokers and nicotine-dependent individuals (59–63). In this respect, an inability to delay gratification might be reflected both in IGD and ND subjects, and this similar tendency on discounting long-term rewards faster could play an important role in the development of these two disordered behaviors among the youths (24, 65). Furthermore, the partial correlations in our study did not find significant relationships between gaming/smoking severity with delay-discounting degrees (k values) in IGD and ND groups (**Supplementary Table 1**), probably suggesting that the poor delay gratification might not be aggravated by the severity of IGD or ND among these individuals. However, given the cross-sectional design of our study, whether the poor delay gratification is a predisposing factor for IGD or ND still needs more powerful longitudinal evidence.

With respect to probability discounting, IGD subjects did not differ from healthy controls on the probability-discounting degrees (log-transformed h values), indicating a normal risk aversion as expected in previous studies (53, 54), though inconsistent with some reports showing that IGD participants chose more probabilistic rewards than recreational Internet game users and controls (66–68). By comparison, the ND group had a lower degree of probability discounting than healthy controls with a medium effect size (Cohen's $d = 0.55$), suggesting a reduction in risk aversion or a greater risk-taking tendency (63, 117). However, as previous research pointed out, the floor effects of low probabilities in different studies might lead to inconsistent results (60, 69–71). Considering that our ND group merely scored lower than the controls on the Part A (i.e., \$20 vs. \$80), but neither on the Part B (i.e., \$40 vs. \$100) nor on the Part C (i.e., \$40 vs. \$60) of the PDT, it appears that the magnitudes of the risky and/or the constant monetary rewards might be also important in the choice of these addicted individuals (118), which calls for further investigations on this interesting topic that to

what extend the probabilities and the magnitudes of monetary rewards may affect the degrees of probability discounting on the PDT.

Cognitive control or inhibitory control plays a crucial part in our goal-directed behaviors (48, 119), as well as in the uncontrolled addictive behaviors (120, 121). Impairments in cognitive control might affect the daily life, family relations, and occupational status of drug-dependent individuals, and are essential in the treatment and relapse of drug addiction (122). Based on the phenomenological and empirical evidence of decreased executive control in adolescents with IGD, some theoretical models of IGD, such as the tripartite neurocognitive model (46) and the Interaction of Person-Affect-Cognition-Execution model (I-PACE) (123), coincidentally underlined the key role of reduced cognitive control or inhibitory control in the development and maintenance of IGD. In the present study, we used the Stroop Color-Word Task and a revised Go/No Go task to test inhibitory control. The data on Stroop task revealed that the Nicotine Dependence (ND) subjects showed a lower correct accuracy than healthy controls in the incongruent trials (Cohen's $d = 0.61$), indicating a dysfunctional inhibitory control in heavy smokers (101), while the IGD subjects had similar performance on the Stroop as the healthy controls did, discordant with previous reports among adolescents showing that high school students with IGD made more errors in the incongruent trials than healthy controls, indicating impaired inhibitory control (85–90). Considering the obvious differences of the IGD samples in ours and other studies (i.e., young adult university students vs. adolescent high-school students), more attention should be paid to these contradictory findings in various samples of IGD. Especially, we noticed that although significantly differing from the healthy controls on the Stroop task, our ND subjects seemed not so "impaired," with an average correct accuracy of 90.81% in the incongruent trials, in contrast to that of 92.80% (IGD group) and 93.50% (HC group). Thus, the task difficulty and complexity issues should be considered in future similar studies using the Stroop task.

More important findings in this study were from the revised Go/No Go task. Our data showed that the IGD and ND groups exhibited similar impaired performance of inhibitory control on this task (i.e., a lower correct accuracy in No-Go trials) than the healthy controls, with a large effect size (Cohen's $d = 1.35$, 1.50, respectively), yet the performance differences in frequent-Go and infrequent-Go trials among the IGD, ND and healthy control groups were not significant. Because of the potential confusions arising from the dual processing of attentional bias related to the novelty and response inhibition related to the no-go signals in traditional Go/No-Go paradigms (i.e., 25% No-Go trials vs. 75% Go trials), the present literature of the performance on the Go/No-Go task has been greatly inconsistent, with some studies reporting reduced inhibitory control functions in adolescents and young adults with IGD (31, 89), while others indicating intact inhibitory control in IGD subjects (86–88) and in heavy smokers (99, 100). Our current study firstly dissociated inhibitory control aspects from attentional bias among IGD and ND samples, using the newly modified and validated Go/No-Go task (89, 90) that contains 75% frequent-Go trials, 12.5% infrequent-Go trials, and 12.5% No-Go trials to directly detect response inhibition by comparing the infrequent-Go trials with No-Go trials. Our data clearly depicted that although the IGD and ND groups performed normally in both frequent-Go and infrequent-Go trials (the average correct accuracy >92%) similar to the healthy controls, these two disordered groups displayed apparent inhibitory impairments in the infrequent No-Go trials (an average correct accuracy of about 60%) compared with healthy controls (about 70% correct) (**Figure 1B**). Furthermore, the IGD individuals who has never used any addictive substance, still manifested a comparable impairment of inhibitory control on this task with the ND subjects, who probably had the concomitant intoxication consequences due to chronic nicotine use (116). These findings might indicate a basic pathology mechanism of cognitive control implicated in IGD as a potential addictive disorder similar to SUD (84). Nevertheless, we did not find a significant correlation between the inhibitory control impairments and the severity of smoking in the ND group, inconsistent with previous reports (96, 97). In light of the non-clinical samples of ND (i.e., university students) in our study, we speculated that a narrow distribution of smoking severity (e.g., an average score of 5.83 ± 1.03 on the FTND) might negatively affect the correlation results, and further studies with a larger ND sample are warranted to detect their accurate relationships.

There are several limitations that should be noted in the present study. Firstly, despite the fact that we mainly included the IGD and ND groups by person-to-person screening interview conducted by a psychiatrist and a clinical psychologist, according to the clinical criteria for IGD and ND, we also used some self-report scales (i.e., the IAT and the FTND) to evaluate the severity of IGD/ND, which might bring subjective biases, thus the results should be explained carefully. Secondly, our samples of IGD and ND primarily consisted of the young adult university students, which could not represent the whole population, so the findings should be further examined with other different samples (e.g., treatment-seeking populations of IGD and ND). Thirdly, we did not combine any neurophysiology measurement together with our behavioral tasks as did in previous studies [e.g., (68, 89, 95, 101)], thus our findings of deficient reward processing and inhibitory control in IGD and ND were short of powerful converged evidence on neurobiological correlates. Actually, the current literature suggests that functional and structural neural alterations in the fronto-striatal and fronto-cingulate regions are closely associated with IGD (81), and abnormal activities in the prefrontal areas (e.g., dorsolateral prefrontal cortex, anterior cingulate cortex, and orbitofrontal cortex/ventromedial prefrontal cortex) may account for the impaired cognitive control and decreased loss sensitivity in IGD and gambling disorder (124, 125) as well as for the craving and impulsivity in comorbid IGD and SUD (126). Thus, neurophysiology measurements should be better integrated with behavioral tasks in future. Additionally, although we contrasted IGD and ND individuals with well-matched healthy controls on multiple tasks, with a larger sample size relative to some previous studies [e.g., (23)], our case-control study design was cross-sectional in nature, therefore our results could not draw a causal conclusion, which should also be interpreted more discreetly.

Despite these limitations, our findings indicated for the first time that in a straightforward comparison, young adults with IGD and those with ND concurrently shared poorer capability of delay gratification as well as impaired inhibitory control, suggesting that IGD was linked to a neuropsychological pattern of anomalous reward discounting and dysfunctional inhibitory control, which was comparable to a typical SUD category (i.e., ND). This study thus might promote a better understanding of the pathogenesis of IGD as a potential addictive disorder similar to SUD. Furthermore, our first direct findings from a comparison between IGD and ND should be beneficial for potential clinical implications in the prevention and treatment of excessive Internet gaming and IGD, for instance, developing possible non-pharmacological therapeutic methods aimed at the restoration of inhibitory control or cognitive control functions (124) and/or reducing the high-level subjective representations of exciting activities or instant craving (127). In this respect, non-invasive neuromodulation methods, such as the repetitive transcranial magnetic stimulation (rTMS), have been proposed as an effective intervention to target cognitive dysfunctions in substance-related addictive disorders including tobacco, alcohol, and cocaine addiction (128). In view of the similar impaired inhibitory control detected in both IGD and ND in our study, future treatment of pathological Internet gaming might also be inspired to yield encouraging results by combining neuromodulation methods (e.g., rTMS) that could be applied on selected brain areas especially the left dorsolateral prefrontal cortex (DLPFC), which has been proved to probably improve the prefrontal top-down executive control and reduce drug craving and consumption in SUD, including ND (128, 129). However, there remains a big need for more accurate studies that can provide deeper insight into the core pathogenesis of IGD so as to advance this field, furnishing the foundation for developing an ideal model for practice in the prevention and treatment of IGD (130).

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 Human Research Ethics Committee at the Guizhou Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

W-SY designed the study, wrote the protocols, directed the study, and wrote a first draft of the manuscript. R-TC, M-ML, and D-HZ performed the task assessments, data collection, and main data analysis. All of the authors contributed to the writing and have approved the final manuscript.

FUNDING

This study was provided by the National Natural Science Foundation of China (Nos.: 32060195, 31560284) to W-SY. These funding sources had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.628933/full#supplementary-material

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Publishing (2013). doi: 10.1176/appi.books.9780890425596
2. Potenza MN, Higuchi S, Brand M. Call for research into a wider range of behavioural addictions. *Nature*. (2018) 555:30. doi: 10.1038/d41586-018-02568-z
3. Pontes HM, Griffiths MD. A new era for gaming disorder research: time to shift from consensus to consistency. *Addict Behav*. (2020) 103:106059. doi: 10.1016/j.addbeh.2019.106059
4. World Health Organization. *The ICD-11 Classification of Mental and Behavioral Disorders: Diagnostic Criteria for Research*. Geneva: World Health Organization (2018).
5. Pontes HM, Stavropoulos V, Griffiths MD. Emerging insights on internet gaming disorder: conceptual and measurement issues. *Addict Behav Rep*. (2020) 11:100242. doi: 10.1016/j.abrep.2019.100242
6. Jo YS, Bhang SY, Choi JS, Lee HK, Lee SY, Kweon YS. Clinical characteristics of diagnosis for internet gaming disorder: comparison of DSM-5 IGD and ICD-11 GD diagnosis. *J Clin Med*. (2019) 8:945. doi: 10.3390/jcm8070945
7. Wu AMS, Chen JH, Tong KK, Yu S, Lau JTF. Prevalence and associated factors of internet gaming disorder among community dwelling adults in Macao, China. *J Behav Addict*. (2018) 7:62–9. doi: 10.1556/2006.7.2018.12
8. Przybylski AK, Weinstein N, Murayama K. Internet gaming disorder: investigating the clinical relevance of a new phenomenon. *Am J Psychiatr*. (2017) 174:230–6. doi: 10.1176/appi.ajp.2016.16020224
9. Petry NM, Rehbein F, Ko CH, O'Brien CP. Internet gaming disorder in the DSM-5. *Curr Psychiatr Rep*. (2015) 17:72. doi: 10.1007/s11920-015-0610-0
10. Stevens MW, Dorstyn D, Delfabbro PH, King DL. Global prevalence of gaming disorder: a systematic review and meta-analysis. *Aust N Z J Psychiatry*. (2020). doi: 10.1177/0004867420962851. [Epub ahead of print].
11. Darvesh N, Radhakrishnan A, Lachance CC, Nincic V, Sharpe JP, Ghassemi M, et al. Exploring the prevalence of gaming disorder and Internet gaming disorder: a rapid scoping review. *Systemat Rev*. (2020) 9:68. doi: 10.1186/s13643-020-01329-2
12. Aarseth E, Bean AM, Boonen H, Colder Carras M, Coulson M, Das D, et al. Scholars' open debate paper on the World Health organization ICD-11 gaming disorder proposal. *J Behav Addict*. (2017) 6:267–70. doi: 10.1556/2006.5.2016.088
13. Petry NM, Rehbein F, Gentile DA, Lemmens JS, Rumpf HJ, Mößle T, et al. An international consensus for assessing internet gaming disorder using the new DSM-5 approach. *Addiction*. (2014) 109:1399–406. doi: 10.1111/add.12457
14. Griffiths MD, van Rooij AJ, Kardefelt-Winther D, Starcevic V, Király O, Pallesen S, et al. Working towards an international consensus on criteria for assessing internet gaming disorder: a critical commentary on Petry et al. (2014). *Addiction*. (2016) 111:167–75. doi: 10.1111/add.13057

15. Kuss DJ, Griffiths MD, Pontes HM. DSM-5 diagnosis of Internet Gaming Disorder: Some ways forward in overcoming issues and concerns in the gaming studies field. *J Behav Addict.* (2017) 6:133–141. doi: 10.1556/2006.6.2017.032
16. van den Brink W. ICD-11 Gaming disorder: needed and just in time or dangerous and much too early? *J Behav Addict.* (2017) 6:290–2. doi: 10.1556/2006.6.2017.040
17. Martin PR, Petry NM. Are non-substance-related addictions really addictions? *Am J Addict.* (2005) 14:1–7. doi: 10.1080/10550490590899808
18. Kuss DJ, Pontes HM, Griffiths MD. Neurobiological correlates in internet gaming disorder: a systematic literature review. *Front Psychiatr.* (2018) 9:166. doi: 10.3389/fpsyt.2018.00166
19. King DL, Delfabbro PH, Potenza MN, Demetrovics Z, Billieux J, Brand M. Internet gaming disorder should qualify as a mental disorder. *Austral N Zealand J Psychiatr.* (2018) 52:615–7. doi: 10.1177/0004867418771189
20. van Rooij AJ, Ferguson CJ, Colder Carras M, Kardefelt-Winther D, Shi J, Aarseth E, et al. A weak scientific basis for gaming disorder: Let us err on the side of caution. *J Behav Addict.* (2018) 7:1–9. doi: 10.31234/osf.io/kc7r9
21. Dullur P, Starcevic V. Internet gaming disorder does not qualify as a mental disorder. *Austral N Zeal J Psychiatr.* (2018) 52:110–1. doi: 10.1177/0004867417741554
22. James RJ, Tunney RJ. The need for a behavioural analysis of behavioural addictions. *Clin Psychol Rev.* (2017) 52:69–76. doi: 10.1016/j.cpr.2016.11.010
23. Choi SW, Kim HS, Kim GY, Jeon Y, Park SM, Lee JY, et al. Similarities and differences among Internet gaming disorder, gambling disorder and alcohol use disorder: a focus on impulsivity and compulsivity. *J Behav Addict.* (2014) 3:246–53. doi: 10.1556/JBA.3.2014.4.6
24. Wölfling K, Duven E, Wejbera M, Beutel ME, Müller KW. Discounting delayed monetary rewards and decision making in behavioral addictions - a comparison between patients with gambling disorder and internet gaming disorder. *Addict Behav.* (2020) 108:106446. doi: 10.1016/j.addbeh.2020.106446
25. Liu SJ, Lan Y, Wu L, Yan WS. Profiles of impulsivity in problematic internet users and cigarette smokers. *Front Psychol.* (2019) 10:772. doi: 10.3389/fpsyg.2019.00772
26. Yan W, Li Y, Sui N. The relationship between recent stressful life events, personality traits, perceived family functioning and internet addiction among college students. *Stress Health.* (2014) 30:3–11. doi: 10.1002/smi.2490
27. Bonnaire C, Baptista D. Internet gaming disorder in male and female young adults: the role of alexithymia, depression, anxiety and gaming type. *Psychiatr Res.* (2019) 272:521–30. doi: 10.1016/j.psychres.2018.12.158
28. Sugaya N, Shirasaka T, Takahashi K, Kanda H. Bio-psychosocial factors of children and adolescents with internet gaming disorder: a systematic review. *Bio Psycho Soc Med.* (2019) 13:3. doi: 10.1186/s13030-019-0144-5
29. Fam JY. Prevalence of internet gaming disorder in adolescents: a meta-analysis across three decades. *Scand J Psychol.* (2018) 59:524–31. doi: 10.1111/sjop.12459
30. Xin M, Xing J, Pengfei W, Houru L, Mengcheng W, Hong Z. Online activities, prevalence of Internet addiction and risk factors related to family and school among adolescents in China. *Addict Behav Rep.* (2018) 7:14–8. doi: 10.1016/j.abrep.2017.10.003
31. Wang L, Tian M, Zheng Y, Li Q, Liu X. Reduced loss aversion and inhibitory control in adolescents with internet gaming disorder. *Psychol Addict Behav.* (2020) 34:484–96. doi: 10.1037/adb0000549
32. Alexander C, Piazza M, Mekos D, Valente T. Peers, schools, and adolescent cigarette smoking. *J Adolescent Health.* (2001) 29:22–30. doi: 10.1016/S1054-139X(01)00210-5
33. Chen X, Li X, Stanton B, Mao R, Sun Z, Zhang H, et al. Patterns of cigarette smoking among students from 19 colleges and universities in Jiangsu Province, China: a latent class analysis. *Drug Alcohol Depend.* (2004) 76:153–63. doi: 10.1016/j.drugalcdep.2004.04.013
34. Reed MB, Wang R, Shillington AM, Clapp JD, Lange JE. The relationship between alcohol use and cigarette smoking in a sample of undergraduate college students. *Addict Behav.* (2007) 32:449–64. doi: 10.1016/j.addbeh.2006.05.016
35. Wang TW, Gentzke A, Sharapova S, Cullen KA, Ambrose BK, Jamal A. Tobacco product use among middle and high school students - United States, 2011-2017. *MMWMorbidity Weekly Rep.* (2018) 67:629–33. doi: 10.15585/mmwr.mm6722a3
36. Di Nicola M, Ferri VR, Moccia L, Panaccione I, Strangio AM, Tedeschi D, et al. Gender differences and psychopathological features associated with addictive behaviors in adolescents. *Front Psychiatr.* (2017) 8:256. doi: 10.3389/fpsyt.2017.00256
37. Ko CH, Liu GC, Yen JY, Yen CF, Chen CS, Lin WC. The brain activations for both cue-induced gaming urge and smoking craving among subjects comorbid with Internet gaming addiction and nicotine dependence. *J Psychiatr Res.* (2013) 47:486–93. doi: 10.1016/j.jpsychires.2012.11.008
38. Marmet S, Studer J, Wicki M, Bertholet N, Khazaal Y, Gmel G. Unique versus shared associations between self-reported behavioral addictions and substance use disorders and mental health problems: a commonality analysis in a large sample of young Swiss men. *J Behav Addict.* (2019) 8:664–77. doi: 10.1556/2006.8.2019.70
39. Burleigh TL, Griffiths MD, Sumich A, Stavropoulos V, Kuss DJ. A systematic review of the co-occurrence of gaming disorder and other potentially addictive behaviors. *Curr Addic Rep.* (2019) 6:383–401. doi: 10.1007/s40429-019-00279-7
40. Mérelle S, Kleiboer A, Schotanus M, Cluitmans TL, Waardenburg CM, Kramer D, et al. Which health-related problems are associated with problematic video-gaming or social media use in adolescents? *Clin Neuropsychiatr.* (2017) 14:11–9.
41. Ge X, Sun Y, Han X, Wang Y, Ding W, Cao M, et al. Difference in the functional connectivity of the dorsolateral prefrontal cortex between smokers with nicotine dependence and individuals with internet gaming disorder. *BMC Neurosci.* (2017) 18:54. doi: 10.1186/s12868-017-0375-y
42. Noël X, Brevers D, Bechara A. A neurocognitive approach to understanding the neurobiology of addiction. *Curr Opin Neurobiol.* (2013) 23:632–8. doi: 10.1016/j.conb.2013.01.018
43. Turel O, Bechara A. A triadic reflective-impulsive-interoceptive awareness model of general and impulsive information system use: behavioral tests of neuro-cognitive theory. *Front Psychol.* (2016) 7:601. doi: 10.3389/fpsyg.2016.00601
44. Zheng H, Hu Y, Wang Z, Wang M, Du X, Dong G. Meta-analyses of the functional neural alterations in subjects with Internet gaming disorder: Similarities and differences across different paradigms. *Progr Neuro-Psychopharmacol Biol Psychiatr.* (2019) 94:109656. doi: 10.1016/j.pnpbp.2019.109656
45. Wang M, Dong H, Zheng H, Du X, Dong GH. Inhibitory neuromodulation of the putamen to the prefrontal cortex in Internet gaming disorder: how addiction impairs executive control. *J Behav Addict.* (2020) 9:312–24. doi: 10.1556/2006.2020.00029
46. Wei L, Zhang S, Turel O, Bechara A, He Q. A tripartite neurocognitive model of internet gaming disorder. *Front Psychiatr.* (2017) 8:285. doi: 10.3389/fpsyt.2017.00285
47. Ernst M, Pine DS, Hardin M. Triadic model of the neurobiology of motivated behavior in adolescence. *Psychol Med.* (2006) 36:299–312. doi: 10.1017/S0033291705005891
48. Somerville LH, Casey BJ. Developmental neurobiology of cognitive control and motivational systems. *Curr Opin Neurobiol.* (2010) 20:236–241. doi: 10.1016/j.conb.2010.01.006
49. Kirby KN, Petry NM, Bickel WK. Heroin addicts have higher discount rates for delayed rewards than non-drug-using controls. *J Exp Psychol.* (1999) 128:78–87. doi: 10.1037/0096-3445.128.1.78
50. Dixon MR, Marley J, Jacobs EA. Delay discounting by pathological gamblers. *J Appl Behav Anal.* (2003) 36:449–58. doi: 10.1901/jaba.2003.36-449
51. Madden GJ, Petry NM, Johnson PS. Pathological gamblers discount probabilistic rewards less steeply than matched controls. *Exp Clin Psychopharmacol.* (2009) 17:283–90. doi: 10.1037/a0016806
52. Rachlin H, Raineri A, Cross D. Subjective probability and delay. *J Exp Analysis Behav.* (1991) 55:233–44. doi: 10.1901/jeab.1991.55-233
53. Li Q, Tian M, Taxer J, Zheng Y, Wu H, Sun S, et al. Problematic internet users' discounting behaviors reflect an inability to delay gratification, not risk taking. *Cyberpsychol Behav Soc Netw.* (2016) 19:172–8. doi: 10.1089/cyber.2015.0295

54. Tian M, Tao R, Zheng Y, Zhang H, Yang G, Li Q. et al. Internet gaming disorder in adolescents is linked to delay discounting but not probability discounting. *Computers Human Behav.* (2018) 80:59–66. doi: 10.1016/j.chb.2017.10.018
55. Weinstein A, Abu HB, Timor A, Mama Y. Delay discounting, risk-taking, and rejection sensitivity among individuals with internet and video gaming disorders. *J Behav Addict.* (2016) 5:674–82. doi: 10.1556/2006.5.2016.081
56. Wang Y, Hu Y, Xu J, Zhou H, Lin X, Du X, et al. Dysfunctional prefrontal function is associated with impulsivity in people with internet gaming disorder during a delay discounting task. *Front Psychiatr.* (2017) 8:287. doi: 10.3389/fpsyt.2017.00287
57. Wang Y, Wu L, Wang L, Zhang Y, Du X, Dong G. Impaired decision-making and impulse control in Internet gaming addicts: evidence from the comparison with recreational Internet game users. *Addict Biol.* (2017) 22:1610–21. doi: 10.1111/adb.12458
58. Wang Y, Wu L, Zhou H, Lin X, Zhang Y, Du X, et al. Impaired executive control and reward circuit in Internet gaming addicts under a delay discounting task: independent component analysis. *Eur Arch Psychiatr Clin Neurosci.* (2017) 267:245–55. doi: 10.1007/s00406-016-0721-6
59. Bickel WK, Odum AL, Madden GJ. Impulsivity and cigarette smoking: delay discounting in current, never, and ex-smokers. *Psychopharmacology.* (1999) 146:447–54. doi: 10.1007/PL00005490
60. Białaszek W, Marcowski P, Cox DJ. Differences in delay, but not probability discounting, in current smokers, e-cigarette users, never smokers. *Psychol Record.* (2017) 67:223–30. doi: 10.1007/s40732-017-0244-1
61. Amlung M, MacKillop J. Clarifying the relationship between impulsive delay discounting and nicotine dependence. *Psychol Addict Behav.* (2014) 28:761–8. doi: 10.1037/a0036726
62. García-Rodríguez O, Secades-Villa R, Weidberg S, Yoon JH. A systematic assessment of delay discounting in relation to cocaine and nicotine dependence. *Behav Proces.* (2013) 99:100–5. doi: 10.1016/j.beproc.2013.07.007
63. Reynolds B, Richards JB, Horn K, Karraker K. Delay discounting and probability discounting as related to cigarette smoking status in adults. *Behav Proces.* (2004) 65:35–42. doi: 10.1016/S0376-6357(03)00109-8
64. Sweitzer MM, Donny EC, Dierker LC, Flory JD, Manuck SB. Delay discounting and smoking: association with the Fagerström Test for Nicotine Dependence but not cigarettes smoked per day. *Nicotine Tobacco Res.* (2008) 10:1571–5. doi: 10.1080/14622200802323274
65. Weidberg S, Secades-Villa R, García-Pérez Á, González-Roz A, Fernández-Hermida JR. The synergistic effect of cigarette demand and delay discounting on nicotine dependence among treatment-seeking smokers. *Exp Clin Psychopharmacol.* (2019) 27:146–52. doi: 10.1037/pha0000248
66. Lin X, Zhou H, Dong G, Du X. Impaired risk evaluation in people with Internet gaming disorder: fMRI evidence from a probability discounting task. *Progr Neuro-psychopharmacol Biol Psychiatr.* (2015) 56:142–8. doi: 10.1016/j.pnpbp.2014.08.016
67. Wang L, Wu L, Lin X, Zhang Y, Zhou H, Du X, et al. Dysfunctional default mode network and executive control network in people with Internet gaming disorder: independent component analysis under a probability discounting task. *Eur Psychiatr.* (2016) 34:36–42. doi: 10.1016/j.eurpsy.2016.01.2424
68. Wang Z, Liu X, Hu Y, Zheng H, Du X, Dong G. Altered brain functional networks in Internet gaming disorder: independent component and graph theoretical analysis under a probability discounting task. *CNS Spectrums.* (2019) 24:544–56. doi: 10.1017/S1092852918001505
69. Reynolds B, Patak M, Shroff P, Penfold RB, Melanko S, Duhig AM. Laboratory and self-report assessments of impulsive behavior in adolescent daily smokers and nonsmokers. *Exp Clin Psychopharmacol.* (2007) 15:264–71. doi: 10.1037/1064-1297.15.3.264
70. Ohmura Y, Takahashi T, Kitamura N. Discounting delayed and probabilistic monetary gains and losses by smokers of cigarettes. *Psychopharmacology.* (2005) 182:508–15. doi: 10.1007/s00213-005-0110-8
71. Yi R, Chase WD, Bickel WK. Probability discounting among cigarette smokers and nonsmokers: molecular analysis discerns group differences. *Behav Pharmacol.* (2007) 18:633–9. doi: 10.1097/FBP.0b013e3282effbd3
72. Yi R, Landes RD. Temporal and probability discounting by cigarette smokers following acute smoking abstinence. *Nicotine Tobacco Res.* (2012) 14:547–58. doi: 10.1093/ntr/ntr252
73. Bechara A, Berridge KC, Bickel WK, Morón JA, Williams SB, Stein JS. A neurobehavioral approach to addiction: implications for the opioid epidemic and the psychology of addiction. *Psychol Sci Public Interest.* (2019) 20:96–127. doi: 10.1177/1529100619860513
74. Hester R, Lubman DI, Yücel M. The role of executive control in human drug addiction. *Curr Top Behav Neurosci.* (2010) 3:301–18. doi: 10.1007/7854_2009_28
75. Tanabe J, Regner M, Sakai J, Martinez D, Gowin J. Neuroimaging reward, craving, learning, and cognitive control in substance use disorders: review and implications for treatment. *Br J Radiol.* (2019) 92:20180942. doi: 10.1259/bjr.20180942
76. Smith DG, Jones PS, Bullmore ET, Robbins TW, Ersche KD. Cognitive control dysfunction and abnormal frontal cortex activation in stimulant drug users and their biological siblings. *Translational Psychiatr.* (2013) 3:e257. doi: 10.1038/tp.2013.32
77. Goldstein RZ, Volkow ND. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nature Rev.* (2011) 12:652–69. doi: 10.1038/nrn3119
78. Dong G, Li H, Wang L, Potenza MN. Cognitive control and reward/loss processing in Internet gaming disorder: results from a comparison with recreational Internet game-users. *Eur Psychiatr.* (2017) 44:30–8. doi: 10.1016/j.eurpsy.2017.03.004
79. Wang H, Jin C, Yuan K, Shakir TM, Mao C, Niu X, et al. The alteration of gray matter volume and cognitive control in adolescents with internet gaming disorder. *Front Behav Neurosci.* (2015) 9:64. doi: 10.3389/fnbeh.2015.00064
80. Meng Y, Deng W, Wang H, Guo W, Li T. The prefrontal dysfunction in individuals with Internet gaming disorder: a meta-analysis of functional magnetic resonance imaging studies. *Addiction Biol.* (2015) 20:799–808. doi: 10.1111/adb.12154
81. Yao YW, Liu L, Ma SS, Shi XH, Zhou N, Zhang JT, et al. Functional and structural neural alterations in Internet gaming disorder: a systematic review and meta-analysis. *Neurosci Biobehav Rev.* (2017) 83:313–24. doi: 10.1016/j.neubiorev.2017.10.029
82. Cools R, D' Esposito. M. Inverted-U-shaped dopamine actions on human working memory and cognitive control. *Biol Psychiatr.* (2011) 69:e113–25. doi: 10.1016/j.biopsych.2011.03.028
83. Brand M, Young KS, Laier C. Prefrontal control and internet addiction: a theoretical model and review of neuropsychological and neuroimaging findings. *Front Human Neurosci.* (2014) 8:375. doi: 10.3389/fnhum.2014.00375
84. Antons S, Brand M, Potenza MN. Neurobiology of cue-reactivity, craving, and inhibitory control in non-substance addictive behaviors. *J Neurol Sci.* (2020) 415:116952. doi: 10.1016/j.jns.2020.116952
85. Cai C, Yuan K, Yin J, Feng D, Bi Y, Li Y, et al. Striatum morphometry is associated with cognitive control deficits and symptom severity in internet gaming disorder. *Brain Imaging Behav.* (2016) 10:12–20. doi: 10.1007/s11682-015-9358-8
86. Xing L, Yuan K, Bi Y, Yin J, Cai C, Feng D, et al. Reduced fiber integrity and cognitive control in adolescents with internet gaming disorder. *Brain Res.* (2014) 1586:109–117. doi: 10.1016/j.brainres.2014.08.044
87. Yuan K, Qin W, Yu D, Bi Y, Xing L, Jin C, et al. Core brain networks interactions and cognitive control in internet gaming disorder individuals in late adolescence/early adulthood. *Brain Structure Funct.* (2016) 221:1427–42. doi: 10.1007/s00429-014-0982-7
88. Yuan K, Yu D, Cai C, Feng D, Li Y, Bi Y, et al. Frontostriatal circuits, resting state functional connectivity and cognitive control in internet gaming disorder. *Addict Biol.* (2017) 22:813–22. doi: 10.1111/adb.12348
89. Li Q, Wang Y, Yang Z, Dai W, Zheng Y, Sun Y, et al. Dysfunctional cognitive control and reward processing in adolescents with Internet gaming disorder. *Psychophysiology.* (2020) 57:e13469. doi: 10.1111/psyp.13469
90. Kim YJ, Lim JA, Lee JY, Oh S, Kim SN, Kim DJ, et al. Impulsivity and compulsivity in Internet gaming disorder: a comparison with obsessive-compulsive disorder and alcohol use disorder. *J Behav Addic.* (2017) 6:545–53. doi: 10.1556/2006.6.2017.069
91. Ding WN, Sun JH, Sun YW, Chen X, Zhou Y, Zhuang ZG, et al. Trait impulsivity and impaired prefrontal impulse inhibition function in

adolescents with internet gaming addiction revealed by a Go/No-Go fMRI study. *Behav Brain Funct.* (2014) 10:20. doi: 10.1186/1744-9081-10-20
92. Chen CY, Huang MF, Yen JY, Chen CS, Liu GC, Yen CF, et al. Brain correlates of response inhibition in internet gaming disorder. *Psychiatr Clin Neurosci.* (2015) 69:201–9. doi: 10.1111/pcn.12224
93. Ko CH, Hsieh TJ, Chen CY, Yen CF, Chen CS, Yen JY, et al. Altered brain activation during response inhibition and error processing in subjects with Internet gaming disorder: a functional magnetic imaging study. *Eur Arch Psychiatr Clin Neurosci.* (2014) 264:661–72. doi: 10.1007/s00406-013-0483-3
94. Chikazoe J, Jimura K, Asari T, Yamashita K, Morimoto H, Hirose S, et al. Functional dissociation in right inferior frontal cortex during performance of go/no-go task. *Cereb Cortex.* (2009) 19:146–52. doi: 10.1093/cercor/bhn065
95. Froeliger B, McConnell PA, Bell S, Sweitzer M, Kozink RV, Eichberg C, et al. Association between baseline corticothalamic-mediated inhibitory control and smoking relapse vulnerability. *JAMA Psychiatr.* (2017) 74:379–86. doi: 10.1001/jamapsychiatry.2017.0017
96. Spinella M. Correlations between orbitofrontal dysfunction and tobacco smoking. *Addiction Biol.* (2002) 7:381–4. doi: 10.1080/1355621021000005964
97. Yakir A, Rigbi A, Kanyas K, Pollak Y, Kahana G, Karni O, et al. Why do young women smoke? IIAttention I, and impulsivity as neurocognitive predisposing factors. *Eur Neuropsychopharmacol.* (2007) 17:339–51. doi: 10.1016/j.euroneuro.2006.09.004
98. Charles-Walsh K, Furlong L, Munro DG, Hester R. Inhibitory control dysfunction in nicotine dependence and the influence of short-term abstinence. *Drug Alcohol Depend.* (2014) 143:81–6. doi: 10.1016/j.drugalcdep.2014.07.008
99. Dinn WM, Aycicegi A, Harris CL. Cigarette smoking in a student sample: neurocognitive and clinical correlates. *Addict Behav.* (2004) 29:107–26. doi: 10.1016/j.addbeh.2003.07.001
100. Lesage E, Sutherland MT, Ross TJ, Salmeron BJ, Stein EA. Nicotine dependence (trait) and acute nicotinic stimulation (state) modulate attention but not inhibitory control: converging fMRI evidence from Go-Nogo and Flanker tasks. *Neuropsychopharmacology.* (2020) 45:857–65. doi: 10.1038/s41386-020-0623-1
101. Yuan K, Yu D, Zhao M, Li M, Wang R, Li Y, et al. Abnormal frontostriatal tracts in young male tobacco smokers. *NeuroImage.* (2018) 183:346–55. doi: 10.1016/j.neuroimage.2018.08.046
102. Young KS. Internet addiction: the emergence of a new clinical disorder. *CyberPsychol Behav.* (1998) 1:237–44. doi: 10.1089/cpb.1998.1.237
103. Khazaal Y, Billieux J, Thorens G, Khan R, Louati Y, Scarlatti E, et al. French validation of the internet addiction test. *Cyberpsychol Behav.* (2008) 11:703–6. doi: 10.1089/cpb.2007.0249
104. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed., text revision (DSM-IV-TR). Washington, DC: American Psychiatric Association (2000).
105. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström Test for Nicotine dependence: a revision of the Fagerström Tolerance Questionnaire. *Br J Addict.* (1991) 86:1119–27. doi: 10.1111/j.1360-0443.1991.tb01879.x
106. Fagerström KO, Kunze M, Schoberberger R, Breslau N, Hughes JR, Hurt RD, et al. Nicotine dependence versus smoking prevalence: comparisons among countries and categories of smokers. *Tobacco Control.* (1996) 5:52–6. doi: 10.1136/tc.5.1.52
107. Ríos-Bedoya CF, Snedecor SM, Pomerleau CS, Pomerleau OF. Association of withdrawal features with nicotine dependence as measured by the Fagerström Test for Nicotine Dependence (FTND). *Addict Behav.* (2008) 33:1086–9. doi: 10.1016/j.addbeh.2008.04.005
108. Sun Y, Li S. Testing the effect of risk on intertemporal choice in the Chinese cultural context. *J Soc Psychol.* (2011) 151:517–522. doi: 10.1080/00224545.2010.503719
109. Yan WS, Zhang RR, Lan Y, Li ZM, Li YH. Questionnaire-based maladaptive decision-coping patterns involved in binge eating among 1013 college students. *Front Psychol.* (2018) 9:609. doi: 10.3389/fpsyg.2018.00609
110. Golden CJ. A group version of the Stroop Color and Word Test. *J Personal Assessment.* (1975) 39:386–8. doi: 10.1207/s15327752jpa3904_10
111. Adleman NE, Menon V, Blasey CM, White CD, Warsofsky IS, Glover GH, et al. A developmental fMRI study of the Stroop color-word task. *NeuroImage.* (2002) 16:61–75. doi: 10.1006/nimg.2001.1046
112. Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt impulsiveness scale. *J Clin Psychol.* (1995) 51:768–74. doi: 10.1002/1097-4679(199511)51:6<768::aid-jclp2270510607>3.0.co;2-1
113. Ryu H, Lee JY, Choi A, Park S, Kim DJ, Choi JS. The relationship between impulsivity and internet gaming disorder in young adults: mediating effects of interpersonal relationships and depression. *Int J Environ Res Public Health.* (2018) 15:458. doi: 10.3390/ijerph15030458
114. Kale D, Stautz K, Cooper A. Impulsivity related personality traits and cigarette smoking in adults: a meta-analysis using the UPPS-P model of impulsivity and reward sensitivity. *Drug Alcohol Depend.* (2018) 185:149–67. doi: 10.1016/j.drugalcdep.2018.01.003
115. Zahalka EA, Seidler FJ, Lappi SE, McCook EC, Yanai J, Slotkin TA. Deficits in development of central cholinergic pathways caused by fetal nicotine exposure: differential effects on choline acetyltransferase activity and [3H] hemicholinium-3 binding. *Neurotoxicol Teratol.* (1992) 14:375–82. doi: 10.1016/0892-0362(92)90047-E
116. DeBry SC, Tiffany ST. Tobacco-induced neurotoxicity of adolescent cognitive development (TINACD): a proposed model for the development of impulsivity in nicotine dependence. *Nicotine Tobacco Res.* (2008) 10:11–25. doi: 10.1080/14622200701767811
117. Poltavski DV, Weatherly JN. Delay and probability discounting of multiple commodities in smokers and never-smokers using multiple-choice tasks. *Behav Pharmacol.* (2013) 24:659–67. doi: 10.1097/FBP.0000000000000010
118. Sloan FA, Wang Y. Economic theory and evidence on smoking behavior of adults. *Addiction.* (2008) 103:1777–85. doi: 10.1111/j.1360-0443.2008.02329.x
119. Dalley JW, Everitt BJ, Robbins TW. Impulsivity, compulsivity, and top-down cognitive control. *Neuron.* (2011) 69:680–94. doi: 10.1016/j.neuron.2011.01.020
120. Naish KR, Vedelago L, MacKillop J, Amlung M. Effects of neuromodulation on cognitive performance in individuals exhibiting addictive behaviors: a systematic review. *Drug Alcohol Depend.* (2018) 192:338–51. doi: 10.1016/j.drugalcdep.2018.08.018
121. Everitt BJ, Robbins TW. Drug addiction: updating actions to habits to compulsions ten years on. *Annual Rev Psychol.* (2016) 67:23–50. doi: 10.1146/annurev-psych-122414-033457
122. Teichner G, Horner MD, Roitzsch JC, Herron J, Thevos A. Substance abuse treatment outcomes for cognitively impaired and intact outpatients. *Addict Behav.* (2002) 27:751–63. doi: 10.1016/S0306-4603(01)00207-6
123. Brand M, Young KS, Laier C, Wölfling K, Potenza MN. Integrating psychological and neurobiological considerations regarding the development and maintenance of specific Internet-use disorders: an Interaction of Person-Affect-Cognition-Execution (I-PACE) model. *Neurosci Biobehav Rev.* (2016) 71:252–66. doi: 10.1016/j.neubiorev.2016.08.033
124. Moccia L, Pettorruso M, De Crescenzo F, De Risio L, di Nuzzo L, Martinotti G, et al. Neural correlates of cognitive control in gambling disorder: a systematic review of fMRI studies. *Neurosci Biobehav Rev.* (2017) 78:104–16. doi: 10.1016/j.neubiorev.2017.04.025
125. Fauth-Bühler M, Mann K. Neurobiological correlates of internet gaming disorder: similarities to pathological gambling. *Addict Behav.* (2017) 64:349–56. doi: 10.1016/j.addbeh.2015.11.004
126. Di Nicola M, Tedeschi D, De Risio L, Pettorruso M, Martinotti G, Ruggeri F, et al. Co-occurrence of alcohol use disorder and behavioral addictions: relevance of impulsivity and craving. *Drug Alcohol Dependence.* (2015) 148:118–25. doi: 10.1016/j.drugalcdep.2014.12.028
127. King DL, Delfabbro PH, Griffiths MD, Gradisar M. Assessing clinical trials of Internet addiction treatment: a systematic review and CONSORT evaluation. *Clin Psychol Rev.* (2011) 31:1110–6. doi: 10.1016/j.cpr.2011.06.009
128. Antonelli M, Fattore L, Sestito L, Di Giuda D, Diana M, Addolorato G. Transcranial magnetic stimulation: a review about its efficacy in the treatment of alcohol, tobacco and cocaine addiction.

Addictive behav. (2020) 114:106760. doi: 10.1016/j.addbeh.2020.106760

129. Lefaucheur JP, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014-2018). *Clin Neurophysiol.* (2020) 131:474–528. doi: 10.1016/j.clinph.2020.02.003
130. King DL, Delfabbro PH, Wu A, Doh YY, Kuss DJ, Pallesen S, et al. Treatment of Internet gaming disorder: An international systematic review and CONSORT evaluation. *Clin Psychol Rev.* (2017) 54:123–33. doi: 10.1016/j.cpr.2017.04.002

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.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 04 March 2021
doi: 10.3389/fpsyt.2021.644882

Behavioral Inhibition/Activation Systems and Depression Among Females With Substance Use Disorder: The Mediating Role of Intolerance of Uncertainty and Anhedonia

Jinlan Xie[1†], *Ping Fang*[1†], *Zhihao Zhang*[2,3], *Ronglei Luo*[2] *and Bibing Dai*[2*]

[1] *Department of Psychology, Capital Normal University, Beijing, China,* [2] *Department of Psychiatry and Psychology, School of Basic Medical Sciences, Tianjin Medical University, Tianjin, China,* [3] *Xiangya Nursing School, Central South University, Changsha, China*

OPEN ACCESS

Edited by:
Xingchao Wang,
Shanxi University, China

Reviewed by:
Guohua Zhang,
Wenzhou Medical University, China
Liangsuo Ma,
University of Texas Health Science Center at Houston, United States
Mauro Pettorruso,
University of Studies G. d'Annunzio Chieti and Pescara, Italy

***Correspondence:**
Bibing Dai
daibibing@tmu.edu.cn

†These authors have contributed equally to this work

Specialty section:
This article was submitted to Addictive Disorders, a section of the journal Frontiers in Psychiatry

Received: *22 December 2020*
Accepted: *10 February 2021*
Published: *04 March 2021*

Citation:
Xie J, Fang P, Zhang Z, Luo R and Dai B (2021) Behavioral Inhibition/Activation Systems and Depression Among Females With Substance Use Disorder: The Mediating Role of Intolerance of Uncertainty and Anhedonia. Front. Psychiatry 12:644882. doi: 10.3389/fpsyt.2021.644882

Previous studies have shown that the behavioral inhibition/activation systems (BIS/BAS) have substantial effects on substance use disorder and emotional disorders, and substance use disorder and emotional disorders often occur; in particular, females with substance use disorder are more likely to also have serious emotional disorders including depression than their male counterparts. However, the associations between the BIS/BAS and depression in females with substance use disorder have received little attention. Furthermore, the underlying mechanisms of these relations are largely unknown. The present study examines the mediating roles of intolerance of uncertainty and anhedonia in the associations between the BIS/BAS and depression among females with substance use disorder from the Research Domain Criteria (RDoC) framework. A total of 303 females with substance use disorder from a compulsory substance abuse detention center were tested using a cross-sectional survey involving BIS/BAS Scales, Intolerance of Uncertainty Scale, Snaith-Hamilton Pleasure Scale, and Center for Epidemiologic Studies Depression Scale. The path analysis model revealed that both the BIS and BAS had a direct effect on depression, that the BIS had an indirect effect on depression through intolerance of uncertainty, and that the BAS had an indirect effect on depression via anhedonia. These findings contribute to a more thorough understanding of how the BIS/BAS influence depression among females with substance use disorder and suggest that the utility of targeting these associations in treatments would help reduce depression in females with substance use disorder.

Keywords: behavioral inhibition/activation systems, intolerance of uncertainty, anhedonia, depression, females with substance use disorder

INTRODUCTION

Globally, substance use disorder (SUD) has been increasing rapidly over the past decade (1). In addition, SUD prevalences were generally greater for males compared to females at most ages until the 70s (2). For example, the prevalences of 12-month DSM-V SUD for males and females were 4.9 and 3.0% in the United States, respectively (3). Similarly, the prevalences of 12-month DSM-IV SUD for males and females were 3.6 and 0.3% in China, respectively (4). SUD can be defined as a chronic relapsing brain disease that urges patients with SUD to seek and compulsorily use substances, despite their significant adverse consequences (5), especially in patients with certain biological, psychological or physical vulnerabilities (6, 7). SUD can cause a range of acute and long-term negative consequences for individuals, such as hyperemesis syndrome, neurocognitive impairments, HIV infection, and premature death (1, 8). SUD are also associated with substantial societal costs from lost productivity, poverty, health care costs, violent and property crime (3). In addition, there is a close relationship between SUD and psychiatric comorbidities, especially, the high prevalence of the SUD-depression comorbidity (9, 10), and some common risk factors appear to lead both to SUD and psychiatric disorders (e.g., depression, anxiety, schizophrenia, bipolar disorder) (9, 11, 12). Furthermore, compared to suffering from only one disorder, suffering from comorbid SUD and depression is strongly correlated to more serious consequences (e.g., greater symptom severity, impairment, suicidality) (13). However, it is still unclear what common risk factors play an important role and how to influence both SUD and depression. In addition, women are likely to suffer from SUD faster when using substances occasionally and are more vulnerable to relapse than men (14). Furthermore, females with SUD are twice as likely as male with SUD to suffer from psychiatric disorders (e.g., depression, anxiety, schizophrenia, bipolar disorder), almost 30 vs. 16%, respectively (15). Thus, to promote the prevention and early intervention of depression, it is imperative to identify risk factors and underlying mechanisms for depression in females with SUD.

The National Institute of Mental Health (NIMH) recently launched the Research Domain Criteria (RDoC) initiative, which provides a new classification framework with transdiagnostic psychopathological dimensions for research on psychiatric disorders (16). These continuous dimensions which are important factors in the context of precision medicine for psychiatry, vary from the general population to individuals with psychiatric disorders (17). Furthermore, these transdiagnostic dimensions can be associated with a range of psychiatric disorders and be used to distinguish the different pathophysiological disease subtypes and serve as potential predictors of treatment outcomes (18). In addition, two objectives of the RDoC initiative are to explore the mechanisms common to a clustering of psychiatric disorders and the unique mechanisms corresponding to specific psychiatric symptoms serving as indicators of differential risk factors among these symptoms (19). Because depression is the first leading cause of global burden among psychiatric disorders (20) and there is high co-occurring SUD and depression in female (9, 15). Therefore, it is very important to explore the common and specific mechanisms for depression in females with SUD within the RDoC framework. To explore these mechanisms, we adopted the Interaction of Person-Affect-Cognition-Execution (I-PACE) theory (21) in the SUD field to build the present research model. The prior theoretical model suggests that potential predisposing variables and vulnerability factors, such as personality variables, cognition and affect-vulnerability factors, may moderately mediate the development and maintenance of psychiatric disorders.

Gray's neuropsychological reinforcement sensitivity theory postulates that two basic dimensions of motivation, including a behavioral inhibition system (BIS) and a behavioral activation system (BAS), govern avoidance and approach behaviors in response to various types of stimuli (11, 22). According to this theory, the BIS is sensitive to stimuli of punishment or non-reward, which may drive individuals to avoid potentially negative or harmful consequences. Therefore, individuals with high levels of BIS activation are more likely to avoid loss and to show a blunted response to reward (23). However, the BAS generates behaviors corresponding to all conditioned and unconditioned appetitive stimuli and displays close relationships with the enhancement of reward or the termination of punishment. Thus, individuals with high levels of BAS activation may show greater proneness to seek reward and to approach novelty (23). As transdiagnostic personality traits, the BIS and the BAS provide an important view for understanding and explaining psychopathology, such as anxiety disorders, depression, eating disorders, and SUD (11). Previous studies found that individuals with SUDs reported higher BAS levels than controls and that the BAS was positively associated with lifetime diagnoses of substance abuse without comorbid anxiety disorders (24, 25). However, the associations between the BIS and substance use problems are still inconsistent. Some studies have found a significant negative correlation between the BIS and substance use problems (26), while some studies have indicated that the BIS is not significantly associated with substance use problems (27). These inconsistencies may be caused by considering different kinds of substance use and different study populations (e.g., age groups, sex ratio) (28). In addition, a large amount of evidence supports the significant associations between the BIS/BAS and depression (11). Previous results indicated that low BAS sensitivity not only is a potential marker of vulnerability to depression but also may be useful in predicting the course of the disorder (29, 30). Furthermore, behavioral activation treatments aim to modify the pattern of low approach in depressed patients by positive activity scheduling and have played an important role in treating depressive episodes and reducing relapses (31). Although previous researchers initially considered the BIS a specific diathesis for anxiety rather than depression, many studies have recently indicated that BIS reactivity is positively related to depression (29, 32). For example, compared to a control group, a depressed group showed higher BIS levels. Furthermore, BIS scores have been shown to have a more positive association with depression scores in a major depressive disorder group than in a control group. Although the above results could indicate that Gray's neuropsychological reinforcement

sensitivity theory may be useful for understanding and explaining psychiatric disorders, the inconsistent results on the association between SUD and depression require more research to explore the associations between the BIS/BAS and depression in a specific context, especially in females with SUD. Furthermore, although most previous studies have shown that the BIS/BAS contribute to depression, little is known about the mediating mechanisms underlying these associations in females with SUD. However, two important transdiagnostic psychopathological dimensions—intolerance of uncertainty as cognitive bias and anhedonia as emotion and motivation deficits—may be among the mechanisms for linking the BIS/BAS to depression in females with SUD.

Life is full of uncertainty, but the extent to which uncertainty is tolerable varies across individuals. Intolerance of uncertainty (IU) is a cognitive bias that influences individuals' perceptions, interpretations, and responses to uncertain scenarios at the cognitive, emotional, and behavioral levels (33). Individuals with a high level of IU experience stress and disturbance in response to uncertainty, hold a negative attitude toward uncertainty, believe uncertainty causes dysfunctional behavior, and regard uncertainty as unfair and to be avoided (34). Recently, IU has been explained as "an individual's dispositional incapacity to endure the aversive response triggered by the perceived absence of salient, key, or sufficient information, and sustained by the associated perception of uncertainty" (35). Although previous studies have suggested that IU plays an important and specific role in the development and maintenance of high levels of worry and generalized anxiety disorder (33, 36), an increasing number of researchers regard IU as a transdiagnostic risk factor for a range of psychiatric disorders, such as generalized anxiety disorder, obsessive-compulsive disorder, eating disorders, depression, and SUD (37–39). For example, several studies have found that compared to healthy individuals, individuals with SUD perceive higher levels of IU (12, 40). While the researchers who conducted these studies also suggested that although IU is a feature of SUD, it may not play a unique role. First, the BIS is related to attempts to escape from or avoid novel, threatening or uncertain environments, which may cause individuals to interpret ambiguous situations more negatively (41). Thus, individuals with high BIS levels may show enhanced associative learning and learn to avoid an aversive situation easily (42). Because both the BIS and IU are closely correlated with information processing biases about dangerous or ambiguous stimuli, the BIS seems to be an important predictor of IU (43). The BAS predisposes an individual to pursue reward and novel sources, while individuals with high levels of IU are likely to select low-probability immediate rewards rather than high-probability delayed rewards (44). Furthermore, compared to a control group, individuals with higher levels of IU were less sensitive to the previously rewarded context (40). Therefore, the BAS may have no association with IU. Second, individuals with higher IU tend to perceive uncertainty negatively and adopt negative coping strategies and poor problem orientations, which explains why IU can correlate positively with depression (45). For example, people diagnosed with depression have been shown to possess higher levels of IU than community and undergraduate samples (46). Furthermore, IU has been shown to predict not only current depressive symptoms but also depression levels 6 weeks later (47). Although previous studies have suggested that IU may act as a mediator between the BIS and depression, no study has explored these associations in females with SUD.

Traditionally, anhedonia has been conceptualized as the inability to experience pleasure or interest in things (5). Recently, anhedonia has been recognized as an important transdiagnostic psychopathological dimension according to the RDoC by the NIMH (48). Anhedonia is known as an important symptom across psychiatric diagnoses, including affective disorders, obsessive-compulsive disorder, schizophrenia and SUD (19, 49). In particular, anhedonia seems to play an important role in the pathogenesis of both SUD and mood disorders but is more likely to be associated with the cooccurrence of SUD and depression (9). The BAS has a strong relationship with reward seeking, and individuals with high BAS levels exhibit enhanced reward dependence and novelty processing (28). Previous studies have found low BAS levels and reduced motivation to pursue rewarding stimuli to be positively linked to anhedonia in a healthy population (50) and physical activity engagement to be negatively associated with anhedonia (51). Furthermore, Veldhoven, Roozen, and Vingerhoets (52) found that the BAS was negatively correlated with anhedonia in patients with an alcohol use disorder. A range of studies adopting multiple methods from self-report, behavioral and neurophysiological levels have provided strong evidence that reduced approach motivation and reward hyposensitivity reflect motivational deficits in anhedonia (52–54). However, individuals with high levels of BIS activation exhibit enhanced sensitivity toward punishment and threat stimuli, and they show a blunted responsivity to reward (23), which suggests that the BIS may not play an important role in anhedonia. In addition, cross-sectional and longitudinal studies have shown that anhedonia plays an important role in the development of depression (55, 56). Furthermore, anhedonia can predict poorer responsivity to pharmacological and psychological interventions for depression (57). Although previous studies have suggested that anhedonia is a potential mediator between the BAS and depression, the role of anhedonia in these associations has not been thoroughly studied in females with SUD.

The purpose of the present study was to examine how the BIS/BAS influence depression in females with SUD. Specifically, this study explored the mediating effects of IU and anhedonia on the BIS/BAS and depression. A previous study found that high BIS levels had an indirect effect on depression via increased rumination and that low BAS levels had an indirect effect on depression through decreased self-reflection in a sample of participants who had attempted suicide (58). To our knowledge, this is the first comprehensive empirical study incorporating the BIS/BAS, IU, anhedonia and their roles in depression among females with SUD within the RDoC framework. On the basis of the I-PACE theory, the proposed model is presented in **Figure 1**. It is plausible to hypothesize that IU and anhedonia act as mediators of the BIS/BAS and depression relationship. Therefore, our hypotheses are as follows: (1) There is a high prevalence of depression in females with SUD; (2) the BIS and

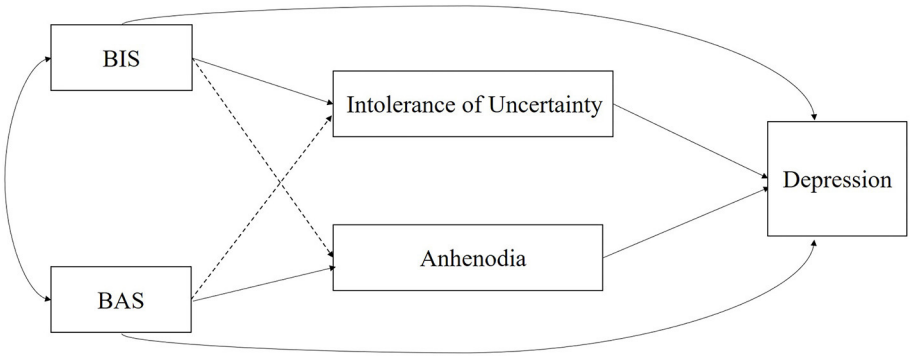

FIGURE 1 | The supposed model.

BAS directly influence depression; (3) IU, rather than anhedonia mediates the relationship between the BIS and depression; and (4) anhedonia, rather than IU, mediates the relationship between BAS and depression.

MATERIALS AND METHODS

Participants

Participants were recruited from a compulsory substance abuse detention center inTianjin, a Representative Municipality city of China. Inclusion criteria included: current diagnosis SUD, between the ages of 18–59, being sufficiently fluency in Chinese to complete the research questionnaires, and being willing to provide written informed consent prior to their inclusion. In addition, exclusion criteria comprised the following: traumatic brain injury and severe suicide risk. Based on the cluster sampling method, a total of 303 Chinese females with SUD were eligible. Of the participants (M_{age} = 34.97 years, SD = 8.52 years, age range: 18–57 years) included 41.9% were unmarried, 21.5% were married, 35.0% were divorced and 1.7% had missing marital status data. More detailed sociodemographic information is shown in **Table 1**. This cross-sectional design research was approved by the Institutional Review Board of Department of Psychology, Capital Normal University in China. All participants gave written informed consent and they could quit the study at any time without being penalized.

Measures

The Behavioral Inhibition System/Behavioral Activation System Scales

The BIS/BAS scales are useful tools for studying individual differences in behavioral inhibition systems and behavioral activation systems (22). A validated Chinese version of the BIS/BAS scales was used to assess the BIS and BAS (59). The BIS/BAS scales comprise 18 items, including the BAS scale (13 items) and the BIS scale (5 items). The former scale is divided into three subscales: drive (BAS-drive, 4 items), reward responsiveness (BAS-reward, 5 items), and fun seeking (BAS-fun, 4 items). All items were assessed on a 4-point Likert scale from 1 (totally disagree) to 4 (totally agree). Sample items are "When I get something I want, I feel excited and energized (BAS)" and "I feel pretty worried or upset when I think or know somebody is angry at me (BIS)." In the present study, scores for all 13 BAS items were summed to yield a single BAS score, while scores for all five BIS items were added up to generate a single BIS score. Higher BAS and BIS scores reflect higher BAS and BIS levels, respectively. The Cronbach's alpha coefficients for the BAS and BIS in the current sample were 0.881 and 0.620, respectively.

The Intolerance of Uncertainty Scale

The IUS is widely used to assess individuals' extent of intolerance of uncertainty by rating 27 items on a scale from 1 (Not at all characteristic of me) to 5 (Entirely characteristic of me) (60). The IUS includes four subscales: uncertainty is stressful and upsetting (e.g., "Uncertainty makes life intolerable."), uncertainty leads to the inability to act (e.g., "When it's time to act, uncertainty paralyzes me."), uncertain events are negative and should be avoided (e.g., "One should always look ahead to avoid surprises."), and uncertainty is unfair (e.g., "I think it's unfair that other people seem to be sure about their future.") (34). The overall IU score is determined by summing all item scores, with higher scores indicating greater IU. The Chinese language version demonstrates excellent internal consistency, good test-retest reliability over a 5-week period, and adequate convergent and discriminant validity (61, 62). In the present study, the Cronbach's alpha coefficient for the Chinese IUS was 0.909.

The Snaith-Hamilton Pleasure Scale

The SHAPS is a self-administered scale including 14 items that is used to assess anhedonia (63). Each of the items has a set of four response categories: Strongly Agree (=1), Agree (=2), Disagree (=3), and Strongly Disagree (=4). A sample item is "I would enjoy being with my family or close friends." Total scores range from 14 to 56, with higher scores indicating a higher level of anhedonia. The Chinese language version shows excellent internal consistency, good construct validity, and adequate convergent and discriminant validity (64). In the present study, the Cronbach's alpha coefficient for the Chinese SHAPS was 0.915.

TABLE 1 | Sociodemographic variables of participants ($N = 303$).

Characteristic	*n*	%
Marital status		
Unmarried	127	41.9
Married	65	21.5
Divorced	106	35.0
Missing	5	1.7
Education		
Primary school and below	67	22.1
Junior high school	145	47.9
High school	68	22.4
University and above	18	5.9
Missing	5	1.7
Occupational status		
Institutional personnel	4	1.3
Company employee	14	4.6
Freelancer	140	46.2
Other	137	45.2
Missing	8	2.6
Duration of substance use (y)		
1	17	5.6
2	36	11.9
3	32	10.6
4	37	12.2
5 or over 5	178	58.7
Missing	3	1
Number of compulsory detoxification		
1	142	46.9
2	106	35.0
3 or over 3	49	16.2
Missing	6	2
Type of substance used		
New substances (ecstasy, meth, etc.)	225	74.3
Traditional substance (heroin)	67	22.1
Missing	11	3.6

The Center for Epidemiological Studies Depression Scale

The CES-D is used to assess depressive symptoms and includes 20 items in Likert format, using four possible responses anchored by 0 (rarely or none of the time) and 3 (most or all of the time) (65). Total scores range from 0 to 60, with higher scores indicating a higher level of depression. Respondents with scores equal to or >16 are defined as depressed (66). The CES-D has been extensively validated in Chinese populations (67). In the present study, the Cronbach's alpha coefficient for the Chinese CES-D was 0.878.

Procedure

The participants were given a packet of questionnaires that included instructions on how to respond to the questions and assurances of anonymity as well as questions regarding their basic sociodemographic information (i.e., age, marital status, and education), the BIS/BAS scales, IUS, SHAPS, and CES-D. All scales were administered to the participants individually. All scales were printed in the Chinese language and took approximately 25 min to finish. No personal identifying information was collected, and all the information collected was confidential.

Data Analysis

Because the proportion of data missing from each scale was low (<5%), mean substitution was used to deal with missing data. First, we conducted descriptive statistics and Pearson's correlation analysis with IBM SPSS statistics 24.0. Specifically, we analyzed the influence of demographic variables on depression among females with SUD using Student's *t*-test or analysis of variance (ANOVA). Next, Mplus 7.0 was used to test the hypothesized model. Because depression may be correlated with a variety of sociodemographic factors, the hypothesized model was conducted by adding age, marital status (married or not), education, duration of substance use, number of compulsory detoxifications, and type of substance used as control variables, which is a common statistical method to reduce the confounding effects of personal characteristics (68). A path analysis model was conducted to test the mediating roles of IU and anhedonia in the relationships between the BIS/BAS and depression in females with SUD. In the current study, several goodness-of-fit indices were adopted to test the model-data fit. The chi-square statistic and its associated *p*-value were reported. If the *p*-value is not significant, it may show good model-data fit. Other model fit indices include the Tucker-Lewis Index (TLI) (69), the comparative fit index (CFI) (70), the standardized root mean square residual (SRMR) (71) and the root mean square error of approximation (RMSEA) (72). A TLI and CFI greater than 0.95 and an SRMR and RMSEA <0.08 indicate good model fit (71). The bias-corrected percentile bootstrap method (5,000 bootstrap samples) with 95% confidence intervals (CIs) was performed to examine the significance of mediation effects. The 95% CIs that do not contain zero show that the effects are significant. The predictive and explanatory powers of the model were assessed using path coefficients and R^2.

RESULTS

Impact of Demographic Features on Depression

Briefly speaking, there were no significant differences in depression between two kinds of marital status including married or not ($t_{(296)} = 1.60$, $p = 0.11$), among education groups ($F(3, 294) = 1.12$, $p = 0.34$), among occupational status groups ($F(3, 291) = 1.20$, $p = 0.31$), among duration of substance use groups ($F(4, 295) = 0.40$, $p = 0.81$), and among number of compulsory detoxification groups ($F(2, 294) = 0.04$, $p = 0.96$). However, there was a significant difference in depression between the two types of substance used groups ($t_{(290)} = 2.37$, $p = 0.02$). Females with traditional substance (M ± SD = 17.37±9.46) had higher level of depression than others with new substance (M ± SD = 14.41 ± 8.85). In addition, according to a CES-D cutoff score

of ≥16 indicating depressive symptoms, there were 137 (45.2%) depressed females in our sample.

Descriptive Statistics and Correlations

The descriptions and correlations of all variables from these scales are presented in **Table 2**. Specifically, the BIS was positively associated with IU but negatively associated with anhedonia. The BAS was negatively correlated with anhedonia and depression. Both IU and anhedonia were positively associated with depression.

Path Analysis Model

The results of the initial hypothesized model with age, marital status, education, duration of substance use, number of compulsory detoxifications, and type of substance used as control variables ($\chi 2 = 36.810$, $\chi 2/df = 1.472$, $p = 0.060$, TLI = 0.889, CFI = 0.897, SRMR = 0.040, RMSEA = 0.041) showed that the fit of the model was suboptimal, but there were eight non-significant pathways for age and depression ($\beta = 0.008$, $p = 0.905$), marital status and depression ($\beta = -0.104$, $p = 0.056$), education and depression ($\beta = 0.046$, $p = 0.424$), duration of substance use and depression ($\beta = 0.093$, $p = 0.091$), number of compulsory detoxification and depression ($\beta = 0.016$, $p = 0.823$), type of substance used and depression ($\beta = -0.021$, $p = 0.748$), the BIS and anhedonia ($\beta = -0.042$, $p = 0.555$), and the BAS and IU ($\beta = -0.114$, $p = 0.076$) in this model. After removing these eight pathways, the results of the measurement showed that the modified model fit the data excellently ($\chi^2 = 3.922$, $\chi^2/df = 1.307$, $p = 0.270$, TLI = 0.976, CFI = 0.992, SRMR = 0.021, RMSEA = 0.033). Standardized pathway coefficients within factors are displayed in **Figure 2**. The final model accounted for 16.6% of the total variance in depression among females with SUD.

When the final model was chosen, bias-corrected bootstrapping was performed to further test the significance of the mediators. Compared to traditional mediation analyses, bootstrapping as a non-parametric resampling procedure can provide greater statistical power to test indirect effects (73). The results of the bootstrap analyses indicated that the direct effect of the BIS on depression was significant ($\beta = 0.201$, $p = 0.001$, 95% CI = [0.080, 0.323]), and the specific indirect effect of the BIS on depression through IU was also significant ($\beta = 0.054$, $p = 0.001$, 95% CI = [0.021, 0.087]). In addition, the results of the bootstrap analyses showed that the direct effect of the BAS on depression was significant ($\beta = -0.219$, $p < 0.001$, 95% CI = [−0.336, −0.103]), and the specific indirect effect of the BAS on depression *via* anhedonia was also significant ($\beta = -0.095$, $p < 0.001$, 95% CI = [−0.148, −0.043]).

DISCUSSION

To the best of our knowledge, this is the first study to explore the direct and indirect effects of the BIS/BAS on depression through IU and anhedonia in females with SUD within the RDoC framework. The present results provide strong evidence supporting our proposed model. We found a high prevalence of depression in this population and that the BIS significantly positively predicted depression, while the BAS significantly negatively predicted depression. In addition, IU was a significant mediator between the BIS and depression, while anhedonia was a significant mediator between the BAS and depression in this population. Considering that SUD differ in course and outcome between women and men, the present results for females with SUD could contribute to understanding depression status, understanding the mechanism of depression, and providing important guidelines for the identification, intervention and treatment of depression in this special population.

In the current study, 45.2% of the females with SUD reported having depression, which is much higher than the rates in other populations (e.g., general women, male with SUD) in previous studies (15, 74). Several reasons may explain why there was a high prevalence rate found in the present study. First, depression is one of the most common psychiatric disorders and a major public health problem in the Chinese population, especially among women, because great social and economic transformation, as well as rapid urbanization and modernization in China, brought dramatic changes to society, including increased personal and contextual stressors (i.e., faster pace of life, job loss, marital divorce or separation, traffic congestion, overcrowded living conditions), disintegration of China's traditional large family, and decline in family support by weakening family ties (75). Most of these factors have been considered risk factors for depression in a previous study (76) and may correlate with the increased depression prevalence rate found in females with SUD. In the present study, 78.2% of the sample was unmarried or divorced, which was likely to cause difficulties in the availability of family support, one of the most important sources of social support in Chinese culture. Second, compared to general women, females with SUD may experience more stressful events, such as underemployment, broad socioeconomic disadvantage and poor health status, which are potential risk factors for depression. Third, compared to male with SUD, substances could have more serious negative consequences in females with SUD. These consequences include higher substance use dependence, easier relapse, less response to treatment, more severe SUD syndrome, and higher comorbidity of SUD and depression (14, 15).

Compared to the positive predictors of high BIS and BAS levels for SUD found in a previous study (24, 25), the current results indicated that high BIS levels and low BAS levels directly positively predict depression in females with SUD, which is supported by the theory that both avoidance motivation and approach deficits play an important role in weakening positive experiences and reinforcement for non-depressed behaviors, leading to the onset and maintenance of depression (11). On the one hand, individuals with reward hypersensitivity are more likely to be susceptible to SUD by means of substance-triggered excessive reward activation states. When their reward systems switch to excessively deactivate responsivity to unresolved failures or losses because of the termination of substance use in the compulsory substance abuse detention center, they become more vulnerable to depression, which is supported by electrophysiological studies (30). For example, a previous study found that low BAS levels measured by ERPs prospectively predict depression onset in adolescent girls (77). Furthermore,

TABLE 2 | Mean, standard deviation, and correlations among all variables.

	M	SD	1	2	3	4	5
1. BIS	15.73	2.45	1				
2. BAS	43.29	6.12	0.54**	1			
3. IU	78.79	15.62	0.29**	0.08	1		
4. Anhedonia	22.71	5.97	−0.22**	−0.40**	−0.09	1	
5. Depression	14.93	9.14	0.08	−0.20**	0.19**	0.28**	1

*BIS, behavioral inhibition system; BAS, behavioral activation system; IU, intolerance of uncertainty; **$p < 0.01$.*

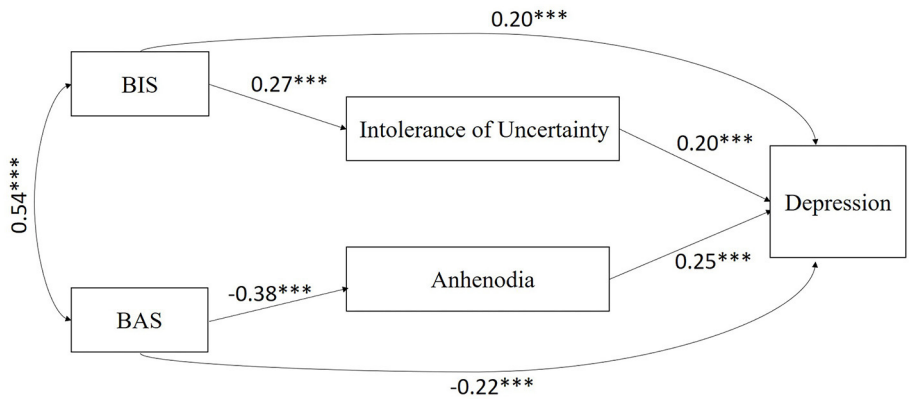

FIGURE 2 | The relationships between BIS/BAS and depression mediated by intolerance of uncertainty and anhedonia. ***$p < 0.001$.

a longitudinal fMRI reward process study has indicated that compared with healthy controls, individuals with depression who consistently exhibited less striatal activation to reward stimuli suffered from increasing depressive symptoms (78). On the other hand, females with high BIS levels, who are more likely to show hypersensitivity to punishment stimuli (e.g., failure or loss, criticism or scolding), are more vulnerable to substance overuse to escape loneliness and life problems. Meanwhile, females with SUD with high BIS levels have been shown to be prone to depression because the BIS is positively correlated with neuroticism, which is a risk personality trait for depression (79).

In the current study, we found that IU mediated the relationships between the BIS and depression and that anhedonia served as a mediator of the relationships between the BAS and depression among females with SUD, which shows that these variables serve as indicators of differential risk factors with great importance to support the unique mechanisms corresponding to depressive symptoms in females with SUD within the RDoC framework (19). On the one hand, the BIS can intensify individual reactions to withdraw from or avoid novel, uncertain or threatening contexts, which may trigger individuals to interpret ambiguous information more negatively (41). Especially for females with SUD who suffer from more negative life events and more uncertainty within their environment, high BIS levels could induce high IU, thus leading to a higher level of depression than the individuals with low BIS levels. Because individuals with high levels of IU show blunted reward responsiveness (40), the BAS cannot have an indirect impact on depression through IU. On the other hand, the BAS has a close relationship with reward seeking, and individuals with high BAS sensitivity show a high preference for novelty processing and reward dependence (23). The BAS may play an important role in individuals' motivations to conduct goal-directed behavior (52). However, individuals with a high level of anhedonia take part in less pleasant activities on the non-substance-related activities list and less physical activities (e.g., walking frequency, moderate-intensity physical activity frequency and duration, and vigorous-intensity physical activities and duration), which are associated with higher physical activity enjoyment and a lower level of depressive symptoms (51, 52). Thus, females with SUD with low BAS levels lose their motivation to pursue meaningful and rewarding stimuli and experience more anhedonia in daily life, which exacerbates their depression. However, individuals with high BIS sensitivity show an enhanced preference for punishment and threat stimuli rather than pleasure or reward stimuli (23), which could explain why the BIS did not indirectly influence depression via anhedonia in females with SUD in the present study.

The present study may have some theoretical and practical implications. From a theoretical perspective, these results provide strong evidence in support of the RDoC initiative. First, consistent with previous findings (29, 46, 47, 55), the present study found that the BIS, the BAS, IU, and anhedonia have close relationships with depression in females with SUD, which indicates that these variables are transdiagnostic features across different psychiatric disorders. Second, the BIS had an indirect

influence on depression through IU, while the BAS had an indirect influence on depression *via* anhedonia in the present study, which suggests that it is imperative to explore the specific mechanisms unique to specific psychiatric symptoms (19). From a practical perspective, the current results could aid evidence-based prevention and interventions to decrease depression among females with SUD. Based on our model, prevention and interventions considering the BIS/BAS, IU, and anhedonia may be helpful for establishing effective strategies for females with SUD with depression. First, when identifying a target population for further prevention and intervention programs among females with SUD, combinations of these risk factors (e.g., low BAS levels, high BIS levels, high IU, and high anhedonia) should be adopted according to the present results. Second, and even more importantly, our results provide invaluable knowledge on how to prevent and intervene in depression among females with SUD. Specifically, interventions to decrease BIS levels and to increase BAS levels could decrease depression in females with SUD. In addition, the findings of this study that IU mediates the associations between the BIS and depression and that anhedonia mediate the relationships between the BAS and depression has important implications for practice. On the one hand, to prevent and intervene in depression in females with SUD with high BIS levels, CBT-IU techniques should be exploited to enhance females with SUD' acceptance of uncertainty because these techniques include psychoeducation on reappraising uncertainty, cognitive modifications for unrealistically positive illusions about seeking certainty, and exposure training for uncertainty (37). On the other hand, to prevent and intervene in depression in females with SUD with low BAS levels, specific behavioral activation therapy unique to these populations should be given more attention and deserve further exploration (57).

However, there are some limitations in the present study that have to be addressed. First, there was the absence of structured assessment data to validate the clinical diagnoses of depression in the sample, although the CES-D has been widely used to assess depression in epidemiological research (75). Thus, future studies should try to assess depression in females with SUD based on a clinical diagnosis system (e.g., DSM-V or ICD-11). Second, this study was a cross-sectional survey study, which prevented the identification of any causal relations among these variables. Future studies should conduct experimental research or use longitudinal designs to strictly explore the causal relationships among these variables. Third, this study adopted the self-report method, which may restrict the validity of the data because of social desirability and memory or response biases. Therefore, future studies should take efforts to collect data from multiple informants (e.g., females with SUD, supervisors and peers) and use multi-index methods, including objective markers and subjective reports. Fourth, the physical health status of the sample was not assessed in the present study, that may ignore the potential influence of physical health on the present results. Therefore, future studies should try to assess physical health status in females with SUD. Finally, although the results from removing the subjects with missing data and redoing the analysis were the same as the present results, some potential errors may appear through the methods that some missing data were replaced with corresponding mean values and then were included in the analysis. Thus, future studies may increase sample size and improve their survey response quality to provide more strong evidence supporting the present findings.

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 ethics committee of Department of Psychology, Capital Normal University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JX and PF designed the study and wrote the protocol. BD and ZZ collected the research data. JX and BD conducted the statistical analyses and wrote the manuscript. RL conducted the literature searches and created the figures. All authors approved the final version of the manuscript.

FUNDING

This study was supported by the Humanities and Social Science Research of the Ministry of Education of China (18YJC190002).

REFERENCES

1. United Nations. *World Drug Report 2020*. United Nations (2020).
2. Vasilenko SA, Evans-Polce RJ, Lanza ST. Age trends in rates of substance use disorders across ages 18–90: differences by gender and race/ethnicity. *Drug Alcohol Depend.* (2017) 180:260–4. doi: 10.1016/j.drugalcdep.2017.08.027
3. Grant BF, Saha TD, Ruan WJ, Goldstein RB, Chou SP, Jung J, et al. Epidemiology of DSM-5 drug use disorder: results from the national epidemiologic survey on alcohol and related conditions–III. *JAMA Psychiatry*. (2016) 73:39–47. doi: 10.1001/jamapsychiatry.2015.2132
4. Huang Y, Wang Y, Wang H, Liu Z, Yu X, Yan J, et al. Prevalence of mental disorders in China: a cross-sectional epidemiological study. *Lancet Psychiatry*. (2019) 6:211–24. doi: 10.1016/S2215-0366(18)30511-X
5. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)*. Washington, DC: American Psychiatric Pub (2013).
6. Alipour A, Ghorbani T, Farzad V. The difference in the profile of working memory, auditory working memory, and spatial working memory between drug, stimulant, and methadone abusers and normal people. *Res Addict.* (2015) 9:9–17. Available online at: http://etiadpajohi.ir/article-1-266-en.html
7. Seyed Hashemi SG, Merghati Khoei E, Hosseinnezhad S, Mousavi M, Dadashzadeh S, Mostafaloo T, et al. Personality traits and substance use disorders: comparative study with drug user and non-drug user population. *Pers Individ Differ.* (2019) 148:50–6. doi: 10.1016/j.paid.2019.05.015
8. Karila L, Roux P, Rolland B, Benyamina A, Reynaud M, Aubin HJ, et al. Acute and long-term effects of cannabis use: a review. *Curr Pharm Design.* (2014) 20:4112–8. doi: 10.2174/13816128113199990620

9. Destoop M, Morrens M, Coppens V, Dom G. Addiction, anhedonia, and comorbid mood disorder. A narrative review. *Front Psychiatry.* (2019) 10:311. doi: 10.3389/fpsyt.2019.00311
10. Robertson AG, Easter MM, Lin H-J, Khoury D, Pierce J, Swanson J, et al. Gender-specific participation and outcomes among jail diversion clients with co-occurring substance use and mental health disorders. *J Subst Abus Treat.* (2020) 115:108035. doi: 10.1016/j.jsat.2020.108035
11. Bijttebier P, Beck I, Claes L, Vandereycken W. Gray's reinforcement sensitivity theory as a framework for research on personality–psychopathology associations. *Clin Psychol Rev.* (2009) 29:421–30. doi: 10.1016/j.cpr.2009.04.002
12. Garami J, Haber P, Myers CE, Allen MT, Misiak B, Frydecka D, et al. Intolerance of uncertainty in opioid dependency – Relationship with trait anxiety and impulsivity. *PLoS ONE.* (2017) 12:e0181955. doi: 10.1371/journal.pone.0181955
13. Prior K, Mills K, Ross J, Teesson M. Substance use disorders comorbid with mood and anxiety disorders in the Australian general population. *Drug Alcohol Rev.* (2017) 36:317–24. doi: 10.1111/dar.12419
14. Bobzean SAM, DeNobrega AK, Perrotti LI. Sex differences in the neurobiology of drug addiction. *Exp Neurol.* (2014) 259:64–74. doi: 10.1016/j.expneurol.2014.01.022
15. Epstein J, Barker P, Vorburger M, Murtha C. *Serious Mental Illness and Its Co-Occurrence With Substance Use Disorders, 2002.* Rockville, MD: Department of Health and Human Services, Substance Abuse and Mental Health Services Administration (2004).
16. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry.* (2010) 167:748–51. doi: 10.1176/appi.ajp.2010.09091379
17. Insel TR. The NIMH research domain criteria (RDoC) project: precision medicine for psychiatry. *Am J Psychiatry.* (2014) 171:395–7. doi: 10.1176/appi.ajp.2014.14020138
18. Fusar-Poli P, Solmi M, Brondino N, Davies C, Chae C, Politi P, et al. Transdiagnostic psychiatry: a systematic review. *World Psychiatry.* (2019) 18:192–207. doi: 10.1002/wps.20631
19. Nusslock R, Alloy LB. Reward processing and mood-related symptoms: an RDoC and translational neuroscience perspective. *J Affect Disord.* (2017) 216:3–16. doi: 10.1016/j.jad.2017.02.001
20. GBD 2016 Disease and injury incidence and prevalence collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the global burden of disease study 2016. *Lancet.* (2016) 390:1211–59. doi: 10.1016/S0140-6736(17)32154-2
21. Brand M, Wegmann E, Stark R, Müller A, Wölfling K, Robbins TW, et al. The interaction of person-affect-cognition-execution (I-PACE) model for addictive behaviors: update, generalization to addictive behaviors beyond internet-use disorders, and specification of the process character of addictive behaviors. *Neurosci Biobehav Rev.* (2019) 104:1–10. doi: 10.1016/j.neubiorev.2019.06.032
22. Carver CS, White TL. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: the BIS/BAS Scales. *J Pers Soc Psychol.* (1994) 67:319–33. doi: 10.1037/0022-3514.67.2.319
23. Li Q, Wang Y, Yang Z, Dai W, Zheng Y, Sun Y, et al. Dysfunctional cognitive control and reward processing in adolescents with Internet gaming disorder. *Psychophysiology.* (2020) 57:e13469. doi: 10.1111/psyp.13469
24. Johnson SL, Turner RJ, Iwata N. BIS/BAS levels and psychiatric disorder: an epidemiological study. *J Psychopathol Behav Assess.* (2003) 25:25–36. doi: 10.1023/A:1022247919288
25. Staiger PK, Kambouropoulos N, Dawe S. Should personality traits be considered when refining substance misuse treatment programs? *Drug Alcohol Rev.* (2007) 26:17–23. doi: 10.1080/09595230601036952
26. Simons JS, Dvorak RD, Batien BD. Methamphetamine use in a rural college population: associations with marijuana use, sensitivity to punishment, and sensitivity to reward. *Psychol Addict Behav.* (2008) 22:444–9. doi: 10.1037/0893-164X.22.3.444
27. O'Connor RM, Stewart SH, Watt MC. Distinguishing BAS risk for university students' drinking, smoking, and gambling behaviors. *Pers Individ Differ.* (2009) 46:514–9. doi: 10.1016/j.paid.2008.12.002
28. Li Q, Dai W, Zhong Y, Wang L, Dai B, Liu X. The mediating role of coping styles on impulsivity, behavioral inhibition/approach system, and internet addiction in adolescents from a gender perspective. *Front Psychol.* (2019) 10:2402. doi: 10.3389/fpsyg.2019.02402
29. Allen TA, Lam RW, Milev R, Rizvi SJ, Frey BN, MacQueen GM, et al. Early change in reward and punishment sensitivity as a predictor of response to antidepressant treatment for major depressive disorder: a CAN-BIND-1 report. *Psychol Med.* (2019) 49:1629–38. doi: 10.1017/S0033291718002441
30. Moriarity DP, Ng T, Titone MK, Chat IKY, Nusslock R, Miller GE, et al. Reward responsiveness and ruminative styles interact to predict inflammation and mood symptomatology. *Behav Ther.* (2020) 51:829–42. doi: 10.1016/j.beth.2019.11.007
31. Cuijpers P, van Straten A, Warmerdam L. Behavioral activation treatments of depression: a meta-analysis. *Clin Psychol Rev.* (2007) 27:318–26. doi: 10.1016/j.cpr.2006.11.001
32. Wang X, Zhou X, Dai Q, Ji B, Feng Z. The role of motivation in cognitive reappraisal for depressed patients. *Front Hum Neurosci.* (2017) 11:516. doi: 10.3389/fnhum.2017.00516
33. Dugas MJ, Schwartz A, Francis K. Brief report: intolerance of uncertainty, worry, and depression. *Cogn Ther Res.* (2004) 28:835–42. doi: 10.1007/s10608-004-0669-0
34. Buhr K, Dugas MJ. The intolerance of uncertainty scale: psychometric properties of the English version. *Behav Res Ther.* (2002) 40:931–45. doi: 10.1016/S0005-7967(01)00092-4
35. Carleton RN. Into the unknown: a review and synthesis of contemporary models involving uncertainty. *J Anxiety Disord.* (2016) 39:30–43. doi: 10.1016/j.janxdis.2016.02.007
36. Dugas MJ, Freeston MH, Ladouceur R. Intolerance of uncertainty and problem orientation in worry. *Cogn Ther Res.* (1997) 21:593–606. doi: 10.1023/A:1021890322153
37. Gillett CB, Bilek EL, Hanna GL, Fitzgerald KD. Intolerance of uncertainty in youth with obsessive-compulsive disorder and generalized anxiety disorder: a transdiagnostic construct with implications for phenomenology and treatment. *Clin Psychol Rev.* (2018) 60:100–8. doi: 10.1016/j.cpr.2018.01.007
38. McEvoy PM, Hyett MP, Shihata S, Price JE, Strachan L. The impact of methodological and measurement factors on transdiagnostic associations with intolerance of uncertainty: a meta-analysis. *Clin Psychol Rev.* (2019) 73:101778. doi: 10.1016/j.cpr.2019.101778
39. Rozgonjuk D, Elhai JD, Täht K, Vassil K, Levine JC, Asmundson GJG. Non-social smartphone use mediates the relationship between intolerance of uncertainty and problematic smartphone use: Evidence from a repeated-measures study. *Comput Hum Behav.* (2019) 96:56–62. doi: 10.1016/j.chb.2019.02.013
40. Radell ML, Allen MT, Favaloro B, Myers CE, Haber P, Morley K, et al. Intolerance of uncertainty and conditioned place preference in opioid addiction. *PeerJ.* (2018) 6:e4775. doi: 10.7717/peerj.4775
41. Radell ML, Myers CE, Beck KD, Moustafa AA, Allen MT. The personality trait of intolerance to uncertainty affects behavior in a novel computer-based conditioned place preference task. *Front Psychol.* (2016) 7:1175. doi: 10.3389/fpsyg.2016.01175
42. Sheynin J, Beck KD, Pang KCH, Servatius RJ, Shikari S, Ostovich J, et al. Behaviourally inhibited temperament and female sex, two vulnerability factors for anxiety disorders, facilitate conditioned avoidance (also) in humans. *Behav Processes.* (2014) 103:228–35. doi: 10.1016/j.beproc.2014.01.003
43. Mihić L, Colović P, Ignjatović I, Smederevac S, Novović Z. Anxiety between personality and cognition: the gray zone. *Pers Individ Differ.* (2015) 78:19–23. doi: 10.1016/j.paid.2015.01.013
44. Luhmann CC, Ishida K, Hajcak G. Intolerance of uncertainty and decisions about delayed, probabilistic rewards. *Behav Therapy.* (2011) 42:378–86. doi: 10.1016/j.beth.2010.09.002
45. Zhang G, Dai B. A summary of research on intolerance of uncertainty. *J Cap Norm Univ.* (2012) 205:124–30.
46. Carleton RN, Mulvogue MK, Thibodeau MA, McCabe RE, Antony MM, Asmundson GJG. Increasingly certain about uncertainty: intolerance of uncertainty across anxiety and depression. *J Anxiety Disord.* (2012) 26:468–79. doi: 10.1016/j.janxdis.2012.01.011
47. Miranda R, Fontes M, Marroquín B. Cognitive content-specificity in future expectancies: role of hopelessness and intolerance of uncertainty

in depression and GAD symptoms. *Behav Res Ther.* (2008) 46:1151–9. doi: 10.1016/j.brat.2008.05.009
48. Bedwell JS, Gooding DC, Chan CC, Trachik BJ. Anhedonia in the age of RDoC. *Schizophr Res.* (2014) 160:226–7. doi: 10.1016/j.schres.2014.10.028
49. Spano MC, Lorusso M, Pettorruso M, Zoratto F, Di Giuda D, Martinotti G, et al. Anhedonia across borders: transdiagnostic relevance of reward dysfunction for noninvasive brain stimulation endophenotypes. *CNS Neurosci Ther.* (2019) 25:1229–36. doi: 10.1111/cns.13230
50. Germans MK, Kring AM. Hedonic deficit in anhedonia: support for the role of approach motivation. *Pers Individ Differ.* (2000) 28:659–72. doi: 10.1016/S0191-8869(99)00129-4
51. Leventhal AM. Relations between anhedonia and physical activity. *Am J Health Behav.* (2012) 36:860–72. doi: 10.5993/AJHB.36.6.12
52. Veldhoven DT-v, Roozen H, Vingerhoets A. The association between reward sensitivity and activity engagement: the influence of delay discounting and anhedonia. *Alcohol Alcohol.* (2020) 55:215–24. doi: 10.1093/alcalc/agz105
53. Liu W-h, Wang L-z, Shang H-r, Shen Y, Li Z, Cheung EFC, et al. The influence of anhedonia on feedback negativity in major depressive disorder. *Neuropsychologia.* (2014) 53:213–20. doi: 10.1016/j.neuropsychologia.2013.11.023
54. Treadway MT, Bossaller NA, Shelton RC, Zald DH. Effort-based decision-making in major depressive disorder: a translational model of motivational anhedonia. *J Abnorm Psychol.* (2012) 121:553–8. doi: 10.1037/a0028813
55. Jordan DG, Winer ES, Salem T, Kilgore J. Longitudinal evaluation of anhedonia as a mediator of fear of positive evaluation and other depressive symptoms. *Cogn Emotion.* (2018) 32:1437–47. doi: 10.1080/02699931.2017.1289895
56. Winer ES, Bryant J, Bartoszek G, Rojas E, Nadorff MR, Kilgore J. Mapping the relationship between anxiety, anhedonia, and depression. *J Affect Disord.* (2017) 221:289–96. doi: 10.1016/j.jad.2017.06.006
57. Craske MG, Meuret AE, Ritz T, Treanor M, Dour HJ. Treatment for anhedonia: a neuroscience driven approach. *Depress Anxiety.* (2016) 33:927–38. doi: 10.1002/da.22490
58. Khosravani V, Baseri A, Kamali Z, Mohammadzadeh A, Amirinezhad A. Direct and indirect effects of behavioral inhibition/activation systems on depression and current suicidal ideation through rumination and self-reflection. *Arch Suicide Res.* (2020) 24:568–88. doi: 10.1080/13811118.2019.1649224
59. Li Y-Z, Zhang Y, Jiang Y, Li H, Mi S, Yi G-J, et al. The Chinese version of the BIS/BAS scale: reliability and validity. *Chin Ment Health J.* (2008) 22:613–6. doi: 10.3724/SP.J.1041.2008.00418
60. Freeston MH, Rhéaume J, Letarte H, Dugas MJ, Ladouceur R. Why do people worry? *Pers Individ Differ.* (1994) 17:791–802. doi: 10.1016/0191-8869(94)90048-5
61. Yang Z. Psychometric properties of the Intolerance of Uncertainty Scale (IUS) in a Chinese-speaking population. *Behav Cogn Psychother.* (2013) 41:500–4. doi: 10.1017/s1352465812000975
62. Yang Z, Chen H, Zhang X, Wang R, Ding J. The online version of the chinese intolerance of uncertainty scale: psychometric properties. *Cyberpsychol Behav Soc Netw.* (2016) 19:217–22. doi: 10.1089/cyber.2015.0149
63. Snaith RP, Hamilton M, Morley S, Humayan A, Hargreaves D, Trigwell P. A scale for the assessment of hedonic tone the Snaith-Hamilton Pleasure Scale. *Br J Psychiatry.* (1995) 167:99–103. doi: 10.1192/bjp.167.1.99
64. Liu W-h, Wang L-z, Zhu Y-h, Li M-h, Chan RCK. Clinical utility of the Snaith-Hamilton-Pleasure scale in the Chinese settings. *BMC Psychiatry.* (2012) 12:184. doi: 10.1186/1471-244X-12-184
65. Radloff LS. The CES-D scale:a self-report depression scale for research in the general population. *Appl Psychol Meas.* (1977) 1:385–401. doi: 10.1177/014662167700100306
66. Radloff LS, Locke BZ. The community mental health assessment survey and the CES-D scale. *Community Surv Psychiatr Disord.* (1986) 4:177–89.
67. Rankin SH, Galbraith ME, Johnson S. Reliability and validity data for a chinese translation of the center for epidemiological studies-depression. *Psychol Rep.* (1993) 73(3_suppl):1291–8. doi: 10.2466/pr0.1993.73.3f.1291
68. Hew J-J, Leong L-Y, Tan GW-H, Lee V-H, Ooi K-B. Mobile social tourism shopping: a dual-stage analysis of a multi-mediation model. *Tourism Manage.* (2018) 66:121–39. doi: 10.1016/j.tourman.2017.10.005
69. Tucker LR, Lewis C. A reliability coefficient for maximum likelihood factor analysis. *Psychometrika.* (1973) 38:1–10. doi: 10.1007/BF02291170
70. Rigdon EE. CFI versus RMSEA: a comparison of two fit indexes for structural equation modeling. *Struct Equ Modeling.* (1996) 3:369–79. doi: 10.1080/10705519609540052
71. Hooper D, Coughlan J, Mullen M. Structural equation modeling: guidelines for determining model fit. *Electron J Bus Res Methods.* (2007) 6:53–60. doi: 10.3109/03005364000000039
72. Browne MW, Cudeck R. Alternative ways of assessing model fit. In: Bollen KA, Long JS, editors. *Testing Structural Equation Models*. Newbury Park, CA: Sage (1993). p. 136–62.
73. MacKinnon DP, Lockwood CM, Williams J. Confidence limits for the indirect effect: distribution of the product and resampling methods. *Multivariate Behav Res.* (2004) 39:99–128. doi: 10.1207/s15327906mbr3901_4
74. Noble RE. Depression in women. *Metabolism.* (2005) 54(5, Suppl):49–52. doi: 10.1016/j.metabol.2005.01.014
75. Wang R, Xue D, Liu Y, Chen H, Qiu Y. The relationship between urbanization and depression in China: the mediating role of neighborhood social capital. *Int J Equity Health.* (2018) 17:105. doi: 10.1186/s12939-018-0825-x
76. Parker G, Gladstone G, Chee KT. Depression in the planet's largest ethnic group: the Chinese. *Am J Psychiatry.* (2001) 158:857–64. doi: 10.1176/appi.ajp.158.6.857
77. Bress JN, Foti D, Kotov R, Klein DN, Hajcak G. Blunted neural response to rewards prospectively predicts depression in adolescent girls. *Psychophysiology.* (2013) 50:74–81. doi: 10.1111/j.1469-8986.2012.01485.x
78. Morgan JK, Olino TM, McMakin DL, Ryan ND, Forbes EE. Neural response to reward as a predictor of increases in depressive symptoms in adolescence. *Neurobiol Dis.* (2013) 52:66–74. doi: 10.1016/j.nbd.2012.03.039
79. Keiser HN, Ross SR. Carver and Whites' BIS/FFFS/BAS scales and domains and facets of the Five Factor Model of personality. *Pers Individ Differ.* (2011) 51:39–44. doi: 10.1016/j.paid.2011.03.007

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.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 09 April 2021
doi: 10.3389/fpsyt.2021.608317

The Mediating Roles of Emotional Regulation on Negative Emotion and Internet Addiction Among Chinese Adolescents From a Development Perspective

Lijuan Liang[1], *Mingrui Zhu*[2], *Jiali Dai*[3], *Min Li*[4] *and Ya Zheng*[5]*

[1] *Department of Psychology, The First Affiliated Hospital, Hainan Medical University, Haikou, China,* [2] *Department of Neurology, The People's Hospital of Liaoning Province, Shenyang, China,* [3] *Daqing No.3 Hospital, Daqing, China,* [4] *HeBei Institute of International Business and Economics, Qinghuangdao, China,* [5] *Department of Psychology, Dalian Medical University, Dalian, China*

Previous researches indicated that emotional regulation can be associated with depression and anxiety, which may be an important mediating factor between emotional regulation and internet addiction. However, the mechanism between these associations has received little attention and it is still unclear. This study has examined 716 Chinese adolescents, 341 were males (47.6%), aged 13 to 18(Mean = 14.58, SD = 1.50), using a cross-sectional survey involving Young's Diagnostic Questionnaire for Internet Addiction, the nine-item Patient Health Questionnaire (PHQ-9), the seven-item Generalized Anxiety (GAD-7) scale, and the Emotion Regulation Questionnaire (ERQ). Correlation analysis, multiple-group analysis and structural equation modeling were carried out in SPSS Statistics version 23 (IBM, Armonk, NY) and AMOS version 21. Cognitive reappraisal had a significantly negative direct effect on Internet addiction ($\beta = -0.118$, $p < 0.05$). Furthermore, negative emotions mediated the relationships between expression suppression and Internet addiction [$\beta = 0.149$, 95% CI = (0.099, 0.212)] and the relationship between cognitive reappraisal and Internet addiction [$\beta = -0.101$, 95% CI = (−0.147, −0.065)]. The differences in the structure path coefficients for different development stages demonstrated that recognitive reappraisal showed more protective roles for negative emotion ($p < 0.01$), and negative emotion also predict Internet addiction more effectively in high school students ($p < 0.001$). However, cognitive reappraisal directly predicted negative Internet addiction in junior high school students. Therefore, the intervention on adolescents for internet addiction should not only focus on emotional regulation and negative emotion, but also development stages of adolescents.

Keywords: depression, anxiety, stress, internet addiction, expressive suppression, cognitive reappraisal

OPEN ACCESS

Edited by:
Xingchao Wang,
Shanxi University, China

Reviewed by:
Dai Bibing,
Tianjin Medical University, China
Yan Dong,
Renmin University of China, China

***Correspondence:**
Ya Zheng
zhengya@dmu.edu.cn

Specialty section:
This article was submitted to Addictive Disorders, a section of the journal Frontiers in Psychiatry

Received: *20 September 2020*
Accepted: *10 March 2021*
Published: *09 April 2021*

Citation:
Liang L, Zhu M, Dai J, Li M and Zheng Y (2021) The Mediating Roles of Emotional Regulation on Negative Emotion and Internet Addiction Among Chinese Adolescents From a Development Perspective. Front. Psychiatry 12:608317. doi: 10.3389/fpsyt.2021.608317

INTRODUCTION

With the development of society and information technology, the internet has brought convenience, but also some problems, especially for adolescents. Physical and psychological characteristics show that adolescents have relatively poor self-control and immature psychology and behavior. Adolescents may be prone to internet addiction (IA), which can affect their physical

(1) and mental health (2) and academic performance (3), even generating suicidal ideation (4). Internet addiction is characterized by psychological dependence, tolerance, and withdrawal symptoms and is included in the "Internet Addiction" chapter of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V; American Psychiatric Association, 2013) (5). The prevalence of internet addiction among Chinese adolescents was found to be 10.4% (6). Many adolescents with internet addiction show more problematic internet usage, which may be associated with significantly more negative emotion and greater deficits in emotional regulation (7). There are obvious differences between boys and girls in Internet addiction. For example, adolescents with masculine temperament prefer competitive games, while adolescents with feminine temperament show low preference for competitive games. However, due to the virtuality of cyberspace, there may be cross gender behavior in adolescents' online behavior (8). Meanwhile, adolescents experience more negative emotions, which may be related to the contradiction between the demand for emotional autonomy and immature emotion regulation in adolescence (9). However, fewer studies simultaneously focused on the mediating roles of cognitive reappraisal and expressive suppression in internet addiction and the model invariance across gender and age.

Depression, Anxiety and Internet Addiction

Owing to factors that pertain to academic performance (10), interpersonal problems (11), and family (12), many adolescents suffered from emotion problems, especially negative emotion of depression and anxiety (13). Many studies have considered that depression and anxiety may be the main risk factors for internet addiction among adolescents (14, 15). Internet addiction should be a negative coping style of avoiding problems. Therefore, the behavior of internet addiction may further aggravate the symptoms of negative emotions. The internal mechanism between emotion problems and internet addiction has played an important role in intervention and the treatment of internet addiction (16, 17). A possible explanation for these associations is that individuals with depression and anxiety may try to self-regulate emotional states through internet addictive behaviors (18). Positive emotional regulation strategies may be mediating roles between emotion problems and internet addiction.

According to Cognitive Behavior Theory (CBT), anxiety and depression of adolescents may be the mediator variables between emotional regulation and problem behavior (19). The problem behaviors of adolescents mainly include internalization and externalization. Internalization problems include all kinds of over-inhibited or inward-directed behavior, such as anxiety and depression, while externalization problems include all kinds of uninhibited or outward-focused behavior, such as internet addiction and aggression. Therefore, internet addiction as an externalized behavior may also be influenced by emotion regulation, but few researches have explored the relationship and psychological mechanism between emotion regulation and internet addiction.

The Mediating Role of Expressive Suppression and Cognitive Reappraisal

Emotional regulation deficits have been theoretically and empirically associated with affective disorders and addiction. Some studies have tried to intervene in internet addiction in adolescents with cognitive behavioral therapy (CBT) (20). Cognitive factors may be key factors in internet addiction. Some studies have supported the notion that the ability to regulate emotions may predict internet addiction, and therefore producing changes in cognition may be an effective intervention method (21, 22). Cognitive reappraisal, as an adaptive strategy, is defined as cognitively transforming a situation in order to modify its impact on one's emotions (23). Cognitive reappraisal may help individuals to re-evaluate a situation of maladjustment and improve the ability of self-control. However, expressive suppression is a maladaptive strategy defined as inhibiting emotion expressive behavior (24). Some studies have shown that adolescents with internet addiction had greater difficulty in emotional regulation, manifested by excessive expressive suppression and too little cognitive reappraisal (25, 26). Owing to excessive suppression of negative emotional experiences, the correlation between negative and internet addiction may be enhance. Therefore, a deficit of emotional regulation may further strengthen the association between negative emotions and internet addiction.

According to previous studies, depression (27) and anxiety (28) are positively associated with internet addiction, and emotional regulation may have a mediating role between negative emotion and internet addiction.

The Effect of Age and Gender

Many related studies have shown that internet addiction and emotional features of adolescents vary with age and sex (29). Although the related research supports the fact that negative emotion, such as depression and anxiety, play important roles in the severity of internet addiction, gender also plays an important role in the structural equation model (30). In addition, compared with boys, girls were found to be at a higher risk of mood symptoms only and of comorbid IA and mood symptoms (13). However, few studies have referred to the invariance of the structural model relating negative emotion and internet addiction, and some research shows that the path relating emotion and internet addiction shows no difference, which assumed negative emotion as mediator between school climate problematic internet use and ignore the comparison of progressive equivalence models (31). According to the different psychological mechanisms of age and gender, the treatment of internet addiction should consider the variables of age (32) and gender (33, 34).

The Present Study

Emotion problems, such as depression (35) and anxiety (36) have been associated with internet addiction, so emotion problems may be risk factors for internet addiction. Expressive suppression may be a risk mediating factor between emotion problems and internet addiction. Internet addiction is affected directly by depression and anxiety, and indirectly by expressive suppression

and cognitive reappraisal. Given the mediating effects of gender and age, we also considered the roles of gender and age in this model to determine whether the model developed for all participants was suitable for all adolescents regardless of age and gender.

MATERIALS AND METHODS

Participants

A total of 716 adolescents participated in the study. The valid data set comprised 690 participants after deleting invalid data, and the data efficiency was 96.37%. All adolescents gave informed consent before starting to fill out the form by choosing whether agree to participate in this study or not.

Procedure

The participants in this study were students who completed a self-reported questionnaire from the provinces of Sichuan and Hainan. They were first asked to read an informed consent declaration and entered the survey only if they agreed by QR (quick response) code or web page. They could opt to remain anonymous or use their real name when filling in the questionnaire.

Ethics Statement

Ethical approval for this study was obtained from the Hainan Medical University Ethics Committee (HYLL2020005). Parents and schools were informed to obtain the consent prior to the study. All participants were volunteered to participate in the study and receive individual psychometric results at the end of the measurement.

Measurement

Depression

The nine-item Patient Health Questionnaire (PHQ-9) has been widely utilized to assess symptoms of depression (37). The nine items of the PHQ correspond to the diagnostic criteria of depressive symptoms in DSM-V. The PHQ-9requiresparticipants to self-report the frequency of related symptoms over the past 2 weeks. As a severity measure, the PHQ-9 score can range from 0 to 27, because each of the nine items is scored from 0 (not at all) to 3 (nearly every day). Cronbach's alpha for the PHQ-9 was 0.911 in the current sample.

Anxiety

The seven-item Generalized Anxiety Disorder (GAD) scale is generally utilized to measure anxiety symptoms among adolescents (38). The GAD asks participants to self-report on the status and frequency of symptoms during the last 2 weeks (39). The score for the GAD can range from 0 to 21, and the Cronbach's alpha was 0.924 among all participants in this study.

Expressive Suppression and Cognitive Reappraisal

The Chinese version of the Emotion Regulation Questionnaire (ERQ) consists of 10 items that measure two factors: expressive suppression (four items) and cognitive reappraisal (six items). Each item of the ERQ is scored one (completely disagree) to seven (completely agree). Scores of for all four expressive suppression items were summed to generate a single expressive suppression score, while scores for all six cognitive reappraisal items were added up to yield a single cognitive reappraisal scores (40, 41). The Chinese version of the ERQ shows good internal consistency, adequate validity in Chinese individuals. In the present study, the Cronbach's alpha coefficients for the expressive suppression and the cognitive reappraisal were 0.752 and 0.857, respectively.

Internet Addiction

Young's Diagnostic Questionnaire for Internet Addiction (YDQ) was applied to assess Internet addiction (42). The YDQ was modified according to the DSM-IV criteria for pathological gambling and consists of eight "yes" or "no" questions. The total score of the eight items ranged from 0 to 8, which also showed good reliability and validity in Chinese adolescents. Cronbach's alpha was 0.771 in this study.

Data Analysis

First, we conducted descriptive statistics, Student's *t*-test, correlation analyses using SPSS Statistics version 23 (IBM, Armonk, NY). Next, Amos 21.0 was adopted to examine the hypothesized models. Structural equation modeling (SEM) was performed to test the mediating role of negative emotions in the relationships among expressive suppression, cognitive reappraisal and Internet addiction. Specially, The SEM analysis was conducted in two steps. Firstly, we tested the measurement model to examine whether the observed variables were properly chosen for the indicators of the latent variables. Secondly, we tested the structural model to examine the proposed associations among the latent variables. Indirect effects were also calculated using bias-corrected bootstrapping (5,000 bootstrap samples) with 95% confidence intervals (CIs) (43). The 95% CIs not including zero shows a significant effect. Furthermore, to assess the structural equivalence across gender and developmental stages, two multi-group (by adolescent gender or developmental stages of adolescents) SEMs were performed.

In the present study, several goodness-of-fit indices were adopted to assess the model-data fit. The first one was the Chi-square statistic and its associated p value. If the p value is not significant, it may show good model-data fit. However, the Chi-square statistic is sensitive to sample size (44). Therefore, we adopted the Chi-square to degrees of freedom ratio (χ^2/df) to assess the model fit. A χ^2/df ratio of <3 indicated a good model fit. Other substitutive indices were also used in the current study, including the Tucker-Lewis Index (TLI) (45), the comparative fit index (CFI) (46), the standardized root mean square residual (SRMR) (47), and the root mean square error of approximation (RMSEA) (48). A TLI and CFI larger than 0.95 and a SRMR and RMSEA <0.08 show good model fit (48). For the comparison of the nested models, differences in the χ^2 ($\Delta\chi^2$) and the degree of freedom (Δdf) were employed to compare the models with the goodness of fit to test the model that best fit the data (49, 50). Specifically, the standard of comparison between the two nested models is as follows: when the degrees of freedom increase with a significant increase in the corresponding Chi-square value (that is, $\Delta\chi^2/\Delta$df is significant), the better model is the one with a smaller degrees of freedom. Otherwise, the larger degrees of

freedom model are better. The predictive and explanatory powers of the model were assessed using path coefficients and R^2.

RESULTS

Descriptive Statistics and *t*-Tests

The characteristics of the participants and the distribution of Interent addiction are shown in **Table 1**. The average age of the adolescents in the current study was 14.59 (SD = 1.50) years, and the age range was 12 to 18 years; the study included 332 boys (48.1%) and 358 girls (51.9%). According to the standard definition of Interent addiction, the prevalence of Interent addiction was 10.72% ($n = 74$) among the adolescent internet users in this study. There were no gender differences in expressive suppression, cognitive reappraisal, Internet addiction, while depression and anxiety yielded significant gender differences. Compared with boys, girls had higher scores on the depression and anxiety scales. Forthermore, there were no developmental stages differences in expressive suppression, cognitive reappraisal, and Internet addiction, while depression and anxiety yielded significant developmental stages differences. High school students showed higher level of depression and anxiety than the junior high school students (**Table 1**).

Correlation Analysis

For all participants, expressive suppression was significantly positively related to depression, anxiety and Interent addiction ($r = 0.298$, $p < 0.001$, $r = 0.309$, $p < 0.001$, $r = 0.08$, $p < 0.05$, respectively), while cognitive reappraisal was significantly negatively associated with depression, anxiety and Internet addiction ($r = -0.243$, $p < 0.001$ and $r = -0.219$, $p < 0.001$, $r = -0.180$, $p < 0.001$, respectively). In addition, depression and anxiety were significantly correlated to Internet addiction ($r = 0.332$, $p < 0.001$ and $r = 0.323$, $p < 0.001$, respectively) (**Table 2**).

Mediational Model Analysis

Firstly, the hypothesized measurement model contained 20 observed variables and five latent variables: expression suppression, cognitive reappraisal, depression, anxiety and Internet addiction (**Figure 1**). Depression and anxiety were loaded on the latent variable of negative emotion, while other all items were loaded on their corresponding latent variables in the measurement model. For example, the total eight items in the YDQ were loaded on the latent variable of Internet addiction. The measurement model was a good fit to the data, ($\chi^2 = 275.551$, $\chi^2/df = 1.680$, TLI = 0.969, CFI = 0.974, SRMR = 0.038, RMSEA = 0.032). The indicators loaded well-onto each latent variable with standardized factor loadings ranging from 0.470 to 0.903. When evaluating the structural model, we analyzed the significance of the entire model as well as the significance of the relationship and variances among the multiple factors in the model. According to the fit standards, our model fits well with the empirical data ($\chi^2 = 275.551$, $\chi^2/df = 1.680$, TLI = 0.969, CFI = 0.974, SRMR = 0.038, RMSEA = 0.032). Expression suppression had no significant direct effect on Internet addiction ($\beta = -0.071$, $p > 0.05$), while cognitive reappraisal had a significantly negative direct effect on Internet addiction ($\beta = -0.118$, $p < 0.05$). Furthermore, negative emotions mediated the relationships between expression suppression and Internet addiction [$\beta = 0.149$, 95% CI = (0.099, 0.212)]. In addition, negative emotions also mediated the associations between cognitive reappraisal and Internet addiction [$\beta = -0.101$, 95% CI = (-0.147, -0.065)]. Finally, we found that 17.2% variance of Internet addiction could be explained by this model.

Structural Invariance of the Mediated Model Analysis

To assess the structural invariance of the mediated model across gender and developmental stages of adolescents, two nested models were estimated, respectively. The first model allowed the structure coefficient of the two models to be estimated freely according to gender, while the second model was conducted for the structure path coefficients to be equal. The results found that these two models were not significantly different, $\Delta\chi^2[(5), N = 676] = 7.012$, $p = 0.220$, indicating that they were not differed according to gender. In addition, the first model allowed the structure coefficient of the two models to be estimated freely according to the developmental stages of adolescents, while the second model was conducted for the structure path coefficients to be equal. The results found that these two models were also not significantly different, $\Delta\chi^2[(5), N = 676] = 18.058$, $p = 0.003$, indicating that they differed according to the developmental stages of adolescents. In addition, we utilized critical ratios of differences (CRDs) as an index to examine the differences in the structure path coefficients between junior high school students and high school students. If the CRD was larger than 1.96, then the associations between these two variables would demonstrate a significant developmental stages difference as $p < 0.05$. First, the results showed that the structure path from cognitive reappraisal to negative emotions revealed a significant developmental stages difference (CRD = -2.065, $P < 0.05$). More specifically, first, the path coefficient for junior high school students was $\beta = -0.23$, $p < 0.01$, while the path coefficient for high school students was $\beta = -0.35$, $p < 0.01$. Therefore, cognitive reappraisal had a far greater protective role against the negative emotions among high school students than junior high school students. Second, the results showed that the structure path from negative emotions to Internet addiction revealed a significant developmental stages difference (CRD = 3.057, $P < 0.001$). More specifically, the path coefficient for junior high school students was $\beta = 0.28$, $p < 0.01$, while the path coefficient for high school students was $\beta = 0.70$, $p < 0.001$. Therefore, negative emotions had a far greater prediction to Internet addiction among high school students than junior high school students. Finally, the results showed that the structure path from cognitive reappraisal to Internet addiction revealed a significant developmental stages difference (CRD = 2.711, $p < 0.01$). More specifically, the path coefficient for junior high school students was $\beta = -0.19$, $p < 0.01$, while the path coefficient for high school students was $\beta = 0.11$, $p > 0.05$. Therefore, cognitive reappraisal had a far greater direct prediction to Internet addiction among junior high school students than high school students. Thus, there were the

TABLE 1 | Descriptive statistics among the variables.

Variables	Gender					Developmental stage of adolescents				
	Girls ($N = 358$)		Boys ($N = 332$)		t	Junior high school students ($N = 504$)		High school students ($N = 186$)		t
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Expressive suppression	15.20	4.77	14.97	4.73	0.65	14.99	4.94	15.35	4.20	−0.95
Cognitive reappraisal	29.08	5.92	28.71	6.74	0.77	29.00	6.47	28.63	5.93	0.69
Depression	6.36	6.13	4.69	5.16	3.87**	5.09	5.57	6.83	6.02	−3.58**
Anxiety	6.19	5.11	4.92	4.56	3.43**	5.29	4.80	6.34	5.06	−2.51*
Internet addiction	1.65	2.38	1.72	2.71	−0.40	1.65	2.58	1.77	2.45	−0.54

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

TABLE 2 | Correlation among the main variables for all sample.

	Range	Mean + SD	1	2	3	4	5
1. Expressive suppression	4–28	15.09 ± 4.75	–				
2. Cognitive reappraisal	6–42	28.91 ± 6.32	−0.003	–			
3. Depression	0–27	5.56 ± 5.74	0.298***	−0.243***	–		
4. Anxiety	0–21	5.58 ± 4.89	0.309***	−.219***	0.804***	–	
Internet addiction	0–8	1.85 ± 2.01	0.080*	−0.180***	0.332***	0.323***	–

*$p < 0.05$; ***$p < 0.001$.

structural invariance of the mediated model across gender, while the developmental stages of adolescents played the moderating effects in the structural paths in the mediated model.

DISCUSSION

Gender and Age Differences

Our study showed that symptoms of depression and anxiety were significantly more common in girls than in boys. This result is consistent with most previous studies that female sex may be a risk factor for depression and anxiety (51). Among adolescents, the high school students showed significantly higher levels of depression and anxiety symptoms than junior school students, which may be related to more academic pressure, as well as emotional problems linked with physical and mental development.

Correlation Among Main Variables

Expressive suppression showed significant positive correlation with depression, anxiety and Internet addiction. Depression and anxiety are highly comorbid, which is broadly characterized by an overreliance on expressive suppression. Previous researched also supported that expressive suppression was associated with negative emotion consequences (52). Negative emotion of depression and anxiety is also characterized by ineffective utilization of cognitive reappraisal, which inhibits the potential positive emotion. Similar with previous researches, cognitive reappraisal showed negative correlation to depression and anxiety (53, 54). The high school students may suffer from stressful or uncontrollable situations, due to underutilization of cognitive reappraisal. For negative emotion, treatment intervention may appear to increase cognitive reappraisal but decrease expressive suppression. In addition, expressive suppression was negative correlated with Internet addiction, but cognitive reappraisal was positively correlated with Internet addiction. The results were consistent with related research that emotion dysregulation may be a potential risk factor for Internet addiction (55). Because of the outbreak of COVID-19, adolescence may also have troubles, for example, lack of social communication, lack of peer communication and academic pressure. However, there are some difficulties in emotion regulation among some adolescents, which may enhance the negative emotion. Negative emotions may lead to externalized behaviors, such as Internet addiction. Therefore, dysregulated negative emotions in adolescents may be a risk factor for psychopathology, but appropriate emotion regulation strategy may be a protective factor for psychopathology (56).

Mediating Effect of Negative Emotion

This study demonstrated that expressive suppression couldn't predict Interent addiction directly, cognitive reappraisal could predict Internet addiction directly. Negative emotion of depression and anxiety conducted mediating variables between emotional regulation and Interent addiction. On the one hand, similar to previous research, negative emotion was the partial mediating factor between cognitive reappraisal and Interent addiction (57–59). Negative emotion are important mechanisms in the relationship between emotional regulation and Interent addiction. The higher the score of cognitive reappraisal corresponded to the lower the negative emotion and the less the Interent addiction. On the other hand, depression and anxiety were also completely mediating factor between expressive

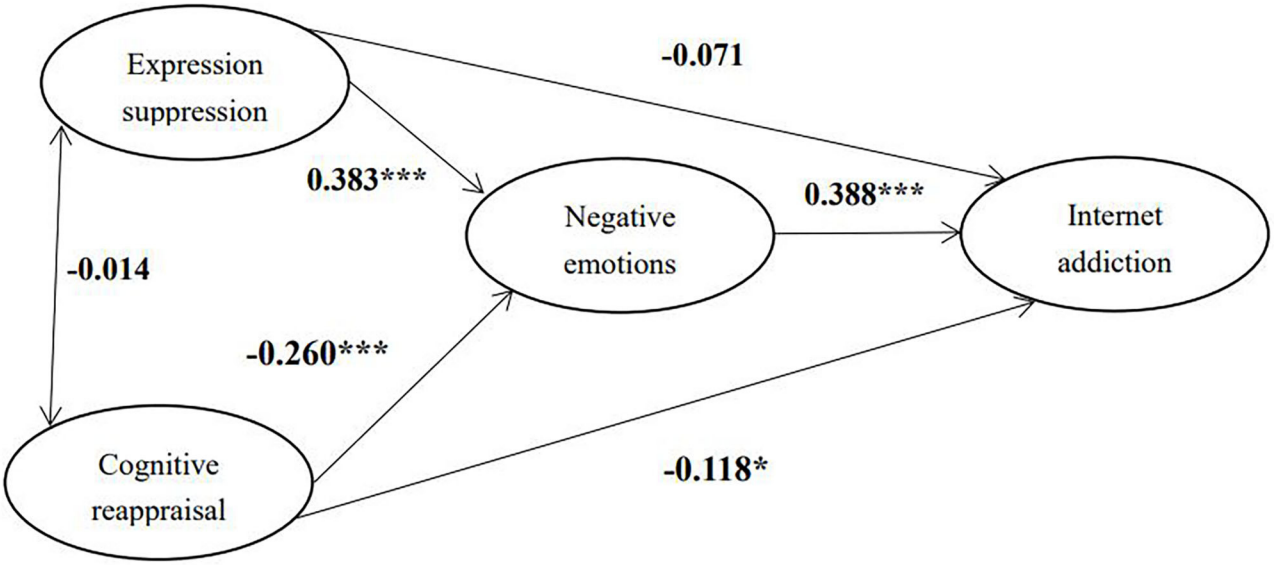

FIGURE 1 | Standardized estimates of the mediated model. *$p < 0.05$; ***$p < 0.001$.

suppression and Interent addiction. The higher the score of expressive suppression predicted the higher the negative emotion and the more the Interent addiction. Cognitive reappraisal allows individuals to reframe negative emotional situations and reassess emotional events, which enables them to have better adaptability to negative situations, and to gain more control (23). Expressive suppression is a negative coping style, which may enhance negative emotional experience, leading to deterioration of self-control, cognitive bias, and maladaptive behavior problems (24). At the same time, expressive suppression may also be harmful for an individual's social functioning and reduce the acquisition of social support (60, 61). For younger adolescents, there are a lot of social support from parents, teachers, friends and so on. Compared with older adolescents, they also confront with less academy stress. This study demonstrated that expressive suppression may be not the important mediating role between negative emotions and internet. Adolescents may still be more inclined to express their emotions rather than over restrain them. Cognitive reappraisal could be beneficial in enabling individuals to distinguish negative emotions, experience lower emotional intensity, and adopt more and various emotional regulation strategies. Research has shown that cognitive reappraisal reduced not only emotional experience but also bilateral amygdala activation (62).

Invariance of the Model

To determine whether both different genders and different development stages of adolescents are applicable in the models, an invariance study of the structural models was conducted. The results showed that structural invariance across gender was accepted, but the invariance across different development stages of adolescents was not established. The structure models could be suitable for both boys and girls. Previous studies revealed that over-suppression of negative emotion may be harmful to the relief of negative emotions and lead to more behavioral problems and physical diseases, especially in females (63, 64). In our study, almost of adolescents are in the early stage of adolescents, psychological and behavioral differences between boys and girls haven't appeared particularly significance. With the development of adolescents, the differences may be more and more significant. As a result of social expectations, males are less likely to express themselves when they are faced with depression and anxiety, but are more willing to take on negative emotions and deal with bad situations by themselves.

According to invariance across different development stage of adolescents, the structure models couldn't also suitable for different stages of adolescents. Compared with junior high school students, cognitive reappraisal could be more protective factors for negative emotion of depression and anxiety among high school students. With the development of adolescents, cognitive function gradually improved, high school students could be better at cognitive reappraisal than junior high school students (65). The cognitive-affective process suggested that the improvement of cognitive level may be beneficial to the improvement of negative emotional experience. Similar with previous studies, anxiety and depression positively predicted Internet addiction of adolescents (15). However, negative emotion of high school students could be more effectively predicting roles in Internet addiction than junior high school students. Compared with junior high school students, high school students have more academic pressure, which is associated with more negative emotions. Finally, cognitive reappraisal is more effective in predicting Internet addiction of junior high school students. Related studies have demonstrated that emotion dysregulation is risk factors for Internet addiction. More

cognitive reappraisal predicted greater reduction in negative emotion (66).

Conclusion

According to cognitive behavior theory, emotional regulation plays important roles in Internet addiction. The way of emotion regulation affects emotional experience, which directly positively predicts Internet addiction. In this study, expressive suppression was a risk factor of negative emotion and Internet addiction, while expressive reappraisal was a protective factor of negative emotion and Internet addiction. Expressive suppression affects Internet addiction through negative emotions, while cognitive reappraisal affects Internet addiction directly. At the same time, there are some differences in the path coefficient of the model among the different development stages of high school students. This found reminds that psychological intervention should consider emotional regulation and negative emotion, but also development stages of adolescents.

LIMITATIONS AND IMPLICATIONS

Longitudinal study may be more beneficial to explore the psychological development mechanism between negative emotions and Interent addiction. Insufficient of older adolescents may affect this invariance of age, we should increase the sample of older adolescents in the future. According to the result, relief of depression and anxiety could be main intervention strategies to decrease Interent addiction for adolescent. In addition, cognitive reappraisal should be benefit for reducing of Interent addiction, which played a positive mediating role between depression, anxiety and Interent addiction.

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 Hainan Medical University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

LL carried out experiments, conducted the statistical analysis, and wrote the manuscript. MZ, JD, and ML conducted data collection work and revised the manuscript. YZ designed experiments and critically reviewed the manuscript. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Alaca N. The impact of internet addiction on depression, physical activity level and trigger point sensitivity in Turkish university students. *J Back Musculoskelet Rehabil.* (2020) 33:623–30. doi: 10.3233/BMR-171045
2. Lam LT. The roles of parent-and-child mental health and parental internet addiction in adolescent internet addiction: does a parent-and-child gender match matter? *Front Public Health.* (2020) 8:142. doi: 10.3389/fpubh.2020.00142
3. Fossion P, Antonetti S, Lays C. Internet: abuse, addiction and benefits. *Rev Med Brux.* (2018) 39:250–4.
4. Lu L, Jian SY, Dong M, Gao J, Zhang TT., Chen XQ, et al. Childhood trauma and suicidal ideation among chinese university students: the mediating effect of internet addiction and school bullying victimisation. *Epidemiol Psychiatr Sci.* (2020) 29:108. doi: 10.1017/S2045796020000682
5. Block JJ. Issues for DSM-V: internet addiction. *Am J Psychiat.* (2008) 165:306–7. doi: 10.1176/appi.ajp.2007.07101556
6. Dong B, Zhao F, Wu XS, Wang WJ, Li YF, Zhang ZH, et al. Social anxiety may modify the relationship between internet addiction and its determining factors in chinese adolescents. *Int J Mental Health Addict.* (2019) 17:1508–20. doi: 10.1007/s11469-018-9912-x
7. Drach RD, Orloff NC, Hormes JM. The emotion regulatory function of online social networking: preliminary experimental evidence. *Addict Behav.* (2020) 112:106559. doi: 10.1016/j.addbeh.2020.106559
8. Yeh YC, Ko HC, Wu JY, Cheng CP. Gender differences in relationships of actual and virtual social support to internet addiction mediated through depressive symptoms among college students in Taiwan. *Cyberpsychol Behav.* (2008) 11:485–7. doi: 10.1089/cpb.2007.0134
9. Marusak HA, Thomason ME, Sala-Hamrick K, Crespo L, Rabinak CA. What's parenting got to do with it: emotional autonomy and brain and behavioral responses to emotional conflict in children and adolescents. *Dev Sci.* (2018) 21:e12605. doi: 10.1111/desc.12605
10. Cardenas SD, Vergara KA, Simancas-Pallares M. Internet addiction and academic performance in dental students. *Rev Colomb Psiquiatr.* (2019) 48:198–207. doi: 10.1016/j.rcpeng.2018.03.009
11. Simcharoen S, Pinyopornpanish M, Haoprom P, Kuntawong P, Wongpakaran N, Wongpakaran T. Prevalence, associated factors and impact of loneliness and interpersonal problems on internet addiction: a study in chiang mai medical students. *Asian J Psychiatr.* (2018) 31:2–7. doi: 10.1016/j.ajp.2017.12.017
12. Copello A, Templeton L, Orford J, Velleman R, Patel A, Moore L, et al. The relative efficacy of two levels of a primary care intervention for family members affected by the addiction problem of a close relative: a randomized trial. *Addiction.* (2009) 104:49–58. doi: 10.1111/j.1360-0443.2008.02417.x
13. Gao T, Li M, Hu Y, Qin Z, Cao R, Mei S, et al. When adolescents face both internet addiction and mood symptoms: a crosssectional study of comorbidity and its predictors. *Psychiatr Res.* (2020) 284. doi: 10.1016/j.psychres.2020.112795. [Epub ahead of print].
14. Seki T, Hamazaki K, Natori T, Inadera H. Relationship between internet addiction and depression among Japanese university students. *J Affect Disord.* (2019) 256:668–72. doi: 10.1016/j.jad.2019.06.055
15. Li G, Hou G, Yang D, Jian H, Wang W. Relationship between anxiety, depression, sex, obesity, and internet addiction in chinese adolescents: a short-term longitudinal study. *Addict Behav.* (2019) 90:421–7. doi: 10.1016/j.addbeh.2018.12.009
16. Santos VA, Freire R, Zugliani M, Cirillo P, Santos HH, Nardi AE, et al. Treatment of internet addiction with anxiety disorders: treatment protocol and preliminary before-after results involving pharmacotherapy and modified cognitive behavioral therapy. *JMIR Res Protoc.* (2016) 5:e46. doi: 10.2196/resprot.5278
17. Zhang YY, Chen JJ, Ye H, Volantin L. Psychological effects of cognitive behavioral therapy on internet addiction in adolescents: a systematic review protocol. *Medicine.* (2020) 99:e18456. doi: 10.1097/MD.0000000000018456
18. Scimeca G, Bruno A, Cava L, Pandolfo G, Muscatello MR, Zoccali R. The relationship between alexithymia, anxiety, depression, and internet addiction

severity in a sample of Italian high school students. *Sci World J.* (2014) 2014:504376. doi: 10.1155/2014/504376
19. Herbert JD, Gaudiano BA, Forman EM. The importance of theory in cognitive behavior therapy: a perspective of contextual behavioral science. *Behav Ther.* (2013) 44:580–91. doi: 10.1016/j.beth.2013.03.001
20. Kim S, Noh D. The current status of psychological intervention research for internet addiction and internet gaming disorder. *Issues Ment Health Nurs.* (2019) 40:335–41. doi: 10.1080/01612840.2018.1534910
21. King DL, Delfabbro PH, Griffiths MD, Gradisar M. Cognitive-behavioral approaches to outpatient treatment of internet addiction in children and adolescents. *J Clin Psychol.* (2012) 68:1185–95. doi: 10.1002/jclp.21918
22. Tsai JK, Lu WH, Hsiao RC, Hu HF, Yen CF. Relationship between difficulty in emotion regulation and internet addiction in college students: a one-year prospective study. *Int J Environ Res Public Health.* (2020) 17:1–11. doi: 10.3390/ijerph17134766
23. Gross JJ, John OP. Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. *J Pers Soc Psychol.* (2003) 85:348–62. doi: 10.1037/0022-3514.85.2.348
24. Gross JJ, Levenson RW. Emotional suppression: physiology, self-report, and expressive behavior. *J Pers Soc Psychol.* (1993) 64:970–86. doi: 10.1037/0022-3514.64.6.970
25. Karaer Y, Akdemir D. Parenting styles, perceived social support and emotion regulation in adolescents with internet addiction. *Compr Psychiatry.* (2019) 92:22–7. doi: 10.1016/j.comppsych.2019.03.003
26. Hormes JM, Kearns B, Timko CA. Craving facebook? Behavioral addiction to online social networking and its association with emotion regulation deficits. *Addiction.* (2014) 109:2079–88. doi: 10.1111/add.12713
27. Senormanci O, Saracli O, Atasoy N, Senormanci G, Kokturk F, Atik L. Relationship of internet addiction with cognitive style, personality, and depression in university students. *Compr Psychiatry.* (2014) 55:1385–90. doi: 10.1016/j.comppsych.2014.04.025
28. Yucens B, Uzer A. The relationship between internet addiction, social anxiety, impulsivity, self-esteem, and depression in a sample of Turkish undergraduate medical students. *Psychiatry Res.* (2018) 267:313–8. doi: 10.1016/j.psychres.2018.06.033
29. Duan L, Shao X, Wang Y, Huang Y, Miao J, Yang X, et al. An investigation of mental health status of children and adolescents in china during the outbreak of COVID-19. *J Affect Disord.* (2020) 275:112–8. doi: 10.1016/j.jad.2020.06.029
30. Jeonga B, Lee JY, Kim BM, Park E, Kwon JG, Kim DJ, et al. Associations of personality and clinical characteristics with excessive internet and smartphone use in adolescents: a structural equation modeling approach. *Addict Behav.* (2020) 110. doi: 10.1016/j.addbeh.2020.106485. [Epub ahead of print].
31. Zhai B, Li D, Li X, Liu Y, Zhang J, Sun W, et al. Perceived school climate and problematic internet use among adolescents: mediating roles of school belonging and depressive symptoms. *Addict Behav.* (2020) 110. doi: 10.1016/j.addbeh.2020.106501. [Epub ahead of print].
32. Hsieh KY, Hsiao RC, Yang YH, Liu TL, Yen CF. Predictive effects of sex, age, depression, and problematic behaviors on the incidence and remission of internet addiction in college students: a prospective study. *Int J Environ Res Public Health.* (2018) 15: 1–10. doi: 10.3390/ijerph15122861
33. Jang MH, Ji ES. Gender differences in associations between parental problem drinking and early adolescents' internet addiction. *J Spec Pediatr Nurs.* (2012) 17:288–300. doi: 10.1111/j.1744-6155.2012.00344.x
34. Li Q, Dai W, Zhong Y, Wang L, Dai B, Liu X. The mediating role of coping styles on impulsivity, behavioral inhibition/approach system, and internet addiction in adolescents from a gender perspective. *Front Psychol.* (2019) 10:2402. doi: 10.3389/fpsyg.2019.02402
35. Chi X, Liu X, Guo T, Wu M, Chen X. Internet addiction and depression in chinese adolescents: a moderated mediation model. *Front Psychiatry.* (2019) 10:816. doi: 10.3389/fpsyt.2019.00816
36. Kim K, Ryu E, Chon MY, Yeun EJ, Choi SY, Seo JS, et al. Internet addiction in Korean adolescents and its relation to depression and suicidal ideation: a questionnaire survey. *Int J Nurs Stud.* (2006) 43:185–92. doi: 10.1016/j.ijnurstu.2005.02.005
37. Lai J, Ma S, Wang Y, Cai Z, Hu J, Wei N, et al. Factors associated with mental health outcomes among health care workers exposed to coronavirus disease 2019. *JAMA Netw Open.* (2020) 3:e203976. doi: 10.1001/jamanetworkopen.2020.3976
38. Bartolo A, Monteiro S, Pereira A. Factor structure and construct validity of the generalized anxiety disorder 7-item (GAD-7) among portuguese college students. *Cad Saude Publica.* (2017) 33:e00212716. doi: 10.1590/0102-311x00212716
39. Tiirikainen K, Haravuori H, Ranta K, Kaltiala-Heino R, Marttunen M. Psychometric properties of the 7-item generalized anxiety disorder scale (GAD-7) in a large representative sample of Finnish adolescents. *Psychiatry Res.* (2019) 272:30–5. doi: 10.1016/j.psychres.2018.12.004
40. Hutchison AN, Yeung DY, Gerstein LH, Wettersten KB. Psychometric comparison of chinese and english versions of the emotion regulation questionnaire with bilingual Hong Kong chinese students. *Int J Psychol.* (2021) 56:296–303. doi: 10.1002/ijop.12699
41. Liu W, Chen L, Tu X. Chinese adaptation of emotion regulation questionnaire for children and adolescents (ERQ-CCA): a psychometric evaluation in chinese children. *Int J Psychol.* (2017) 52:398–405. doi: 10.1002/ijop.12233
42. Young KS. Internet addiction: the emergence of a new clinical disorder. *Cyberpsychol Behav.* (1998) 1:237–44. doi: 10.1089/cpb.1998.1.237
43. Hayes AF. *Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach*. New York, NY: Guilford Press (2013).
44. Bollen KA. A new incremental fit index for general structural equation models. *Sociol Meth Res.* (1989) 17:303–16. doi: 10.1177/0049124189017003004
45. Tucker LR, Lewis C. A reliability coefficient for maximum likelihood factor analysis. *Psychometrika.* (1973) 38:1–10. doi: 10.1007/BF02291170
46. Rigdon EE. CFI versus RMSEA: a comparison of two fit indexes for structural equation modeling. *Struct Equ Model A Multidis J.* (1996) 3:369–79. doi: 10.1080/10705519609540052
47. Browne MW, Cudeck R. Alternative ways of assessing model fit. In: Bollen KA, Long JS, editors. *Testing Structural Equation Models*. SAGE Focus Editions ed. Newbury Park; Sage Publication (1993). p. 136–62.
48. Hooper D, Coughlan J, Mullen MR. Structural equation modelling: guidelines for determining model fit. *Electron J Bus Res Methods.* (2008) 6:53–60.
49. Heijmans RDH, Pollock DSG, Satorra A. *Scaled and Adjusted Restricted tests in Multi-sample Analysis of Moment Structures. Innovations in Multivariate Statistical Analysis: A Festschrift for Heinz Neudecker*. Boston, MA: Springer US (2000). p. 233–47.
50. Byrne BM, Stewart SM. Teacher's corner: the MACS approach to testing for multigroup invariance of a second-order structure: a walk through the process. structural equation modeling: a multidisciplinary journal. *Struct Equ Model A Multidis J.* (2006) 13:287–321. doi: 10.1207/s15328007sem1302_7
51. Pospos S, Tal I, Iglewicz A, Newton IG, Tai-Seale M, Downs N, et al. Gender differences among medical students, house staff, and faculty physicians at high risk for suicide: a HEAR report. *Dep Anxiety.* (2019) 36:902–20. doi: 10.1002/da.22909
52. Dryman MT, Heimberg RG. Emotion regulation in social anxiety and depression: a systematic review of expressive suppression and cognitive reappraisal. *Clin Psychol Rev.* (2018) 65:17–42. doi: 10.1016/j.cpr.2018.07.004
53. Goldin PR, Ziv M, Jazaieri H, Hahn K, Heimberg R, Gross JJ. Impact of cognitive behavioral therapy for social anxiety disorder on the neural dynamics of cognitive reappraisal of negative self-beliefs: randomized clinical trial. *JAMA Psychiatry.* (2013) 70:1048–56. doi: 10.1001/jamapsychiatry.2013.234
54. Andreotti C, Thigpen JE, Dunn MJ, Watson K, Potts J, Reising MM, et al. Cognitive reappraisal and secondary control coping: associations with working memory, positive and negative affect, and symptoms of anxiety/depression. *Anxiety Stress Coping.* (2013) 26:20–35. doi: 10.1080/10615806.2011.631526
55. Mo PKH, Chan VWY, Chan SW, Lau JTF. The role of social support on emotion dysregulation and internet addiction among chinese adolescents: a structural equation model. *Addict Behav.* (2018) 82:86–93. doi: 10.1016/j.addbeh.2018.01.027
56. Gilbert KE. The neglected role of positive emotion in adolescent psychopathology. *Clin Psychol Rev.* (2012) 32:467–81. doi: 10.1016/j.cpr.2012.05.005
57. Chung MC, Di X, Wan KH. Exploring the interrelationship between alexithymia, defense style, emotional suppression, homicide-related

posttraumatic stress disorder and psychiatric co-morbidity. *Psychiatry Res.* (2016) 243:373–81. doi: 10.1016/j.psychres.2016.05.057
58. Ottonello M, Fiabane E, Pistarini C, Spigno P, Torselli E. Difficulties in emotion regulation during rehabilitation for alcohol addiction: correlations with metacognitive beliefs about alcohol use and relapse risk. *Neuropsychiatr Dis Treat.* (2019) 15:2917–25. doi: 10.2147/NDT.S214268
59. Gullone E, Taffe J. The emotion regulation questionnaire for children and adolescents (ERQ-CA): a psychometric evaluation. *Psychol Assess.* (2012) 24:409–17. doi: 10.1037/a0025777
60. Cundiff JM, Jennings JR, Matthews KA. Social stratification and risk for cardiovascular disease: examination of emotional suppression as a pathway to risk. *Pers Soc Psychol Bull.* (2019) 45:1202–15. doi: 10.1177/0146167218808504
61. Chung MC, Symons C, Gilliam J, Kaminski ER. Posttraumatic stress disorder, emotional suppression and psychiatric co-morbidity in patients with chronic idiopathic urticaria: a moderated mediation analysis. *J Ment Health.* (2018) 27:442–9. doi: 10.1080/09638237.2018.1437601
62. Chen S, Chen C, Yang J, Yuan J. Trait self-consciousness predicts amygdala activation and its functional brain connectivity during emotional suppression: an fMRI analysis. *Sci Rep.* (2017) 7:117. doi: 10.1038/s41598-017-00073-3
63. Brandao T, Schulz MS, Gross JJ, Matos PM. The emotion regulation questionnaire in women with cancer: a psychometric evaluation and an item response theory analysis. *Psychooncology.* (2017) 26:1647–53. doi: 10.1002/pon.4356
64. Baziliansky S, Cohen M. Emotion regulation and psychological distress in cancer survivors: a systematic review and meta-analysis. *Stress Health.* (2021) 37:3–18. doi: 10.1002/smi.2972
65. Li Y, Wang Y, Ren Z, Gao M, Liu Q, Qiu C, et al. The influence of environmental pressure on internet use disorder in adolescents: the potential mediating role of cognitive function. *Addict Behav.* (2020) 101:105976. doi: 10.1016/j.addbeh.2019.04.034
66. Pettorruso M, Valle S, Cavic E, Martinotti G, di Giannantonio M, Grant JE. Problematic internet use (PIU), personality profiles and emotion dysregulation in a cohort of young adults: trajectories from risky behaviors to addiction. *Psychiatry Res.* (2020) 289:113036. doi: 10.1016/j.psychres.2020.113036

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.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 09 June 2021
doi: 10.3389/fpsyt.2021.660810

Effects of Psychopathy on Neurocognitive Domains of Impulsivity in Abstinent Opiate and Stimulant Users

Elena Psederska[1,2], *Nicholas D. Thomson*[3,4], *Kiril Bozgunov*[1], *Dimitar Nedelchev*[1], *Georgi Vasilev*[1] *and Jasmin Vassileva*[5,6]*

[1] Bulgarian Addictions Institute, Sofia, Bulgaria, [2] Department of Cognitive Science and Psychology, New Bulgarian University, Sofia, Bulgaria, [3] Division of Acute Care Surgical Services, Department of Surgery, Virginia Commonwealth University Health, Richmond, VA, United States, [4] Department of Psychology, University of Durham, Durham, United Kingdom, [5] Institute for Drug and Alcohol Studies, Virginia Commonwealth University, Richmond, VA, United States, [6] Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, United States

OPEN ACCESS

Edited by:
Qi Li,
University of Chinese Academy of Sciences, China

Reviewed by:
Aleksander Hagen Erga,
Stavanger University Hospital, Norway
Erica Nicole Grodin,
University of California, Los Angeles, United States

***Correspondence:**
Jasmin Vassileva
jasmin.vassileva@vcuhealth.org

Specialty section:
This article was submitted to Addictive Disorders, a section of the journal Frontiers in Psychiatry

Received: 29 January 2021
Accepted: 03 May 2021
Published: 09 June 2021

Citation:
Psederska E, Thomson ND, Bozgunov K, Nedelchev D, Vasilev G and Vassileva J (2021) Effects of Psychopathy on Neurocognitive Domains of Impulsivity in Abstinent Opiate and Stimulant Users. Front. Psychiatry 12:660810. doi: 10.3389/fpsyt.2021.660810

Background: Psychopathy and substance use disorders (SUDs) are both characterized by neurocognitive impairments reflecting higher levels of impulsivity such as reward-driven decision-making and deficient inhibitory control. Previous studies suggest that psychopathy may exacerbate decision-making deficits, but it may be unrelated to other neurocognitive impairments among substance dependent individuals (SDIs). The aim of the present study was to examine the role of psychopathy and its interpersonal-affective and impulsive-antisocial dimensions in moderating the relationships between dependence on different classes of drugs and neurocognitive domains of impulsivity.

Method: We tested 693 participants (112 heroin mono-dependent individuals, 71 heroin polysubstance dependent individuals, 115 amphetamine mono-dependent individuals, 76 amphetamine polysubstance dependent individuals, and 319 non-substance dependent control individuals). Participants were administered the Psychopathy Checklist: Screening Version (PCL:SV) and seven neurocognitive tasks measuring impulsive choice/decision-making (Iowa Gambling Task; Cambridge Gambling Task; Kirby Delay Discounting Task; Balloon Analog Risk Task), and impulsive action/response inhibition (Go/No-Go Task, Immediate Memory Task, and Stop Signal Task).

Results: A series of hierarchical multiple regressions revealed that the interpersonal-affective dimension of psychopathy moderated the association between decision-making, response inhibition and both amphetamine and heroin dependence, albeit differently. For amphetamine users, low levels of interpersonal-affective traits predicted poor decision-making on the Iowa Gambling Task and better response inhibition on the Stop Signal task. In contrast, in heroin users high interpersonal-affective psychopathy traits predicted lower risk taking on the Cambridge Gambling Task and better response inhibition on the Go/No-Go task. The impulsive-antisocial dimension of psychopathy predicted poor response inhibition in both amphetamine and heroin users.

Conclusions: Our findings reveal that psychopathy and its dimensions had both common and unique effects on neurocognitive function in heroin and amphetamine dependent individuals. Our results suggest that the specific interactions between psychopathy dimensions and dependence on different classes of drugs may lead to either deficient or superior decision-making and response inhibition performance in SDIs, suggesting that psychopathy may paradoxically play a protective role for some neurocognitive functions in specific subtypes of substance users.

Keywords: opioid use disorder, stimulant use disorder, psychopathy, impulsivity, decision-making, response inhibition

INTRODUCTION

Impulsivity and Substance Use Disorders

Impulsivity, defined as a "predisposition toward rapid, unplanned reactions to internal or external stimuli without regards to the negative consequences of these reactions" (1) is considered a key etiological factor in current conceptualizations of substance use disorders (SUDs) (2). Deficits in impulse control are considered both as vulnerability factors that increase the risk of initiation and maintenance of SUDs (3, 4), as well as consequences of chronic drug use reflecting long-term neuroadaptive changes in the brain linked to specific neurocognitive impairments (5, 6). Despite the strong associations of impulsivity with SUDs, recent advances in the literature have drawn attention to the multifactorial nature of impulsivity and the heterogeneity of SUDs, suggesting that specific impulsivity dimensions might be differentially implicated in distinct types of SUDs and in different stages of the addiction cycle (2, 4, 7).

Impulsivity is a multidimensional construct comprised of a variety of characteristics reflecting the personality dimensions of trait impulsivity, as well as a number of neurobehavioral manifestations, reflecting more fluctuating neurocognitive dimensions of state impulsivity (8). Trait impulsivity is a stable personality dimension, widely acknowledged as a general risk factor for SUDs (9), which is usually measured by self-report questionnaires such as the Barratt Impulsiveness Scale-11 [BIS-11; (10)] and the UPPS Impulsive Behavior Scale [UPPS; (11)]. Trait impulsivity is considered to be on a continuum between lower, more adaptive levels and higher, more extreme and maladaptive levels, which feature prominently in externalizing psychiatric disorders that originate in childhood and are commonly comorbid with SUDs, such as attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), conduct disorder, and antisocial personality disorder (ASPD) (12). In contrast to trait impulsivity, neurocognitive dimensions of impulsivity are more fluctuating and dependent on environmental influences and the current state of the individual (9). Therefore, neurocognitive domains of impulsivity reflect more imminent risk and are typically measured in the laboratory with performance-based computerized tasks.

Neurocognitive impulsivity is additionally subdivided into two broad domains: impulsive action, involving deficits in rapid response inhibition (13) and impulsive choice, indicating deficits in decision-making (14). This distinction is supported by findings from preclinical studies, which show that impulsive choice and impulsive action are differentially involved in distinct stages of the addiction cycle and are mediated by different neural circuits (15). Impulsive action reflects response disinhibition and is typically measured by Stop Signal Tasks [SST; (16)], which examine the ability to cancel an already initiated motor response, and/or Go/No-Go type of paradigms (17, 18), measuring the ability to inhibit a prepotent or dominant behavioral response. Impulsive choice reflects a reward-driven decision-making style associated with higher risk-taking and preference for immediate over delayed rewards. Common tasks of impulsive choice include delay discounting tasks (19, 20) such as the Monetary Choice Questionnaire [MCQ; (21)] and simulated gambling tasks measuring sensitivity to risk and reward, such as the Iowa Gambling Task [IGT; (22)] measuring decision-making under ambiguity or the Cambridge Gambling Task [CGT; (23)] and the Balloon Analog Risk Task [BART; (24)], measuring decision-making under risk.

Neurocognitive Impulsivity in Substance Use Disorders

Impairments in neurocognitive impulsivity have long been implicated in SUDs. Increased response disinhibition and aberrant decision-making are some of the most common findings in people with SUDs (23, 25–31). Deficits in neurocognitive dimensions of impulsivity have gained increased research interest in the addiction literature as predictors of drug initiation and poor treatment outcomes. Studies reveal that higher delay discounting and compromised decision-making are predictive of post-treatment relapse and can negatively affect one's ability to achieve and maintain abstinence from substance use (32–37). Although response disinhibition on Stop Signal and Go/No-Go tasks has not been consistently related to treatment retention and abstinence (34, 35), it has proven to be among the most reliable predictors of drug use initiation (38–41).

Though individuals with SUDs manifest marked impairments on virtually all tasks of impulsive choice and impulsive action (23, 25, 28, 30, 31), recent studies suggest that the type of deficits demonstrated by individuals with SUDs might also be affected by the unique properties of the type of substance

they are using. In line with the precision medicine approach, current models of addiction emphasize the increasing need for identifying substance-specific personality and neurocognitive risk profiles that reflect the specific psychopharmacological effects of different classes of drugs and the distinct positive and negative reinforcement mechanisms implicated in different types of SUDs (2, 42, 43). Research increasingly reveals differences in neurocognitive dimensions of impulsivity in individuals with different SUDs, such as stimulant and opioid use disorder. Although there is accumulating evidence for impaired response inhibition on impulsive action tasks in individuals with both stimulant- (28, 31, 44–46) and opioid use disorders (47–49), studies directly comparing opiate and stimulant users reveal that stimulant users are characterized by more pronounced response inhibition deficits than opiate users (31, 50). Studies investigating impulsive choice in individuals with stimulant and opioid use disorders have yielded somewhat mixed findings. Some studies have shown that individuals who preferentially use stimulants are characterized by more impulsive decision-making than opiate users (20, 23, 50, 51), whereas others have failed to find any performance differences between stimulant and opiate users (31, 52, 53). Machine-learning approaches also reveal that heroin and amphetamine dependence are characterized by unique substance-specific neurocognitive impairments (54, 55), with heroin dependence uniquely predicted by impaired decision-making, lower risk-taking and intact response inhibition, whereas amphetamine dependence was predicted by higher delay discounting and longer reaction times (54).

However, there are several methodological limitations that limit the conclusions that can be drawn from previous studies in the field. Polysubstance use is one of the most significant confounds in studies aiming to dissociate the specific effects of different classes of drugs. With few exceptions (7, 52, 54), most studies examining differences in neurocognitive impulsivity between opiate and stimulant users are based on samples of polysubstance users whose drug of choice was either opiates or stimulants (23, 31, 50, 51, 53). Another methodological limitation is related to differences in the length of abstinence across studies of neurocognitive function in substance users. The majority of neurocognitive studies on impulsivity explore the effects of chronic substance use or the effects of early remission (<12 months) (20, 23, 25, 28, 31, 45–47, 50, 51, 53). A few studies have focused on elucidating the effects of protracted abstinence (>12 months) on different dimensions of neurocognitive impulsivity (7, 52, 53, 56–58). Differences in the length of abstinence (early vs. protracted) of participants with SUDs may explain some of the conflicting findings in the literature, as some neurocognitive deficits have been shown to recover with abstinence (59–61). However, few neurocognitive studies in SDIs have addressed the protracted abstinence stage of the addiction cycle. Finally, neurocognitive studies often fail to control for the confounding effects of externalizing traits among people with SUDs, such as antisocial and psychopathic traits, which are characterized by similar neurocognitive impairments as those observed in substance users and may further exacerbate neurocognitive impairments in SDIs.

Effects of Psychopathy on Neurocognitive Impulsivity in Substance Users

Psychopathy is a personality disorder characterized by a cluster of personality and behavioral traits, which fall into two factors. Factor 1 is characterized by affective (e.g., callousness, lack of remorse) and interpersonal traits (e.g., manipulativeness, superficial charm), whereas Factor 2 consists of lifestyle (e.g., impulsivity, irresponsibility) and antisocial traits (e.g., early behavior problems, poor behavioral controls) (62). This distinction is reflected in the Psychopathy Checklist-Revised [PCL-R; (63, 64)], the most widely used instrument for measuring psychopathy, which differentiates between interpersonal-affective and impulsive-antisocial features of psychopathy (65, 66), closely resembling the traditional distinction between primary and secondary psychopathy (67–69). Studies with the PCL-R reveal that Factor 1 is uniquely related to lower levels of anxiety and impulsivity, whereas Factor 2 is associated with negative emotionality, impulsivity, and substance misuse (63, 70, 71).

Psychopathy often co-occurs with SUDs (72–74) and is associated with a variety of negative outcomes in people with SUDs, including high treatment attrition, substance use during treatment, high relapse rates, and increased risk for post-treatment violent offending (73, 75–77). Studies using machine-learning approaches reveal that psychopathy is the highest and the only common predictor of dependence on different classes of drugs, including heroin, amphetamine, cannabis, nicotine, and alcohol (54, 55). This suggests that psychopathy may be an important diagnostic marker for SUDs, regardless of drug class.

Psychopathy has been associated with impairments in neurocognitive domains of impulsivity, similar to those observed in individuals with SUDs. With few exceptions (78, 79), most studies on impulsive choice in psychopathy have found that psychopathic individuals manifest suboptimal decision-making, associated with risky decision-making style and inability to learn from feedback (80–86). Results are less consistent in the impulsive action domain, with some studies reporting higher response disinhibition (87–90), whereas others suggest intact or even superior response inhibition in psychopathic individuals (87, 91–93). Inconsistencies across findings may be explained by the heterogeneity of psychopathy, which has not been addressed by the majority of studies, which are typically based on PCL total sum scores that do not take into account the distinction between interpersonal-affective and impulsive-antisocial aspects of psychopathy. Focusing exclusively on total sum scores may lead to conflicting results and conceal important differential relationships that could deepen our understanding of psychopathy (94). Studies that have addressed the distinction between the interpersonal-affective and impulsive-antisocial dimensions of psychopathy reveal that only Factor 2 (impulsive-antisocial) is related to impulsive choice, manifested by risky and less advantageous decision-making (80, 95, 96). With regards to impulsive action, studies demonstrate that higher scores on PCL-R Factor 2 and lower scores on Factor 1 were related to poor response inhibition, suggesting that the affective-interpersonal

aspects of psychopathy may in fact exert some protective effects on neurocognitive functioning (97, 98).

Given that both psychopathy and SUDs are associated with neurocognitive deficits in impulsivity, it has been suggested that their co-occurrence may increase some impulse-control deficits in individuals with SUDs (86). In two related studies, Vassileva et al. (86, 92) examined differences in various neurocognitive domains of impulsivity in psychopathic and non-psychopathic mono-substance dependent ("pure") heroin users. Findings revealed that comorbid psychopathy exacerbated decision-making deficits in heroin dependent individuals (86), but psychopathy was unrelated to delay discounting and response inhibition in this population (92). However, the role of psychopathy and its dimensions on neurocognitive functioning in SUDs is still not well-understood and has been particularly understudied among individuals dependent on different classes of drugs and in different stages of the addiction cycle. This is an important line of inquiry as Factor 1 and 2 may be differentially related to neurocognitive functioning and impulsivity (99, 100), which could in turn influence the associations between SUDs and neurocognitive function.

The aim of the current study was to examine if psychopathy and its dimensions moderate the relationships between addiction to different classes of drugs (stimulants vs. opiates) and neurocognitive domains of impulsivity (impulsive choice and impulsive action) in substance users in protracted abstinence.

MATERIALS AND METHODS

Participants

Participants were recruited from a larger study on impulsivity among substance users in Bulgaria via flyers placed at substance abuse clinics, therapeutic communities, social venues, as well as through the study's web page and Facebook page. Participants were initially screened via telephone on their medical and substance use histories. All participants had to meet the following inclusion criteria: (1) age between 18 and 50 years, (2) Raven's Progressive Matrices (101) estimated IQ higher than 75; (3) minimum of 8th grade education; (4) being able to read and write in Bulgarian; (5) HIV-seronegative status; (6) negative breathalyzer test for alcohol and negative urine toxicology screen for amphetamines, methamphetamines, cocaine, opiates, methadone, cannabis, benzodiazepines, barbiturates, and MDMA. Exclusion criteria included history of neurological illness, head injury with loss of consciousness of more than 30 min, and history of psychotic disorders and/or use of antipsychotic medication.

Participants included 693 individuals (64% male), with a mean age of 28.57 years (SD = 7.09). Three hundred seventy-four participants (74.1% male) had a DSM-IV history of substance dependence, of whom 183 were dependent on heroin (77% male) (112 mono-dependent, 71 polysubstance dependent) and 191 were dependent on amphetamines (71.2% male) (115 mono-dependent, 76 polysubstance dependent). The majority of participants with a history of substance dependence (69%) were in protracted abstinence at the time of testing (i.e., full sustained remission for more than 12 months by DSM-IV criteria) (102). In addition, 319 participants (53% male) had no past or current history of abuse or dependence on any substance, of whom 62 were non-substance dependent siblings of heroin users (44% male), and 48 were non-substance dependent siblings of amphetamine users (40% male).

Procedures

The study was approved by the Institutional Review Boards of Virginia Commonwealth University and the Medical University in Sofia on behalf of the Bulgarian Addictions Institute. Subjects who met inclusion criteria were invited to participate in the study. All participants gave written informed consent. Abstinence from alcohol and drug use at the time of testing was verified by breathalyzer test (Alcoscan AL7000) and urine toxicology screen for amphetamines, barbiturates, benzodiazepines, cannabis, cocaine, MDMA, methadone, methamphetamines, and opiates. All participants were HIV-seronegative, determined by rapid HIV testing.

Testing was conducted by an experienced team of trained psychologists at the Bulgarian Addictions Institute in Sofia, Bulgaria. Data were collected in two sessions of approximately 4 hours each, conducted on two separate days. The assessment battery included a combination of clinical interviews, self-report questionnaires and computer-based neurobehavioral tests. The first session included assessment of substance use disorders, externalizing psychopathology (e.g., psychopathy, antisocial personality disorder, ADHD) and intelligence. The second session included completion of neurocognitive tasks and self-report measures of externalizing and internalizing personality traits and disorders (e.g., impulsivity, sensation seeking, depression, alexithymia). Participants were paid a total of 80 Bulgarian leva (approximately 50 USD) for participation in the study.

Measures

Assessment of SUDs and Psychopathy

Substance dependence was assessed with the *Structured Clinical Interview for DSM-IV—Substance Abuse Module* [SCID-SAM; (103)]. The SCID-SAM is a semi-structured clinical interview designed to determine whether an individual meets criteria for any SUD (alcohol-, cannabis-, stimulant-, hallucinogen-, opioid use disorders) according to the DSM-IV (102). Raters assess the presence of DSM-IV symptoms of substance abuse and dependence using a three-point scale (0 = not present, 1 = subthreshold, 2 = present). A diagnosis of substance dependence is made if the participant displayed three (or more) of the seven substance dependence criteria within a 12-month period. A symptom count of the number of criteria met for heroin- and amphetamine dependence (range 0–7) was used as the main SUD index in the analyses.

The Psychopathy Checklist: Screening Version [PCL:SV; (104)], an abbreviated version of the Psychopathy Checklist–Revised [PCL-R; (63)] was used to measure psychopathy. The PCL:SV consists of a semi-structured interview, which involves the assessment of 12 characteristics of psychopathy scored on a 3-point rating scale (0 = absent, 1 = somewhat present, 2 = definitely present). The PCL:SV is comprised of two factors.

Factor 1 consists of six items reflecting the interpersonal and affective characteristics of psychopathy (grandiosity, manipulativeness, lack of empathy, lack of remorse), while the remaining six items from Factor 2 measure impulsive and antisocial behaviors (impulsivity, irresponsibility, poor behavioral controls, antisocial behavior in adolescence and adulthood). Items reflecting interpersonal-affective (Factor 1) and impulsive-antisocial (Factor 2) characteristics of psychopathy were summed to provide a total factor scores ranging from 0 to 12 points for each psychopathy dimension.

The semi-structured interview for the PCL:SV was conducted by researchers who were initially trained by the senior author, who is the author of the Bulgarian version of the PCL-R with its publisher Multi Health Systems. Additional training and supervision were further provided by two of the co-authors, who had participated in formal training workshops led by Robert Hare, the author of the PCL instruments. In line with earlier findings (105), the PCL:SV showed good internal consistency for its total score ($\alpha = 0.89$) and its two factors ($\alpha = 0.78$, and $\alpha = 0.85$) in the current sample.

Neurocognitive Measures of Impulsivity

Measures of Impulsive Choice

Iowa Gambling Task [IGT; (22, 106)] measures decision-making under uncertainty and requires learning by trial-and-error. Examinees are presented with four decks of cards and instructed to select cards to maximize earnings. Decks A and B are associated with higher rewards but also higher occasional penalties. Selecting from Decks C and D yields lower rewards and lower occasional penalties and is a more advantageous long-term strategy. The performance measure used was the "net score" (IGT Net score), reflecting the total number of advantageous choices minus the total number of disadvantageous choices.

Cambridge Gambling Task [CGT; (23)] assesses risky decision-making, which does not involve learning. Examinees are presented with 10 boxes colored red or blue and are asked to guess whether a token is hidden under a red or a blue box. The ratios of red:blue boxes vary from 1:9 to 9:1 in pseudorandom order. Participants earn points based on correct performance. The second phase of the task asks participants to gamble points based on the confidence of their decisions, by selecting from an array of bets ranging from 5 to 95% of their earned points, presented in ascending and descending order. Two performance indices were used in the analyses: (1) Quality of decision-making (CGT Quality of decision-making), reflecting the tendency to bet on the more likely outcome; and (2) Risk taking (CGT Risk taking), the average number of points scored after the most probable result has been selected.

Monetary Choice Questionnaire [MCQ; (21)] was used to measure delay discounting. The questionnaire consists of 27 choices between smaller rewards available on the day of testing and larger rewards available from 1 week to 6 months in the future, thereby capturing the tendency to discount rewards that are delayed in time. The 27 questions were grouped in one of three categories based on the approximate magnitudes of the delayed rewards: small ($25–35), medium ($50–60) and large ($75–85). Analyses utilized the discount-rate parameter k, calculated using the hyperbolic discount function $V = A/[1 + kD]$, where V is the value of reward A available at delay D. Two performance indices were used in the analyses: (1) the overall temporal discounting rate (i.e., MCQ Overall k); (2) the temporal discounting rate of small magnitude rewards (i.e., MCQ Small k), which typically has the highest effect sizes from the three reward magnitudes. We used the log transformed values of both discounting rates due to the non-normal distribution of MCQ scores in our sample.

Balloon Analog Risk Task [BART; (24)] is a decision-making task assessing risk-taking behavior. The participant is presented with a balloon on the computer screen, along with a balloon pump, a button for collecting the monetary rewards earned by pumping the balloon, a temporary bank, and a permanent bank, where the collected money from each balloon are kept. The task consists of a total of 30 balloons (trials) presented sequentially one at a time. At any point during each trial, the examinee can stop pumping the balloon and click the button to collect the money, which transfers the earnings accumulated from that balloon to the permanent bank. In contrast, when a balloon explodes, the balloon disappears, the money in the temporary bank is lost for that trial, and the next trial begins. The adjusted average number of pumps on unexploded balloons (BART Pumps adjusted average) was used as a measure of risk-taking, with higher scores indicative of greater risk-taking propensity.

Measures of Impulsive Action

Go/No-Go Task [GNGT; (18)] is a measure of response inhibition where a series of two-element visual stimuli arrays are presented on a screen for 500 ms and examinees are instructed to respond when the two elements are identical ("Go") and to inhibit responding when the stimuli are discrepant ("No-Go"). On "No-Go" trials, the position of the inhibitory element is random, requiring the examinee to scan both elements. Errors of commission/false alarms (GNG False alarms) were used as an index of impulsivity in the regression analyses.

Immediate Memory Task [IMT; (17)] is a modified continuous performance task with higher complexity and sensitivity. A series of five-digit numbers are shown on a computer screen for 500 ms each, with examinees instructed to respond only if a stimulus is identical to the preceding one. Errors of commission (i.e., false alarms), measuring incorrect responding to a non-target stimulus (IMT Commission errors) were used as an index of impulsivity.

Go Stop Task [SST; (107)] is a stop-signal paradigm, which presents examinees with a series of five-digit numbers displayed for 500 ms each. Examinees are instructed to respond when a stimulus is identical to the previous display ("Go") and to withhold responding when the stimulus matches, but then changes color from black to red ("Stop"). Stop signals occurred at 50, 150, 250, and 350 ms intervals after the appearance of the target "go" stimulus. The performance measure used in the analyses was the 150 ms inhibition ratio (SST 150 ms inhibition), calculated by dividing the failures to inhibit a response on "Stop trials" by correct detections on "Go trials" at the 150 ms stop-signal delay, which is the index most commonly used in the literature (107). Higher scores reflect better inhibition or lower impulsivity.

Data Analytic Plan

Our main goal was to examine the moderating role of the two psychopathy dimensions on neurocognitive domains of impulsivity in heroin and amphetamine users. First, descriptive statistics and group differences in demographic characteristics, psychopathy scores and indices of impulsive choice and impulsive action were performed. Second, a series of hierarchical multiple regressions were conducted to examine the moderating role of psychopathy dimensions on the relation between substance dependence (heroin and amphetamine) and neurocognitive function (impulsive choice and impulsive action). All regressions followed the same steps. Step 1 included biological sex (1 = male, 2 = female), Raven's estimated IQ, heroin dependence symptoms, and amphetamine dependence symptoms. Step 2 added Factor 1 (interpersonal-affective) and Factor 2 (impulsive-antisocial) of psychopathy. Step 3 included the interaction terms between heroin dependence and psychopathy factors, and amphetamine dependence and psychopathy factors. All tests were conducted using an alpha of 0.05. Significant interactions were probed using simple slopes analysis (108).

RESULTS

Descriptive Statistics and Group Differences

Group differences in demographic characteristics were examined using ANOVA. There were significant differences in age [$F_{(2, 689)} = 41.92$, $p < 0.01$], estimated IQ [$F_{(2, 690)} = 5.90$, $p < 0.01$] and years of education [$F_{(2, 687)} = 29.46$, $p < 0.01$] across groups. Tukey's *post-hoc* comparisons showed that amphetamine users were significantly younger than the two other groups, followed by control participants and heroin users (ps < 0.01) With regards to estimated IQ, both control participants and amphetamine users scored higher than heroin users (ps < 0.05). In addition, control participants reported higher education as compared to both substance dependent groups (ps < 0.01). Group differences in substance use variables were examined using Independent Sample *t*-test. Amphetamine dependent individuals had lower length of abstinence [$t_{(280)} = 5.10$, $p < 0.01$] and lower symptoms count [$t_{(372)} = 9.82$, $p < 0.01$] compared to heroin dependent individuals. Group differences in indices of psychopathy and neurocognitive domains of impulsivity were examined using ANOVA followed by Tukey's *post-hoc* comparisons. There were significant group differences in both interpersonal-affective [$F_{(2, 690)} = 173.22$, $p < 0.01$] and impulsive-antisocial [$F_{(2, 690)} = 384.09$, $p < 0.01$] psychopathy dimensions, as well as in psychopathy total score [$F_{(2, 690)} = 343.71$, $p < 0.01$], where heroin users scored the highest, followed by amphetamine users and control participants (ps < 0.01). With regards to neurocognitive indices of impulsivity, groups differed in MCQ Overall k index of delay discounting [$F_{(2, 653)} = 6.66$, $p < 0.01$]. Tukey's *post-hoc* comparisons reveal that control participants had lower discounting rates than heroin users. In addition, there were group differences in MCQ Small k index of delay discounting, measuring the temporal discounting rate of small magnitude rewards [$F_{(2, 653)} = 7.66$, $p < 0.01$], where both amphetamine- and heroin users had higher discounting rates than control participants ($p < 0.05$). Please see **Tables 1**, **2** for participants' characteristics. **Table 1** provides descriptive statistics and group differences in demographic and substance use variables. **Table 2** provides descriptive statistics and group differences in indices of psychopathy, impulsive choice, and impulsive action.

All main analyses were performed using groups of heroin and amphetamine users, consisting of both mono-dependent, and polysubstance dependent individuals. For detailed participants characteristics across groups of heroin- and amphetamine mono- and polysubstance dependent individuals, please see **Supplementary Tables 1, 2**.

Regression Analyses

Impulsive Choice

Iowa Gambling Task (**IGT Net score**). Step 1 was significant, $F_{(4, 675)} = 7.25$, $p < 0.001$. Higher IGT Net scores were associated with higher IQ ($p < 0.001$) and fewer symptoms of heroin dependence ($p = 0.042$) and amphetamine dependence ($p = 0.031$). Step 2 added the PCL:SV factors to step 1 [$F_{(6, 673)} = 5.17$, $p < 0.001$]. Both heroin ($p = 0.229$) and amphetamine dependence ($p = 0.221$) became nonsignificant, and the psychopathy factors were not significant predictors of IGT Net score. Step 3 added the interaction term between psychopathy and substance dependence, [$F_{(10, 669)} = 3.61$, $p < 0.001$]. The change in R^2 was not significant ($p = 0.283$). The interaction between factor 1 and amphetamine was significant ($p = 0.044$). Probing this interaction using simple slopes analysis revealed that amphetamine dependence symptoms were related to IGT Net score at low levels of Factor 1 ($p = 0.031$) and not at high levels of Factor 1 ($p = 0.401$). Thus, lower Factor 1 scores contribute to the association between amphetamine dependence symptoms and poor performance on IGT Net score, whereas higher Factor 1 scores may serve as a buffer in the association between amphetamine dependence and IGT Net score performance, as indicated by the nonsignificant difference (see **Figure 1**, **Table 3**).

Cambridge Gambling Task. **(1) CGT Quality of decision-making**. Step 1 was significant, $F_{(4, 648)} = 5.03$, $p = 0.001$. IQ ($p < 0.001$) and biological sex ($p = 0.038$) were positively related to CGT Quality of decision-making ($p < 0.001$). Step 2 [$F_{(6, 646)} = 3.46$, $p = 0.002$] and step 3 were significant [$F_{(10, 642)} = 2.13$, $p = 0.020$], but no significant variables emerged. Therefore, higher IQ and being female was associated with higher quality of decision-making (see **Table 3**). **(2) CGT Risk taking**. Step 1 was significant, $F_{(4, 648)} = 8.53$, $p < 0.001$. Being male ($p < 0.001$) and higher amphetamine dependence symptoms ($p = 0.028$) were related to higher CGT Risk taking scores. Step 2 was significant [$F_{(6, 646)} = 6.30$, $p < 0.001$] but no new variables were significant. Step 3 was significant [$F_{(10, 642)} = 4.67$, $p < 0.001$] and R^2 change approached significance ($p = 0.071$). The interaction between heroin dependence and PCL:SV Factor 1 was significant ($p = 0.009$). The simple slopes analysis was significant for high levels of Factor 1 ($p = 0.022$) but not for low levels ($p = 0.177$; See

TABLE 1 | Descriptive statistics and group differences in demographic and substance use variables.

	Controls (1)	HDIs (2)	ADIs (3)	*p*	Contrasts
N	319	183	191	–	–
Age	28.41 (7.64)	31.96 (5.98)	25.61 (5.57)	**0.000**	2 > 1 > 3
Biological sex (N/% male)	169 (53%)	141 (77%)	136 (71.2%)	**0.000**	-
Raven's estimated IQ	109.19 (13.94)	105.20 (12.87)	109.05 (12.68)	**0.003**	1, 3 > 2
Years education	14.51 (2.76)	12.86 (2.55)	13.20 (2.18)	**0.000**	1 > 2, 3
Length of abstinence	–	5.67 (5.57)	2.96 (3.00)	**0.000**	2 > 3
N of symptoms heroin/amphetamine dependence	–	6.20 (0.97)	4.74 (1.76)	**0.000**	2 > 3

HDIs, heroin dependent individuals; ADIs, amphetamine dependent individuals. Values in bold are significant.

TABLE 2 | Descriptive statistics and group differences in indices of psychopathy, decision-making, and response inhibition.

	Controls (1)	HDIs (2)	ADIs (3)	*p*	Contrasts
PCL:SV factor 1	1.52 (1.76)	5.45 (2.75)	3.81 (2.75)	**0.000**	2 > 3 > 1
PCL:SV factor 2	1.81 (2.15)	7.79 (2.74)	6.39 (2.92)	**0.000**	2 > 3 > 1
PCL:SV total score	3.32 (3.46)	13.25 (4.96)	10.20 (4.98)	**0.000**	2 > 3 > 1
IGT net score	4.17 (27.52)	−1.41 (26.09)	0.58 (26.27)	0.069	–
CGT quality of decision-making	0.89 (0.13)	0.86 (0.14)	0.87 (0.14)	0.073	–
CGT risk taking	0.57 (0.15)	0.59 (0.14)	0.59 (0.15)	0.161	–
MCQ overall *k*	−3.66 (1.55)	−3.17 (1.36)	−3.35 (1.46)	**0.001**	2 > 1
MCQ small *k*	−3.18 (1.47)	−2.69 (1.29)	−2.82 (1.38)	**0.001**	2, 3 > 1
BART pumps adjusted average	40.06 (12.99)	39.77 (13.20)	41.05 (14.95)	0.622	–
GNG false alarms	15.15 (9.3.)	17.16 (16.67)	17.35 (9.28)	0.063	–
IMT commission errors	38.17 (14.92)	39.47 (14.41)	39.18 (13.12)	0.568	–
SST 150 ms inhibition	71.68 (21.34)	71.58 (19.94)	71.79 (21.26)	0.995	–

HDIs, heroin dependent individuals; ADIs, amphetamine dependent individuals. PCL:SV Factor 1, Psychopathy Checklist: Screening Version Factor 1; PCL:SV Factor 2, Psychopathy Checklist: Screening Version Factor 2; PCL:SV Total score, Psychopathy Checklist: Screening Version Total score; MCQ Overall k, MCQ Overall temporal discounting rate; MCQ Small k, MCQ Temporal discounting rate of small magnitude rewards; BART Pumps adjusted average, adjusted average number of pumps on unexploded balloons. Values in bold are significant.

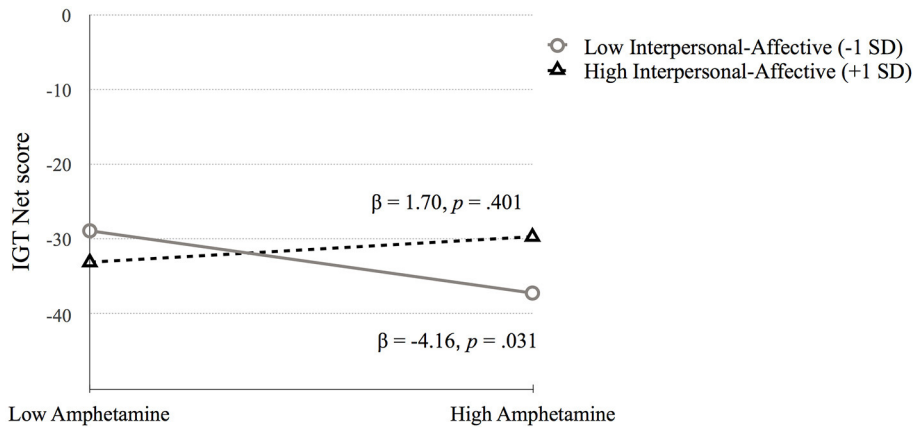

FIGURE 1 | The moderating effect of Interpersonal-affective psychopathy dimension on the association between amphetamine dependence and IGT Net score. Low and high values represent +1.0 and −1.00 *SD* from the mean.

Figure 2). High PCL:SV Factor 1 scores in individuals with more symptoms of heroin dependence was associated with less risky decision-making (see **Table 3**).

Monetary Choice Questionnaire. **(1) MCQ Overall k**. Step 1 was significant, $F_{(4, 660)} = 5.78$, $p < 0.001$. Biological sex ($p = 0.036$) and IQ ($p = 0.001$) were related to MCQ Overall k. Step 2

TABLE 3 | Substance use and psychopathy as predictors of (1) IGT Net score, (2) CGT Quality of decision-making, and (3) CGT Risk taking.

	IGT net score				CGT quality of decision-making				CGT risk taking			
	B	***SE B***	β	**ΔR^2**	***B***	***SE B***	β	**ΔR^2**	***B***	***SE B***	β	**ΔR^2**
Step 1				0.04**				0.03**				0.05**
Biological sex	−2.13	2.15	−0.04		0.02	0.01	0.08*		−0.06	0.01	−0.20***	
Raven's estimated IQ	0.34	0.08	0.17***		0.00	0.00	0.14***		0.00	0.00	−0.02	
Heroin	−2.13	1.05	−0.08*		−0.01	0.01	−0.04		0.00	0.01	−0.02	
Amphetamine	−2.21	1.02	−0.08*		0.00	0.01	−0.01		0.01	0.01	0.09*	
Step 2				0.00				0.00				0.01
Biological sex	−1.88	2.32	−0.03		0.02	0.01	0.08		−0.06	0.01	−0.18	
Raven's estimated IQ	0.33	0.08	0.16***		0.00	0.00	0.13**		0.00	0.00	−0.01	
Heroin	−1.63	1.35	−0.06		0.00	0.01	−0.01		−0.01	0.01	−0.08	
Amphetamine	−1.54	1.26	−0.06		0.00	0.01	0.01		0.01	0.01	0.03	
Factor 1	1.78	1.60	0.07		0.00	0.01	0.01		0.00	0.01	0.02	
Factor 2	−2.41	1.79	−0.09		−0.01	0.01	−0.05		0.02	0.01	0.10	
Step 3				0.01				0.00				0.07
Biological sex	−2.20	2.33	−0.04		0.02	0.01	0.07		−0.05	0.01	−0.17	
Raven's estimated IQ	0.34	0.08	0.17		0.00	0.00	0.13**		0.00	0.00	−0.01	
Heroin	−2.29	1.55	−0.09		0.00	0.01	0.00		−0.01	0.01	−0.03	
Amphetamine	−1.23	1.34	−0.05		0.00	0.01	0.00		0.00	0.01	0.02	
Factor 1	0.83	1.68	0.03		0.00	0.01	0.01		0.01	0.01	0.06	
Factor 2	−1.65	1.82	−0.06		−0.01	0.01	−0.05		0.01	0.01	0.08	
Heroin X factor 1	0.65	1.51	0.02		0.00	0.01	−0.01		−0.02	0.01	−0.15*	
Heroin X factor 2	0.76	1.74	0.03		0.00	0.01	−0.01		0.01	0.01	0.04	
Amphetamine X factor 1	2.93	1.45	0.11*		0.00	0.01	0.02		−0.01	0.01	−0.05	
Amphetamine X factor 2	−2.06	1.62	−0.07		0.00	0.01	0.00		0.01	0.01	0.04	

*Biological sex, Male (1), Female (2); *p < 0.05; **p < 0.01; ***p < 0.001.*

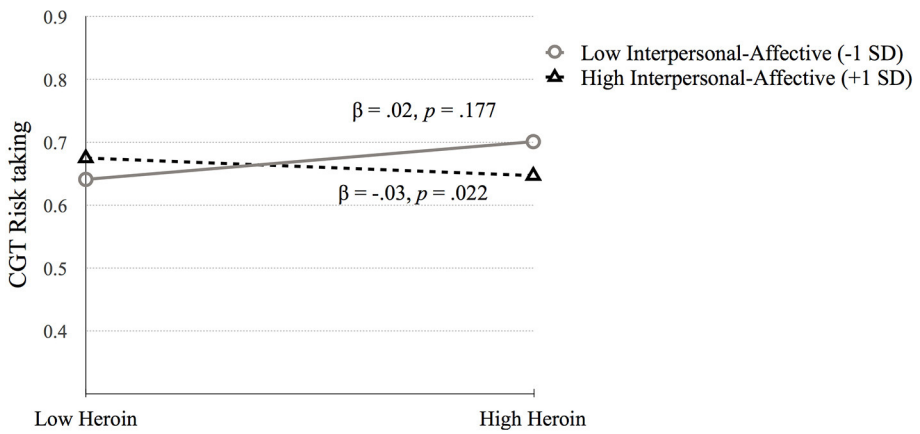

FIGURE 2 | The moderating effect of Interpersonal-affective psychopathy dimension on the association between heroin dependence and CGT Risk taking. Low and high values represent +1.0 and −1.00 *SD* from the mean.

$[F_{(6, 658)} = 4.71, p = 0.001]$ and step 3 were significant $[F_{(10, 654)} = 3.32, p < 0.001]$, but no significant predictors emerged. Therefore, being male and having lower IQ were related to higher delay discounting (see **Table 4**). **(2) MCQ Small k**. Step 1 was significant, $F_{(4, 660)} = 5.71, p < 0.001$. Lower IQ ($p = 0.004$) and higher amphetamine dependence symptoms ($p = 0.042$) were associated with MCQ Small k. Step 2 $[F_{(6, 658)} = 4.03, p = 0.001]$ and step 3 were significant $[F_{(10, 654)} = 3.16, p = 0.001]$, but no significant predictors emerged (see **Table 4**).

Balloon Analog Risk Task (**BART Pumps adjusted average**). Results of the hierarchical regression analyses with BART Pumps adjusted average are displayed in **Table 4**. Step 1, which

TABLE 4 | Substance use and psychopathy as predictors of (1) MCQ Overall *k,* (2) MCQ Small *k*, and (3) BART Pumps adjusted average.

	MCQ overall *k*				MCQ small *k*				BART pumps adjusted average			
	B	***SE B***	β	ΔR^2	***B***	***SE B***	β	ΔR^2	***B***	***SE B***	β	ΔR^2
Step 1				0.03***				0.03***				0.03**
Biological sex	−0.25	0.12	−0.08*		−0.22	0.12	−0.08**		−1.70	1.09	−0.06	
Raven's estimated IQ	−0.01	0.00	−0.13**		−0.01	0.00	−0.11		0.15	0.04	0.15***	
Heroin	0.09	0.06	0.06		0.10	0.06	0.07		0.11	0.54	0.01	
Amphetamine	0.09	0.06	0.06		0.11	0.06	0.08*		0.29	0.52	0.02	
Step 2				0.01				0.00				0.00
Biological sex	−0.15	0.13	−0.05		−0.18	0.12	−0.06		−1.65	1.18	−0.06	
Raven's estimated IQ	−0.01	0.00	−0.11**		−0.01	0.00	−0.11**		0.15	0.04	0.15***	
Heroin	−0.02	0.08	−0.01		0.05	0.07	0.03		−0.14	0.69	−0.01	
Amphetamine	0.00	0.07	0.00		0.06	0.07	0.05		0.03	0.64	0.00	
Factor 1	0.08	0.09	0.05		0.01	0.08	0.00		−0.36	0.81	−0.03	
Factor 2	0.13	0.10	0.09		0.09	0.10	0.07		0.76	0.91	0.06	
Step 3				0.01				0.01				0.00
Biological sex	−0.15	0.13	−0.05		−0.18	0.12	−0.06		−1.51	1.19	−0.05	
Raven's estimated IQ	−0.01	0.00	−0.11**		−0.01	0.00	−0.10*		0.15	0.04	0.15***	
Heroin	0.03	0.09	0.02		0.07	0.09	0.05		0.05	0.79	0.00	
Amphetamine	0.03	0.08	0.02		0.11	0.07	0.08		−0.01	0.68	0.00	
Factor 1	0.09	0.09	0.06		0.02	0.09	0.02		−0.01	0.85	0.00	
Factor 2	0.11	0.10	0.08		0.07	0.10	0.05		0.48	0.93	0.04	
Heroin X factor 1	−0.02	0.08	−0.02		−0.05	0.08	−0.04		−0.32	0.77	−0.02	
Heroin X factor 2	−0.10	0.10	−0.06		−0.05	0.09	−0.03		−0.18	0.89	−0.01	
Amphetamine X factor 1	0.01	0.08	0.01		−0.01	0.08	0.00		−0.96	0.73	−0.07	
Amphetamine X factor 2	−0.12	0.09	−0.08		−0.15	0.09	−0.10		0.49	0.82	0.03	

*Biological sex = Male (1), Female (2); *p < 0.05; **p < 0.01; ***p < 0.001.*

included biological sex, IQ, heroin dependence symptoms, and amphetamine dependence symptoms was significant, $F_{(4, 686)} = 4.33$, $p = 0.002$. IQ was positively related to BART Pumps adjusted average ($p < 0.001$). Step 2 added the psychopathy factors, which was significant, $F_{(6, 684)} = 29.99$, $p = 0.007$. However, no new significant variables emerged. Step 3 added the interaction between the psychopathy factors and substance dependence, which was significant, $F_{(10, 680)} = 2.02$, $p = 0.029$ but no interaction terms were significant. In sum, the only predictor to emerge was IQ, which was positively associated with risk taking (BART Pumps adjusted average).

Impulsive Action

Go/No-Go Task (**GNG False alarms**). Step 1 was significant, $F_{(4, 683)} = 6.72$, $p < 0.001$. Higher GNG False alarms were associated with lower IQ ($p = 0.001$) and higher amphetamine dependence symptoms ($p < 0.001$). Step 2 added the psychopathy factors to step 1 [$F_{(6, 681)} = 5.52$, $p < 0.001$]. Amphetamine dependence ($p = 0.221$) became non-significant, and Factor 2 was positively associated with GNG False alarms ($p = 0.021$). Step 3 added the interaction terms between psychopathy and substance dependence [$F_{(10, 677)} = 5.04$, $p < 0.001$] but the change in R^2 was not significant ($p = 0.573$). The interactions between heroin dependence and Factor 1 ($p = 0.003$) and Factor 2 ($p < 0.001$) were significant. In addition, the interaction between amphetamine dependence and Factor 2 was significant ($p = 0.041$). Each of these interactions were probed using simple slopes analysis, which revealed that GNG False alarms performance was related to high heroin dependence symptoms for those with high Factor 1 scores ($p = 0.031$; See **Figure 3**; **Table 5**).

Simple slopes analysis testing the interaction between heroin dependence and Factor 2 indicated that higher GNG False alarms scores were related to high heroin dependence symptoms at high Factor 2 scores ($p = 0.010$), while lower GNG False alarms scores were related to high heroin at low Factor 2 scores ($p = 0.007$; see **Figure 4**).

The simple slopes model for the interaction term between amphetamine and Factor 2 suggests that higher scores of GNG False alarms are related to high amphetamine dependence symptoms at high factor 2 scores (see **Figure 5**).

Immediate Memory Task (**IMT Commission errors**). Step 1 was significant, $F_{(4, 693)} = 6.16$, $p < 0.001$, which showed that higher IMT Commission errors were associated with lower IQ ($p = 0.001$). Step 2 [$F_{(6, 691)} = 4.60$, $p < 0.001$] and step 3 were significant [$F_{(10, 687)} = 3.21$, $p < 0.001$], but no significant variables emerged. Thus, lower IQ was related to higher errors of commission (see **Table 5**).

Go Stop Task (**SST 150ms inhibition**). **Table 5** presents the results of the hierarchical regression. Neither step 1 [$F_{(4, 688)} =$

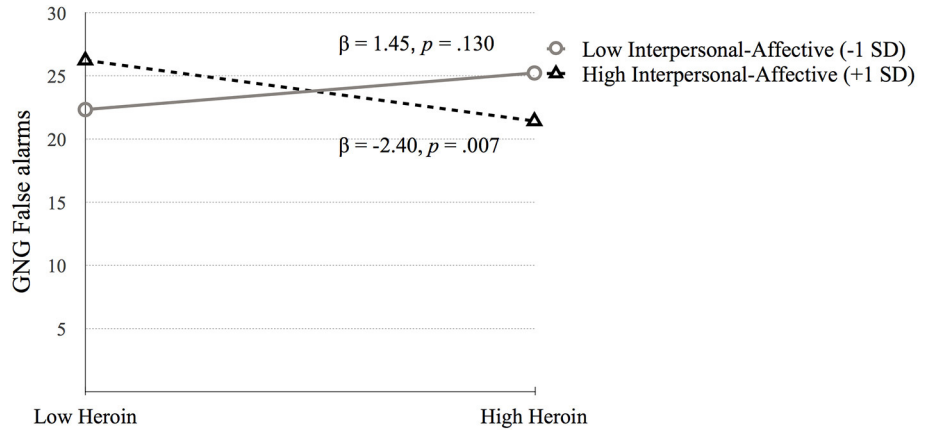

FIGURE 3 | The moderating effect of Interpersonal-affective psychopathy dimension on the association between heroin dependence and GNG False alarms. Low and high values represent +1.0 and −1.00 *SD* from the mean.

TABLE 5 | Substance use and psychopathy as predictors of (1) GNG False alarms, (2) IMT Commission errors, and (3) SST 150 ms inhibition.

	GNG false alarms				IMT commission errors				SST 150 ms inhibition			
	B	***SE B***	β	**Δ*R*²**	***B***	***SE B***	β	**Δ*R*²**	***B***	***SE B***	β	**Δ*R*²**
Step 1				0.04***				0.03***				0.04**
Biological sex	1.30	0.93	0.05		−0.86	1.14	−0.03		−4.45	1.69	−0.10	
Raven's estimated IQ	−0.12	0.03	−0.13**		−0.19	0.04	−0.18***		−0.04	0.06	−0.03**	
Heroin	0.65	0.46	0.06		−0.19	0.56	−0.01		0.17	0.83	0.01	
Amphetamine	1.60	0.44	0.14***		0.82	0.54	0.06		0.33	0.80	0.02	
Step 2				0.01*				0.00				0.00
Biological sex	1.77	1.01	0.07		−0.14	1.23	−0.01		−5.17	1.83	−0.12	
Raven's estimated IQ	−0.10	0.03	−0.12**		−0.18	0.04	−0.17***		−0.05	0.06	−0.03**	
Heroin	−0.16	0.58	−0.01		−0.93	0.71	−0.06		0.44	1.06	0.02	
Amphetamine	0.83	0.54	0.07		0.24	0.66	0.02		0.36	0.99	0.02	
Factor 1	−0.33	0.68	−0.03		0.61	0.83	0.04		−1.59	1.23	−0.08	
Factor 2	1.79	0.77	0.15*		0.88	0.95	0.06		0.85	1.41	0.04	
Step 3				0.02**				0.01				0.01
Biological sex	1.83	1.00	0.08		−0.27	1.23	−0.01		−4.84	1.82	−0.11	
Raven's estimated IQ	−0.10	0.03	−0.12**		−0.17	0.04	−0.16***		−0.05	0.06	−0.03**	
Heroin	−0.48	0.66	−0.04		−1.08	0.82	−0.08		−0.35	1.21	−0.02	
Amphetamine	0.66	0.57	0.06		0.44	0.71	0.03		0.30	1.05	0.01	
Factor 1	0.02	0.71	0.00		0.34	0.87	0.02		−0.82	1.29	−0.04	
Factor 2	1.76	0.78	0.15*		1.15	0.97	0.08		0.40	1.43	0.02	
Heroin X factor 1	−1.93	0.64	−0.17**		−0.64	0.80	−0.04		−0.03	1.18	0.00	
Heroin X factor 2	2.61	0.74	0.21***		0.72	0.92	0.05		1.69	1.37	0.07	
Amphetamine X factor 1	−0.60	0.61	−0.05		1.20	0.75	0.08		−3.05	1.11	−0.15**	
Amphetamine X factor 2	1.40	0.69	0.11*		−1.18	0.85	−0.08		2.73	1.26	0.12*	

*Biological sex = Male (1), Female (2); *p < 0.05; **p < 0.01; ***p < 0.001.*

2.11, $p = 0.078$) nor step 2 [$F_{(6, 686)} = 1.68$, $p = 0.122$] were significant. Step 3, which included the interaction terms between psychopathy and SUD was significant, $F_{(10, 682)} = 2.05$, $p = 0.027$. SST 150 ms inhibition was associated with amphetamine dependence when moderated by Factor 1 ($p = 0.006$) and Factor 2 ($p = 0.031$). Factor 1 of psychopathy moderated the association between amphetamine dependence and SST 150 ms inhibition at low levels of Factor 1 ($p = 0.025$) but not at high levels of Factor 1 ($p = 0.079$; **Figure 6**). In contrast, Factor 2 moderated the relation between amphetamine dependence and SST 150 ms inhibition at high levels of Factor 2 ($p = 0.032$) but not at low levels of Factor 2 ($p = 0.187$; **Figure 7**). Thus, amphetamine

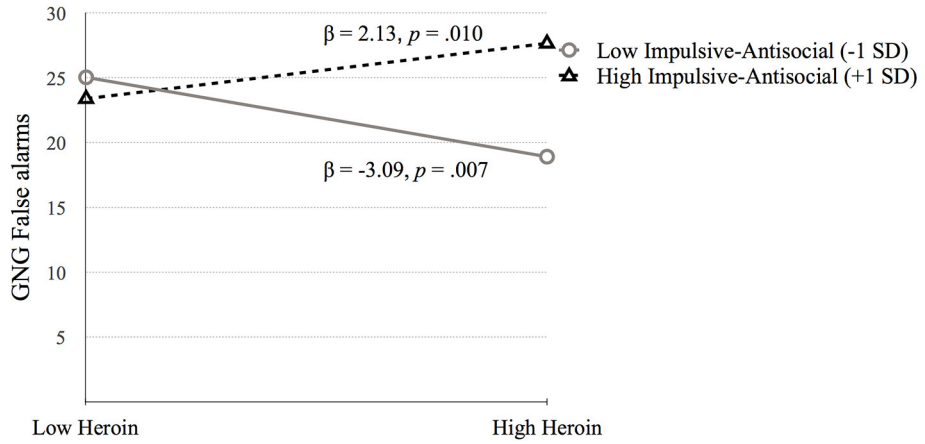

FIGURE 4 | The moderating effect of Impulsive-antisocial psychopathy dimension on the association between heroin dependence and GNG False alarms. Low and high values represent +1.0 and −1.00 *SD* from the mean.

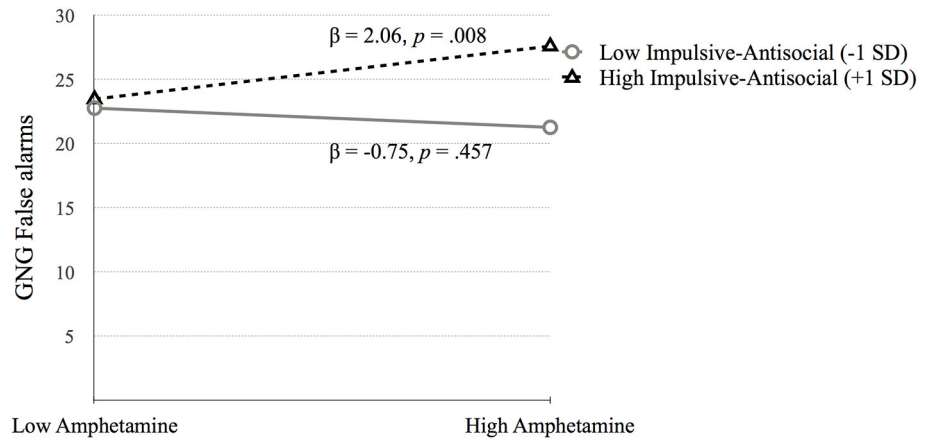

FIGURE 5 | The moderating effect of Impulsive-antisocial psychopathy dimension on the association between amphetamine dependence and GNG False alarms. Low and high values represent +1.0 and 1.00 *SD* from the mean.

dependence was related to higher SST 150 ms inhibition scores (i.e., lower impulsivity) when individuals had either low Factor 1 psychopathy scores or high Factor 2 psychopathy scores. This result highlights that psychopathy factors can differentially serve as both risk and protective factors for neurocognitive function in people with amphetamine dependence.

DISCUSSION

The aims of the present study were to examine the effects of psychopathy and its two dimensions (interpersonal-affective and impulsive-antisocial) on the relationships between dependence on different classes of drugs (stimulants and opioids) and distinct neurocognitive domains of impulsivity (impulsive choice/decision-making and impulsive action/response inhibition). Our findings suggest that the two dimensions of psychopathy had both common and unique moderating effects on decision-making and response inhibition in individuals dependent on stimulants or opiates.

Within the domain of impulsive choice, our results demonstrate that the interpersonal-affective dimension of psychopathy (Factor 1) moderates the associations between quality of decision-making, risk-taking, and dependence in a similar manner for opiates and stimulants. Specifically, lower risk taking on the CGT was predicted by the combination of more symptoms of heroin dependence and high scores on the interpersonal-affective dimension of psychopathy (PCL:SV Factor 1). With few exceptions (78, 79), previous studies conducted separately with psychopathic individuals (80–84, 95) and with opioid dependent individuals (47–49, 56, 61, 109) report that both groups are characterized by riskier and less advantageous decision-making. To our knowledge, only one study to date has examined the effects of co-occurring psychopathy and opioid dependence on decision-making. Vassileva et al. (86) reported that psychopathic

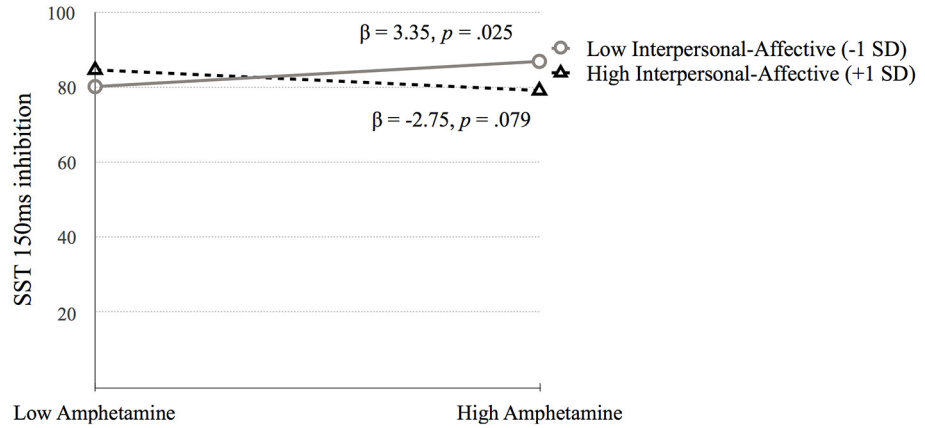

FIGURE 6 | The moderating effect of Interpersonal-affective psychopathy dimension on the association between amphetamine dependence and SST 150 ms inhibition. Low and high values represent +1.0 and −1.00 *SD* from the mean.

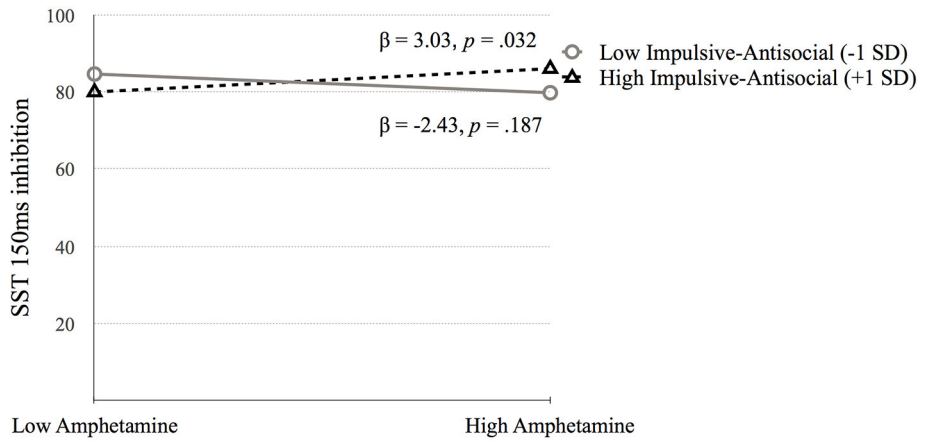

FIGURE 7 | The moderating effect of Impulsive-antisocial psychopathy dimension on the association between amphetamine dependence and SST 150 ms inhibition. Low and high values represent +1.0 and −1.00 *SD* from the mean.

heroin users were characterized by more impaired decision-making than non-psychopathic heroin users, suggesting that psychopathy may exacerbate decision-making deficits in opiate dependent individuals. However, Vassileva et al. (86) considered psychopathy as a unitary categorical construct rather than examining its underlying dimensions, therefore it remained unclear which features of psychopathy were associated with more impaired decision-making in heroin users and whether some psychopathic traits may act as a buffer against disadvantageous and risky decision-making within the context of opioid addiction. The current study builds upon previous findings and indicates that the interpersonal-affective features of psychopathy (Factor 1) may paradoxically play a protective role and reduce the predisposition toward risky decision-making in heroin users.

Findings related to the utility of the two psychopathy dimensions for predicting decision-making in individuals with amphetamine dependence were somewhat consistent with those observed among heroin users. Specifically, results revealed that poor performance on the IGT was predicted by the combination of more symptoms of amphetamine dependence and lower scores on the PCL:SV Factor 1, suggesting that the interpersonal-affective dimension of psychopathy may have similarly protective effect on decision-making in amphetamine dependent individuals as it does in heroin dependent individuals. Interestingly, these results reveal that although the PCL:SV Factor 1 might have common protective effect on reward-based decision-making in both opiate and stimulant dependent individuals, it affects different types of decision-making in heroin and amphetamine users. Specifically, it was related to decision-making under ambiguity in amphetamine users, whereas it was associated with decision-making under risk in heroin users (58, 110). Therefore, our data suggest that the interpersonal-affective dimension of psychopathy may be a key factor that may account for the differential neurocognitive impulsivity profiles observed in individuals dependent on opiates vs. stimulants.

Our findings are also consistent with previous studies that have found that the interpersonal-affective traits of psychopathy were either unrelated or negatively related to overall decision-making deficits (80, 95, 96). Unlike previous studies, which fail to address the unique effects of different dimensions of psychopathy on decision-making in substance users, our study was focused on the predictive utility of the two psychopathy dimensions on the quality of decision-making in different types of SUDs and on different reward-based decision-making tasks. Our findings reveal that the interpersonal-affective rather than the impulsive-antisocial dimension of psychopathy contributes significantly to intact decision-making in the context of both opioid and stimulant addictions, and appears to be the key factor of psychopathy that moderates reward-based decision-making in individuals with SUDs, regardless of specific drug class.

Within the domain of impulsive action, both the interpersonal-affective and the impulsive-antisocial dimensions of psychopathy predicted varying levels of response disinhibition among individuals dependent on opioids or stimulants. High scores on the impulsive-antisocial Factor 2 of psychopathy exacerbated response inhibition deficits on the Go/No-Go task in both amphetamine- and heroin users. These results are in line with previous findings from studies conducted separately with psychopathic individuals (87, 88, 97) and individuals dependent on stimulants (28, 31, 44–46) and/or opioids (31, 47–49), suggesting that psychopathy and dependence on both classes of drugs are related to poor response inhibition. Some studies on psychopathy have also implicated specifically the impulsive-antisocial dimension of psychopathy as the key factor underlying the response inhibition deficits observed in psychopathic individuals (97, 98, 111). Our findings suggest that increased levels of impulsive-antisocial psychopathic traits in the context of addiction may exert additive effects on the already compromised response inhibition performance in substance users.

In contrast, the interpersonal-affective (Factor 1) dimension of psychopathy had differential effects on response inhibition in individuals dependent on opiates vs. stimulants, such that it exacerbated the response inhibition deficits in amphetamine dependent individuals, whereas it was related to better response inhibition in heroin dependent individuals. These results are in line with studies reporting opposite relationships between trait impulsivity and neurocognitive impulsivity in heroin and amphetamine users, where increased trait impulsivity was associated with worse response inhibition in amphetamine dependent individuals, but with better response inhibition in heroin dependent individuals (7). There are reports that the interpersonal-affective dimension of psychopathy is related to superior response inhibition among psychopathic individuals (92, 97, 98). However, research findings to date are equivocal, with some studies finding positive associations between interpersonal-affective psychopathic traits and response inhibition (97, 98), while others have failed to find any relationships or have reported negative relationships (112, 113). These conflicting findings may be explained at least partially by the highly heterogenous samples across studies, e.g., criminal offenders (97, 98) vs. students (112, 113). In addition, inconsistencies between studies could be due to differences in the assessment of psychopathy [interview-based measures such as the PCL (97, 98) vs. self-report measures (112, 113)], differences in the paradigms used to assess response inhibition which may lead to task-specific effects, and the lack of control for concurrent SUDs. Our results are limited to opiate and stimulant use disorders and are focused on the effects of specific combinations between dependence on different classes of drugs (stimulants and opioids) and psychopathy dimensions as predictors of response inhibition. Our findings suggest that drug of choice may interact uniquely with the interpersonal-affective traits of psychopathy and result either in better response inhibition in heroin dependent individuals, or poor response inhibition in amphetamine dependent individuals. It is important to note that in the current sample the levels of the interpersonal-affective dimension of psychopathy were significantly higher among heroin users than in amphetamine users. Therefore, it is possible that more pronounced interpersonal-affective traits can contribute to intact response inhibition, irrespective of the unique effects of the drug of choice. In addition, our results suggest that the effects of the PCL:SV Factor 1 on response inhibition might be task dependent in heroin and amphetamine users. That is, in amphetamine dependent individuals the interpersonal-affective psychopathy dimension predicted diminished ability to cancel an already initiated response as measured by the Go Stop task, whereas in heroin dependent individuals it was associated with the ability to inhibit a prepotent motor response that has not been triggered yet as measured by the Go/No-Go task.

One surprising finding was that the combination of more symptoms of amphetamine dependence and higher impulsive-antisocial features of psychopathy predicted increased inhibitory control on the Stop Signal Task. This indicates that the impulsive-antisocial dimension of psychopathy had differential effects on different tasks of impulsive action in amphetamine users, facilitating the cancellation of an already triggered prepotent motor reaction, while exacerbating the difficulties in the ability to inhibit a dominant response that has not been triggered yet. These findings are in line with previous studies, which have suggested that distinct impulsive action tasks (e.g., Go/No-Go, Stop Signal Tasks) reflect independent cognitive processes, such as "controlled top-down inhibition" in Stop Signal Tasks vs. "automatic bottom-up inhibition" in Go/No-Go Tasks (114) that are mediated by different neural circuits (115–117). Therefore, our results provide further evidence for the distinction between different types of neurocognitive impulsivity and the need to evaluate them separately when examining the specific profiles of neurocognitive impairments in individuals with different types of psychopathology.

In summary, our findings suggest that psychopathy dimensions could play an important role in explaining the decision-making and response inhibition deficits commonly observed in substance users, which may have important clinical implications. First, our results suggest that although screening for psychopathy is rarely conducted in SUDs treatment programs, it would provide valuable information, which could facilitate the development of more personalized interventions aimed at decreasing the negative treatment outcomes related

to specific personality and neurocognitive risk factors. For example, the development and implementation of treatment interventions targeting the impulsive-antisocial aspects of psychopathy could be of particular importance when working with substance users with impaired response inhibition and higher scores on PCL:SV Factor 2. On the other hand, detecting higher interpersonal-affective psychopathic traits could be a resource for improving the quality of decision-making among substance users. Such interventions could potentially help reduce relapse rates in substance users, which are commonly predicted by higher response disinhibition and impaired decision-making (32–37) and may be significantly influenced by certain personality characteristics. Nevertheless, our findings require further investigation and replication in samples with other types of SUDs (e.g., alcohol-, cannabis use disorders) and at different stages of the addiction cycle. In addition, other personality profiles could be tested as predictors of neurocognitive impairments among substance users, which could lead to the development of enriched variety of interventions and therapeutic techniques that are not uniformly applied among substance users, but are rather tailored to the individual characteristics of the highly heterogeneous group of substance users.

LIMITATIONS AND FUTURE DIRECTIONS

A few important limitations need to be considered. First, our findings are specific to the protracted abstinence stage of opiate and stimulant addiction and should not be generalized to other stages of the addiction cycle or to other types of SUDs. Future studies should examine whether psychopathy dimensions have similar moderating effects on decision-making and response inhibition in individuals dependent on other classes of drugs. Second, our findings were based on the traditional two-factor model of psychopathy and should be examined with other models, such as the 4-facet model, which includes interpersonal, affective, lifestyle and antisocial dimensions (118) and has been proposed to provide a more sensitive approach in studying the associations between psychopathy and other variables (119). Future studies should also examine whether psychopathy dimensions predict neurocognitive impairments differently in mono- vs. polysubstance-dependent individuals. Third, we used a community sample of Bulgarian substance users. Therefore, caution is warranted in generalizing the conclusions of our findings before they are replicated cross-culturally. Another limitation of the current study is that there was no comprehensive evaluation of co-occurring psychiatric disorders, that are commonly comorbid with SUDs, such as affective, neurodevelopmental and personality disorders. Future studies could examine more thoroughly the possible effects of comorbid psychopathology on the relationships between psychopathy dimensions and neurocognitive impulsivity among substance users. Finally, statistical tests were uncorrected for multiple comparisons and conducted using an alpha level of 0.05. An alternative would be to apply the Bonferroni correction, which may change the interpretation of some results. However, this method could be overly conservative when conducting multiple regressions, resulting in a type I error rate much smaller than the desired alpha, therefore all tests were conducted using an unadjusted alpha (120).

CONCLUSION

In summary, our results reveal that distinct dimensions of psychopathy have both common and unique moderating effects on neurocognitive impulsivity in individuals in protracted abstinence who are dependent on different classes of drugs (stimulants vs. opiates). In heroin dependent individuals the interpersonal-affective features of psychopathy may play a protective role on both response inhibition and decision-making, whereas in amphetamine dependent individuals lower scores on this dimension of psychopathy were associated with poor decision-making and superior response inhibition. These findings suggest that the interpersonal-affective features of psychopathy have similar effects on decision-making and opposite effects on response inhibition in heroin- and amphetamine dependent individuals. In contrast, higher scores on the impulsive-antisocial dimension of psychopathy predicted response disinhibition in both heroin- and amphetamine dependent individuals, suggesting that the PCL:SV Factor 2 had common deleterious effects on the ability to inhibit prepotent motor responses in people with SUDs, regardless of drug of choice. In addition, impulsive-antisocial psychopathic traits were uniquely related to increased ability to cancel an already initiated response in amphetamine dependent individuals. Overall, our results suggest that not psychopathy *per se*, but rather the interaction between its two dimensions and dependence on specific classes of drugs may lead to either deficient or superior response inhibition and decision-making performance in individuals with SUDs in protracted abstinence.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

All subjects gave written informed consent in accordance with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Boards of Virginia Commonwealth University and the Medical University in Sofia on behalf of the Bulgarian Addictions Institute.

AUTHOR CONTRIBUTIONS

EP, NT, and JV conceived the study. NT performed the statistical analyses and drafted the analysis and results sections. EP drafted the Introduction, Methods, and Discussion sections. EP, KB, DN, and GV collected and managed the data. JV supervised

the data collection and analyses and drafted portions of the manuscript. All authors discussed the results and contributed to the final manuscript.

FUNDING

This research was supported by grant R01DA021421 (JV) from the National Institute on Drug Abuse (NIDA) and the Fogarty International Center (FIC). NT work on this article was supported by the Centers for Disease Control and Prevention: 1R01CE003296-01 and 5K01CE003160-02.

ACKNOWLEDGMENTS

We would like to thank all volunteers for their participation in this study. We express our gratitude to Rada Naslednikova, Ivaylo Raynov, Emiliya Peneva, and Victoria Dobrojalieva for assistance with recruitment and testing of study participants.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.660810/full#supplementary-material

REFERENCES

1. Moeller FG, Barratt ES, Dougherty DM, Schmitz JM, Swann AC. Psychiatric aspects of impulsivity. *Am J Psychiatry.* (2001) 158:1783–93. doi: 10.1176/appi.ajp.158.11.1783
2. Vassileva J, Conrod PJ. Impulsivities and addictions: a multidimensional integrative framework informing assessment and interventions for substance use disorders. *Philoso Trans R Soc B.* (2019) 374:20180137. doi: 10.1098/rstb.2018.0137
3. Bird J, Schenk S. Contribution of impulsivity and novelty-seeking to the acquisition and maintenance of MDMA self-administration. *Addict Biol.* (2013) 18:654–64. doi: 10.1111/j.1369-1600.2012.00477.x
4. Kreek MJ, Nielsen DA, Butelman ER, LaForge KS. Genetic influences on impulsivity, risk taking, stress responsivity and vulnerability to drug abuse and addiction. *Nat Neurosci.* (2005) 8:1450–7. doi: 10.1038/nn1583
5. Crews FT, Boettiger CA. Impulsivity, frontal lobes and risk for addiction. *Pharmacol Biochem Behav.* (2009) 93:237–47. doi: 10.1016/j.pbb.2009.04.018
6. de Wit H. Impulsivity as a determinant and consequence of drug use: a review of underlying processes. *Addict Biol.* (2009) 14:22–31. doi: 10.1111/j.1369-1600.2008.00129.x
7. Vassileva J, Paxton J, Moeller FG, Wilson MJ, Bozgunov K, Martin EM, et al. Heroin and amphetamine users display opposite relationships between trait and neurobehavioral dimensions of impulsivity. *Addict Behav.* (2014) 39:652–9. doi: 10.1016/j.addbeh.2013.11.020
8. Evenden JL. Varieties of impulsivity. *Psychopharmacology.* (1999) 146:348–61. doi: 10.1007/PL00005481
9. Cyders MA, Coskunpinar A. Measurement of constructs using self-report and behavioral lab tasks: is there overlap in nomothetic span and construct representation for impulsivity? *Clin Psychol Rev.* (2011) 31:965–82. doi: 10.1016/j.cpr.2011.06.001
10. Patton JH, Stanford MS, Barratt ES. Factor structure of the barratt impulsiveness scale. *J Clin Psychol.* (1995) 51:768–74. doi: 10.1002/1097-4679(199511)51:6,768::AID-JCLP2270510607.3.0.CO;2-1
11. Whiteside SP, Lynam DR. The five factor model and impulsivity: using a structural model of personality to understand impulsivity. *Pers Indiv Diff.* (2001) 30:669–89. doi: 10.1016/S0191-8869(00)00064-7
12. Beauchaine TP, Zisner AR, Sauder CL. Trait impulsivity and the externalizing spectrum. *Ann Rev Clin Psychol.* (2017) 13:343–68. doi: 10.1146/annurev-clinpsy-021815-093253
13. Hamilton KR, Littlefield AK, Anastasio NC, Cunningham KA, Fink LHL, Wing VC, et al. Rapid-response impulsivity: definitions, measurement issues, clinical implications. *Pers Disord Theory Res Treat.* (2015) 6:168–81. doi: 10.1037/per0000100
14. Hamilton KR, Mitchell MR, Wing VC, Balodis IM, Bickel WK, Fillmore M, et al. Choice impulsivity: definitions, measurement issues, clinical implications. *Pers Disord Theory Res Treat.* (2015) 6:182–98. doi: 10.1037/per0000099
15. Diergaarde L, Pattij T, Poortvliet I, Hogenboom F, de Vries W, Schoffelmeer AN, et al. Impulsive choice and impulsive action predict vulnerability to distinct stages of nicotine seeking in rats. *Biol Psychiatry.* (2008) 63:301–8. doi: 10.1016/j.biopsych.2007.07.011
16. Paterson NE, Wetzler C, Hackett A, Hanania T. Impulsive action and impulsive choice are mediated by distinct neuropharmacological substrates in rat. *Int J Neuropsychopharmacol.* (2012) 15:1473–87. doi: 10.3389/fpsyt.2018.00503
17. Dougherty DM, Marsh DM, Mathias CW. Immediate and delayed memory tasks: a computerized behavioral measure of memory, attention, and impulsivity. *Behav Res Methods Instrum Comput.* (2002) 34:391–8. doi: 10.3758/bf03195467
18. Lane SD, Moeller FG, Steinberg JL, Buzby M, Kosten TR. Performance of cocaine dependent individuals and controls on a response inhibition task with varying levels of difficulty. *Am J Drug Alcohol Abuse.* (2007) 33:717–26. doi: 10.1080/00952990701522724
19. Bickel WK, Miller ML, Yi R, Kowal BP, Lindquist DM, Pitcock JA. Behavioral and neuroeconomics of drug addiction: competing neural systems and temporal discounting processes. *Drug Alcohol Depend.* (2007) 90:85–91. doi: 10.1016/j.drugalcdep.2006.09.016
20. Kirby KN, Petry NM. Heroin and cocaine abusers have higher discount rates for delayed rewards than alcoholics or non-drug-using controls. *Addiction.* (2004) 99:461–71. doi: 10.1111/j.1360-0443.2003.00669.x
21. Kirby KN, Petry NM, Bickel WK. Heroin addicts have higher discount rates for delayed rewards than non-drug-using controls. *J Exp Psychol Gen.* (1999) 128:78–87. doi: 10.1037//0096-3445.128.1.78
22. Bechara A, Damasio AR, Damasio H, Anderson SW. Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition.* (1994) 50:7–15. doi: 10.1016/0010-0277(94)90018-3
23. Rogers RD, Everitt BJ, Baldacchino A, Blackshaw AJ, Swainson R, Wynne K, et al. Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteers: evidence for monoaminergic mechanisms. *Neuropsychopharmacology.* (1999) 20:322–39. doi: 10.1016/S0893-133X(98)00091-8
24. Lejeuz CW, Richards JB, Read JP, Kahler CW, Ramsey SE, Stuart GL, et al. Evaluation of a behavioral measure of risk taking: the balloon analogue risk task (BART). *J Exp Psychol Appl.* (2002) 8:75–84. doi: 10.1037/1076-898X.8.2.75
25. Bechara A, Dolan S, Denburg N, Hindes A, Anderson SW, Nathan PE. Decision-making deficits, linked to a dysfunctional ventromedial prefrontal cortex, revealed in alcohol and stimulant abusers. *Neuropsychologia.* (2001) 39:376–89. doi: 10.1016/s0028-3932(00)00136-6
26. Bickel WK, Mellis AM, Snider SE, Athamneh LN, Stein JS, Pope DA. 21st century neurobehavioral theories of decision making in addiction: review and evaluation. *Pharmacol Biochem Behav.* (2018) 164:4–21. doi: 10.1016/j.pbb.2017.09.009
27. Gowin JL, Sloan ME, Ramchandani VA, Paulus MP, Lane SD. Differences in decision-making as a function of drug of choice. *Pharmacol Biochem Behav.* (2018) 164:118–24. doi: 10.1016/j.pbb.2017.09.007

28. Hester R, Simoes-Franklin C, Garavan H. Post-error behavior in active cocaine users: poor awareness of errors in the presence of intact performance adjustments. *Neuropsychopharmacology.* (2007) 32:1974–84. doi: 10.1038/sj.npp.1301326
29. MacKillop J, Amlung MT, Few LR, Ray LA, Sweet LH, Munaf,ò MR. Delayed reward discounting and addictive behavior: a meta-analysis. *Psychopharmacology.* (2011) 216:305–21. doi: 10.1007/s00213-011-2229-0
30. Petry NM. Discounting of money, health, and freedom in substance abusers and controls. *Drug Alcohol Depend.* (2003) 71:133–41. doi: 10.1016/S0376-8716(03)00090-5
31. Verdejo-García AJ, Perales JC, Pérez-García M. Cognitive impulsivity in cocaine and heroin polysubstance abusers. *Addict Behav.* (2007) 32:950–66. doi: 10.1016/j.addbeh.2006.06.032
32. Bowden-Jones H, McPhillips M, Rogers R, Hutton S, Joyce E. Risk-taking on tests sensitive to ventromedial prefrontal cortex dysfunction predicts early relapse in alcohol dependency: a pilot study. *J Neuropsychiatry Clin Neurosci.* (2005) 17:417–20. doi: 10.1176/jnp.17.3.417
33. De Wilde B, Verdejo-García A, Sabbe B, Hulstijn W, Dom G. Affective decision-making is predictive of three-month relapse in polysubstance-dependent alcoholics. *Euro Addict Res.* (2013) 19:21–8. doi: 10.1159/000339290
34. Passetti F, Clark L, Mehta MA, Joyce E, King M. Neuropsychological predictors of clinical outcome in opiate addiction. *Drug Alcohol Depend.* (2008) 94:82–91. doi: 10.1016/j.drugalcdep.2007.10.008
35. Passetti F, Clark L, Davis P, Mehta MA, White S, Checinski K, et al. Risky decision-making predicts short-term outcome of community but not residential treatment for opiate addiction. Implications for case management. *Drug Alcohol Depend.* (2011) 118:12–8. doi: 10.1016/j.drugalcdep.2011.02.015
36. Stevens L, Goudriaan AE, Verdejo-Garcia A, Dom G, Roeyers H, Vanderplasschen W. Impulsive choice predicts short-term relapse in substance-dependent individuals attending an in-patient detoxification programme. *Psychol Med.* (2015) 45:2083–93. doi: 10.1017/S003329171500001X
37. Washio Y, Higgins ST, Heil SH, McKerchar TL, Badger GJ, Skelly JM, et al. Delay discounting is associated with treatment response among cocaine-dependent outpatients. *Exp Clin Psychopharmacol.* (2011) 19:243–8. doi: 10.1037/a0023617
38. Fernie G, Peeters M, Gullo MJ, Christiansen P, Cole JC, Sumnall H, et al. Multiple behavioural impulsivity tasks predict prospective alcohol involvement in adolescents. *Addiction.* (2013) 108:1916–23. doi: 10.1111/add.12283
39. Mahmood OM, Goldenberg D, Thayer R, Migliorini R, Simmons AN, Tapert SF. Adolescents' fMRI activation to a response inhibition task predicts future substance use. *Addict Behav.* (2013) 38:1435–41. doi: 10.1016/j.addbeh.2012.07.012
40. Nigg JT, Wong MM, Martel MM, Jester JM, Puttler LI, Glass JM, et al. Poor response inhibition as a predictor of problem drinking and illicit drug use in adolescents at risk for alcoholism and other substance use disorders. *J Am Acad Child Adolesc Psychiatry.* (2006) 45:468–75. doi: 10.1097/01.chi.0000199028.76452.a9
41. Norman AL, Pulido C, Squeglia LM, Spadoni AD, Paulus MP, Tapert SF. Neural activation during inhibition predicts initiation of substance use in adolescence. *Drug Alcohol Depend.* (2011) 119:216–23. doi: 10.1016/j.drugalcdep.2011.06.019
42. Badiani A, Belin D, Epstein D, Calu D, Shaham Y. Opiate versus psychostimulant addiction: the differences do matter. *Nat Rev Neurosci.* (2011) 12:685–700. doi: 10.1038/nrn3104
43. Wise RA, Koob GF. The development and maintenance of drug addiction. *Neuropsychopharmacology.* (2014) 39:254–62. doi: 10.1038/npp.2013.261
44. Fillmore MT, Rush CR. Impaired inhibitory control of behavior in chronic cocaine users. *Drug Alcohol Depend.* (2002) 66:265–273. doi: 10.1016/s0376-8716(01)00206-x
45. Kaufman JN, Ross TJ, Stein EA, Garavan H. Cingulate hypoactivity in cocaine users during a GO-NOGO task as revealed by event-related functional magnetic resonance imaging. *J Neurosci.* (2003) 23:7839–43. doi: 10.1523/JNEUROSCI.23-21-07839.2003
46. Monterosso JR, Aron AR, Cordova X, Xu J, London ED. Deficits in response inhibition associated with chronic methamphetamine abuse. *Drug Alcohol Depend.* (2005) 79:273–7. doi: 10.1016/j.drugalcdep.2005.02.002
47. Forman SD, Dougherty GG, Casey BJ, Siegle GJ, Braver TS, Barch DM, et al. Opiate addicts lack error-dependent activation of rostral anterior cingulate. *Biol Psychiatry.* (2004) 55:531–7. doi: 10.1016/j.biopsych.2003.09.011
48. Fu LP, Bi GH, Zou ZT, Wang Y, Ye EM, Ma L, et al. Impaired response inhibition function in abstinent heroin dependents: an fMRI study. *Neurosci Lett.* (2008) 438:322–6. doi: 10.1016/j.neulet.2008.04.033
49. Mintzer MZ, Stitzer ML. Cognitive impairment in methadone maintenance patients. *Drug Alcohol Depend.* (2002) 67:41–51. doi: 10.1016/S0376-8716(02)00013-3
50. Verdejo-García A, Pérez-García M. Profile of executive deficits in cocaine and heroin polysubstance users: common and differential effects on separate executive components. *Psychopharmacology.* (2007) 190:517–30. doi: 10.1007/s00213-006-0632-8
51. Bornovalova MA, Daughters SB, Hernandez GD, Richards JB, Lejuez CW. Differences in impulsivity and risk-taking propensity between primary users of crack cocaine and primary users of heroin in a residential substance-use program. *Exp Clin Psychopharmacol.* (2005) 13:311–8. doi: 10.1037/1064-1297.13.4.311
52. Ahn WY, Vasilev G, Lee SH, Busemeyer JR, Kruschke JK, Bechara A, et al. Decision-making in stimulant and opiate addicts in protracted abstinence: evidence from computational modeling with pure users. *Front Psychol.* (2014) 5:849. doi: 10.3389/fpsyg.2014.00849
53. Ersche KD, Fletcher PC, Lewis SJG, Clark L, Stocks-Gee G, London M, et al. Abnormal frontal activations related to decision-making in current and former amphetamine and opiate dependent individuals. *Psychopharmacology.* (2005) 180:612–23. doi: 10.1007/s00213-005-2205-7
54. Ahn WY, Vassileva J. Machine-learning identifies substance-specific behavioral markers for opiate and stimulant dependence. *Drug Alcohol Depend.* (2016) 161:247–57. doi: 10.1016/j.drugalcdep.2016.02.008
55. Vassileva J, Shahidi R, Taylor BA, Moeller FG, Ahn WY. Machine learning identifies common and specific markers of dependence on five different classes of drugs. *Biolog Psychiatry.* (2019) 85:S209.
56. Li X, Zhang F, Zhou Y, Zhang M, Wang X, Shen M. Decision-making deficits are still present in heroin abusers after short- to long-term abstinence. *Drug Alcohol Depend.* (2013) 130:61–7. doi: 10.1016/j.drugalcdep.2012.10.012
57. Morie KP, Garavan H, Bell RP, De Sanctis P, Krakowski MI, Foxe JJ. Intact inhibitory control processes in abstinent drug abusers (II): a high-density electrical mapping study in former cocaine and heroin addicts. *Neuropharmacology.* (2014) 82:151–60. doi: 10.1016/j.neuropharm.2013.02.023
58. Wilson MJ, Vassileva J. Decision-making under risk, but not under ambiguity, predicts pathological gambling symptoms in discrete types of abstinent substance users. *Front Psychiatry.* (2018) 9:239. doi: 10.3389/fpsyt.2018.00239
59. Garavan H, Brennan KL, Hester R, Whelan R. The neurobiology of successful abstinence. *Curr Opin Neurobiol.* (2013) 23:668–74. doi: 10.1016/j.conb.2013.01.029
60. Salo R, Nordahl TE, Galloway GP, Moore CD, Waters C, Leamon MH. Drug abstinence and cognitive control in methamphetamine-dependent individuals. *J Substan Abuse Treat.* (2009) 37:292–7. doi: 10.1016/j.jsat.2009.03.004
61. Zhang XL, Shi J, Zhao LY, Sun LL, Wang J, Wang GB, et al. Effects of stress on decision-making deficits in formerly heroin-dependent patients after different durations of abstinence. *Am J Psychiatry.* (2011) 168:610–6. doi: 10.1176/appi.ajp.2010.10040499
62. Hare RD, Neumann CS. Psychopathy as a clinical and empirical construct. *Annu Rev Clin Psychol.* (2008) 4:217–46. doi: 10.1146/annurev.clinpsy.3.022806.091452
63. Hare RD. *Manual for the Hare Psychopathy Checklist–Revised*. Toronto, ON: Multi-Health Systems (1991).
64. Hare RD. *Manual for the Hare Psychopathy Checklist – Revised, 2nd Edn*. Toronto, ON: Multi-Health Systems (2003).

65. Hare RD, Harpur TJ, Hakstian AR, Forth AE, Hart SD, Newman JP. The revised psychopathy checklist: reliability and factor structure. *Psychol Assess J Consult Clin Psychol.* (1990) 2:338–41. doi: 10.1037/1040-3590.2.3.338
66. Harpur TJ, Hare RD, Hakstian AR. Two-factor conceptualization of psychopathy: construct validity and assessment implications. *Psychol Assess J Consult Clin Psychol.* (1989) 1:6–17. doi: 10.1037/1040-3590.1.1.6
67. Blackburn R. An empirical classification of psychopathic personality. *Br J Psychiatry.* (1975) 127:456–60.
68. Karpman B. The myth of the psychopathic personality. *Am J Psychiatry.* (1948) 104:523–34. doi: 10.1176/ajp.104.9.523
69. Vassileva J, Kosson DS, Abramowitz C, Conrod P. Psychopathy versus psychopathies in classifying criminal offenders. *Legal Criminol Psychol.* (2005) 10:27–43. doi: 10.1348/135532504X15376
70. Hicks BM, Markon KE, Patrick CJ, Krueger RF, Newman JP. Identifying psychopathy subtypes on the basis of personality structure. *Psychol Assess.* (2004) 16:276–88. doi: 10.1037/1040-3590.16.3.276
71. Snowden RJ, Gray NS. Impulsivity and psychopathy: associations between the barrett impulsivity scale and the psychopathy checklist revised. *Psychiatry Res.* (2011) 187:414–7. doi: 10.1016/j.psychres.2011.02.003
72. Derefinko KJ, Lynam DR. Using the FFM to conceptualize psychopathy: a test using a drug abusing sample. *J Pers Disord.* (2007) 21:638–56. doi: 10.1521/pedi.2007.21.6.638
73. Smith SS, Newman JP. Alcohol and drug abuse-dependence disorders in psychopathic and nonpsychopathic criminal offenders. *J Abnorm Psychol.* (1990) 99:430–9. doi: 10.1037/0021-843x.99.4.430
74. Taylor J, Lang AR. Psychopathy and substance use disorders. In: Patrick CJ, editor. *Handbook of Psychopathy.* The Guilford Press (2006). p. 495–511.
75. Alterman AI, Rutherford MJ, Cacciola JS, McKay JR, Boardman CR. Prediction of 7 months methadone maintenance treatment response by four measures of antisociality. *Drug Alcohol Depend.* (1998) 49:217–23. doi: 10.1016/s0376-8716(98)00015-5
76. O'Neill ML, Lidz V, Heilbrun K. Adolescents with psychopathic characteristics in a substance abusing cohort: treatment process and outcomes. *Law Hum Behav.* (2003) 27:299–313. doi: 10.1023/A:1023435924569
77. Richards HJ, Casey JO, Lucente SW. Psychopathy and treatment response in incarcerated female substance abusers. *Crim Justice Behav.* (2003) 30:251–76. doi: 10.1177/0093854802251010
78. Lösel F, Schmucker M. Psychopathy, risk taking, and attention: a differentiated test of the somatic marker hypothesis. *J Abnorm Psychol.* (2004) 113:522–9. doi: 10.1037/0021-843X.113.4.522
79. Schmitt WA, Brinkley CA, Newman JP. Testing Damasio's somatic marker hypothesis with psychopathic individuals: risk takers or risk averse? *J Abnorm Psychol.* (1999) 108:538–43. doi: 10.1037/0021-843X.108.3.538
80. Beszterczey S, Nestor PG, Shirai A, Harding S. Neuropsychology of decision making and psychopathy in high-risk ex-offenders. *Neuropsychology.* (2013) 27:491–7. doi: 10.1037/a0033162
81. Blair RJ, Colledge E, Mitchell DG. Somatic markers and response reversal: is there orbitofrontal cortex dysfunction in boys with psychopathic tendencies? *J Abnorm Child Psychol.* (2001) 29:499–511. doi: 10.1023/A:1012277125119
82. Blair KS, Morton J, Leonard A, Blair RJR. Impaired decision-making on the basis of both reward and punishment information in individuals with psychopathy. *Pers Indivi Diff.* (2006) 41:155–65. doi: 10.1016/j.paid.2005.11.031
83. Boulanger C, Habib M, LanAon C. Impaired making-decision and empathy disorder in psychopathy. *Euro Psychiatry.* (2008) 23:92. doi: 10.1037/a0030261
84. Mitchell DG, Colledge E, Leonard A, Blair RJ. Risky decisions and response reversal: is there evidence of orbitofrontal cortex dysfunction in psychopathic individuals? *Neuropsychologia.* (2002) 40:2013–22. doi: 10.1016/S0028-3932(02)00056-8
85. van Honk J, Hermans EJ, Putman P, Montagne B, Schutter DJ. Defective somatic markers in sub-clinical psychopathy. *Neuroreport.* (2002) 13:1025–7. doi: 10.1097/00001756-200206120-00009
86. Vassileva J, Petkova P, Georgiev S, Martin EM, Tersiyski R, Velinov V, et al. Impaired decision making in psychopathic heroin addicts. *Drug Alcohol Depend.* (2007) 86:287–9. doi: 10.1016/j.drugalcdep.2006.06.015
87. Kim YY, Jung YS. Reduced frontal activity during response inhibition in individuals with psychopathic traits: An sLORETA study. *Biol Psychol.* (2014) 97:49–59. doi: 10.1016/j.biopsycho.2014.02.004
88. Krakowski MI, Foxe J, de Sanctis P, Nolan K, Hoptman MJ, Shope C, et al. Aberrant response inhibition and task switching in psychopathic individuals. *Psychiatry Res.* (2015) 229:1017–23. doi: 10.1016/j.psychres.2015.06.018
89. Lapierre D, Braun CM, Hodgins S. Ventral frontal deficits in psychopathy: neuropsychological test findings. *Neuropsychologia.* (1995) 33:139–51. doi: 10.1016/0028-3932(94)00110-b
90. Roussy S, Toupin J. Behavioral inhibition deficits in juvenile psychopaths. *Aggress Behav.* (2000) 26:413–24. doi: 10.1002/1098-2337(200011)26:6<413::AID-AB1>3.0.CO;2-Q
91. Munro GE, Dywan J, Harris GT, McKee S, Unsal A, Segalowitz SJ. Response inhibition in psychopathy: the frontal N2 and P3. *Neurosci Lett.* (2007) 418:149–53. doi: 10.1016/j.neulet.2007.03.017
92. Vassileva J, Georgiev S, Martin EM, Gonzalez R, Segal,à L. Psychopathic heroin addicts are not uniformly impaired across neurocognitive domains of impulsivity. *Drug Alcohol Depend.* (2011) 114:194–200. doi: 10.1016/j.drugalcdep.2010.09.021
93. Verona E, Sprague J, Sadeh N. Inhibitory control and negative emotional processing in psychopathy and antisocial personality disorder. *J Abnorm Psychol.* (2012) 121:498–510. doi: 10.1037/a0025308
94. Thomson ND. *Understanding Psychopathy: The Biopsychosocial Perspective.* New York, NY: Routledge (2019).
95. Dean AC, Altstein LL, Berman ME, Constans JI, Sugar CA, McCloskey MS. Secondary psychopathy, but not primary psychopathy, is associated with risky decision-making in noninstitutionalized young adults. *Personality and individual differences.* (2013) 54:272–277. doi: 10.1016/j.paid.2012.09.009
96. Miranda R Jr, MacKillop J, Meyerson LA, Justus A, Lovallo WR. Influence of antisocial and psychopathic traits on decision-making biases in alcoholics. *Alcohol Clin Exp Res.* (2009) 33:817–25. doi: 10.1111/j.1530-0277.2009.00901.x
97. Feilhauer J, Cima M, Korebrits A, Kunert HJ. Differential associations between psychopathy dimensions, types of aggression, response inhibition. *Aggress Behav.* (2012) 38:77–88. doi: 10.1002/ab.20415
98. Weidacker K, Snowden RJ, Boy F, Johnston SJ. Response inhibition in the parametric Go/No-Go task in psychopathic offenders. *Psychiatry Res.* (2017) 250:256–63. doi: 10.1016/j.psychres.2017.01.083
99. Baskin-Sommers AR, Curtin JJ, Newman JP. Altering the cognitive-affective dysfunctions of psychopathic and externalizing offender subtypes with cognitive remediation. *Clin Psychol Sci.* (2015) 3:45–57. doi: 10.1177/2167702614560744
100. Thomson ND, Vassileva J, Kiehl KA, Reidy D, Aboutanos M, McDougle R, et al. Which features of psychopathy and impulsivity matter most for prison violence? New evidence among female prisoners. *Int J Law Psychiatry.* (2019) 64:26–33. doi: 10.1016/j.ijlp.2019.01.001
101. Raven J. The raven's progressive matrices: change and stability over culture and time. *Cognit Psychol.* (2000) 41:1–48. doi: 10.1006/cogp.1999.0735
102. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR, 2000).* Washington, DC: American Psychiatric Association (2000).
103. First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV).* Washington, DC: American Psychiatric Press (1996).
104. Hart SD, Cox DN, Hare RD. *Hare Psychopathy Checklist: Screening Version.* North Tonowanda, NY: Multi-Health Systems (1995).
105. Wilson MJ, Abramowitz C, Vasilev G, Bozgunov K, Vassileva J. Psychopathy in Bulgaria: the cross-cultural generalizability of the hare psychopathy checklist. *J Psychopathol Behav Assess.* (2014) 36:389–400. doi: 10.1007/s10862-014-9405-6
106. Bechara A, Tranel D, Damasio H. Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. *Brain.* (2000) 123:2189–202. doi: 10.1093/brain/123.11.2189
107. Dougherty DM, Mathias CW, Marsh DM, Jagar AA. Laboratory behavioral measures of impulsivity. *Behav Res Methods.* (2005) 37:82–90. doi: 10.3758/bf03206401

108. Aiken LS, West SG, Reno RR. *Multiple Regression: Testing and Interpreting Interactions*. Thousand Oaks, CA: Sage, (1991).
109. Kriegler J, Wegener S, Richter F, Scherbaum N, Brand M, Wegmann E. Decision making of individuals with heroin addiction receiving opioid maintenance treatment compared to early abstinent users. *Drug Alcohol Depend.* (2019) 205:107593. doi: 10.1016/j.drugalcdep.2019.107593
110. Krain AL, Wilson AM, Arbuckle R, Castellanos FX, Milham MP. Distinct neural mechanisms of risk and ambiguity: a meta-analysis of decision-making. *Neuroimage.* (2006) 32:477–84. doi: 10.1016/j.neuroimage.2006.02.047
111. Heritage AJ, Benning SD. Impulsivity and response modulation deficits in psychopathy: evidence from the ERN and N1. *J Abnorm Psychol.* (2013) 122:215–22. doi: 10.1037/a0030039
112. Sellbom M, Verona E. Neuropsychological correlates of psychopathic traits in a non-incarcerated sample. *J Res Pers.* (2007) 41:276–94. doi: 10.1016/j.jrp.2006.04.001
113. Weidacker K, Whiteford S, Boy F, Johnston SJ. Response inhibition in the parametric go/no-go task and its relation to impulsivity and subclinical psychopathy. *Q J Exp Psychol.* (2017) 70:473–87. doi: 10.1080/17470218.2015.1135350
114. Verbruggen F, Logan GD. Automatic and controlled response inhibition: associative learning in the go/no-go and stop-signal paradigms. *J Exp Psychol Gen.* (2008) 137:649–72. doi: 10.1037/a0013170
115. Eagle DM, Bari A, Robbins TW. The neuropsychopharmacology of action inhibition: cross-species translation of the stop-signal and go/no-go tasks. *Psychopharmacology.* (2008) 199:439–56. doi: 10.1007/s00213-008-1127-6
116. Lenartowicz A, Kalar DJ, Congdon E, Poldrack RA. Towards an ontology of cognitive control. *Topics Cognit Sci.* (2010) 2:678–92. doi: 10.1111/j.1756-8765.2010.01100.x
117. Littman R, Takács Á. Do all inhibitions act alike? A study of go/no-go and stop-signal paradigms. *PLoS ONE.* (2017) 12:e0186774. doi: 10.1371/journal.pone.0186774
118. Neumann CS, Hare RD, Newman JP. The super-ordinate nature of the psychopathy checklist-revised. *J Pers Disord.* (2007) 21:102–17. doi: 10.1521/pedi.2007.21.2.102
119. Thomson ND, Bozgunov K, Psederska E, Vassileva J. Sex differences on the four-facet model of psychopathy predict physical, verbal, indirect aggression. *Aggress Behav.* (2019) 45:265–274. doi: 10.1002/ab.21816
120. Mundfrom DJ, Perrett JJ, Schaffer J, Piccone A, Roozeboom M. Bonferroni adjustments in tests for regression coefficients. *Mult Linear Regress Viewpoints.* (2006) 32:1–6. Available online at: http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.490.7640&rep=rep1&type=pdf

Conflict of Interest: GV has ownership interests in the Bulgarian Addictions Institute, where data collection took place.

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.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 23 July 2021
doi: 10.3389/fpsyt.2021.647615

Effects of Chronic Alcohol Use Disorder on the Visual Tilt Illusion

Guoqing Gao [1,2,3], Liangshuang Yin [4], Jun Cheng [1,2,3], Rui Tao [1,2,3], Yu Liu [1,2,3], Liangjun Pang [1,2,3] and Zhengchun Wang [5]**

[1] Department of Psychiatry, Affiliated Psychological Hospital of Anhui Medical University, Hefei, China, [2] Department of Psychiatry, Heifei Fourth People's Hospital, Hefei, China, [3] Department of Psychiatry, Anhui Mental Health Center, Hefei, China, [4] Department of Psychiatry, General Hospital for Prison in Anhui Province, Hefei, China, [5] The Affiliated People's Hospital of Ningbo University, Ningbo, China

Rationale: Among the serious consequences of alcohol use disorder (AUD) is the reduced ability to process visual information. It is also generally agreed that AUD tends to occur with disturbed excitation–inhibition (EI) balance in the central nervous system. Thus, a specific visual behavioral probe could directly qualify the EI dysfunction in patients with AUD. The tilt illusion (TI) is a paradigmatic example of contextual influences on perception of central target. The phenomenon shows a characteristic dependence on the angle between the inducing surround stimulus and the central target test. For small angles, there is a repulsion effect; for larger angles, there is a smaller attraction effect. The center-surround inhibition in tilt repulsion is considered to come from spatial orientational interactions between orientation-tuned neurons in the primary visual cortex (V1), and tilt attraction is from higher-level effects of orientation processing in the visual information processing.

Objectives: The present study focuses on visual spatial information processing and explores whether chronic AUD patients in abstinence period exhibited abnormal TI compared with healthy controls.

Methods: The participants are 30 male volunteers (20–46 years old) divided into two groups: the study group consists of 15 clinically diagnosed AUD patients undergoing abstinence from alcohol, and the control group consists of 15 healthy volunteers. The TI consists of a center target surround with an annulus (both target and annulus are sinusoidal grating with spatial frequency = 2 cycles per degree). The visual angle between center and surround is a variable restricted to 0°, ±15°, ±30°, or ±75°. For measuring the TI, participants have to report whether the center target grating orientation tilted clockwise or counterclockwise from the internal vertical orientation by pressing corresponding keys on the computer keyboard. No feedback is provided regarding response correctness.

Results: The results reveal significantly weaker tilt repulsion effect under surround orientation ±15° ($p < 0.05$) and higher lapse rate (attention limitation index) under all

OPEN ACCESS

Edited by:
Qi Li,
University of Chinese Academy of Sciences, China

Reviewed by:
Sally Adams,
University of Bath, United Kingdom
Guochun Yang,
Institute of Psychology, Chinese Academy of Sciences (CAS), China

****Correspondence:***
Liangjun Pang
pljdr@ahmhcentre.com
Zhengchun Wang
wangzhengchun@nbu.edu.cn

Specialty section:
This article was submitted to Addictive Disorders, a section of the journal Frontiers in Psychiatry

Received: *30 December 2020*
Accepted: *18 June 2021*
Published: *23 July 2021*

Citation:
Gao G, Yin L, Cheng J, Tao R, Liu Y, Pang L and Wang Z (2021) Effects of Chronic Alcohol Use Disorder on the Visual Tilt Illusion. Front. Psychiatry 12:647615. doi: 10.3389/fpsyt.2021.647615

tested surround orientations (all ps < 0.05) in patients with chronic AUD compared with health controls.

Conclusions: These results provide psychophysical evidence that visual perception of center-contextual stimuli is different between AUD and healthy control groups.

Keywords: alcohol use disorder, tilt illusion, visual perception, inhibition, primary visual cortex

INTRODUCTION

Chronic extensive alcohol consumption affects basically all organs, including most brain areas (1–4). Particularly, the primary visual cortex (V1) is vulnerable to any noxious input, such as bisphenol A (5), methanol (6), or organic solvents (7). Alcohol consumption, sporadically or chronically, impairs visual function, as documented in animal research (8–11), human imaging studies (12), and psychophysical measurements (13–15).

Alcohol use disorder (AUD) is characterized by a chronic disorder of alcohol dependence (16). AUD patients who have been craving alcoholic beverage, developing tolerance to the intoxicating effects, and developing neurologic signs of withdrawal when they stop drinking (17–19). The neurotoxic effects of chronic alcohol ingestion on the central nervous system include structural, cognitive, and behavioral dysfunctions (20–23). Moreover, an abnormal excitation/inhibition ratio is associated with ethanol-related cortical deficits in AUD patients (24). It is demonstrated that chronic alcohol consumption increases the number of glutamate receptors and reduces the number of GABA receptors (24). Particularly, the impaired visual processing abilities induced by chronic extensive alcohol consumption are explained by altered metabolism in the primary visual cortex (12), impaired brain electrical activities (25), and reduced activation of occipital areas (26).

The perceived orientation of center target was biased by the simultaneously presented surround stimulus (**Figure 1A**), a phenomenon known as tilt illusion (TI) (27). Particularly, the physical orientation of center target was strongly misperceived by participants when the surround orientation had an angular difference between 0° and 50° (repulsion effect), while a systematic weaker effect was observed when angular difference was around 75° (attraction effect) (example in **Figure 2A**) (28, 29). Lateral inhibition between neurons tuned to different orientations at the same location, as well as between those tuned to the same orientation at different locations, is proposed as the neural mechanism of repulsive and attractive TI (28, 30, 31). The TI has been proven a valuable tool in establishing the extent of unconscious processing in human visual cortex and in investigating the degree of cue invariance with which orientation is processed (27).

Given that AUD patients suffer from disturbed excitation/inhibition balance (24), for example, increased glutamate receptors and reduced GABA receptors (24), we expect that AUD patients should possess decreased overall inhibition. We investigate this hypothesis by using the center-surround TI scenario as a probe of inhibition changes, such that the weakened inhibitory system should decrease the magnitude of TI.

MATERIALS AND METHODS

Subjects

The study includes 15 AUD subjects and 15 healthy individuals. All study participants are male between 20 and 46 years of age. The alcohol-dependent subjects are recruited from the Anhui Mental Health Center and meet the criteria for alcohol dependence (**Table 1**). All subjects are examined by an ophthalmologist before psychophysical testing. No subject has anatomical abnormalities that could be detected by ophthalmological examination. This is particularly important for the chronic AUD subjects because permanent damage to the papillomacular bundle can occur in advanced forms of alcoholism, which can be detected by retinoscopy (32).

Patients are included in the present study if they fulfilled the following criteria: (1) current diagnosis of AUD as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V); (2) normal or corrected to normal visual acuity (20/20 visual acuity) and no history of past or present ocular or neural diseases that could affect visual functions; (3) no current blood alcohol and alcohol misuse maintained until hospitalization (in order to ensure that all patients are tested within their first month of detoxification, most of the subjects are abstinent for more than 20 days before the date of the study). Patients are excluded if they (1) are diagnosed with a disorder in the psychotic spectrum or (2) regularly used other addictive substances (except nicotine).

Control participants are recruited from the local community, who have normal or corrected to normal visual acuity (20/20 visual acuity) and no report of current or past history of alcoholism, neurological and/or psychiatric disease, or medication. None of them presents a personal or family history of chronic alcoholism. Alcohol-related data of patients and controls are shown in **Table 1**.

Ethics Statement

This research has been approved by the ethics committee of the Mental Health Center of Anhui Province. All participants are provided with informed consent forms before taking part in the psychophysical assessment, which followed The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

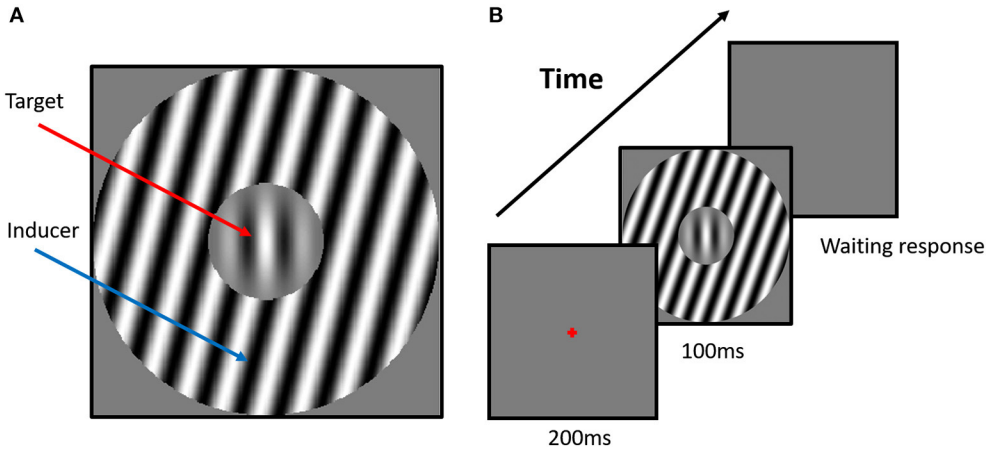

FIGURE 1 | Example stimuli and experiment scenario. **(A)** The stimulus configuration for the tilt repulsion condition. In this case, the orientation of the surround inducer is +15°, and the central target is oriented vertically (0°), which induces a repulsion in the perceived orientation of the center grating, now appearing to be tilted left of vertical. **(B)** The scenario of the tilt illusion (TI) experiment. The classical one-interval task was used in the current experiments. The surround orientation could have one of seven values (−75°, −30°, −15°, 0°, +15°, +30°, +75°) relative to the orientation of the center grating, and we manipulated the center orientation in each trial with respect to vertical according to the participant's responses to measure each subject's perceived vertical.

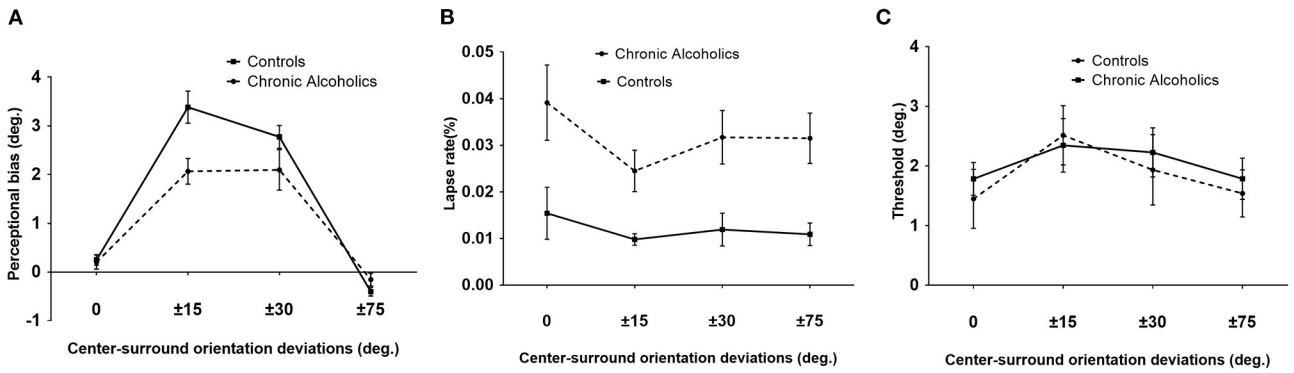

FIGURE 2 | Tilt illusion (TI) results. **(A)** TI effects, indicated by perceptual orientation bias necessary to perceive the center as vertical, as a function of various angles between surround inducer and center target for patients with chronic alcoholism (broken line) and healthy controls. Perceptual biases of ±15° and ±30° are tilt repulsion effects, while those under ±75° were attraction effects. **(B)** Lapse rate values for chronic alcoholics (broken line) and controls. **(C)** Orientation thresholds around perceived verticality for chronic alcoholics (broken line) and controls (blue). Error bars are SEM.

Equipment and Stimulus

The visual stimuli are displayed on a 17-inch CRT monitor (Sony G520, Sony Corporation, Tokyo Japan; 85 Hz, resolution of 1,280 × 960 pixels) and generated by self-programmed Matlab functions (MathWorks Inc.) with PsychToolBox-3 extensions (33). The original 8 bits per pixel luminance range digitization is extended above 10 bits with the contrast box switcher (34), and the monitor is calibrated daily with a custom laboratory automated procedure.

A chair is set at 200 cm from the video screen, with a support for the chin and forehead to control the distance, and the stimuli are viewed binocularly. A black cardboard with a 30-cm-diameter circular window is delimited in front of the monitor to avoid any local cues of the vertical/horizontal position (35). All tests are performed in a dark room with 0.01 cd/m^2 of background luminance. The stimuli used to measure the TI are defined by center-surround configuration with a central Gabor patch (target) surrounded by an annulus of the sine-wave grating (inducer). The Gabor patch is defined as previous reports (35, 36).

The stimulus in each trial is presented for nine frames (∼100 ms) after 17 frames (∼200 ms) fixation, and no feedback is provided regarding the response correctness (**Figure 1B**). The orientation of the inducer is defined with respect to the orientation of the central target and is one of seven predefined values (−75°, −30°, −15°, 0°, +15°, +30°, +75°). Particularly, a 0° inducer indicates that the orientation of the inducer has the same orientation as the central target. Positive and negative values corresponded to clockwise and counterclockwise orientations from 0°, respectively (**Figure 1**). There are 280 trials (40 trials × 7 surround orientations) in the orientation

TABLE 1 | Demographic and alcohol-related data for patients and controls.

	Alcohol-dependent subjects	Healthy subjects
N	15	15
Age, years	36.53 ± 1.74	33.93 ± 1.52
Education, years	8.80 ± 0.64	14.87 ± 1.03
Left eye (logMAR)[a]	0.09 ± 0.05	0.03 ± 0.03
Right eye (logMAR)	0.04 ± 0.03	0.04 ± 0.03
Alcohol consumption[b]	195.90 ± 21.31	/
Abstinence, days[c]	31.73 ± 2.95	/
Age in years at first drinking	17.93 ± 0.92	/
Age in years at onset of dependence	27.13 ± 1.59	/
Duration of dependence, years	10 ± 1.58	/

[a]LogMAR indicates the logarithm of the minimum angle of resolution. [b]Alcohol consumption was defined as grams of pure alcohol per day preceding detoxification. [c]The abstinence for these subjects was calculated from the date of admission to the hospital to the date of the study. Data are expressed as mean ± SEM.

discrimination task, and all conditions are pseudo-randomly presented to each subject. The target orientation is altered across the trials to estimate each subject's perceived upward orientation of the target under a surround orientation. A weighted up–down adaptive procedure is used for psychometric curve measurement. For each surround orientation, two staircases are assigned with up/down steps of 3/1 and 1/3 in steps of 1°, respectively. Each staircase contains 20 trials, with a starting direction of −21°/+21° positioned at the opposite side of the convergence point, which allows for rapid measurement within the transition region of the psychometric function. All stimuli are achromatic and are presented in real time at the center of the screen.

Psychophysical Procedures

Before the examination, the trial procedures and aims are clearly and carefully explained to each of the subjects. Each participant undergoes an ophthalmological visual examination and answers questionnaires with demographic questions (information about age, gender, education, duration of abstinence and dependence, alcohol consumption, age at first drinking, and onset of dependence).

Experiments are initiated by subjects with a predefined keyboard press. A small red dot in the center of the CRT is provided as a fixation point on which observers are to hold their gazes. After the stimulus disappeared from the screen, participants have to report whether the target orientation is tilted clockwise or counterclockwise from his internal vertical upward orientation by pressing corresponding keys (right or left arrows) on the computer keyboard. Each observer has a practice session prior to the collection of actual experimental data. That is, a few easy trials (strong target tilts) are conducted to ensure that each observer could understand and perform the trial accurately. The duration of the visual tilt procedure is about 10 min.

Data Analysis

The magnitude of the TI at each surround orientation is determined by the angular difference between the perceived and physical orientations. The raw data of each surround orientation and condition is fitted with a logistic function that consisted of the proportion of clockwise responses as $p_i = y_i/n_i$, where n_i is the number of occurrences under the current target orientation (x), and y_i is the number of clockwise responses. Thus, the psychometric function is:

$$\mathrm{p}\,(x) = l + \frac{1-2l}{1+\exp\left(-\frac{log(21/4)}{\sigma}\,(x-\mu)\right)}$$

where l is the subject's lapse rate, μ and σ are the perceived vertical orientation (also called "bias") for the given surround orientation and the threshold of the subject for perceiving a deviation from verticality, respectively. The "perceptual bias" corresponds to the perceived vertical reference direction (midpoint) in a given surround condition. The discrimination threshold describes the deviation from the seen reference value for reliably (above p = 0.84) seeing a deviation from the perceived reference. The function is adjusted to the data using Bayesian fitting. Prior parameters are: l–beta probability distribution with parameters Beta (1.2, 15); σ—gamma probability distribution with parameters Gamma (2.5, 2.5); and μ has a uniform prior. The perceptual biases of a given block of measures are adjusted to a mean of zero by subtracting the average. The perceptual bias (μ), threshold (σ), and lapse (l) are extracted using the above methods for each subject, surround direction, and condition.

Statistical Analysis

The differences between patients with alcoholism and healthy controls are analyzed using t-test for age, education, and visual acuity. For the data of the magnitudes of repulsion, a repeated measures analysis of variance (ANOVA) is calculated using "group" (patients–controls) as the between-subject factor and "surround orientation" (0°, ±15°, ±30°, and ±75°) as the within-subject factor. We also perform Bonferroni *post-hoc* multiple comparisons for the repulsions of each test's orientation. All statistical levels used Geisser–Greenhouse epsilon hat when appropriate. Data are expressed as mean ± SE.

RESULTS

Basic demographic information such as age, education, and visual acuity (VA) was collected for all participants and alcohol-related data for patients with chronic alcohol misuse (**Table 1**). All subjects had normal visual acuity or decreased visual acuity that could be corrected to normal using spectacle lenses with appropriate dioptric values, and there was no significant difference [$F_{(3,\,56)} = 0.59$, $p = 0.62$] in the VA. No significant difference between the groups was observed in age ($t = 1.13$, df = 28, $p = 0.27$). Higher levels of education ($t = 5.04$, df = 28, $p < 0.0001$) were observed in controls compared with AUD patients. The experiment was conducted 3 weeks later of

monitored alcohol abstinence for chronic AUD, and the average duration of abstinence was 31.73 ± 2.95 days. The abstinence for these subjects was calculated from the date of admission to the hospital to the date of the study. Age in years at first drinking and age at onset of alcohol dependence were 17.93 ± 0.92 years and 27.13 ± 1.59 years, respectively. By questionnaire investigation, patients with alcoholism reported a mean daily consumption of 195.90 ± 21.31 g/day alcohol during the last month before admission to the hospital and a mean alcoholism history of 10 ± 1.58 years (**Table 1**).

Decreased Tilt Repulsion in Patients With Chronic Alcoholism

A 2 × 4 repeated ANOVA with group (chronic AUD and controls) as the between-subjects factor, surround orientation (0°, ±15°, ±30°, and ±75°) as the within-subject factor, and education as the covariate was conducted. The results revealed that there were significant main effects of surround orientation on TI [$F_{(3, 81)} = 8.25$, $p < 0.001$, $\eta_p^2 = 0.23$] and a significant interaction between surround orientation and group [$F_{(3, 81)} = 3.17$, $p = 0.05$, $\eta_p^2 = 0.11$]. This interaction effect was driven by a reduced ($p = 0.03$, $\eta_p^2 = 0.16$) tilt repulsion in chronic AUD under ±15° surround orientation compared with controls (**Figure 2A**).

Increased Lapse Rate in Patients With Chronic Alcoholism

The lapse rate of an observer indicated an overall attentional state the observer paid to the current task, which was suggested as an indicator of plausible attentional limit changes or deficits. There was no statistical difference between various surround orientations [$F_{(3, 81)} = 0.61$, $p = 0.52$, $\eta_p^2 = 0.02$] or interaction effects [$F_{(3, 81)} = 1.32$, $p = 0.27$, $\eta_p^2 = 0.05$]. However, a significant main effect of group on the lapse rate [$F_{(1, 27)} = 6.67$, $p = 0.016$, $\eta_p^2 = 0.2$] was observed. Bonferroni posttests revealed a higher lapse rate of patients with alcoholism in 0 ($p < 0.01$), ±30° ($p < 0.05$), and ±75° ($p < 0.05$) conditions compared with healthy controls (**Figure 2B**).

Similar Orientation Discrimination Performance in the Two Groups

The discrimination threshold described the deviation of the orientation from the perceived verticality in which the participant reported reliable deviation in 84% of trials. The deviation indicates the difficulty of discriminating two close orientations of the center target. Higher deviation values reflect a worse discrimination ability of the participant. The average thresholds for each group were presented in **Figure 2C**. There was no distinction in orientation discrimination thresholds among various conditions [$F_{(3, 81)} = 1.81$, $p = 0.17$, $\eta_p^2 = 0.06$] and between groups [$F_{(1, 27)} = 0.03$, $p = 0.86$, $\eta_p^2 = 0.001$]. There was no interaction overall [$F_{(3, 81)} = 0.22$, $p = 0.80$, $\eta_p^2 = 0.008$] (**Figure 2C**).

DISCUSSION

The present study investigated the changes in inhibitory mediated TI in abstinent individuals with AUD vs. healthy controls using human psychophysiological measures. Results showed an obvious center-surround interaction in both the patient and control groups. Patients with chronic AUD had no significant difference in the tilt attraction compared with healthy controls, and the threshold values between two groups were similar. However, there was a weaker tilt repulsion effect in individuals with AUD compared with healthy controls, which was demonstrated by the decreased magnitude of tilt repulsion in the chronic AUD patients compared with those of matched controls. Additionally, there was a significantly elevated lapse rate (attention limitation index) in patients with chronic alcoholism compared with healthy controls in all conditions. The current findings provided evidence for the detrimental effect of alcohol dependency on the early visual information processing.

One of the most important aspects of our results was that it allowed to rule out explanations of reduced repulsive TI in chronic AUD patients due to higher-level effects of orientation processing. TI patterns were systematically modulated by surround orientations consistently across all conditions, which meant participants, both chronic AUD patients and healthy controls, reliably represented individual perceptual sensitivities under all conditions. The decrease in perceptual bias only occurred at surround orientations of 15°, while the attractive TI effect was unchanged, which meant there was abnormal visual processing in early levels of visual processing and perception, while these deficits such as more global, higher-order orientation processing were not visibly affected in chronic AUD patients compared with healthy controls. Another was that the current findings allowed to discard specific explanations of reduced repulsive TI in chronic AUD patients due to attentional changes targeting the exact conditions where the repulsive TI appears. The lapse rates globally increased across all surround orientations and indicated that subjects had global changes in attention to the task, and these "high cognitive" effects were unrelated to specific surround conditions. In other words, deteriorated cognition, that is, attention, represented generalized effects.

Several population changes of center orientation tuning characteristics could contribute to the observed TI effect: amplitude inhibition, tuning width change, shift of neuronal preferred orientation, etc. (37, 38). Additionally, by comparing human psychophysics and neurophysiology (39), TI effects involved two spatial mechanisms: one narrowly tuned orientation that was spatially restricted and the other broadly tuned that was spatially widespread. We inferred, for the moment, that the reduced repulsive TI effect in AUD patients came from either broader orientation tuned neuron populations or a weaker surround amplitude of inhibition, until further evidence is available. Future work on training AUD animal model to perform TI task while simultaneously recording single-unit activities in V1 would clarify the present position.

Several neurotransmitter systems [e.g., gamma-aminobutyric acid (GABA), glutamate, dopamine, acetylcholine, and serotonin systems] were vulnerable to effects of alcoholism. Disrupted

GABA, the major inhibitory neurotransmitter, might contribute to the deficits in the V1 inhibition that we observed. Available evidence suggested that acute alcohol potentiated GABA's effects (i.e., it increases inhibition, and often the brain became mildly sedated). However, prolonged and excessive alcohol ingestion reduced the number of GABA receptors. When the person discontinued drinking, decreased inhibition combined with a deficiency of GABA receptors might contribute to overexcitation throughout the brain, including V1. GABAergic system was a major determinant of the level of activity in V1. In the current study, the participants in the patient group were chronic alcohol-dependent people on withdrawal for about 20 days, which meant that the disturbed balance between the inhibitory and the excitatory still exists even during abstinence for about 3 weeks.

It was reported that GABA enhancers ameliorated ethanol withdrawal reaction, which suggested that the GABAergic system is one of the key targets for alcohol toxicity (40). Additionally, levels of GABA(A)-benzodiazepine receptor were reduced in alcohol dependency in the absence of gray matter atrophy (41). Together with current findings of weaker tilt repulsion in chronic AUD, ethanol and GABA interplay might modulate a visual cortical dysfunction in such subjects (11). The inhibitory function was considered to play an important role in the tilt repulsion; the findings of weaker contextual modulations of orientation in chronic alcoholism might imply an altered inhibitory processing in orientation-sensitive neurons in the primary visual cortex (V1) in alcoholism.

There was a significantly elevated lapse rate (attention limitation index) in patients with chronic alcoholism compared with healthy controls. Using the visual probe task, Sinclair et al. (42) explored attentional biases to alcohol, depression, and anxiety related cues and found the reduced attention to depressive and anxiogenic material in abstinent patients. Previous studies suggested an attentional bias toward alcohol-related stimuli at the cost of other stimuli in problematic drinkers (43–45). Research suggested that these stimuli not only attracted attention but that problematic drinkers also found it difficult to disengage their attention from them. Melaugh McAteer et al. (46) investigated both adolescent and adult social drinkers and found comparable alcohol attention bias between them. Recent studies identified abnormal cortical thickness in the superior frontal gyrus, lateral orbitofrontal cortex, and transverse temporal gyrus in alcohol dependence (47). The current findings that increased lapse rate in patients with chronic alcoholism might suggest abnormal attention function in patients with chronic alcoholism.

The "perceptual bias" corresponded to the perceived vertical reference direction (midpoint) in a given surround condition, while the discrimination threshold described the deviation from the seen reference value for reliably (above $p = 0.84$) seeing a deviation from the perceived reference. The deviation indicated the difficulty of discriminating two close orientations of the center target. Higher deviation values reflected a worse discrimination ability of the participant. No difference in orientation discrimination thresholds between the two groups indicated that the difficulty of discriminating two close orientations of the center target was similar between the two groups. The lapse rates indicated subjects' attention to the task. Our results revealed that the lapse rates of AUD patients globally increased across all surround orientations, which indicated that these "high cognitive" effects were unrelated to specific conditions.

Previous studies pointed to an impairment of visual functions caused by alcohol toxicity. Consistently, our results showed a significant decline in amplitude of the tilt repulsion in patients with chronic alcoholism. The latter seemed to be more likely due to the dramatic effects of chronic alcohol ingestion in inhibitory system.

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 the ethics committee of the Mental Health Center of Anhui Province, Declaration of Helsinki. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

The measurements were carried out by ZW and GG. ZW, GG, and LY performed the data analysis. ZW and LP contributed to the supervision of data analysis and to the manuscript writing. Research and study design were carried out by all authors.

FUNDING

This work was supported by the National Natural Science Foundation of China (31800874), Natural Science Foundation of Zhejiang Province (LY21C090001), Applied medicine research project of Hefei Health and Family Planning Commission (hwk2017yb016), and K. C. Wong Magna Fund in Ningbo University and the Fund of Anhui Medical University (2020xkj062).

REFERENCES

1. Pfefferbaum A, Rosenbloom M, Crusan K, Jernigan LT. Brain CT changes in alcoholics: effects of age and alcohol consumption. *Alcohol Clin Exp Res.* (1988) 12:81–7. doi: 10.1111/j.1530-0277.1988.tb00137.x
2. Lishman WA. Alcohol and the brain. *Br J Psychiatry.* (1990) 156:635–44. doi: 10.1192/bjp.156.5.635
3. Kril JJ, Halliday GM, Svoboda MD, Cartwright H. The cerebral cortex is damaged in chronic alcoholics. *Neuroscience.* (1997) 79:983–98. doi: 10.1016/S0306-4522(97)00083-3

4. Heather N, Stockwell T, eds. *International Handbook of Alcohol Dependence and Problems* New York, NY: Wiley (2001).
5. Xu G, Hu F, Wang X, Zhang B, Zhou Y. Bisphenol A exposure perturbs visual function of adult cats by remodeling the neuronal activity in the primary visual pathway. *Arch Toxicol.* (2018) 92:455–68. doi: 10.1007/s00204-017-2047-1
6. Moschos MM, Gouliopoulos NS, Rouvas A, Ladas I. Vision loss after accidental methanol intoxication: a case report. *BMC Res Notes.* (2013) 6:479. doi: 10.1186/1756-0500-6-479
7. Lacerda EM, Lima MG, Rodrigues AR, Teixeira CE, de Lima LJ, Ventura DF, et al. Psychophysical evaluation of achromatic and chromatic vision of workers chronically exposed to organic solvents. *J Environ Public Health.* (2012) 2012:784390. doi: 10.1155/2012/784390
8. Kjellstrom C, Rydenhag B, Sjostrom A, Conradi GN. Alterations in cortical visual evoked response following ethanol feeding in adult rats. *Alcohol Clin Exp Res.* (1994) 18:1392–7. doi: 10.1111/j.1530-0277.1994.tb01441.x
9. Sancho-Tello M, Muriach M, Barcia J, Bosch-Morell F, Genoves JM, Johnsen-Soriano S, et al. Chronic alcohol feeding induces biochemical, histological, and functional alterations in rat retina. *Alcohol Alcohol.* (2008) 43:254–60. doi: 10.1093/alcalc/agn006
10. Lantz CL, Pulimood NS, Rodrigues-Junior WS, Chen CK, Manhaes AC, Kalatsky VA, et al. Visual defects in a mouse model of fetal alcohol spectrum disorder. *Front Pediatr.* (2014) 2:107. doi: 10.3389/fped.2014.00107
11. Brasil A, Castro AJ, Martins IC, Lacerda EM, Souza GS, Herculano AM, et al. Colour vision impairment in young alcohol consumers. *PLoS One.* (2015) 10:e0140169. doi: 10.1371/journal.pone.0140169
12. Bagga D, Khushu S, Modi S, Kaur P, Bhattacharya D, Garg ML, et al. Impaired visual information processing in alcohol-dependent subjects: a proton magnetic resonance spectroscopy study of the primary visual cortex. *J Stud Alcohol Drugs.* (2014) 75:817–26. doi: 10.15288/jsad.2014.75.817
13. Brecher GA, Hartman AP, Leonard DD. Effect of alcohol on binocular vision. *Am J Ophthalmol.* (1955) 39(2 Pt 2):44–52. doi: 10.1016/0002-9394(55)90008-8
14. Wegner AJ, Gunthner A, Fahle M. Visual performance and recovery in recently detoxified alcoholics. *Alcohol Alcohol.* (2001) 36:171–9. doi: 10.1093/alcalc/36.2.171
15. Wang Z, Wang H, Tzvetanov T, Zhou Y. Moderate acute alcohol intoxication increases visual motion repulsion. *Sci Rep.* (2018) 8:1607. doi: 10.1038/s41598-018-19932-8
16. WHO. *Alcohol.* Geneva: WHO (2010).
17. Diamond I, Messing RO. Neurologic effects of alcoholism. *West J Med.* (1994) 161:279–87.
18. Preedy VR, Reilly ME, Patel VB, Richardson PJ, Peters JT. Protein metabolism in alcoholism: effects on specific tissues and the whole body. *Nutrition.* (1999) 15:604–8. doi: 10.1016/S0899-9007(99)00096-9
19. Rudolf H, Priebe S. Subjective quality of life and depressive symptoms in women with alcoholism during detoxification treatment. *Drug Alcohol Depend.* (2002) 66:71–6. doi: 10.1016/S0376-8716(01)00183-1
20. Oscar-Berman M, Marinkovic K. Alcoholism and the brain: an overview. *Alcohol Res Health.* (2003) 27:125–33.
21. Roseribloom MJ, Pfefferbaum A, Sullivan VE. Recovery of short-term memory and psychomotor speed but not postural stability with long-term sobriety in alcoholic women. *Neuropsychology.* (2004) 18:589–97. doi: 10.1037/0894-4105.18.3.589
22. Harper C, Matsumoto I. Ethanol and brain damage. *Curr Opin Pharmacol.* (2005) 5:73–8. doi: 10.1016/j.coph.2004.06.011
23. Oscar-Berman M, Marinkovic K. Alcohol: effects on neurobehavioral functions and the brain. *Neuropsychol Rev.* (2007) 17:239–57. doi: 10.1007/s11065-007-9038-6
24. Porjesz B, Begleiter H. Alcoholism and human electrophysiology. *Alcohol Res Health.* (2003) 27:153–60.
25. Maurage P, Philippot P, Verbanck P, Noel X, Kornreich C, Hanak C, et al. Is the P300 deficit in alcoholism associated with early visual impairments (P100, N170)? *An oddball paradigm. Clin Neurophysiol.* (2007) 118:633–44. doi: 10.1016/j.clinph.2006.11.007
26. Hermann D, Smolka MN, Klein S, Heinz A, Mann K, Braus FD. Reduced fMRI activation of an occipital area in recently detoxified alcohol-dependent patients in a visual and acoustic stimulation paradigm. *Addict Biol.* (2007) 12:117–21. doi: 10.1111/j.1369-1600.2006.00039.x
27. Clifford CW. The tilt illusion: phenomenology and functional implications. *Vision Res.* (2014) 104:3–11. doi: 10.1016/j.visres.2014.06.009
28. O'Toole B, Wenderoth P. The tilt illusion: repulsion and attraction effects in the oblique meridian. *Vision Res.* (1977) 17:367–74. doi: 10.1016/0042-6989(77)90025-6
29. Takao S, Watanabe K, Clifford GCW. Angular tuning of tilt illusion depends on stimulus duration. *Vision Res.* (2020) 175:85–9. doi: 10.1016/j.visres.2020.07.007
30. Blakemore C, Carpenter RH, Georgeson AM. Lateral inhibition between orientation detectors in the human visual system. *Nature.* (1970) 228:37–9. doi: 10.1038/228037a0
31. Blakemore C, Muncey JP, Ridley MR. Stimulus specificity in the human visual system. *Vision Res.* (1973) 13:1915–31. doi: 10.1016/0042-6989(73)90063-1
32. Plant GT, Perry VH. The anatomical basis of the caecocentral scotoma. New observations and a review. *Brain.* (1990) 113 (Pt 5): 1441–57. doi: 10.1093/brain/113.5.1441
33. Brainard DH. The psychophysics toolbox. *Spat Vis.* (1997) 10:433–6. doi: 10.1163/156856897X00357
34. Li X, Lu ZL, Xu P, Jin J, Zhou Y. Generating high gray-level resolution monochrome displays with conventional computer graphics cards and color monitors. *J Neurosci Methods.* (2003) 130:9–18. doi: 10.1016/S0165-0270(03)00174-2
35. Tzvetanov T. A single theoretical framework for circular features processing in humans: orientation and direction of motion compared. *Front Comput Neurosci.* (2012) 6:28. doi: 10.3389/fncom.2012.00028
36. Wang Z, Yu S, Fu Y, Tzvetanov T, Zhou Y. Aging potentiates lateral but not local inhibition of orientation processing in primary visual cortex. *Front Aging Neurosci.* (2018) 10:14. doi: 10.3389/fnagi.2018.00014
37. Gilbert CD, Wiesel TN. The influence of contextual stimuli on the orientation selectivity of cells in primary visual cortex of the cat. *Vision Res.* (1990) 30:1689–701. doi: 10.1016/0042-6989(90)90153-C
38. Schwartz O, Hsu A, Dayan P. Space and time in visual context. *Nat Rev Neurosci.* (2007) 8:522–35. doi: 10.1038/nrn2155
39. Shushruth S, Nurminen L, Bijanzadeh M, Ichida JM, Vanni S, Angelucci A. Different orientation tuning of near- and far-surround suppression in macaque primary visual cortex mirrors their tuning in human perception. *J Neurosci.* (2013) 33:106–19. doi: 10.1523/JNEUROSCI.2518-12.2013
40. Addolorato G, Caputo F, Capristo E, Domenicali M, Bernardi M, Janiri L, et al. Baclofen efficacy in reducing alcohol craving and intake: a preliminary double-blind randomized controlled study. *Alcohol Alcohol.* (2002) 37:504–8. doi: 10.1093/alcalc/37.5.504
41. Lingford-Hughes AR, Acton PD, Gacinovic S, Suckling J, Busatto GF, Boddington SJ, et al. Reduced levels of GABA-benzodiazepine receptor in alcohol dependency in the absence of grey matter atrophy. *Br J Psychiatry.* (1998) 173:116–22. doi: 10.1192/bjp.173.2.116
42. Sinclair JM, Garner M, Pasche SC, Wood TB, Baldwin SD. Attentional biases in patients with alcohol dependence: influence of coexisting psychopathology. *Hum Psychopharmacol.* (2016) 31:395–401. doi: 10.1002/hup.2549
43. Robbins SJ, Ehrman RN. The role of attentional bias in substance abuse. *Behav Cogn Neurosci Rev.* (2004) 3:243–60. doi: 10.1177/1534582305275423
44. Cox WM, Fadardi JS, Pothos ME. The addiction-stroop test: theoretical considerations and procedural recommendations. *Psychol Bull.* (2006) 132:443–76. doi: 10.1037/0033-2909.132.3.443

45. Field M, Cox WM. Attentional bias in addictive behaviors: a review of its development, causes, and consequences. *Drug Alcohol Depend.* (2008) 97:1–20. doi: 10.1016/j.drugalcdep.2008.03.030
46. Melaugh McAteer A, Curran D, Hanna D. Alcohol attention bias in adolescent social drinkers: an eye tracking study. *Psychopharmacology.* (2015) 232:3183–91. doi: 10.1007/s00213-015-3969-z
47. Hahn S, Mackey S, Cousijn J, Foxe JJ, Heinz A, Hester R, et al. Predicting alcohol dependence from multi-site brain structural measures. *Hum Brain Mapp.* (2020) 1–10. doi: 10.1002/hbm.25248

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.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 13 October 2021
doi: 10.3389/fpsyt.2021.692266

Altered Neural Processing of Reward and Punishment in Women With Methamphetamine Use Disorder

Shuguang Wei[1], *Zhaoxia Xue*[2], *Wujun Sun*[3], *Jie Han*[4], *Haiyan Wu*[5]* *and Xun Liu*[6,7]*

[1] *Department of Psychology, College of Education, Hebei Normal University, Shijiazhuang, China,* [2] *Department of Applied Psychology, College of Humanities and Social Sciences, Shanxi Medical University, Taiyuan, China,* [3] *Faculty of Education, Henan Normal University, Xinxiang, China,* [4] *Hebei Female Drug Rehabilitation Center, Shijiazhuang, China,* [5] *Centre for Cognitive and Brain Sciences and Department of Psychology, University of Macau, Macao, Macao, SAR China,* [6] *Key Laboratory of Behavioral Science, Institute of Psychology, Chinese Academy of Sciences, Beijing, China,* [7] *Department of Psychology, University of Chinese Academy of Sciences, Beijing, China*

OPEN ACCESS

Edited by:
Xingchao Wang,
Shanxi University, China

Reviewed by:
Kesong Hu,
Lake Superior State University, United States
Martin Zack,
Centre for Addiction and Mental Health (CAMH), Canada

***Correspondence:**
Haiyan Wu
haiyanwu@um.edu.mo
Xun Liu
liux@psych.ac.cn

Specialty section:
This article was submitted to Addictive Disorders, a section of the journal Frontiers in Psychiatry

Received: *08 April 2021*
Accepted: *10 September 2021*
Published: *13 October 2021*

Citation:
Wei S, Xue Z, Sun W, Han J, Wu H and Liu X (2021) Altered Neural Processing of Reward and Punishment in Women With Methamphetamine Use Disorder. Front. Psychiatry 12:692266. doi: 10.3389/fpsyt.2021.692266

It has been suggested that the altered function of reward and punishment is an important vulnerability factor leading to the development of drug use disorders. Previous studies have identified evidence of neurophysiological dysfunction in the reward process of individuals with substance use disorders. To date, only a few event-related potential (ERP) studies have examined the neural basis of reward and punishment processing in women with methamphetamine (MA) use disorders. The current ERP research aims to investigate the neurophysiological mechanisms of reward and punishment in women with MA use disorder using a monetary incentive delay task. Nineteen women with MA use disorder (MA group) and 20 healthy controls (HC group) were recruited in this study. The behavioral data showed that the reaction time (RT) was faster and the response accuracy (ACC) was higher for the potential reward and punishment conditions compared to neutral conditions. During the monetary incentive anticipation stage, the Cue-P3, and stimulus-preceding negativity (SPN) were larger in the MA group than in the HC group. The SPN under the potential reward condition was larger than that under the neutral condition in the MA group but not in the HC group. During the monetary incentive consummation stage, the feedback-related negativity and feedback P3 (FB-P3) following positive feedback were significantly larger than negative feedback in the potential reward condition for the HC group, but not for the MA group. However, the FB-P3 following negative feedback was significantly larger than positive feedback in the potential punishment condition for the MA group, but not the HC group. The results suggest that women with MUD have stronger expectations of generic reward and stronger response of generic harm avoidance, which could be targeted in designing interventions for women with MA use disorder.

Keywords: methamphetamine (MA) use disorder, reward processing, punishment processing, Cue-P3, stimulus-preceding negativity (SPN), feedback-related negativity (FRN), feedback P3 (FB-P3)

INTRODUCTION

Substance use disorder (SUD) is characterized by chronic relapse, compulsive drug use, and loss of control over drug-taking behavior despite adverse consequences (1). Methamphetamine (MA) is the second most widely used illegal drug worldwide (2), and the use of MA in China has exceeded heroin use as the most widely abused drug in recent years (3). MA can stimulate the rewarding system of the brain and has highly reinforcing effects that lead to abuse and dependence. Chronic MA abuse is associated with significant neurological damage and psychiatric impairment in the cognitive, intellectual, and affective domains (4–6). However, the neural correlates in individuals with MA use disorder (MUD) are not well-understood.

The outcomes of a particular behavior, choice, or environment have a significant influence on motivation and decision-making. These results, whether positive (rewards) or negative (punishments), can strongly influence an individual's behavior (7). Rewards can be defined as stimuli that an organism tries to obtain, while punishments are stimuli that an organism tries to avoid. By definition, reinforcement is a stimulus that can increase the frequency of a behavior, and positive reinforcement and rewards are generally considered to be synonymous. Negative reinforcement refers to a decrease in aversive stimuli leading to an increase in individual behavioral responses. Punishment consists of the presentation of an aversive stimulus or the removal of an appetitive stimulus. Researchers have suggested that the brain mechanisms of positive and negative reinforcement have been considered key to the etiology and maintenance of the pathophysiology of addiction (8–11). Instead of seeking rewards and avoiding punishment, addicts are driven to seek special rewards to compromise other needs or attribute rewards to maladaptive behaviors (12). Therefore, understanding the neural processing mechanisms of rewards and punishments is very important for understanding the brainpower of substance users.

Various experimental paradigms have been used to explain reinforcement processing for individuals with and without mental health disorders. One of the most well-established paradigms is the monetary incentive delay (MID) task (13). A typical trial requires a quick response to a target following a cue-signaling contingency for that trial. Performance-specific feedback is delivered based on the response. The MID task has been used in many functional magnetic resonance imaging (fMRI) studies to effectively delineate the dynamics of brain activity in reward processing [i.e., anticipation and consummation; for a meta-analysis, see (14)]. Individuals with SUD show enhanced reward-related responses to drug-related cues [see meta-analyses (15, 16)]. However, there are still inconsistencies regarding the response to non-drug rewards in the anticipatory and consummatory stages in SUD. Using fMRI, researchers identified that regular smokers show reduced ventral striatum (VS) recruitment in response to monetary anticipatory cues or monetary notifications compared to controls (17–19). However, research on the use of other substances is more inconsistent; several studies found no decrease in VS recruitment by non-drug reward cues or delivery in substance users (20, 21). The results also varied as a function of whether the anticipatory or consummatory component was emphasized. Schmidt et al. (22) found that individuals with gambling disorder showed greater left orbitofrontal cortex and VS activity to erotic relative to monetary reward anticipation compared to healthy volunteers, but generally stronger activity in the VS, ventromedial and dorsolateral prefrontal cortex, and anterior cingulate cortex to both erotic and monetary rewards relative to healthy volunteers. Using an image-based meta-analysis, a systematic literature review (23) concluded that substance users show decreased striatal activation during monetary reward anticipation and increased VS activation during monetary reward consummation.

In addition to the neural mechanisms underlying reward processing, drug-seeking behavior is also a function of punishment processing (9). In the development of addiction, the negative effects of drug withdrawal have become the main motivation for drug use. That is, negative reinforcement plays an important role in the maintenance of addiction. In drug addiction, the withdrawal response brought on by an individual ceasing drug use and that individual's negative emotional state are important reasons for their drug-taking behavior. Compared to reward processing, the neural bases of punishment processing remain largely unexamined in substance users. An fMRI study investigating responses to monetary gains and losses demonstrated that individuals with MUD exhibited less response in the VS to loss anticipation than controls, but more response in the caudate to loss outcomes than to gain outcomes (24). However, other studies indicated that substance users have a blunted response to punishment. For example, one study illustrated that cocaine-dependent participants showed diminished behavioral punishment sensitivity, which was associated with significant deactivation in the dorsal anterior cingulate cortex, right insula, and right prefrontal regions (25). Romanczuk-Seiferth et al. (26) investigated the neural correlates of loss processing in pathological gamblers compared with alcohol-dependent patients and healthy controls, and found that pathological gamblers showed increased activity in the right VS during loss anticipation compared with controls and alcohol-dependent patients. Moreover, pathological gamblers showed decreased activation in the right VS and right medial prefrontal cortex during successful loss avoidance compared with controls. Other studies also confirmed that smokers have a lower error-correction rate and are less sensitive to punishment (27, 28). Compared to reward processing, significant work is required to link punishment processing to specific neural mechanisms in individuals with SUD.

Studies using fMRI demonstrated dissociable patterns of activation in response to monetary outcomes (29, 30). As a complement to neuroimaging research, event-related potentials (ERPs) provide superior millisecond-by-millisecond temporal resolution, thus enabling a full characterization of reward processing. The MID task also allows for exploration of the neurophysiological correlates of reward and punishment processing in one experimental paradigm (31, 32). According to the framework of the MID, several candidate ERP components may be relevant to different stages of reward and punishment processing. The reinforcement anticipatory stage is associated with three ERP components: Cue-P3, contingent negative

variation (CNV), and stimulus-preceding negativity (SPN). First, Cue-P3 is involved in the attention allocation of incentive-contingent cues. Cue-P3 is a late positive-going component that peaks between 300 and 600 ms post-stimulus at centroparietal sites. Cue-P3 is generally more positive for salient, task-relevant, or unexpected stimuli (33), and it is increased for incentive vs. neutral cues in MID tasks (31, 32). Second, the CNV is a slow negative-going potential that occurs between a warning stimulus (cue) and an imperative stimulus (target) (34), and can reflect anticipatory attention, motivation, and motor preparation (32). The third sub-stage within reinforcement anticipation is the interval following the motor reaction, and in anticipation of the outcome present, which should elicit an SPN. Compared to CNV, SPN reflects pure anticipatory processing due to the exclusion of motor preparation (35).

Regarding the consummatory stage, feedback-related negativity (FRN) and feedback P3 (FB-P3) are the relevant ERP components. FRN is typically defined as a negative-going component that peaks at ∼250 ms after outcome onset. It is thought to encode the reward prediction error (the difference between predicted and obtained outcomes) when feedback is better or worse than expected (36). However, more recent research supports the view that FRN is driven by reward delivery (37). FB-P3 is a centroparietal positive-going component approximately peaking at 300–600 ms following feedback. FB-P3 involves the classification of important attentionally driven information related to outcomes, such as context updating and integration of the contents of working memory to maximize future rewards (38). Additionally, FB-P3 may reflect affective processes by signaling the motivational salience of reward feedback (39).

Using ERPs, Morie et al. (40) found that cocaine users demonstrated increased neural response to monetary incentive cues indexed by cue-related negativities and CNV; however, Zhao et al. (41) demonstrated that heroin users showed blunted neural response indexed by disrupted SPN during the reward anticipation stage. In the reward consummatory stage, many studies found that individuals with cocaine and alcohol use disorder showed blunted sensitivity to monetary reward outcomes indexed by decreased FRN and FB-P3 (42–45). However, Zhao et al. (41) found that heroin users showed enhanced neural response to monetary feedback indexed by FRN. In our previous research, using a simple gamble task in a separate MUD group, we found an enhanced neural response to monetary cues and feedback indexed by SPN, FRN, and FB-P3 (46). With the ERP and fMRI studies taken together, the contradictory evidence as to whether individuals with SUD show an enhanced or blunted neural response to monetary rewards calls for more detailed research in this field.

Much of the initial research on SUD came from the studies conducted with male substance users. However, in recent years, some studies have found that, compared with male substance users, female substance users have more sensitive psychomotor-related responses to addictive substances (47), and can more easily transition from recreational use to SUD (48–50). Therefore, exploring the female-specific MA use behaviors is crucial to the development of appropriate MA use prevention and treatment strategies.

The current ERP study aimed to investigate the neurophysiological mechanisms underlying anticipation and consummation of reward and punishment in women with MUD. Therefore, we used the MID task, which included a separate punishment and reward condition. We focused on Cue-P3, CNV, and SPN to examine anticipatory processes and on FRN and FB-P3 to examine consummatory processes. Based on our previous ERP study on women with MUD indicating enhanced neural responsivity to reward, we expected enhanced ERP components (Cue-P3/CNV/SPN/FRN/FB-P3) during reward anticipation and consummation in women with MUD compared to controls. Regarding punishment consummation, as our prior study showed that women with MUD made more risky choices following a loss outcome in a previous trial, we expected blunted ERP components (Cue-P3/CNV/SPN/FB-P3/FRN) during punishment anticipation and consummation in women with MUD compared to controls.

MATERIALS AND METHODS

Participants

Nineteen female MA users (age = 25 ± 4.41 years; drug experience = 23.42 ± 10.05 months; abstinence duration = 14.53 ± 3.84 months) participated in the study as the experimental group (MA group). They were patients from an addiction rehabilitation center in Hebei Province, China. All patients were subjected to a 24-month compulsory isolation treatment, during which they were unable to use cigarettes, alcohol, or addictive substances. Twenty healthy female participants without a history of substance use (age = 27.05 ± 4.75 years) were selected for the healthy control group (HC group). They were recruited using advertisements on the Internet and *via* word-of-mouth from the same geographic area.

The inclusion criteria for the MA group were as follows: (1) a history of MA use corresponding to the diagnosis of stimulant addiction disorder using Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) (51); (2) a drug withdrawal period from 3 to 24 months before the date of screening. The selection criteria for the HC group were similar to the selection criteria for the MA group. In the HC group, all participants reported having no history or current use of illegal drugs. The exclusion criteria were as follows: (1) a history of using other kinds of drugs (e.g., heroin, cocaine), (2) a history of brain injury leading to loss of awareness of more than 30 min, (3) current or a history of brain pathology, and (4) a history of using any psychotropic drug within 2 months of this study registration.

The screening process was similar to that used in a previous study (40). After entering the test room, all participants were asked about their drug use time, abstinence time, cumulative drug dosage, the number of cigarettes consumed, and alcohol usage per day for the month before their treatment. Furthermore, all participants were asked to complete the Barratt Impulsiveness Scale Version 11 (BIS-11) (52) and the Sensation Seeking Scale Version V (SSS-V) (53). Each received a base payment of ¥40 for participating and a bonus of up to ¥10 based on their

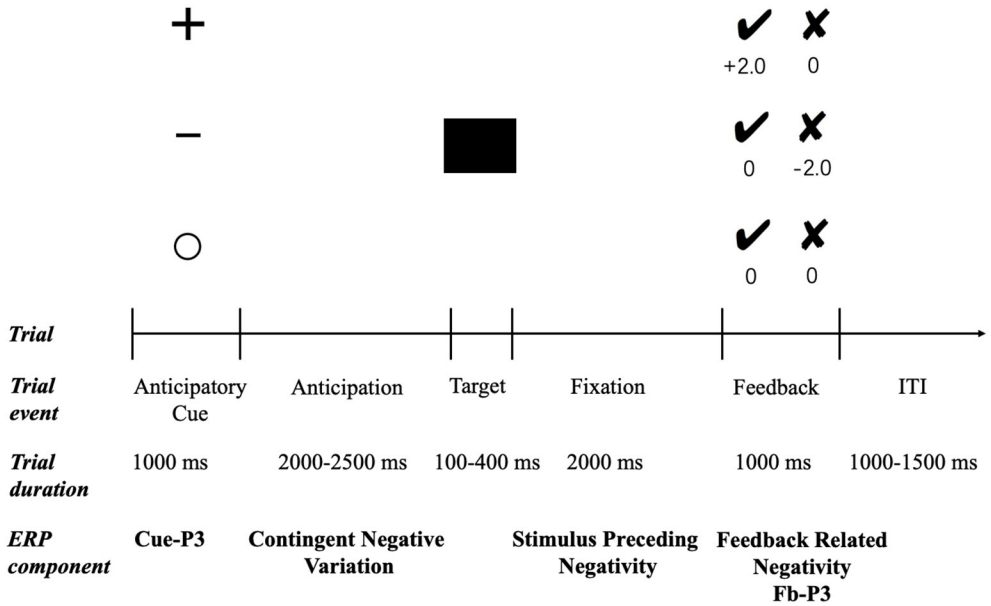

FIGURE 1 | Trial structure and timeline of the MID task. ITI, intertrial interval.

performance in the MID task. All participants were right-handed and had normal or corrected-to-normal visual acuity. Written informed consent was obtained from all participants. The study was conducted under the Declaration of Helsinki and approved by the ethical review board of the Institute of Psychology of the Chinese Academy of Science.

ERP Task—The MID Task

The participants completed the test in a sound-attenuating room. At the start of the experiment, participants were informed that they needed to respond as quickly as possible, and their performance was related to the bonus.

All participants were asked to complete a modified version of the MID (32, 54) (see **Figure 1**). In each trial, one of the three cues depicting the monetary contingency for that trial was presented for 1,000 ms. The plus sign indicated a potential monetary reward (potential reward condition), the minus sign indicated a potential monetary punishment (potential punishment condition), and the empty circle indicated that no monetary outcome would be delivered irrespective of performance (neutral condition). Thus, following a jittered interstimulus interval (ISI; 2,000–2,500 ms), a black square was presented as the target stimulus, and the participants were instructed to respond by pressing a button as quickly as possible. The duration of the target presentation was set to 250 ms initially and then was adapted between 100 and 400 ms according to participants' response times. Specifically, the target duration was decreased by 25 ms after a successful response (i.e., pressing the button during target presentation) and increased by 25 ms after an unsuccessful response (i.e., pressing the button either before or after target presentation). This staircase process resulted in a success rate of ∼50% for all three conditions. Following another ISI (2,000 ms), the performance feedback was presented for 1,000 ms. Positive feedback was indicated by a black tick and negative feedback by a black cross. In potential reward trials, the tick feedback signaled a win of ¥2, whereas the cross feedback signaled a win of ¥0. In potential punishment trials, the tick feedback indicated a loss of ¥0, whereas the cross feedback signaled a loss of ¥2. In neutral trials, both crosses and ticks led to ¥0. All trials in the three conditions were randomly presented during the experiment. The task consisted of three blocks, 240 trials in total (80 trials for each condition), and there was a short break between blocks. Before the formal experimentation, there was a practice session to familiarize participants with the task.

Psychophysiological Recording and Data Analysis

Continuous scalp electroencephalographic (EEG) activity was recorded using an electrode cap with 64 electrodes according to a modified expanded 10–20 system (Brain Products Company, Munich, Germany). The signals were recorded online using the reference electrode FCz and the ground electrode AFz. An electrode was placed ∼2 cm below the right eye to record vertical electrooculogram. The impedance between all the electrodes and the scalp was <5 kΩ.

EEGLAB (55) and ERPLAB (56) were used to analyze the EEG data. All signals were re-referenced to the bilateral mastoid average (TP9/10) and low-pass filtered of 30 Hz (roll-off 6 dB/octave). For the Cue-P3 and CNV, the EEG data were segmented from −200 to 3,000 ms relative to cue onset, with −200 to 0 as the baseline. For the SPN, the EEG data are segmented from −2,000 to 200 ms relative to feedback onset, with −1,900 to −1,700 ms as the baseline. For the FRN and FB-P3, the EEG data were segmented from −200 to 1,000 ms

relative to feedback onset with the activity from −200 to 0 serving as the baseline. Epochs containing artifacts outside −80 to 80 μV were eliminated. Independent component analysis (ICA) (runica) was performed. Subsequently, eye blinking and movement artifacts were selected and removed manually. Thus, the epochs in the same condition were averaged for each participant. In the anticipatory stage, there were 73.58 ± 5.82 (72.45 ± 8.18), 72.79 ± 5.52 (71.1 ± 9.67), and 72.79 ± 5.83 (70.55 ± 11.62) artifact-free trials obtained for the monetary reward, monetary punishment, and neutral conditions in the MA group (HC group). In the consummatory stage, there were 44.79 ± 4.85 (42.40 ± 5.31), 35.47 ± 4.36 (37.30 ± 4.99), 42.79 ± 3.41 (41.75 ± 4.94), 36.53 ± 3.64 (37.90 ± 5.07), 33.36 ± 5.73 (35.75 ± 5.97), and 47.05 ± 5.33 (44.65 ± 6.08) artifact-free trials obtained for the hit and miss of the monetary reward, monetary punishment, and neutral condition in the MA group (HC group), respectively.

Following a previous study, ERP components were quantified using a region-of-interest (ROI) approach (40, 41). Cue-P3 and FB-P3 were measured as the mean amplitude from 300 to 450 ms post-cue or feedback onset over a centroparietal ROI (C1, Cz, C2, CP1, CPz, CP2, P1, Pz, and P2) and the CNV from 2,800 to 3,000 ms post cue onset over the frontal–central ROI (F1, F2, Fz, FC1, FC2, FCz, C1, C2, and Cz). Given a plateau-shaped distribution with a right hemisphere dominance (28), in this study, the SPN was measured as the mean amplitude from −200 to 0 ms before feedback onset over the right frontotemporal ROI (F8, FT8, T8, F6, FC6, C6, F4, FC4, and C4). The FRN was measured as the mean amplitude from 200 to 300 ms post-feedback onset over the frontocentral ROI (F1, F2, Fz, FC1, FC2, FCz, C1, C2, and Cz).

Statistical Analysis

For the demographic characteristics, independent samples *t*-tests were used to compare group differences (MA vs. HC). For behavioral data from the MID task, a 2 (group: MA vs. HC) × 3 (incentive: potential reward vs. potential punishment vs. neutral) repeated-measures ANOVA was performed on the response time (RT) and the response accuracy (ACC), where the group was a between-subjects variable and the incentive was a within-subjects variable.

Separate repeated-measures ANOVAs were used for all ERP data. A 2 (group: MA vs. HC) ×3 (incentive: potential reward vs. potential punishment vs. neutral) repeated-measures ANOVA was performed on the Cue-P3, CNV, and SPN data, with group as a between-subjects variable and incentive as a within-subjects variable. For the FRN and FB-P3, a 2 (groups: MA vs. HC) × 3 (incentive: potential reward vs. potential punishment vs. neutral) × 2 (feedback: positive vs. negative) repeated-measures ANOVA was performed, with group as a between-subjects variable, and incentive and feedback as within-subjects variables. When significant interaction effects were indicated, further simple effect analyses were performed. The Greenhouse–Geisser correction was applied when detecting violations of sphericity, and statistical significance was set at $p < 0.05$. The measures of the proportion between the variance of one experimental factor and the total variance were reported in partial eta squared (η_p^2).

RESULTS

Behavioral Data

Table 1 shows the group differences regarding drug use time, abstinence time, cumulative drug dosage, the number of cigarettes consumed, and alcohol usage per day for 1 month prior to treatment. There were no significant differences between the two groups in age or education (ps > 0.05). The MA group scored significantly higher than the HC group on the subscales for motor impulsiveness and non-planning impulsiveness (ps < 0.05). Similarly, the MA group had significantly higher scores on the Sensation Seeking Scale and its subscales of disinhibition and experience seeking compared with the HC group (ps < 0.01).

Descriptive behavioral data are presented in **Table 2**. RTs were analyzed using a 2 × 3 ANOVA. There was a significant main effect of group [$F_{(1, 37)} = 4.93$, $p < 0.05$, and $\eta_p^2 = 0.12$]. RTs in the MA group (202.16 ms) were significantly faster than those in the HC group (226.94 ms). An independent *t*-test on three incentive conditions showed that RTs in the MA group were

TABLE 1 | Sample characteristics (M ± SD).

	HC group (n = 20)	MA group (n =19)	p-values
Age (years)	27.05 ± 4.75	25 ± 4.41	0.17
Education (years)	9.15 ± 0.67	8.82 ± 2.16	0.51
Drug experience (months)	–	23.42 ± 10.05	
Abstinence time (months)	–	14.53 ± 3.84	
Methamphetamine use, lifetime (g)	–	266.13 ± 407.42	
Number of cigarettes per day	–	8 ± 8.27	
Alcohol use per day (g)	–	23.03 ± 63.23	
BIS-11	63.75 ± 11.02	69.84 ± 9.83	0.08
Attentional impulsiveness	18.3 ± 5.18	17.07 ± 2.99	0.37
Motor impulsiveness	20.56 ± 3.97	23.28 ± 3.78	<0.05*
Non-planning impulsiveness	25.27 ± 5.55	29.49 ± 5.51	<0.05*
SSS-V	12.7 ± 4.07	17.32 ± 4.85	<0.01**
Disinhibition	2.35 ± 2	4.16 ± 2.54	<0.01**
Experience seeking	3.6 ± 1.9	5.23 ± 1.65	<0.01**
Thrill and adventure seeking	4.5 ± 2.97	5.39 ± 2.19	0.3
Boredom susceptibility	2.25 ± 1.4	2.56 ± 1.4	0.5

*BIS-11, Barratt Impulsiveness Scale, Version 11; SSS-V, Sensation Seeking Scale Form V. *p < 0.05, **p < 0.01.*

TABLE 2 | Group means and standard deviations (in brackets) of reaction times (RTs) and response accuracy (ACC) for MA and HC group.

	HC group (n = 20)	MA group (n = 19)
RTs in potential monetary reward trials	224.41 (43.68)	199.23 (22.05)
RTs in potential monetary punishment trials	224.5 (42.95)	202.41 (24.4)
RTs in neutral trials	231.91 (44.01)	204.73 (26.24)
ACC in potential monetary reward trials	0.53 (0.07)	0.56 (0.06)
ACC in potential monetary punishment trials	0.51 (0.1)	0.54 (0.04)
ACC in neutral trials	0.43 (0.09)	0.41 (0.08)

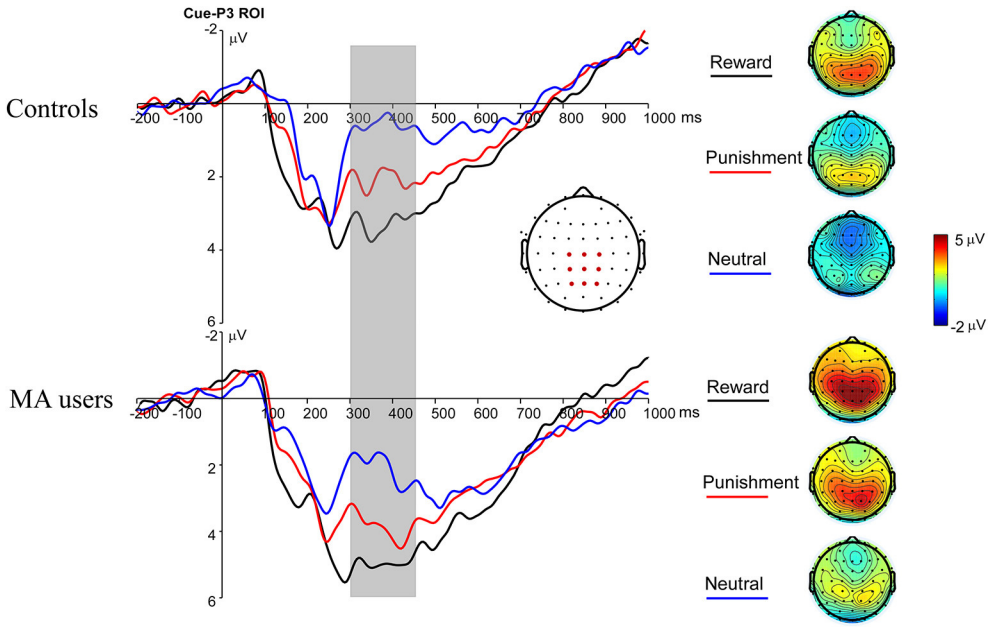

FIGURE 2 | Cue-P3 waveforms after cue presentation for the MA and HC group over centroparietal ROI (C1, Cz, C2, CP1, CPz, CP2, P1, Pz, and P2) (left); topographic maps of the Cue-P3 during 300–450 ms after cue presentation (right).

significantly fast than those in the HC group in the potential reward [$t_{(37)} = 2.25$, $p < 0.05$] and neutral conditions [$t_{(37)} = 2.33$, $p < 0.05$]; the group difference in RTs was marginally significant in the potential punishment condition [$t_{(37)} = 1.96$, $p = 0.06$]. The main effect of the incentive condition was significant [$F_{(2, 74)} = 6.69$, $p < 0.01$, and $\eta_p^2 = 0.15$]. Pairwise comparisons revealed that the RTs were faster for potential reward (211.82 ms) and potential punishment trials (213.46 ms) compared to neutral trials (218.32 ms, $ps < 0.05$). There were no significant differences between the potential reward and potential punishment trials ($p > 0.05$). The interaction effect of group and incentive condition was not significant [$F_{(1, 37)} = 0.96$, $p = 0.34$, and $\eta_p^2 = 0.03$].

The ACC was subjected to a 2 × 3 ANOVA. There was a significant main effect of incentive condition [$F_{(2, 74)} = 27.46$, $p < 0.001$, and $\eta_p^2 = 0.43$]. Pairwise comparisons revealed that the ACC was higher for the potential reward (0.54) and punishment trials (0.53) compared to neutral trials (0.42, $ps < 0.001$). There were no significant differences between the potential reward and potential punishment trials ($p > 0.05$). The main effect of group [$F_{(1, 37)} = 1.25$, $p = 0.27$, and $\eta_p^2 = 0.03$] and the interaction effect of group and incentive condition were not significant [$F_{(2, 74)} = 1.35$, $p = 0.26$, and $\eta_p^2 = 0.04$]. Thus, these results indicate incentive-related accuracy and speed in the MID task.

Electrophysiological Data

Anticipatory ERPs

Cue-P3

A 2 × 3 ANOVA was performed on the Cue-P3 data. There was a significant main effect of incentive condition [$F_{(2, 74)} = 18.34$, $p < 0.001$, and $\eta_p^2 = 0.33$]. Pairwise comparisons revealed that the Cue-P3 was more positive for potential reward (3.66 μV) and punishment trials (2.84 μV) compared to neutral trials (1.81 μV, $ps < 0.001$), and marginally positive for reward trials compared to punishment trials ($p = 0.07$). The main effect of group was also significant [$F_{(1, 37)} = 4.7$, $p < 0.05$, and $\eta_p^2 = 0.11$], with the Cue-P3 being more positive in the MA group (3.69 μV) than in the HC group (1.85 μV). The interaction effect between group and incentive conditions was not significant [$F_{(2, 74)} = 0.19$, $p = 0.83$, and $\eta_p^2 = 0.005$] (**Figures 2**, **7**).

CNV

A 2 × 3 ANOVA was performed on the CNV data. There was no significant group effect on CNV [$F_{(1, 37)} = 0.61$, $p = 0.44$, and $\eta_p^2 < 0.01$]. Neither the incentive effect [$F_{(2, 74)} = 2.23$, $p = 0.12$, and $\eta_p^2 = 0.06$], nor the interaction effect between group and incentive conditions was significant [$F_{(2, 74)} = 0.8$, $p = 0.45$, and $\eta_p^2 = 0.02$] (**Figures 3**, **7**).

SPN

A 2 × 3 ANOVA was performed on the SPN data. The main effect of the group was marginally significant [$F_{(1, 37)} = 3.03$, $p = 0.09$, and $\eta_p^2 = 0.08$], and the SPN in the MA group (−2.59 μV) was larger than that in the HC group (−0.47 μV). The main effect of incentive was not significant [$F_{(2, 74)} = 0.03$, $p = 0.97$]. The interaction between incentive and group was significant [$F_{(2, 74)} = 4.31$, $p < 0.05$, and $\eta_p^2 = 0.1$]. Simple analysis showed that the incentive effect was significant in the MA group, the SPN under the potential reward condition (−3.36 μV) was larger than in the neutral condition (−1.93 μV, $p < 0.05$), and no significant difference existed between potential punishment and neutral conditions. However, the incentive effect was not significant in the HC group. The SPN in potential reward

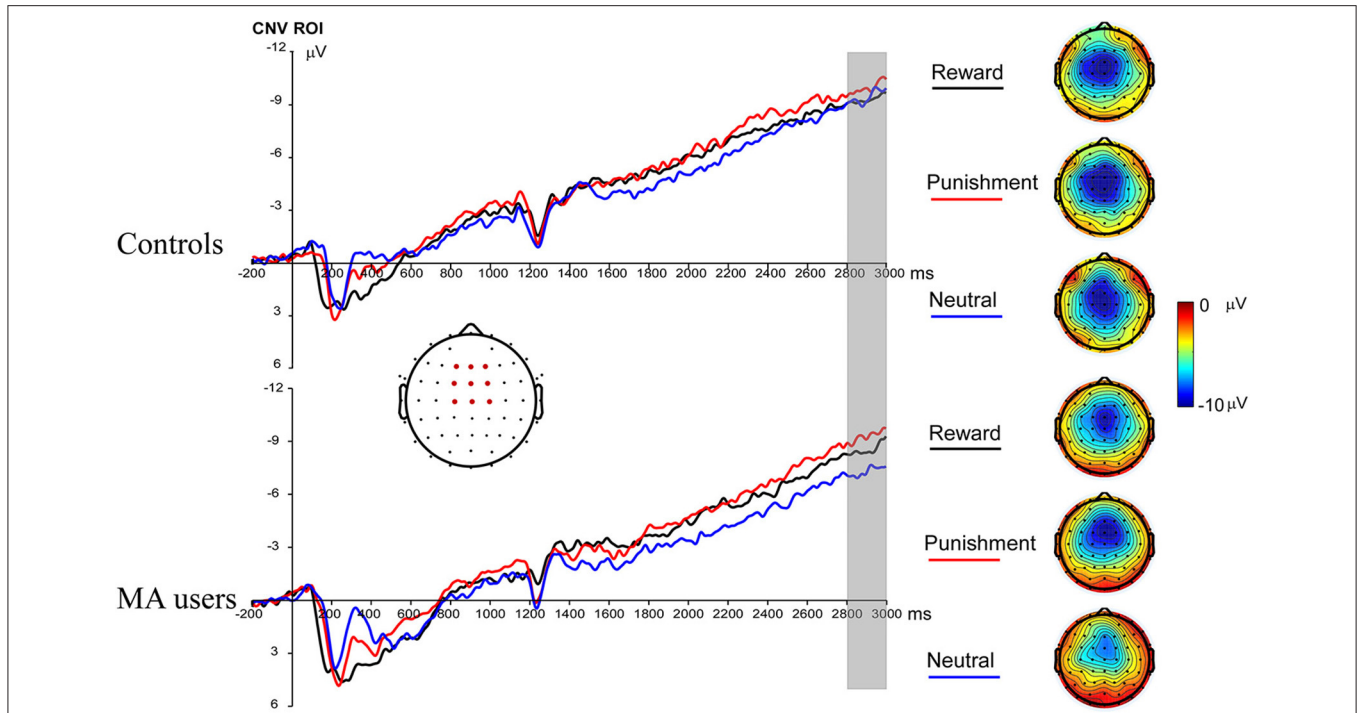

FIGURE 3 | Contingent negative variation (CNV) waveforms before choice making for the MA and HC group over frontocentral ROI (F1, F2, Fz, FC1, FC2, FCz, C1, C2, and Cz) (left); topographic maps of the CNV during 2,800–3,000 ms post cue onset (right).

condition was significantly larger in the MA group (−3.36 μV, $p < 0.05$) compared to the HC group (0.41 μV), but not in the potential punishment ($p = 0.14$, −0.68 μV in the HC group) and neutral conditions (**Figures 4**, **7**).

Consummatory ERPs

FRN

A 2 × 3 × 2 ANOVA was performed on the FRN data. The main effect of group was significant [$F_{(1, 37)} = 4.6$, $p < 0.05$, and $\eta_p^2 = 0.11$], and the FRN in the MA group (10.96 μV) was more positive than that in the HC group (8.6 μV). The main effect of the incentive condition was significant, [$F_{(2, 74)} = 29.43$, $p < 0.001$, and $\eta_p^2 = 0.44$], and the FRN in the potential reward (10.7 μV) and potential punishment (10.39 μV) conditions was more positive than that in the neutral condition (8.25 μV). The main effect of feedback outcome was significant [$F_{(1, 37)} = 7.02$, $p < 0.05$, and $\eta_p^2 = 0.16$], and the FRN for positive feedback (10.26 μV) was significantly higher than that for negative feedback (9.3 μV). The interaction effect of feedback and incentives was significant [$F_{(2, 74)} = 16.53$, $p < 0.001$, and $\eta_p^2 = 0.31$]. Simple analysis showed that the feedback effect was significant in the potential reward condition ($p < 0.001$, $M = 11.82$ μV following positive feedback, and $M = 9.49$ μV following negative feedback), potential punishment condition ($p < 0.05$, $M = 9.79$ μV following positive feedback, and $M = 10.92$ μV following negative feedback), and neutral condition ($p < 0.01$, $M = 9.07$ μV following positive feedback, and $M = 7.39$ μV following negative feedback). Neither the interaction effect of incentives and group [$F_{(2, 74)} = 2.81$, $p = 0.07$, and $\eta_p^2 = 0.07$], nor the interaction effect of feedback and group was significant [$F_{(1, 37)} < 0.01$, $p = 0.99$, and $\eta_p^2 < 0.01$]. The three-way effect of feedback, incentives, and group was not significant [$F_{(2, 74)} = 0.92$, $p = 0.4$, and $\eta_p^2 = 0.02$].

We further compared the feedback effect under different incentive conditions for the MA and HC groups. Using paired *t*-test, we identified that the FRN following positive feedback was more positive than following negative feedback in the reward condition in the HC group [$t_{(19)} = 4.44$, $p < 0.001$, and $M = 10.46$ μV following positive feedback and $M = 7.71$ μV following negative feedback], but not in the MA group [$t_{(18)} = 2.45$, $p = 0.025 > 0.008$ (after Bonferroni correction), $M = 13.25$ μV following positive feedback, and $M = 11.38$ μV following negative feedback]. The FRN following positive feedback compared to negative feedback in the punishment condition was not significant in either the HC group [$t_{(19)} = -1.58$, $p = 0.13$, and $M = 8.69$ μV following positive feedback, and $M = 9.82$ μV following negative feedback] or the MA group [$t_{(18)} = -2.37$, $p = 0.029 > 0.008$ (after Bonferroni correction), $M = 10.96$ μV following positive feedback, and $M = 12.07$ μV following negative feedback]. The FRN following positive feedback compared to negative feedback in the neutral condition was not significant in either the HC group [$t_{(19)} = 1.37$, $p = 0.19$, and $M = 8.1$ μV following positive feedback, and $M = 6.82$ μV following negative feedback] or the MA group [$t_{(18)} = 2.68$, $p = 0.015 > 0.008$ (after Bonferroni correction), $M = 10.1$ μV following positive feedback, and $M = 8$ μV following negative feedback] (**Figures 5**, **7**).

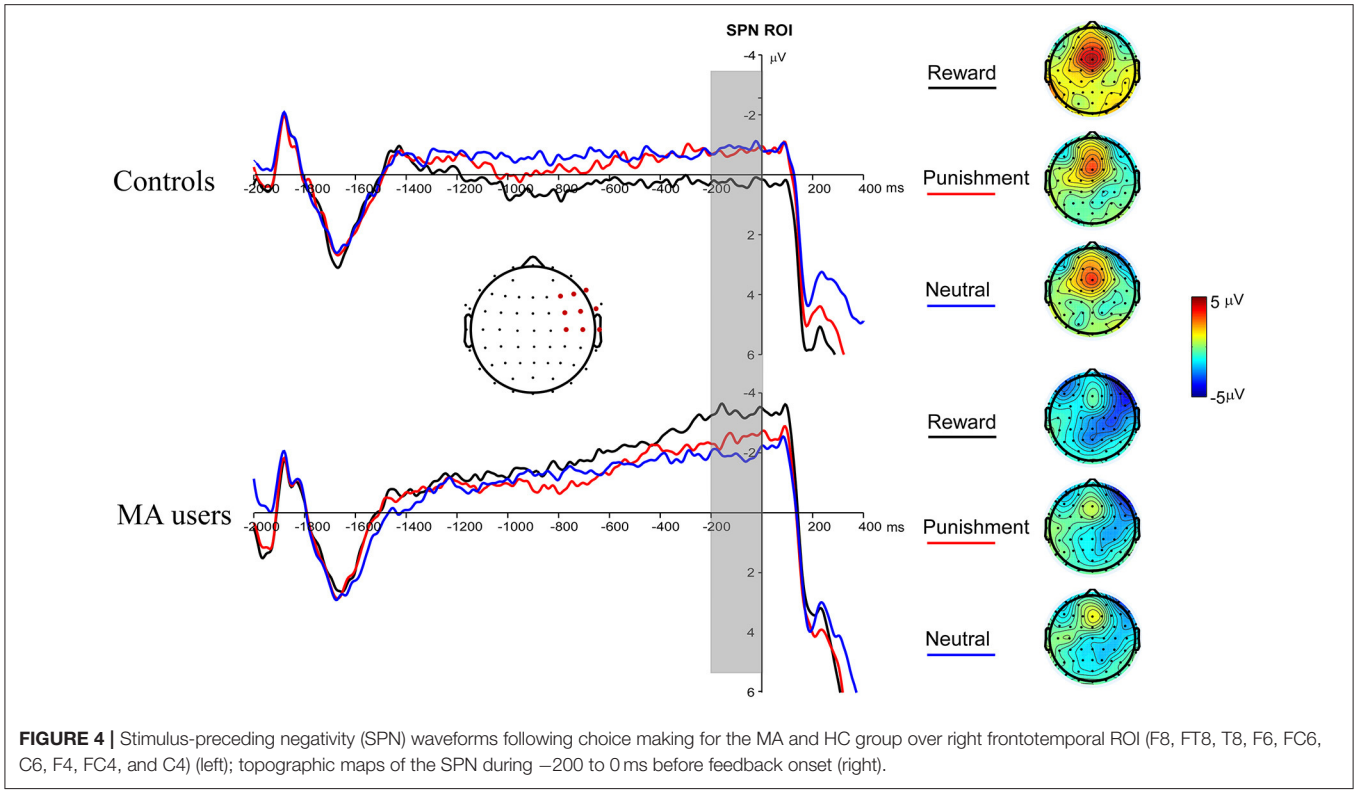

FIGURE 4 | Stimulus-preceding negativity (SPN) waveforms following choice making for the MA and HC group over right frontotemporal ROI (F8, FT8, T8, F6, FC6, C6, F4, FC4, and C4) (left); topographic maps of the SPN during −200 to 0 ms before feedback onset (right).

FB-P3

A 2 × 3 × 2 ANOVA was performed on the FB-P3 data. The main effect of incentive was significant [$F_{(2, 74)} = 26.99$, $p < 0.001$, and $\eta_p{}^2 = 0.42$], the FB-P3 in the reward condition (15.84 μV) and punishment conditions (14.45 μV) was significantly higher than that in the neutral condition (11.57 μV, $ps < 0.001$), and the FB-P3 in the reward condition was significantly higher than that in punishment condition ($p < 0.01$). The main effect of feedback was significant [$F_{(1, 37)} = 4.4$, $p < 0.05$, and $\eta_p{}^2 = 0.11$], and the FB-P3 after positive feedback (14.4 μV) was higher than that of negative feedback (13.5 μV). The main effect of group was not significant [$F_{(1, 37)} = 2.21$, $p = 0.15$, and $\eta_p{}^2 = 0.06$]. The interaction effect of feedback and incentive was significant [$F_{(2, 74)} = 14.25$, $p < 0.001$, and $\eta_p{}^2 = 0.28$]. Simple analysis showed that the feedback effect was significant under the potential reward condition ($p < 0.001$, $M = 17.66$ μV following positive feedback, and $M = 13.96$ μV following negative feedback), potential punishment condition ($p < 0.01$, $M = 13.58$ μV following positive feedback, and $M = 15.27$ μV following negative feedback), but not the neutral condition ($p = 0.36$, $M = 11.92$ μV following positive feedback, and $M = 11.15$ μV following negative feedback). The interaction effect of the incentive and group was not significant [$F_{(2, 74)} = 0.41$, $p = 0.67$, and $\eta_p{}^2 = 0.01$]. The interaction effect of feedback and group was not significant [$F_{(2, 74)} = 3.61$, $p = 0.07$, and $\eta_p{}^2 = 0.09$]. The three-way interaction effect of incentive, feedback, and group was not significant [$F_{(2, 74)} = 0.52$, $p = 0.6$, and $\eta_p{}^2 = 0.01$].

We further compared the feedback effect under different incentive conditions for the MA and HC groups. Using paired *t*-test, we identified that FB-P3 following positive feedback was significantly larger than that following negative feedback in the potential reward condition in the HC group [$t_{(19)} = 5.34$, $p < 0.001$, and $M = 17.02$ μV following positive feedback and $M = 11.96$ μV following negative feedback], but not the MA group [$t_{(18)} = 1.64$, $p = 0.12$, and $M = 18.33$ μV following positive feedback and $M = 16.07$ μV following negative feedback]. However, the FB-P3 following positive feedback was significantly lower than that following negative feedback in the potential punishment condition in the MA group [$t_{(18)} = -5.19$, $p < 0.001$, and $M = 14.11$ μV following positive feedback, and $M = 16.44$ μV following negative feedback], but not in the HC group [$t_{(19)} = -1.44$, $p = 0.17$, and $M = 13.07$ μV following positive feedback, and $M = 14.16$ μV following negative feedback]. The FB-P3 following positive feedback was similar to that following negative feedback in the neutral condition in the MA group [$t_{(18)} = 0.23$, $p = 0.82$, and $M = 12.9$ μV following positive feedback, and $M = 12.58$ μV following negative feedback] and the HC group [$t_{(19)} = 1.29$, $p = 0.21$, and $M = 10.99$ μV following positive feedback, and $M = 9.8$ μV following negative feedback] (**Figures 6**, **7**).

DISCUSSION

In this study, we utilized the MID task to identify the electrophysiological brain responses to potential reward and punishment during the anticipatory and consummatory stages of monetary incentive processing in women with MUD and healthy controls. In particular, we determined that in the anticipatory

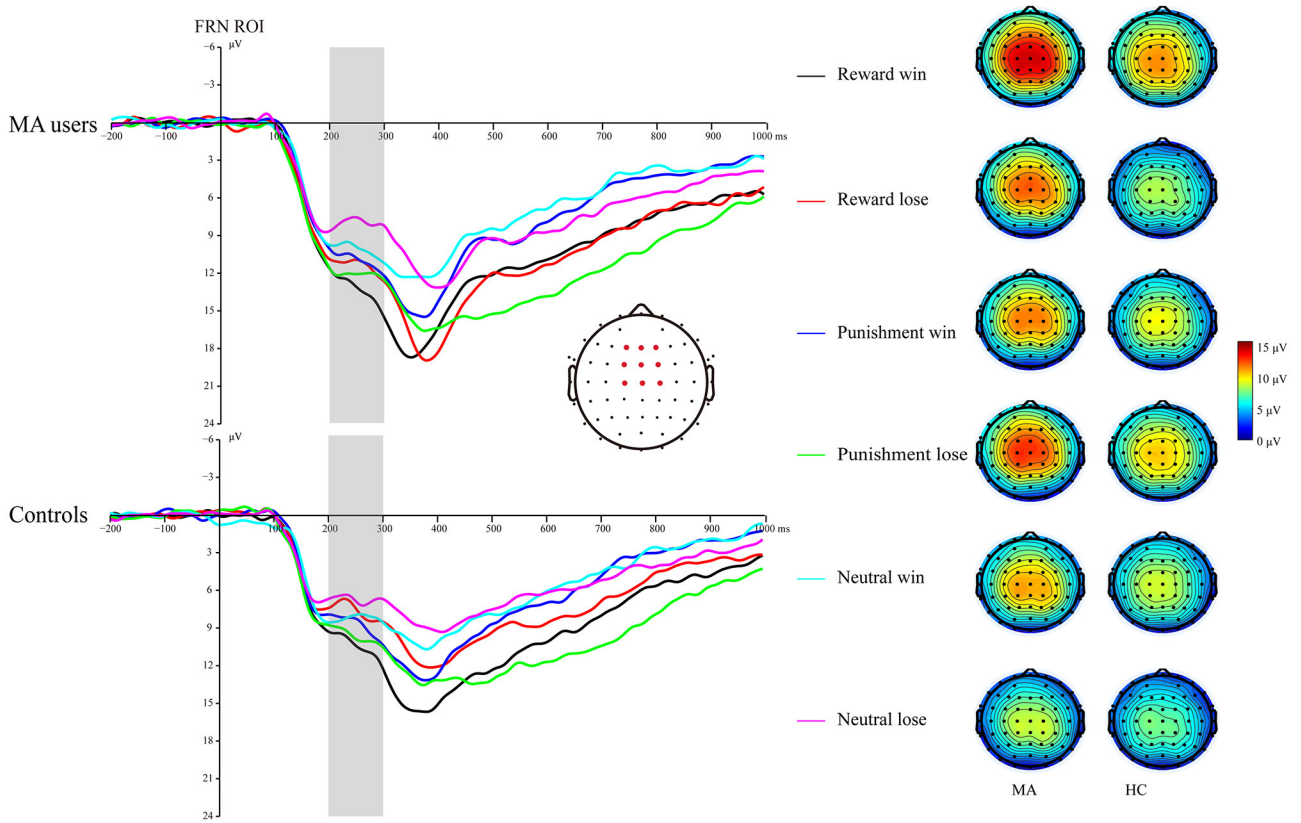

FIGURE 5 | Feedback-related negativity (FRN) waveforms of win and loss for the MA group and HC group over frontocentral ROI (F1, F2, Fz, FC1, FC2, FCz, C1, C2, and Cz) post feedback (left). Topographic maps of the FRN during 200–300 ms following feedback onset (right).

stage of monetary incentive processing, the women with MUD have sensitive neural correlates to the potential reward cues, while in the consummatory stage of the monetary incentive processing, they have more sensitive neural correlates to the delivery of the punishment.

In line with previous research (57, 58), the current study showed that women with MUD had significantly higher scores on the subscales of the BIS and SSS compared with healthy controls, which suggests that women with MUD tend to be impulsive and sensation-seeking. Impulsivity is the core pathological characteristic of SUD (59, 60), which may arise *via* two alternative mechanisms, which are not mutually exclusive. First, a highly impulsive personality may create a vulnerability to recreational substance use when available, and second, chronic substances use can induce changes in brain function, leading to increased impulsivity.

In the current study, for both groups, the behavioral data showed that the response latency under the potential reward and potential punishment conditions was significantly faster than that under neutral conditions, but there were no differences between potential reward and punishment conditions. Similarly, the ACC under the potential reward and punishment conditions was significantly higher than that under the neutral condition, with no differences between potential reward and punishment conditions. The behavioral results of this study confirm previous MID research that the RT in monetary incentive conditions is faster than that in neutral conditions (61–63), which indicated that individuals are more motivated to secure a monetary gain or avoid a monetary loss (64). This study also identified that the RT of women with MUD was faster than that of HC. This finding supports Anderson et al.'s (65) research that links attentional bias for a monetary reward with addiction, which suggests that substance users have heightened attentional capture by stimuli associated with drug and non-drug rewards. However, we also found that under neutral conditions, the RT of the women with MUD was faster than that of the HC. A meta-analysis showed that individuals with MUD have greater deficits in reward- or impulse-related functions and social cognition, and moderate deficits in global cognition, attention, executive functions, language/verbal fluency, language learning and memory, visual memory and working memory, and related control (6). In the current study, individuals with MUD were required to undergo mandatory isolation treatment for 2 years, during which time they could not use drugs or smoke. Thus, the behavioral activation effects caused by the use of substances or cigarettes can be ruled out. Gray proposed the existence of two independent motivational systems: behavioral inhibition system (BIS) and behavioral activation system (BAS) (66, 67).

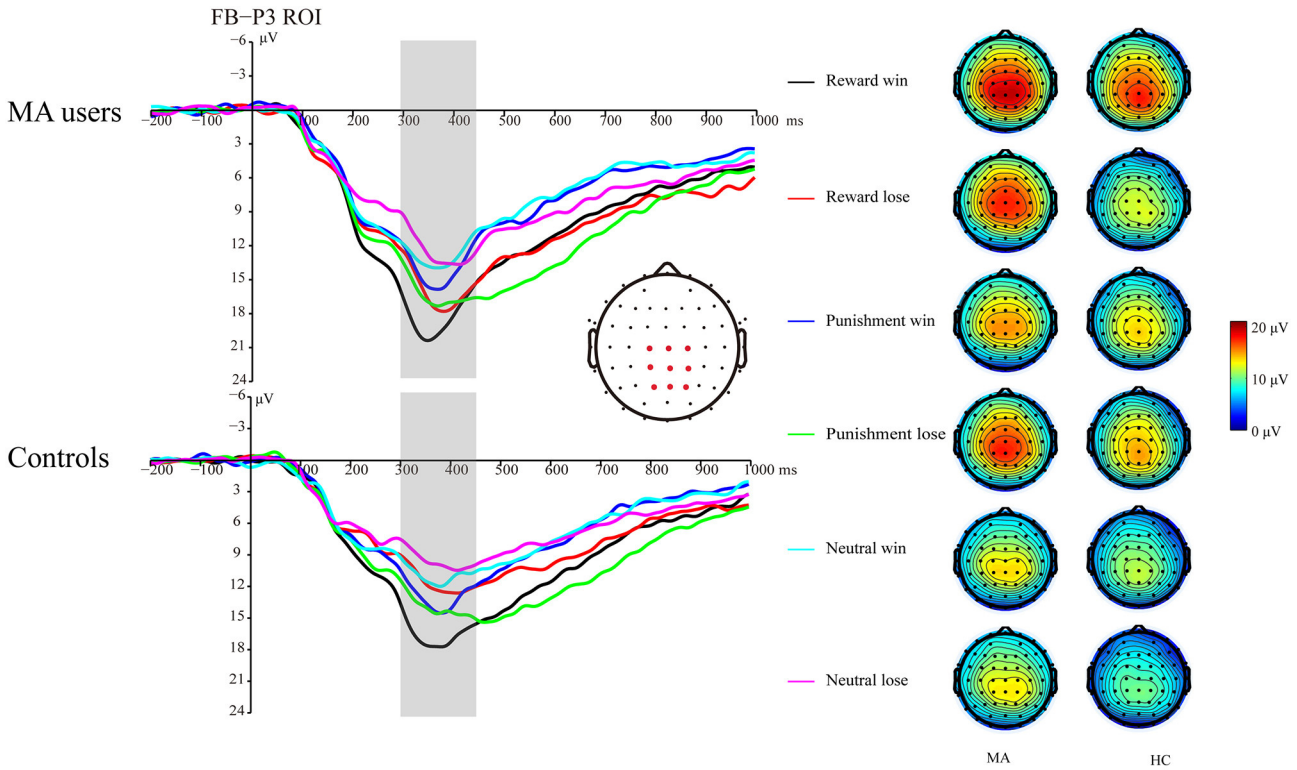

FIGURE 6 | FB-P3 waveforms of win and loss for the MA and HC groups over a centroparietal ROI (C1, Cz, C2, CP1, CPz, CP2, P1, Pz, and P2) post feedback (left). Topographic maps of the FB-P3 during 300–450 ms following feedback onset (right).

The BIS is activated by conditioned signals of punishment and termination of reward. In contrast, the action of the BAS is engaged only by conditioned signals of reward and termination of punishment, which promotes approach and active avoidance behavior. A previous study found that college students' illegal substances use correlated positively with BAS and negatively with BIS personality characteristics (68). Therefore, the faster response in women with MUD in the current study is consistent with a hyper-sensitive "go" or BAS. Prolonged abstinence may have afforded an opportunity to recover whatever deficits active MA or other substance use might have done to undermine the "stop" or BIS.

The findings from this study demonstrate distinct ERP components in the anticipatory and consummatory stages of monetary incentive processing. Concerning anticipatory processes, the Cue-P3 was shown to reflect the allocation of attention to signals for monetary incentive conditions in both groups, such that amplitudes were more positive for potential reward and punishment conditions than neutral conditions. These results are consistent with previous reports (31, 32, 61, 62, 69–71) that confirmed the sensitivity of this component to the salient features of incentives. Moreover, the Cue-P3 was not sensitive to cue valence during incentive processing, in which both reward and punishment cues elicited greater Cue-P3 than neutral stimuli. The results of Cue-P3 are also congruent with a stronger motivation, which accounts for faster response latency and a higher accuracy rate in the monetary incentive conditions. The amplitude of Cue-P3 was significantly higher in the MA group than in the HC group, which indicates that MA users have an increased neural response to cues of monetary incentives than healthy controls.

Furthermore, in this study, the MA group had a greater amplitude of SPN compared with the HC group under the potential reward condition, but there were no differences in the amplitude of SPN between the MA and HC groups under the potential punishment and neutral conditions. The results of Cue-P3 and SPN in this study showed that women with MUD have increased motivation for monetary rewards. These results are consistent with the previous fMRI results indicating increased neural activity during monetary reward anticipation in individuals with alcohol dependence and gambling disorder (22, 72). However, Luijten et al. (23) indicated that individuals with substance and gambling addiction showed decreased striatal activation compared with healthy controls in a meta-analysis. Compared with previous ERP studies, these results are consistent with our previous finding that women with MUD have an increased SPN to reward anticipation in a simple gambling task (46). These results are also consistent with those of Morie et al. (40), who demonstrated that cocaine users showed amplified anticipatory responses to reward predictive cues. However, Zhao et al. (41) showed that abstinent heroin users showed neural hypoactivation during the reward anticipation stage. This

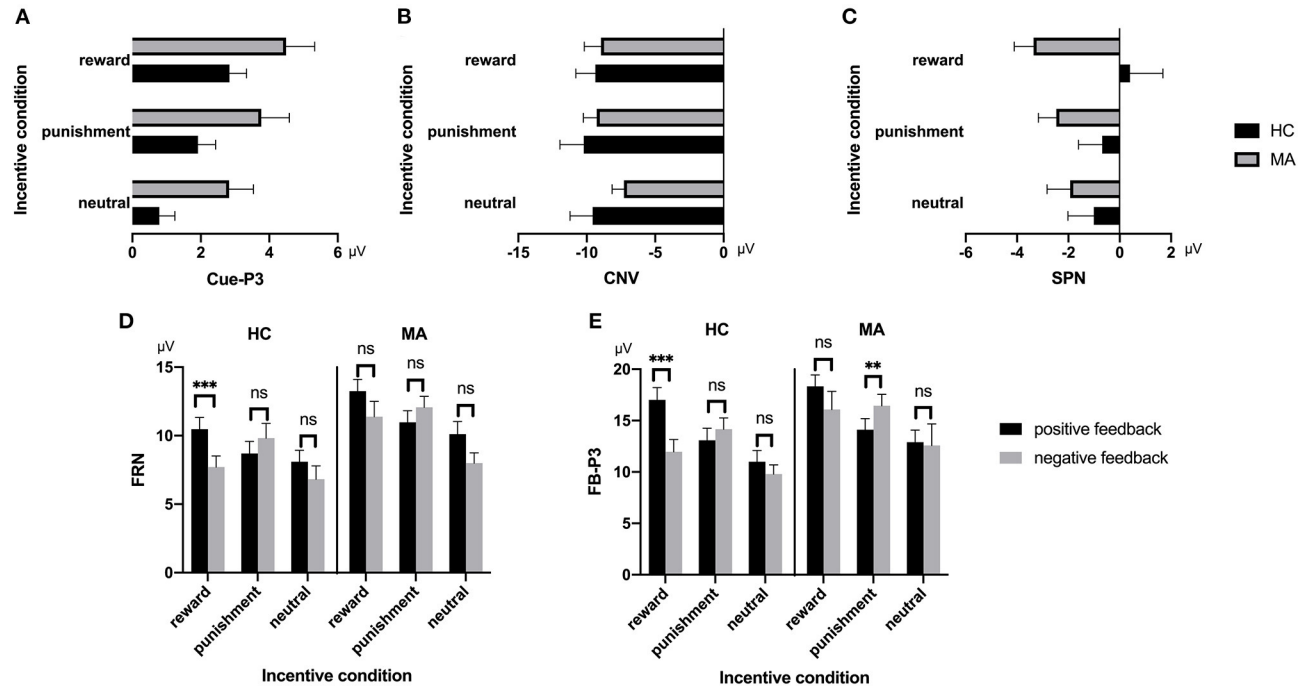

FIGURE 7 | ERP component data. **(A)** Mean amplitude of Cue-P3 (during 300–450 ms after cue presentation) over the centroparietal ROI (C1, Cz, C2, CP1, CPz, CP2, P1, Pz, and P2) for MA and HC groups. **(B)** Mean amplitude of CNV (during 2,800–3,000 ms post-cue onset) before choice making over the frontocentral ROI (F1, F2, Fz, FC1, FC2, FCz, C1, C2, and Cz) for the MA and HC groups. **(C)** Mean amplitude of SPN (during −200 to 0 ms before feedback onset) following choice making over the right frontotemporal ROI (F8, FT8, T8, F6, FC6, C6, F4, FC4, and C4) for the MA and HC groups. **(D)** Mean amplitude of FRN (during 200–300 ms following feedback onset) of win and loss over the frontocentral ROI (F1, F2, Fz, FC1, FC2, FCz, C1, C2, and Cz) post feedback for the MA and HC groups. **(E)** Mean amplitude of FB-P3 (during 300–450 ms following feedback onset) of win and loss over the centroparietal ROI (C1, Cz, C2, CP1, CPz, CP2, P1, Pz, and P2) post feedback for the MA and HC groups. Standard errors are also depicted. ns, not significant, $^{**}p < 0.01$, $^{***}p < 0.001$.

differs from the findings of this study. According to reward-deficiency theory, SUD is associated with a hypodopaminergic reward system (73), which suggests reduced neural responses to non-drug rewards (74). However, substance users have also been shown to exhibit impulsive behavior, particularly involving hyperactive responses to monetary rewards (75). The results could also support the incentive-sensitization theory, which proposes that substance users are characterized by hypersensitive anticipatory reward processing (i.e., the "wanting" process) (76). The focus of sensitized "wanting" in addiction is supposed to be primarily toward drug cues, rather than non-drug rewards (77). However, a previous study further indicated that chronic exposure to substances of abuse could lead to sensitization, which enhances the pursuit of natural rewards in animals (78). Therefore, these results support the impulsivity and incentive-sensitization theories in addiction.

The incentive effect was not observed for CNV, which is consistent with previous studies adopting the MID task to an ERP design (62, 69, 70). However, this is in contrast with other studies that observed a greater CNV following reward and loss cues relative to neutral cues (32, 79). The CNV is hypothesized to consist of anticipatory attention and preparation of the movement (35). The current results suggest that although the substance users had increased anticipatory monetary incentive processing, they also had similar motor preparation for pressing the button in both the monetary incentive and neutral conditions of this study.

Regarding consummatory ERPs, the FRN is sensitive to performance evaluation and reward evaluation during feedback processing and signals greater negativity when an outcome is worse than expected (80, 81). In this study, we identified that the FRN of the negative feedback was significantly greater than that for the positive feedback under the potential reward condition in the HC group, but no feedback effect was indicated under the potential punishment condition. However, the feedback effect of the FRN was displayed in neither the reward context nor the punishment context in the MA group. Similarly, previous studies showed that FRN was more negative for negative feedback than for positive feedback in the gain or win frame, but with no difference between the positive and negative frames in the loss frame (82–84). The framing effect is a well-established phenomenon, in which most people tend to be risk-averse in the gain frame but risk-seeking in the loss frame in risky decision-making (85). The current results support the existence of frame effects in healthy controls, but not women with MUD. The MA users were not sensitive to negative feedback in the potential reward context. Previous studies found that individuals with cocaine and alcohol use disorder showed blunted sensitivity to monetary reward outcomes indexed by decreased FRN (53, 86). The present findings suggest that prolonged abstinence from

stimulants in women with a history of heavy MA use does not alter this deficit, raising the possibility that low FRN may predispose a person to substance addiction. However, there are also studies that showed enhanced FRN to monetary feedback in heroin or MA users (41, 46).

In the monetary incentive consummatory stage, under the potential reward conditions, the FB-P3 of the positive feedback was significantly greater than that of the negative feedback in healthy controls, while the no feedback effect of FB-P3 existed in the MA users. The results suggest that under the potential reward condition, healthy controls were more sensitive to positive. In this study, the HC group was sensitized to positive feedback under the potential reward condition, while the MA group showed a significantly higher neural response to both the positive and negative feedback. However, the MA group was sensitive to negative feedback under the potential punishment condition, while the HC group showed a similar neural response to both positive and negative feedback. The FB-P3 is sensitive to more unexpected outcomes (87) but not sensitive to performance evaluation (88, 89). The current results suggest that the MA users are hyperactive to monetary loss under the potential punishment condition.

Similarly, one previous study identified that MA users exhibited more response in the caudate to loss outcomes than to gain outcomes (36). Another study indicated that smokers had higher academic scores from punishment feedback than non-smoking controls (90). According to early models of addiction (91), addicted individuals take drugs to alleviate or avoid aversive withdrawal syndrome. Solomon and Corbit (92) postulated that the initial effects of addictive drugs are appetitive, but these effects trigger the activation of a negative or opponent process. Solomon concluded that negative reinforcement has the most potent motivational influence on drug use. Recent researchers (8, 93) posit that a negative affect addiction stage, which involves avoidance of negative emotional after-effects of drug use, plays an important role in addiction. According to these theories, withdrawal-based learning makes drug users have a sensitive response to negative affect, which leads to drug use. In our previous study, we found that the individuals with MUD were more likely to make risky decisions following negative feedback (46). Therefore, the MA users' sensitivity to negative feedback under the potential punishment condition may be related to negative reinforcement. However, previous studies have also identified that individuals with SUD or pathological gamblers are less sensitive to punishment than healthy controls (25–27, 94). Since there are relatively few studies on the neural mechanism of addicted individuals in punishment processing, more research is required to clarify this issue.

Although our results provide some new information, some limitations still need to be considered. This study only included women with MUD, and future studies should be cautious when extending these results to male MA users. Moreover, female users were recruited from compulsory addiction rehabilitation centers, and their living environments were isolated from the outside world. Due to these limitations, current research results cannot be extended to men or individuals who do not seek treatment. Further studies are required to verify the current conclusions in other populations.

CONCLUSION

Using a MID task for ERP research, this study examined the incentive processing under the reward and punishment conditions in women with MUD and healthy controls. In this study, we revealed that women with MUD are more sensitive to monetary reward anticipation and monetary punishment consummation than healthy controls. The results suggest that women with MUD have stronger expectations of generic reward and stronger response of generic harm avoidance, which could be targeted in designing interventions for women with MA use disorder.

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 Ethical Review Board of the Institute of Psychology of the Chinese Academy of Science. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SW, HW, and XL conceived and designed this study. SW and ZX designed experimental stimuli and procedures. WS and JH implemented experimental protocols and collected data. SW and WS analyzed data. SW wrote the paper. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the National Key R&D Program of China (2016YFC0800901-Z03), the National Social Science Foundation of China (18BSH128), and in part by the Natural Science Foundation of Guangdong Province (2021A1515012509).

REFERENCES

1. Koob GF, Volkow ND. Neurocircuitry of addiction. *Neuropsychopharmacology.* (2010) 35:217. doi: 10.1038/npp.2009.110

2. Degenhardt L, Hall W. Extent of illicit drug use and dependence, and their contribution to the global burden of disease. *Lancet.* (2012) 379:55–70. doi: 10.1016/S0140-6736(11)61138-0

3. NCBMPS. *Annual Report on Drug Control in China*. Beijing: Narcotics Control Bureau of the Ministry of Public Security (2018).
4. Rawson RA. Current research on the epidemiology, medical and psychiatric effects, and treatment of methamphetamine use. *J Food Drug Anal.* (2013) 21(4 Suppl.):S77–S81. doi: 10.1016/j.jfda.2013.09.039
5. Courtney KE, Ray LA. Methamphetamine: an update on epidemiology, pharmacology, clinical phenomenology, and treatment literature. *Drug Alcohol Depend.* (2014) 143:11–21. doi: 10.1016/j.drugalcdep.2014.08.003
6. Potvin S, Pelletier J, Grot S, Hébert C, Barr AM, Lecomte T. Cognitive deficits in individuals with methamphetamine use disorder: a meta-analysis. *Addict Behav.* (2018) 80:154–60. doi: 10.1016/j.addbeh.2018.01.021
7. Mazur JE. *Learning & Behavior.* New York, NY: Routledge (2016).
8. Koob GF. The dark side of emotion: the addiction perspective. *Eur J Pharmacol.* (2015) 753:73–87. doi: 10.1016/j.ejphar.2014.11.044
9. Wise RA. The neurobiology of craving: implications for the understanding and treatment of addiction. *J Abnorm Psychol.* (1988) 97:118–32. doi: 10.1037/0021-843X.97.2.118
10. Koob GF, Le Moal M. Addiction and the brain antireward system. *Annu Rev Psychol.* (2008) 59:29–53. doi: 10.1146/annurev.psych.59.103006.093548
11. Robinson TE, Berridge KC. Addiction. *Annu Rev Psychol.* (2003) 54:25–53. doi: 10.1146/annurev.psych.54.101601.145237
12. Charney DS, Nestler EJ. *Neurobiology of Mental Illness.* New York, NY: Oxford University Press (2017).
13. Knutson B, Westdorp A, Kaiser E, Hommer D. FMRI visualization of brain activity during a monetary incentive delay task. *Neuroimage.* (2000) 12:20–7. doi: 10.1006/nimg.2000.0593
14. Liu X, Hairston J, Schrier M, Fan J. Common and distinct networks underlying reward valence and processing stages: a meta-analysis of functional neuroimaging studies. *Neurosci Biobehav Rev.* (2011) 35:1219–36. doi: 10.1016/j.neubiorev.2010.12.012
15. Kuhn S, Gallinat J. Common biology of craving across legal and illegal drugs - a quantitative meta-analysis of cue-reactivity brain response. *Eur J Neurosci.* (2011) 33:1318–26. doi: 10.1111/j.1460-9568.2010.07590.x
16. Chase HW, Eickhoff SB, Laird AR, Hogarth L. The neural basis of drug stimulus processing and craving: an activation likelihood estimation meta-analysis. *Biol Psychiatry.* (2011) 70:785–93. doi: 10.1016/j.biopsych.2011.05.025
17. Bühler M, Vollstädt-Klein S, Kobiella A, Budde H, Reed LJ, Braus DF, et al. Nicotine dependence is characterized by disordered reward processing in a network driving motivation. *Biol Psychiatry.* (2010) 67:745–52. doi: 10.1016/j.biopsych.2009.10.029
18. van Hell HH, Vink M, Ossewaarde L, Jager G, Kahn RS, Ramsey NF. Chronic effects of cannabis use on the human reward system: an fMRI study. *Eur Neuropsychopharmacol.* (2010) 20:153–63. doi: 10.1016/j.euroneuro.2009.11.010
19. Lessov-Schlaggar CN, Lepore RL, Kristjansson SD, Schlaggar BL, Barnes KA, Petersen SE, et al. Functional neuroimaging study in identical twin pairs discordant for regular cigarette smoking. *Addict Biol.* (2013) 18:98–108. doi: 10.1111/j.1369-1600.2012.00435.x
20. Bjork JM, Knutson B, Hommer DW. Incentive-elicited striatal activation in adolescent children of alcoholics. *Addiction.* (2008) 103:1308–19. doi: 10.1111/j.1360-0443.2008.02250.x
21. Bjork JM, Smith AR, Chen G, Hommer DW. Mesolimbic recruitment by nondrug rewards in detoxified alcoholics: effort anticipation, reward anticipation, and reward delivery. *Hum Brain Mapp.* (2012) 33:2174–88. doi: 10.1002/hbm.21351
22. Schmidt C, Gleesborg C, Schmidt H, Kvamme TL, Lund TE, Voon V, et al. A bias towards natural rewards away from gambling cues in gamblers undergoing active treatment. *Brain Res.* (2021) 1764:147479. doi: 10.1016/j.brainres.2021.147479
23. Luijten M, Schellekens AF, Kuhn S, Machielse MWJ, Sescousse G. Disruption of reward processing in addiction an image-based meta-analysis of functional magnetic resonance imaging studies. *JAMA Psychiatry.* (2017) 74:387–98. doi: 10.1001/jamapsychiatry.2016.3084
24. Bischoff-Grethe A, Connolly CG, Jordan SJ, Brown GG, Paulus MP, Tapert SF, et al. Altered reward expectancy in individuals with recent methamphetamine dependence. *J Psychopharm.* (2017) 31:17–30. doi: 10.1177/0269881116668590
25. Hester R, Bell RP, Foxe JJ, Garavan H. The influence of monetary punishment on cognitive control in abstinent cocaine-users. *Drug Alcohol Depend.* (2013) 133:86–93. doi: 10.1016/j.drugalcdep.2013.05.027
26. Romanczuk-Seiferth N, Koehler S, Dreesen C, Wustenberg T, Heinz A. Pathological gambling and alcohol dependence: neural disturbances in reward and loss avoidance processing. *Addict Biol.* (2015) 20:557–69. doi: 10.1111/adb.12144
27. Duehlmeyer L, Hester R. Impaired learning from punishment of errors in smokers: Differences in dorsolateral prefrontal cortex and sensorimotor cortex blood-oxygen-level dependent responses. *Neuroimage Clin.* (2019) 23:101819. doi: 10.1016/j.nicl.2019.101819
28. Franken IH, van Strien JW, Kuijpers I. Evidence for a deficit in the salience attribution to errors in smokers. *Drug Alcohol Depend.* (2010) 106:181–5. doi: 10.1016/j.drugalcdep.2009.08.014
29. Worhunsky PD, Malison RT, Rogers RD, Potenza MN. Altered neural correlates of reward and loss processing during simulated slot-machine fMRI in pathological gambling and cocaine dependence. *Drug Alcohol Depend.* (2014) 145:77–86. doi: 10.1016/j.drugalcdep.2014.09.013
30. Bjork JM, Chen G, Smith AR, Hommer DW. Incentive-elicited mesolimbic activation and externalizing symptomatology in adolescents. *J Child Psychol Psychiatry.* (2010) 51:827–37. doi: 10.1111/j.1469-7610.2009.02201.x
31. Novak BK, Novak KD, Lynam DR, Foti D. Individual differences in the time course of reward processing: stage-specific links with depression and impulsivity. *Biol Psychol.* (2016) 119:79–90. doi: 10.1016/j.biopsycho.2016.07.008
32. Novak KD, Foti D. Teasing apart the anticipatory and consummatory processing of monetary incentives: an event-related potential study of reward dynamics. *Psychophysiology.* (2015) 52:1470–82. doi: 10.1111/psyp.12504
33. Polich J, Kok A. Cognitive and biological determinants of P300: an integrative review. *Biol Psychol.* (1995) 41:103–46. doi: 10.1016/0301-0511(95)05130-9
34. Walter WG, Cooper R, Aldridge VJ, McCallum WC, Winter AL. Contingent negative variation: an electric sign of sensorimotor association and expectancy in the human brain. *Nature.* (1964) 203:380–4. doi: 10.1038/203380a0
35. Brunia CHM, Hackley SA, van Boxtel GJM, Kotani Y, Ohgami Y. Waiting to perceive: reward or punishment? *Clin Neurophysiol.* (2011) 122:858–68. doi: 10.1016/j.clinph.2010.12.039
36. Holroyd CB, Coles MGH. The neural basis of human error processing: Reinforcement learning, dopamine, and the error-related negativity. *Psychol Rev.* (2002) 109:679–709. doi: 10.1037/0033-295X.109.4.679
37. Proudfit GH. The reward positivity: from basic research on reward to a biomarker for depression. *Psychophysiology.* (2015) 52:449–59. doi: 10.1111/psyp.12370
38. Polich J. Updating P300: an integrative theory of P3a and P3b. *Clin Neurophysiol.* (2007) 118:2128–48. doi: 10.1016/j.clinph.2007.04.019
39. San Martín R. Event-related potential studies of outcome processing and feedback-guided learning. *Front Hum Neurosci.* (2012) 6:304. doi: 10.3389/fnhum.2012.00304
40. Morie KP, De Sanctis P, Garavan H, Foxe JJ. Regulating task-monitoring systems in response to variable reward contingencies and outcomes in cocaine addicts. *Psychopharmacology.* (2016) 233:1105–18. doi: 10.1007/s00213-015-4191-8
41. Zhao QL, Li HQ, Hu B, Wu HY, Liu QY. Abstinent heroin addicts tend to take risks: ERP and source lolecalization. *Front Neurosci.* (2017) 11:681. doi: 10.3389/fnins.2017.00681
42. Goldstein RZ, Parvaz MA, Maloney T, Alia-Klein N, Woicik PA, Telang F, et al. Compromised sensitivity to monetary reward in current cocaine users: an ERP study. *Psychophysiology.* (2008) 45:705–13. doi: 10.1111/j.1469-8986.2008.00670.x
43. Kamarajan C, Porjesz B, Rangaswamy M, Tang Y, Chorlian DB, Padmanabhapillai A, et al. Brain signatures of monetary loss and gain: outcome-related potentials in a single outcome gambling task. *Behav Brain Res.* (2009) 197:62–76. doi: 10.1016/j.bbr.2008.08.011
44. Parvaz MA, Konova AB, Proudfit GH, Dunning JP, Malaker P, Moeller SJ, et al. Impaired neural response to negative prediction errors in cocaine addiction. *J Neurosci.* (2015) 35:1872–9. doi: 10.1523/JNEUROSCI.2777-14.2015
45. Parvaz MA, Maloney T, Moeller SJ, Woicik PA, Alia-Klein N, Telang F, et al. Sensitivity to monetary reward is most severely

compromised in recently abstaining cocaine addicted individuals: a cross-sectional ERP study. *Psychiatry Res Neuroimaging.* (2012) 203:75–82. doi: 10.1016/j.pscychresns.2012.01.001
46. Wei SG, Zheng Y, Li Q, Dai WN, Sun JX, Wu HY, et al. Enhanced neural responses to monetary rewards in methamphetamine use disordered individuals compared to healthy controls. *Physiol Behav.* (2018) 195:118–27. doi: 10.1016/j.physbeh.2018.08.003
47. Mayo LM, Paul E, DeArcangelis J, Van Hedger K, de Wit H. Gender differences in the behavioral and subjective effects of methamphetamine in healthy humans. *Psychopharmacology (Berl).* (2019) 236:2413–23. doi: 10.1007/s00213-019-05276-2
48. Brecht M-L, O'Brien A, Von Mayrhauser C, Anglin MD. Methamphetamine use behaviors and gender differences. *Addict Behav.* (2004) 29:89–106. doi: 10.1016/S0306-4603(03)00082-0
49. Hser YI, Evans E, Huang YC. Treatment outcomes among women and men methamphetamine abusers in California. *J Subst Abuse Treat.* (2005) 28:77–85. doi: 10.1016/j.jsat.2004.10.009
50. Rawson RA, Gonzales R, Obert JL, McCann MJ, Brethen P. Methamphetamine use among treatment-seeking adolescents in Southern California: participant characteristics and treatment response. *J Subst Abuse Treat.* (2005) 29:67–74. doi: 10.1016/j.jsat.2005.04.001
51. First M, Williams J, Karg R, Spitzer R. *Structured Clinical Interview for DSM-5-Research Version (SCID-5 for DSM-5, Research Version; SCID-5-RV).* Arlington, VA: American Psychiatric Association (2015).
52. Patton JH, Stanford MS. Factor structure of the Barratt impulsiveness scale. *J Clin Psychol.* (1995) 51:768–74. doi: 10.1002/1097-4679(199511)51:6<768::AID-JCLP2270510607>3.0.CO;2-1
53. Zuckerman M, Eysenck SB, Eysenck HJ. Sensation seeking in England and America: cross-cultural, age, and sex comparisons. *J Consult Clin Psychol.* (1978) 46:139–49. doi: 10.1037/0022-006X.46.1.139
54. Knutson B, Adams CM, Fong GW, Hommer D. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *J Neurosci.* (2001) 21:RC159. doi: 10.1523/JNEUROSCI.21-16-j0002.2001
55. Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods.* (2004) 134:9–21. doi: 10.1016/j.jneumeth.2003.10.009
56. Lopez-Calderon J, Luck SJ. ERPLAB: an open-source toolbox for the analysis of event-related potentials. *Front Hum Neurosci.* (2014) 8:213. doi: 10.3389/fnhum.2014.00213
57. Jones HW, Dean AC, Price KA, London ED. Increased self-reported impulsivity in methamphetamine users maintaining drug abstinence. *Am J Drug Alcohol Abuse.* (2016) 42:500–6. doi: 10.1080/00952990.2016.1192639
58. Zhang J, Su H, Tao JY, Xie Y, Sun YM, Li LR, et al. Relationship of impulsivity and depression during early methamphetamine withdrawal in Han Chinese population. *Addict Behav.* (2015) 43:7–10. doi: 10.1016/j.addbeh.2014.10.032
59. Goldstein RZ, Volkow ND. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *Am J Psychiatry.* (2002) 159:1642–52. doi: 10.1176/appi.ajp.159.10.1642
60. Verdejo-Garcia A, Lawrence AJ, Clark L. Impulsivity as a vulnerability marker for substance-use disorders: review of findings from high-risk research, problem gamblers and genetic association studies. *Neurosci Biobehav Rev.* (2008) 32:777–810. doi: 10.1016/j.neubiorev.2007.11.003
61. Zhang YY, Li Q, Wang Z, Liu X, Zheng Y. Temporal dynamics of reward anticipation in the human brain. *Biol Psychol.* (2017) 128:89–97. doi: 10.1016/j.biopsycho.2017.07.011
62. Broyd SJ, Richards HJ, Helps SK, Chronaki G, Bamford S, Sonuga-Barke EJS. An electrophysiological monetary incentive delay (e-MID) task: a way to decompose the different components of neural response to positive and negative monetary reinforcement. *J Neurosci Methods.* (2012) 209:40–9. doi: 10.1016/j.jneumeth.2012.05.015
63. Greimel E, Bakos S, Landes I, Tollner T, Bartling J, Kohls G, et al. Sex differences in the neural underpinnings of social and monetary incentive processing during adolescence. *Cogn Affect Behav Neurosci.* (2018) 18:296–312. doi: 10.3758/s13415-018-0570-z
64. Dillon DG, Pizzagalli DA. Evidence of successful modulation of brain activation and subjective experience during reappraisal of negative emotion in unmedicated depression. *Psychiatry Res Neuroimaging.* (2013) 212:99–107. doi: 10.1016/j.pscychresns.2013.01.001
65. Anderson BA, Faulkner ML, Rilee JJ, Yantis S, Marvel CL. Attentional bias for nondrug reward is magnified in addiction. *Exp Clin Psychopharmacol.* (2013) 21:499–506. doi: 10.1037/a0034575
66. Gray J. *The Neuropsychology of Anxiety: An Enquiry Into the Functions of the Septo-Hippocampal System*. Oxford: Oxford University Press (1982).
67. Gray J, McNaughton N. *The Neuropsychology of Anxiety: An Enquiry Into the Function of the Septo-Hippocampal System, Vol. 2.* Oxford: Oxford University Press (2000).
68. Franken IH, Muris P, Georgieva I. Gray's model of personality and addiction. *Addict Behav.* (2006) 31:399–403. doi: 10.1016/j.addbeh.2005.05.022
69. Goldstein RZ, Cottone LA, Jia Z, Maloney T, Volkow ND, Squires NK. The effect of graded monetary reward on cognitive event-related potentials and behavior in young healthy adults. *Int J Psychophysiol.* (2006) 62:272–9. doi: 10.1016/j.ijpsycho.2006.05.006
70. Pfabigan DM, Seidel E-M, Sladky R, Hahn A, Paul K, Grahl A, et al. P300 amplitude variation is related to ventral striatum BOLD response during gain and loss anticipation: an EEG and fMRI experiment. *Neuroimage.* (2014) 96:12–21. doi: 10.1016/j.neuroimage.2014.03.077
71. Chronaki G, Soltesz F, Benikos N, Sonuga-Barke EJS. An electrophysiological investigation of reinforcement effects in attention deficit/hyperactivity disorder: dissociating cue sensitivity from downstream effects on target engagement and performance. *Dev Cogn Neurosci.* (2017) 28:12–20. doi: 10.1016/j.dcn.2017.10.003
72. van Holst RJ, Clark L, Veltman DJ, van den Brink W, Goudriaan AE. Enhanced striatal responses during expectancy coding in alcohol dependence. *Drug Alcohol Depend.* (2014) 142:204–8. doi: 10.1016/j.drugalcdep.2014.06.019
73. Volkow ND, Wang GJ, Fowler JS, Tomasi D, Telang F. Addiction: beyond dopamine reward circuitry. *Proc Natl Acad Sci U S A.* (2011) 108:15037–42. doi: 10.1073/pnas.1010654108
74. Blum K, Braverman ER, Holder JM, Lubar JF, Monastra VJ, Miller D, et al. Reward deficiency syndrome: a biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors. *J Psychoactive Drugs.* (2000) 32(Suppl. i–iv):1–112. doi: 10.1080/02791072.2000.10736099
75. Bechara A. Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. *Nat Neurosci.* (2005) 8:1458–63. doi: 10.1038/nn1584
76. Robinson TE, Berridge KC. The incentive sensitization theory of addiction: some current issues. *Philos Trans R Soc B.* (2008) 363:3137–46. doi: 10.1098/rstb.2008.0093
77. Robinson TE, Berridge KC. The psychology and neurobiology of addiction: an incentive-sensitization view. *Addiction.* (2000) 95(Suppl. 2):S91–S117. doi: 10.1046/j.1360-0443.95.8s2.19.x
78. Wyvell CL, Berridge KC. Incentive sensitization by previous amphetamine exposure: increased cue-triggered "wanting" for sucrose reward. *J Neurosci.* (2001) 21:7831–40. doi: 10.1523/JNEUROSCI.21-19-07831.2001
79. Plichta MM, Wolf I, Hohmann S, Baumeister S, Boecker R, Schwarz AJ, et al. Simultaneous EEG and fMRI reveals a causally connected subcortical-cortical network during reward anticipation. *J Neurosci.* (2013) 33:14526–33. doi: 10.1523/JNEUROSCI.0631-13.2013
80. Glazer JE, Kelley NJ, Pornpattananangkul N, Mittal VA, Nusslock R. Beyond the FRN: broadening the time-course of EEG and ERP components implicated in reward processing. *Int J Psychophysiol.* (2018) 132(Pt B):184–202. doi: 10.1016/j.ijpsycho.2018.02.002
81. Sambrook TD, Goslin J. A neural reward prediction error revealed by a meta-analysis of ERPs using great grand averages. *Psychol Bull.* (2015) 141:213–35. doi: 10.1037/bul0000006
82. Xu S, Wang M, Liu Q, Wang C, Zhang C. Exploring the valence-framing effect: gain frame enhances behavioral and brain sensitivity to the failure of decision-making under uncertainty. *Int J Psychophysiol.* (2020) 153:166–72. doi: 10.1016/j.ijpsycho.2020.05.006
83. Yu R, Zhang P. Neural evidence for description dependent reward processing in the framing effect. *Front Neurosci.* (2014) 8:56. doi: 10.3389/fnins.2014.00056

84. Zheng Y, Li Q, Wang K, Wu H, Liu X. Contextual valence modulates the neural dynamics of risk processing. *Psychophysiology*. (2015) 52:895–904. doi: 10.1111/psyp.12415
85. Tversky A, Kahneman D. The framing of decisions and the psychology of choice. *Science*. (1981) 211:453–8. doi: 10.1126/science.7455683
86. Soder HE, Webber TA, Bornovalova MA, Park JY, Potts GF. A test of dopamine hyper-and hyposensitivity in alcohol use. *Addict Behav*. (2019) 90:395–401. doi: 10.1016/j.addbeh.2018.12.002
87. Hajcak G, Moser JS, Holroyd CB, Simons RF. It's worse than you thought: the feedback negativity and violations of reward prediction in gambling tasks. *Psychophysiology*. (2007) 44:905–12. doi: 10.1111/j.1469-8986.2007.00567.x
88. Yeung N, Sanfey AG. Independent coding of reward magnitude and valence in the human brain. *J Neurosci*. (2004) 24:6258–64. doi: 10.1523/JNEUROSCI.4537-03.2004
89. Pfabigan DM, Alexopoulos J, Bauer H, Sailer U. Manipulation of feedback expectancy and valence induces negative and positive reward prediction error signals manifest in event-related brain potentials. *Psychophysiology*. (2011) 48:656–64. doi: 10.1111/j.1469-8986.2010.01136.x
90. Rai LA, O'Halloran L, Jollans L, Vahey N, O'Brolchain C, Whelan R. Individual differences in learning from probabilistic reward and punishment predicts smoking status. *Addict Behav*. (2019) 88:73–6. doi: 10.1016/j.addbeh.2018.08.019
91. Wikler A. Recent progress in research on the neurophysiologic basis of morphine addiction. *Am J Psychiatry*. (1948) 105:329–38. doi: 10.1176/ajp.105.5.329
92. Solomon RL, Corbit JD. An opponent-process theory of motivation: I. Temporal dynamics of affect. *Psychol Rev*. (1974) 81:119. doi: 10.1037/h0036128
93. Baker TB, Piper ME, McCarthy DE, Majeskie MR, Fiore MC. Addiction motivation reformulated: an affective processing model of negative reinforcement. *Psychol Rev*. (2004) 111:33. doi: 10.1037/0033-295X.111.1.33
94. Potts GF, Bloom EL, Evans DE, Drobes DJ. Neural reward and punishment sensitivity in cigarette smokers. *Drug Alcohol Depend*. (2014) 144:245–53. doi: 10.1016/j.drugalcdep.2014.09.773

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.

The Handling Editor XW declared a shared affiliation, though no other collaboration, with one of the authors ZX at the time of the review.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: frontiersin.org/about/contact

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership