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# Addiction and the brain: Current knowledge, methods, and perspectives

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# Addiction and the brain: Current knowledge, methods, and perspectives

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# Editorial: Addiction and the brain: current knowledge, methods, and perspectives

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Editorial on the Research Topic
Addiction and the brain: current knowledge, methods, and perspectives

Addiction is commonly considered a disorder that affects the brain and changes behavior. Substance use disorders, among the leading causes of death and disability (1), continue to be major public health challenges. Behavioral addictions, which share certain neurobiological mechanisms with substance use disorders (2), have received increasing attention over the last two decades. Yet, we lack an overarching theoretical framework that integrates the advancements in neurobiological research with the development, progression, and treatment of addiction.

Despite the significant progress in our understanding of addiction (3–5), the translation of this knowledge into effective treatment options remains a critical challenge (6). In this Research Topic, we present selected studies that aim to bridge this gap by carefully assessing relevant cohorts, by evaluating available brain-related interventions, or by developing innovative approaches to the treatment of substance use disorders (see Table 1 for overview).

## Studies on brain-related intervention effects

Chen J. et al. evaluated the commonly adopted treatment approach, methadone maintenance treatment, for heroin use disorder, within a 1-year longitudinal study. The results confirmed the effectiveness of methadone in reducing withdrawal symptoms and preventing relapses. At the imaging level, increased connectivity within the default mode network (DMN) was associated with reduced withdrawal symptoms, while the increased connectivity between the DMN and the salience network might pose risks of relapse given its link to enhanced salience signal of heroin cues. Clinicians may need to evaluate both positive and negative effects of this treatment approach during application.

Mindfulness-based interventions, rooted in neurobiological findings and increasingly being adopted in treatment centers globally, have also emerged as a powerful treatment approach for substance misuse (7), offering the added advantages of ease of access and low costs. Rosenthal et al. aimed to better understand the underlying mechanisms of a short, guided meditation by assessing how changes in environmental cues influence instrumental

TABLE 1 Overview of edited primary studies on addictions.

| Authors | Keyword(s) | Substance, diagnosis | Setting of treatment/ recruitment | Country | Sample size, female %* | Participant age range (mean) | Study type | Intervention/ treatment (experimental) | Additional naturalistic treatment | Primary outcome variable(s) | Follow-up interval |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Studies on brain-related intervention effects** | | | | | | | | | | | |
| Chen J. et al. | Resting-state connectivity | Heroin/methadone, HUD | Heroin treatment program including methadone maintenance treatment | China, East Central | $N = 94$ ($N = 37$ HUD, $N = 57$ controls); 10% and 8% female | — ($M = 37$ and $M = 35$) | Observational, longitudinal, self-controlled, quasi-experimental | — | Methadone maintenance treatment including monthly random urine testing | Coupling of default mode and salience networks, changes in psychological characteristics | One year (HUD group only) |
| Rosenthal et al. | Meditation | Alcohol, AUD | *Ad-hoc* community sample** | Europe, Germany | $N = 62$ ($N = 27$ AUD, $N = 35$ controls); 17% and 59% female | — ($M = 39$ and $M = 38$) | Randomized, within-subject | Audio-guided body scan meditation against a control condition (audio of nature sounds) | — | Pavlovian-to-instrumental transfer effect | Within treatment session |
| van Oort et al. | Resting-state connectivity | Alcohol, AUD | Inpatient AUD treatment center with detoxification | USA, northeast | $N = 64$ ($N = 37$ inpatients, $N = 27$ controls); 40% female | 30–59 years ($M = 47$ and $M = 47$) | Prospective, quasi-experimental, randomized, naturalistic | — | NIAAA treatment program for AUD, including group and individual therapy and pharmacological interventions when appropriate | Left and right frontoparietal networks connectivity, default mode network connectivity | Treatment entry (baseline) to treatment end (follow-up) = 4 weeks ± 9 days |
| Gullett et al. | Resting-state connectivity | Alcohol | *Ad-hoc* community sample | USA, southeast | $N = 35$ with heavy alcohol use; 40% female | 45–75 years ($M = 57$) | Prospective, one-group, controlled, within-subject | Contingency management aiming at drinking reduction rather than abstinence | — | Resting-state functional connectivity of the salience network | 30 days |
| **Studies on brain-centered interventions** | | | | | | | | | | | |
| Hu et al. | rTMS | Alcohol, AUD | Inpatient and outpatient treatment centers (different hospitals) | China (multiple) | $N = 263$; 3.0%−15.2% female | — ($M = 44$–$48$) | Prospective, randomized, double-blind, sham-controlled | Ten sessions rTMS at DLPFC across 2 weeks (starting at baseline) plus either (a) 8 × 60 min CBT across 8 weeks (starting at baseline) or (b) 1 × 10 min clinical interview | Mecobalamin, vitamin B, vitamin C, vitamin E. Temporary short-term low-dose benzodiazepines when appropriate | Relapse (combining self-reports and family member telephone interviews) | 6 months following discharge |
| Upton et al. | rTMS (cTBS, iTBS) | Nicotine, ND | *Ad-hoc* community sample | USA, midwest | $N = 31$; 48% female | — ($M = 47$) | Prospective, within-subject | Two randomized, counterbalanced, neuronavigated TBS sessions to the rIFG—one administering cTBS, and the other administering iTBS | — | Smoking behaviors, fronto-striatal-limbic resting-state functional connectivity | Within treatment session |
| Dong et al. | rTMS (iTBS) | Heroin & methamphetamine concurrently, HUD & MUD | Inpatient addiction treatment center | China, East Central | $N = 56$; 16% female | 40–62 years (—) | Prospective | Twenty sessions of rTMS to the DLPFC | Unspecified inpatient treatment as usual including pharmacological interventions when appropriate | Cognitive functioning, 10 related protein markers in blood serum | Treatment entry (baseline) to treatment end (follow-up) = 4 weeks |
| Chen Y.-H. et al. | rTMS, tDCS | Methamphetamine, MUD | Clinical (review) | — | — | — | Review | rTMS, tDCS, (EEG-fNIRS for assessment) | — | — | — |
| **Studies on relapse prediction using brain parameters** | | | | | | | | | | | |
| Sasaki et al. | fNIRS | Alcohol, AUD | Inpatient treatment centers | East Asia, Japan | $N = 41$; 14.6% female | — ($M = 51.6$–$55.0$) | Prospective, controlled | — | Detoxification treatment (1–2 weeks, including diazepam infusions), subsequent inpatient treatment (3.5 months, treatment based on "12 Step" meetings), optional post-discharge services (outpatient visits, daycare activities, self-help groups) | Associations between relapse status and possible predictors measured during hospitalization (notably task-related brain treatment measured via fNIRS) | 6 months following discharge |

*(Continued)*





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TABLE 1 (Continued)

| Authors | Keyword(s) | Substance, diagnosis | Setting of treatment/ recruitment | Country | Sample size, female %* | Participant age range (mean) | Study type | Intervention/ treatment (experimental) | Additional naturalistic treatment | Primary outcome variable(s) | Follow-up interval |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Martelli et al. | Structural MRI | Alcohol, AUD | Inpatient treatment centers | Europe, France | $N = 23$ ($N = 17$ inpatients, $N = 6$ healthy controls); no females | — ($M = 50.8$–$54.9$) | Prospective, controlled | — | Detoxification treatment finished | Association between AUD/relapse status and regional cerebral volumes | 7 years |
| **Studies on comorbidities with a possible shared brain mechanism** | | | | | | | | | | | |
| Shen et al. | Oxytocin receptor polymorphism | Alcohol, AUD | Hospitals with inpatient detoxification treatment | China, North | $N = 265$; no females | — ($M = 45$) | Non-interventional, cross-sectional | — | Detoxification treatment finished | Interactions between polymorphism and self-reported anxiety & depression | — |
| Luderer et al. | Comorbidity | Alcohol, AUD | Inpatient and outpatient psychiatric treatment institution | Europe, Germany | $N = 47$ patients ($N = 6$ AUD only, $N = 12$ AUD + ADHD, $N = 19$ ADHD only); 6% and 50% and 68% female | — ($M = 44$ and $M = 39$ and $M = 30$) | Non-interventional, cross-sectional | — | — | Comparison of diagnostic utility between self-report scale and a continuous performance test | — |
| Miller et al. | Cohort | Gambling, GD | Outpatient treatment center | Europe, Sweden | $N = 204$; 26.4% female | — ($M = 36.1$) | Non-interventional, cross-sectional, cohort | — | CBT | Demographics, GD severity, prevalence of other psychiatric diagnoses, additional addictive behaviors, quality of life, gambling-related cognitive distortions | — |

*Recalculated for this table when only group sample sizes were presented in the respective paper.

**Including persons with AUD diagnosis but no necessity for detoxification.

—, not reported or not applicable.

AUD, alcohol use disorder; CBT, cognitive-behavioral therapy; cTBS, continuous theta-burst stimulation, a patterned form of rTMS; DLPFC, dorsolateral prefrontal cortex; EEG, electroencephalography; fNIRS, functional near-infrared spectroscopy; GD, gambling disorder; HUD, heroin use disorder; iTBS, intermittent theta-burst stimulation, a patterned form of rTMS; MUD, methamphetamine use disorder; MRI, magnetic resonance imaging; NIAAA, National Institute on Alcohol Abuse and Alcoholism in the USA; ND, nicotine dependence; tDCS, Transcranial direct-current stimulation; rIFG, right inferior frontal gyrus; rTMS, repetitive transcranial magnet stimulation.





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behaviors in a Pavlovian-to-instrumental transfer (PIT) task. The meditation reduced the PIT effect in individuals with alcohol use disorder (AUD), but not in the control group. This pilot study paves the way for future research to further assess the effectiveness of mindfulness-based interventions and to better understand their cognitive mechanisms.

Another promising approach for the development of personalized treatments and recovery is to address problems in early abstinence and their underlying mechanisms. van Oort et al. studied brain network connectivity to find such mechanisms, which may ultimately help individuals to better maintain abstinence. In a related study, Gullett et al. investigated participants (heavy alcohol use; with or without HIV) who attempted abstinence for 30 days via contingency management. Lower baseline connectivity in the salience network, which is linked to susceptibility to environmental cues, predicted reduction in drinking. Although this finding highlights a promising target for intervention, individuals living with HIV, who tend to have lower baseline connectivity in the salience network, may not benefit as much from contingency management as those without HIV.

## Studies on brain-centered interventions

Three studies evaluated non-invasive brain stimulation for treatment, highlighting it as a promising tool owing to its safety, precision, and importantly, potential for combination with other treatments. Hu et al. demonstrated the effectiveness of reducing relapse rates by combining repetitive transcranial magnetic stimulation (rTMS) and cognitive behavioral therapy in a clinical trial with 263 participants diagnosed with alcohol dependence. Building on the concept of rTMS, theta burst stimulation (TBS)—including continuous TBS (cTBS) and intermittent TBS (iTBS)—represents another innovative approach while being safe and efficacious (8). Upton et al. demonstrated the benefits of cTBS on the right inferior frontal gyrus in reducing cravings for smoking and increasing resting-state fronto-striatal functional connectivity over 24 h in individuals with nicotine dependence. Dong et al. investigated patients with polydrug (heroin and methamphetamine) use disorder and revealed the superior effect of iTBS compared to rTMS and sham iTBS in improving cognitive functions, thus highlighting its clinical value.

In their review, Chen Y.-H. et al. propose an intelligent closed-loop TMS neuromodulation system that is informed and repeatedly adapted via measurements from multimodal electroencephalogram–functional near-infrared spectroscopy (EEG-fNIRS) in order to treat methamphetamine addiction and methamphetamine-related craving. This innovative approach has the potential to improve clinical outcomes by providing real-time monitoring and intervention for patients seeking to achieve abstinence from drug use.

All these findings collectively underscore the promise and potential of non-invasive brain stimulation techniques, such as rTMS and TBS, in offering new and effective treatment modalities for various forms of addiction.

## Studies on relapse prediction using brain parameters

While non-invasive brain stimulation has shown promising results, it is important to comprehend the mechanisms that cause some individuals to maintain abstinence while others relapse post-treatment. Two studies aimed to identify (bio)markers predictive of future relapses in individuals with AUD. Sasaki et al. measured fNIRS during cognitive tasks and identified reduced brain responses in right frontotemporal areas to emotional stimuli, along with risk-seeking behavior, as markers for relapse within 6 months. In a 7-year follow-up study, Martelli et al. identified a larger caudate volume as a biomarker for relapse. These studies highlight the potential for identifying specific biomarkers that can predict relapse, thus providing a valuable direction for future research and more individualized interventions.

## Studies on comorbidities with a possible shared brain mechanism

Complementing the two studies that identified specific biomarkers predictive of relapse, Shen et al. provided further insight into the genetic factors that may influence withdrawal symptoms in individuals with AUD. The identification of the oxytocin receptor rs2254298 polymorphism as a significant modulator of mood disorders during alcohol withdrawal adds to our understanding of the genetic basis of addiction and withdrawal. This finding highlights the importance of personalized treatments that consider both genetic and environmental factors.

Given AUD often co-occurs with other mental disorders (9), Luderer et al. investigated the relationship between attention-deficit/hyperactivity disorder (ADHD) and AUD across many dimensions. Hyperactivity emerged as a significant symptom in individuals with both ADHD and AUD, indicating a treatment target for individuals with both conditions.

Lastly, Miller et al. addressed gender differences in gambling disorder, which is particularly relevant given its escalating prevalence and the notable overrepresentation of affected men (10). The study underscored the distinct motivations, patterns, and consequences of gambling behavior between men and women, thereby paving the way for more targeted and effective interventions. This may, in the future, include non-invasive rTMS given that neurobiological links have been found between gambling disorder and several of the substance-related use disorders (11) for which rTMS has been shown to be promising by authors in this Research Topic (Chen Y.-H. et al.; Dong et al.; Hu et al.; Upton et al.).

## Conclusion

The studies presented in this Research Topic provide exciting insights into the current developments in neurobiologically informed addiction treatment, from traditional to innovative

techniques. Several of the presented findings highlight the potential for new and effective treatment modalities that consider the neurobiological mechanisms underlying addiction, as well as the need for personalized interventions informed by both genetic and environmental factors. As we continue to explore the complexities of addiction, it is our hope that these insights will help develop more effective and targeted treatments, ultimately improving outcomes for individuals struggling with substance use disorders and behavioral addictions.

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# Repetitive transcranial magnetic stimulation combined with cognitive behavioral therapy treatment in alcohol-dependent patients: A randomized, double-blind sham-controlled multicenter clinical trial

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**Background:** Alcohol dependence (AD) is a complex addictive disorder with a high relapse rate. Previous studies have shown that both repetitive transcranial magnetic stimulation (rTMS) and cognitive behavioral therapy (CBT) may be effective for AD, and we aim to explore more effective treatment options to reduce relapse rates for AD.

**Materials and methods:** A total of 263 AD patients were recruited. They were divided into six groups according to the location and the type of rTMS: left dorsolateral prefrontal cortex (DLPFC), right DLPFC, sham stimulation, and whether they received CBT treatment: with a fixed schedule (C1) and without a fixed plan (C0). There were included in sham rTMS + C0 group ($n$ = 50), sham rTMS + C1 group ($n$ = 37), right rTMS + C0 group ($n$ = 45), right rTMS + C1 group ($n$ = 42), left rTMS + C0 group ($n$ = 49), left rTMS + C1 group ($n$ = 40). We used obsessive compulsive drinking scale (OCDS), visual analogue scale (VAS), alcohol dependence scale (ADS), montreal cognitive assessment (MoCA), generalized anxiety disorder-7 (GAD-7), patient health

questionnaire-9 items (PHQ-9), and Pittsburgh sleep quality index (PSQI) to assess alcohol cravings, alcohol dependence, cognition, anxiety, depression, and sleep quality. They were followed up and evaluated for relapse.

**Results:** The sham rTMS + C0 group relapse rate was significantly higher than the right rTMS + C1 group ($P$ = 0.006), the left rTMS + C0 group ($P$ = 0.031), the left rTMS + C1 group ($P$ = 0.043). The right rTMS + C0 group showed significantly higher relapse rate compared to the right rTMS + C1 group ($P$ = 0.046). There was no significant difference in relapse rates between other groups. The repeated-measures ANOVA showed an interaction effect between group and time was significant in the rate of patient health questionnaire-9 items (PHQ-9) scale reduction ($P$ = 0.020). Logistic analysis indicated that smoking and alcohol consumption were independent determinants of relapse ($P < 0.05$). At 24 weeks of follow-up, Kaplan–Meier survival analysis reveal that there is statistically significant relapse rate between six groups ($P$ = 0.025), left rTMS + C1 group has the best treatment effect for alcohol dependent patients. Cox regression analysis confirmed that current smoking, total cholesterol, and total bilirubin (TBIL) level were risk factors of relapse ($P < 0.05$).

**Conclusion:** This study is the first to suggest that the combination of rTMS and CBT may be a potentially effective treatment for reducing relapse.

KEYWORDS

**alcohol dependence, repetitive transcranial magnetic stimulation, cognitive behavioral therapy, relapse, combination therapy**

## Introduction

It is currently widely recognized that alcoholism is a complex, multi-dimensional, and multifactorial disease. Notably, 9–17% of drinkers meet the diagnostic criteria for alcohol dependence (AD) (1). AD is a complex addictive disease. In general, addiction formation is closely related to biological factors, and the occurrence and development of addictive behaviors are related to psychological and social factors, such as parenting style (2), family relationships (3), and childhood sexual abuse (4). Because of long-term heavy drinking, the body gradually develops physical and psychological dependence on alcohol, damaging physical, mental, and social functions. AD in all countries in the world is a severe public health problem. With the development of the social economy, and the continuous improvement of people's living standards, alcohol dependence prevalence is gradually rising. In 2018, the World Health Organization's global status report on alcohol and health revealed approximately 283 million AD (accounting for 5.1% of the world's 15 years old and older adults). The prevalence rates vary considerably between countries and are significantly influenced by drinking culture and social norms. Europe has the highest prevalence (8.8% of the adult population), followed by the United States (8.2% of the adult population), while the prevalence of alcohol dependence in China is 2.3% (5). AD is among the highest risk factors for shortening the life cycle and leads to more than 200 health conditions, with a high disease burden, high disability rate, and high mortality (6).

Early long-term AD treatment mainly included drug and behavioral therapy (7). However, these treatments are only moderately helpful, and more than 50% of treated patients relapse within 1 year (8). Even though research over the past 50 years has demonstrated that addiction is a brain disease, we still have no effective treatments based on neural circuits and specific neural targets that directly and specifically target AD. For the first time, a non-invasive neuroendocrine technique called transcranial magnetic stimulation (TMS) appears to be the primary physical therapy approach to fill this gap in developing AD treatment. Dr. Anthony Barker invented TMS technology in Sheffield, UK, in 1984 (9). TMS is based on electromagnetic induction, a brief focused electromagnetic pulse

Abbreviations: AD, alcohol dependence; rTMS, repetitive transcranial magnetic stimulation; CBT, cognitive behavioral therapy; DLPFC, dorsolateral prefrontal cortex; ADS, alcohol dependence scale; OCDS, obsessive compulsive drinking scale; VAS, visual analogue scale; MoCA, montreal cognitive assessment; PSQI, Pittsburgh sleep quality index; GAD-7, generalized anxiety disorder-7; PHQ-9, patient health questionnaire-9.

penetrating the skull without attenuation and stimulating the targeted brain region. Typically, the magnetic field is high enough to induce depolarization of neurons in the cortex region where the coils are located. This technique is called repetitive TMS (rTMS) when TMS pulses are transmitted continuously and repeatedly at a precise frequency. High-frequency repeat transcranial magnetic stimulation (HF-rTMS) (>5 Hz) promoted, while low frequency rTMS (<1 Hz) inhibited motor cortex excitability (10). rTMS can induce changes in brain function for a more extended period by modulating cortical excitability, neurotransmitters, and neuronal plasticity, reducing the desire for addictive substances, improving cognitive function, and ultimately reducing the relapse rate (11). It provides a new therapeutic advantage for alcohol dependence unmatched by pharmacotherapy.

Brodmann regions 9 and 46 are often known as the dorsolateral prefrontal cortex (DLPFC). DLPFC plays an essential role in decision making, reasoning, working memory, inhibition, and outcome prediction, plays a vital role in substance-related cravings, including alcohol, and has gained a recognized reputation as a successful treatment target for TMS in patients with depression (12). Previous studies have shown that rTMS, DLPFC was selected as the stimulation site to show promise for the reduction of craving and substance use in nicotine (13) and cocaine addiction (14), as well as in behavioral addictions (15), which are showing significant development potential. All these suggest that DLPFC may be an ideal target for TMS treatment of AD. However, the treatment duration, frequency of stimulation, and intensity of stimulation frequency of rTMS have not been determined. Also, it has not been clearly answered whether left, right, or bilateral stimulation is the most effective method (16–20).

Another critical aspect of TMS treatment for AD is combining it with existing behavioral therapies for AD. Ultimately, all treatments for AD need to emphasize changing behavior. Cognitive behavioral therapy (CBT) has become a front-line behavioral therapy for AD and other substance use disorders (SUDs) in recent years (21). Drawn up in the 1960s and 1970s in the United States, CBT is a time-limited, multistage intervention designed to address the cognitive, emotional, and environmental risks of drug use, identify and change unreasonable beliefs, and provide training in behavioral self-control skills. By overcoming the desire to seek out and consume alcohol and by dealing with situations that might trigger these desires, to improve patients' psychological defense ability and build psychological defense mechanisms to help individuals achieve and maintain abstinence or reduce drinking cravings (22). A meta-analysis found that Internet-based alcohol interventions guided by health professionals were more effective than unguided (fully automated) interventions (23). However, therapist-guided interventions were not more effective than self-help interventions in the two most recent studies on internet-based cognitive behavioral therapy for alcohol (24, 25). Therefore, the trial hypothesizes that a therapist-guided, fixed-plan model CBT would be more effective in reducing relapse rates than simply providing a standardized basic interview of about 10 min without any therapeutic intervention.

A large part of the disease burden is due to the ongoing effects of alcohol on the central nervous system (26). As a central nervous system depressant, alcohol can, directly and indirectly, act on the central nervous system, leading to cognitive dysfunction (27). Cognitive impairment has increasingly become the focus of AD research. Depending on studies, 50–80% of AD patients have cognitive impairment (28). In addition, people with AD often experience an intense, uncontrollable desire for alcohol, also known as craving (29). Combining perceived desires with reduced cognitive control can lead to problems managing cravings, leading to relapse (30). AD is often associated with various psychiatric and social behavioral comorbidities, including severe sleep disorders, anxiety, and depression (31, 32).

Therefore, the biggest problem plaguing AD is its extraordinary relapse rate. There are limited treatment methods for AD relapse, and a high relapse rate will hinder the treatment effect. Depending on statistics, although the early treatment is beneficial, up to 85% of AD patients still drink again (33), significantly the highest within 6–12 months after treatment (34). This suggests a critical need to understand factors associated with relapse. The evidence is inconsistent regarding the potential impact of smoking on recovery from alcohol dependence. Although some studies have found that smoking negatively affects the treatment outcome of alcohol dependent patients (35), however, there is also evidence that smoking does not pose a risk to sobriety in AD (36). Variables associated with nicotine dependence may be predictors of future alcohol dependence (37). Alcohol biomarkers have become valuable tools for objectively assessing treatment outcomes (38). Routine blood tests may help predict the long-term development of alcohol withdrawal treatment and may become a more feasible and cost-effective method for assessing relapse risk (39). This study explored the relationship between pre-treatment predictors (demographics and laboratory tests), post-treatment predictors (rTMS and CBT), and relapse. We hypothesized that treatment-related variables would be best helpful in predicting the prognosis of alcohol dependent patients receiving treatment. Even though AD profoundly impacts individuals' work, social life, and interpersonal relationships (40), the treatment rate of AD is extremely low, and the establishment of effective treatment is essential.

Although rTMS and CBT have positive effects on all dimensions of AD, there is currently more heterogeneity in the outcomes of rTMS and CBT for AD compared with pharmacological AD treatment. There are no studies on whether there is an advantage of combined treatment with CBT and rTMS. Therefore, we conducted a randomized, double-blind sham-controlled multicenter clinical trial in which sham rTMS,

left DLPFC rTMS, right DLPFC rTMS, and combined with CBT were utilized to treat AD patients. The ADS, VAS, OCDS, PHQ-9, GAD-7, PSQI, and MoCA scales were regularly used to evaluate the patients' alcohol dependence, drinking desire, cognitive function anxiety, depression, and sleep. And during the follow-up period, whether the patients relapsed were recorded by a self-assessment diary of alcohol consumption. The primary objectives of this study: assess the effectiveness of rTMS in combination with CBT for AD in reducing relapse and investigate the risk factors of relapse. The secondary objectives of this study: whether different treatment modalities improve anxiety, depression, cognitive function, and craving and indirectly reduce the rate of relapse to drinking, and provide new directions for AD treatment.

# Materials and methods

## Participants

We selected patients with AD who were outpatients and inpatients at the First Affiliated Hospital of Harbin Medical University, Sun Yat-sen Memorial Hospital, the First Affiliated Hospital of Zhengzhou University, Mudanjiang Medical University, Beijing Anding Hospital Affiliated to Capital Medical University, Shenzhen Kangning Hospital, Hunan Provincial Brain Hospital, the Second Affiliated Hospital of Kunming Medical University from March 2019 to September 2021 as the study population. The Ethics Committee endorsed the study, and all participants obtained informed consent from themselves and signed informed consent. **Supplementary Figure 1** shows the CONSORT diagram of the flow of participants through the trial.

Inclusion criteria: (1) 18–65 years old; (2) Meet the diagnostic criteria of DSM-IV alcohol dependence; (3) No history of neurological diseases or family history of mental disorders.

Exclusion criteria: (1) Clinical Institute Alcohol Withdrawal Syndrome Scale (CIWA-Ar) > 9 points in acute alcohol withdrawal reaction stage; (2) Severe neurological or mental diseases caused by other diseases other than chronic alcohol dependence, such as stroke, intracranial infection, brain tumors, schizophrenia, etc.; (3) Have experienced a traumatic brain injury or other brain tissue damage; (4) Is taking or has taken any other psychotropic drugs or is dependent on other drugs or other substances; (5) Contraindications of rTMS therapy: a. Acute infectious diseases; b. Presence of metallic foreign bodies in the skull; c. After craniotomy; d. Intracranial aneurysm or other vascular malformation; e. Epilepsy history; f. Severe cardiovascular disease, especially those with pacemakers or cardiac stents.

Experimental termination criteria: (1) Severe adverse reactions occurred during the study; (2) Subjects did not cooperate with treatment and had poor compliance.

# Research methods

## General clinical data

We collected general clinical data: self-designed case report form, general physical examination, basic vital signs, hematology routine, and blood biochemistry test results. And during the follow-up period, whether the patients relapsed were recorded by a self-assessment diary of alcohol consumption. Based on the self-assessment diary of alcohol consumption, combined with regular telephone follow-up with family members at week 0, week 2, week 8, week 12, and week 24, and outpatient follow-up, to ensure the authenticity of the self-assessment diary of alcohol consumption.

(1) Self-designed case report form, including gender, age, drinking years, alcohol consumption, drinking type, frequency of alcohol consumption, and current smoking.
(2) General physical examination and basic vital signs, including body mass index, heart rate, systolic blood pressure, and diastolic blood pressure.
(3) Hematology routine including white blood cell, red-blood-cell, Platelets, and hemoglobin.
(4) Blood biochemistry, including fasting glucose, uric acid, serum creatinine, alanine transaminase, aspartate aminotransferase, gamma-glutamyl transpeptidase, total bilirubin, direct bilirubin, indirect bilirubin, Total cholesterol, Triglycerides, low-density lipoprotein, high-density lipoprotein.

## Treatment plan

(1) Repetitive transcranial magnetic stimulation procedure:

Treatment device: Use of "8" coil transcranial magnetic stimulation instrument (using the YiRuiDe® CCY-1 classic magnetic stimulator device; YiRuiDe Group, Wuhan, China).

Treatment duration: Starting at baseline, stimulated on five consecutive days (W1), suspended on weekends, treatment continued for five consecutive working days in the second week (W2), total of 10 sessions.

Treatment: The individual motor threshold (MT) for the right/left abductor pollicis brevis muscle was determined using single-pulse TMS in combination with motor-evoked potentials (MEP). The MT was considered the lowest intensity to induce a visual MEP on electromyography (EMG). A stimulation intensity of 110% of the subject's resting MT was used for the study. a. Left DLPFC rTMS: the Left dorsolateral prefrontal cortex was selected as the stimulation site, and the location was determined by the international 10–20 electroencephalography system (the location of the left DLPFC corresponds to the F3). Treatment parameters were set (stimulation intensity: 110% threshold, stimulation frequency: high-frequency 10 Hz, train duration: 5 s, intertrain interval: 20 s, total trains per session: 30 trains, total 10 sessions). b. Right DLPFC rTMS: the Right dorsolateral prefrontal cortex was selected as the

stimulation site. The international 10–20 electroencephalogram system was used for localization (the location of the right DLPFC corresponds to the F4). The treatment parameters were the same as the left rTMS group. c. Sham rTMS: The spiral edge was placed at the stimulation site, and the stimulation intensity was set to 0 or 1%. The other treatment parameters were fixed as above. All subjects were unaware of the type of stimulation they received; they wore earplugs. The study was conducted in conformity with the current safety guidelines (41).

(2) Cognitive behavioral therapy procedure:

Treatment duration: Starting at baseline, once a week for 8 weeks (W1–W8), for a total of eight sessions per subject.

Treatment: Cognitive behavioral therapy with a fixed plan is 60 min per session, and each session is divided into three phases preparation, work, and summary, each phase being 20 min. According to the abstinence treatment research paradigm (pre-action stage, planning stage, preparation stage, action stage, maintenance/consolidation stage, and termination/relapse stage), this study designed eight individual cognitive-behavioral therapy sessions with different themes. The eight themes were: a. Individual motivational feedback; b. Identification and handling of predisposing factors; c. Transformation of negative cognition; d. Negative emotion control and management; e. Enrichment of drink-refusal skills; f. Improvement of interpersonal relationships; g. Establishment of a recovery support system; h. Reduction of relapse risk. The CBT group, without a fixed plan, provided only about 10 min of a standardized basic interview without any therapeutic intervention. The CBT treatment protocol was designed with reference to the studies of Johansson M (42) and Magill M (43), with appropriate adaptations. One of the treatment regimens was randomly assigned to CBT with a fixed plan (C1); CBT without a fixed plan (C0).

(3) Treatment as usual:

All subjects received routine drug therapy with the same treatment period, and dose, including the use of mecobalamin and vitamin B to nourish nerves, antioxidant damage with vitamin C and vitamin E. Temporary short-term low-dose Benzodiazepines were given to patients when necessary.

## Research group

(1) Randomization and double-blind method: a clinical research assistant who is not involved in other clinical treatment, scale, and outcome evaluation will automatically randomize subjects by the computer algorithm. Neither the subject nor the clinical investigator knew which treatment group the subject was assigned. TMS investigators, and CBT study personnel, are unaware of changes in subject outcomes.

(2) This study was divided into six groups:

a. TAU + sham rTMS + CBT without a fixed plan (sham rTMS + C0 group).
b. TAU + sham rTMS + CBT with a fixed plan (sham rTMS + C1 group).
c. TAU + right DLPFC rTMS + CBT without a fixed plan (right rTMS + C0 group).
d. TAU + right DLPFC rTMS + CBT with a fixed plan (right rTMS + C1 group).
e. TAU + left DLPFC rTMS + CBT without a fixed plan (left rTMS + C0 group).
f. TAU + left DLPFC rTMS + CBT with a fixed plan (left rTMS + C1 group).

## Scale evaluation

The CIWA-Ar (44) assessment was performed at enrollment to exclude patients in the acute alcohol withdrawal phase. The obsessive-compulsive drinking scale (OCDS) (45) and visual analogue scale (VAS) (46) were administered to measure the severity of alcohol cravings. The alcohol dependence scale (ADS) (47) was used to assess the severity of alcohol dependence. Montreal Cognitive Assessment (MoCA) (48) was used to measure the overall cognitive level of the patients. Pittsburgh Sleep Quality Index (PSQI) (49) was utilized to evaluate the Sleep Quality of patients. Generalized anxiety disorder-7 (GAD-7) (50) was used to assess the severity of anxiety symptoms. Patient Health Questionnaire-9 items (PHQ-9) (51) assess the patient's depressive symptoms. The above scales of OCDS, VAS, PSQI, GAD-7, PHQ-9 were evaluated at week 0, week 2, week 8, week 12, and week 24. MoCA was evaluated at week 0, week 8, week 12, and week 24. ADS was evaluated at week 0, week 12, and week 24.

## Statistical analysis

The Kolmogorov–Smirnov test was used to test normal distribution. Continuous variables were expressed as the mean ± standard deviation. One-way analysis of variance (ANOVA) model was used to analyze the differences in the treatment effects of different treatment regimens on relapse in AD patients. Categorical variables were analyzed using the chi-squared test or Fisher's exact test. Repeated measures ANOVA was used to explore the interaction of different treatment modalities with changes in the rate of scale score reduction over treatment time, using baseline period, 2 weeks, 2 months, 3 months, and 6 months of treatment scores as relevant measures. And further simple effect analysis was performed for a significant interaction effect between group and time. Binary logistic regression analysis was performed to identify independent variables influencing relapse. Relapse rate of six groups were compared using Kaplan–Meier survival analysis. Risk factors for the relapse rate were assessed using Cox regression model analysis. Statistical analyses were performed in SPSS-23 (IBM). Insert additional missing values using the maximum expected value method. Differences

TABLE 1 Comparison of basic clinical information and laboratory test levels of patients recruited for the study.

| | Sham rTMS + C0 | Sham rTMS + C1 | Right rTMS + C0 | Right rTMS + C1 | Left rTMS + C0 | Left rTMS + C1 | *P* |
|---|---|---|---|---|---|---|---|
| **Demographics** | | | | | | | |
| Age, years | 48 ± 10 | 46 ± 10 | 47 ± 12 | 44 ± 10 | 45 ± 11 | 48 ± 11 | 0.409 |
| Male, n% | 34 (87.2) | 28 (96.6) | 29 (85.3) | 32 (97) | 36 (94.7) | 28 (84.8) | 0.253 |
| Drinking duration (year) | 22 ± 10 | 23 ± 11 | 23 ± 11 | 21 ± 10 | 20 ± 11 | 24 ± 12 | 0.627 |
| Frequency of drinking (day/week) | 5.5 ± 2.1 | 5.2 ± 2.2 | 5.8 ± 1.8 | 5.6 ± 2.0 | 5.8 ± 1.8 | 5.9 ± 1.7 | 0.647 |
| Alcohol consumption, ml | 930 ± 1028 | 756 ± 1164 | 1141 ± 1327 | 983 ± 1380 | 894 ± 964 | 849 ± 873 | 0.735 |
| Current smoking | 39 (78) | 27 (73) | 26 (57.8) | 29 (69) | 28 (57.1) | 23 (57.5) | 0.130 |
| BMI, kg/m$^2$ | 23.12 ± 3.37 | 23.23 ± 3.37 | 22.80 ± 3.74 | 23.54 ± 3.62 | 22.52 ± 4.79 | 22.20 ± 3.59 | 0.625 |
| Heart rate, bpm | 87.77 ± 14.69 | 87.89 ± 12.55 | 90.44 ± 12.61 | 86.96 ± 16.13 | 90.38 ± 17.30 | 84.67 ± 15.72 | 0.471 |
| Systolic blood pressure, mmHg | 128.46 ± 13.33 | 133.78 ± 21.50 | 131.54 ± 14.05 | 130.82 ± 16.14 | 133.64 ± 18.43 | 130.10 ± 17.52 | 0.636 |
| Diastolic blood pressure, mmHg | 83.98 ± 10.60 | 85.32 ± 12.28 | 84.27 ± 9.46 | 84.01 ± 12.46 | 86.75 ± 11.22 | 85.22 ± 9.45 | 0.811 |
| **Laboratory tests** | | | | | | | |
| WBC, $\times 10^9$/L | 7.05 ± 1.956 | 7.18 ± 2.776 | 6.60 ± 1.882 | 6.27 ± 1.879 | 6.93 ± 1.779 | 6.54 ± 1.660 | 0.272 |
| RBC, $\times 10^{12}$/L | 4.57 ± 0.84 | 4.63 ± 0.676 | 4.30 ± 0.543 | 4.47 ± 0.557 | 4.35 ± 0.610 | 4.31 ± 0.465 | 0.068 |
| Platelets, $\times 10^9$/L | 229.41 ± 58.785 | 227.52 ± 70.213 | 230.57 ± 72.348 | 192.70 ± 66.912 | 230.82 ± 79.573 | 221.07 ± 96.455 | 0.137 |
| HGB, g/L | 141.97 ± 25.480 | 144.10 ± 21.102 | 139.87 ± 16.004 | 141.33 ± 15.767 | 141.32 ± 17.014 | 140.35 ± 18.670 | 0.949 |
| Fasting glucose, mmol/L | 4.42 ± 9.539 | 12.29 ± 50.617 | 5.06 ± 7.823 | 5.99 ± 6.323 | 5.86 ± 10.818 | 7.73 ± 16.886 | 0.614 |
| UA, μmol/L | 439.97 ± 760.166 | 312.80 ± 269.687 | 373.30 ± 168.878 | 315.02 ± 175.239 | 363.24 ± 212.268 | 317.07 ± 177.631 | 0.556 |
| Serum creatinine, μmol/L | 65.32 ± 12.976 | 64.93 ± 12.900 | 66 ± 16.081 | 66.81 ± 13.458 | 71.92 ± 14.460 | 68.41 ± 13.625 | 0.155 |
| ALT, U/L | 30.74 ± 27.301 | 27.21 ± 16.937 | 40.87 ± 39.751 | 43.36 ± 61.099 | 45 ± 41.402 | 40.99 ± 37.858 | 0.217 |
| AST, U/L | 40.12 ± 44.113 | 35.39 ± 38.326 | 49.43 ± 57.091 | 50.99 ± 57.294 | 53.98 ± 61.308 | 49.94 ± 48.022 | 0.541 |
| GGT, U/L | 166.08 ± 274.690 | 90.66 ± 125.281 | 133.48 ± 201.295 | 146.97 ± 214.172 | 131.05 ± 284.344 | 103.28 ± 128.302 | 0.643 |
| TBIL, μmol/L | 17.83 ± 10.153 | 14.65 ± 6.789 | 16.46 ± 18.047 | 19.27 ± 16.250 | 15.25 ± 11.226 | 13.00 ± 10.756 | 0.264 |
| DBIL, μmol/L | 5.40 ± 3.675 | 5.67 ± 5.003 | 4.96 ± 4.721 | 6.64 ± 6.858 | 4.62 ± 3.939 | 4.91 ± 3.853 | 0.411 |
| IBIL, μmol/L | 12.35 ± 7.725 | 9.58 ± 5.25 | 11.45 ± 15.212 | 11.62 ± 9.116 | 10.55 ± 8.830 | 8.72 ± 6.648 | 0.488 |
| Total cholesterol, mmol/L | 15.90 ± 65.423 | 8.81 ± 12.813 | 3.50 ± 14.260 | 5.73 ± 12.382 | 4.72 ± 9.807 | 6.28 ± 12.745 | 0.397 |
| Triglycerides, mmol/L | 1.91 ± 1.160 | 1.90 ± 1.391 | 1.87 ± 1.717 | 1.64 ± 1.049 | 1.81 ± 1.153 | 1.70 ± 0.859 | 0.896 |
| LDL, mmol/L | 2.61 ± 0.874 | 2.82 ± 0.888 | 2.77 ± 0.957 | 2.51 ± 0.820 | 2.56 ± 1.111 | 2.55 ± 0.869 | 0.566 |
| HDL, mmol/L | 1.42 ± 0.616 | 1.21 ± 0.630 | 1.41 ± 0.577 | 1.37 ± 0.458 | 1.41 ± 0.624 | 1.33 ± 0.471 | 0.562 |
| **Scale evaluation** | | | | | | | |
| MoCA | 17.442 ± 9.028 | 19.679 ± 8.319 | 18.730 ± 8.251 | 19.019 ± 9.055 | 20.015 ± 8.981 | 19.610 ± 9.428 | 0.756 |
| ADS | 14.781 ± 9.189 | 15.742 ± 9.680 | 17.515 ± 9.120 | 14.246 ± 9.676 | 14.863 ± 9.659 | 14.748 ± 10.542 | 0.648 |
| CIWA-Ar | 9.407 ± 6.889 | 10.108 ± 10.452 | 9.056 ± 7.654 | 8.926 ± 8.640 | 10.494 ± 8.240 | 6.566 ± 6.547 | 0.306 |
| GAD-7 | 5.14 ± 4.540 | 4.744 ± 4.487 | 4.240 ± 3.717 | 5.463 ± 5.611 | 5.736 ± 4.290 | 5.517 ± 4.557 | 0.645 |
| PHQ-9 | 7.049 ± 6.054 | 7.796 ± 6.129 | 6.577 ± 5.830 | 7.512 ± 7.694 | 7.664 ± 6.149 | 6.253 ± 5.763 | 0.841 |
| PSQI | 9.18 ± 7.870 | 10.379 ± 8.773 | 9.609 ± 7.708 | 8.997 ± 9.662 | 10.743 ± 11.005 | 9.431 ± 9.229 | 0.935 |
| VAS | 4.103 ± 3.429 | 4.732 ± 3.550 | 3.939 ± 3.483 | 3.887 ± 3.245 | 3.839 ± 3.513 | 4.178 ± 3.144 | 0.869 |
| OCDS | 18.470 ± 10.546 | 17.731 ± 9.535 | 18.924 ± 8.685 | 17.454 ± 11.290 | 18.880 ± 9.018 | 18.923 ± 11.084 | 0.971 |

C1, cognitive behavioral therapy with a fixed schedule; C0, cognitive behavioral therapy without a fixed plan; BMI, body mass index; WBC, white blood cell; RBC, red-blood-cell; HGB, hemoglobin; UA, uric acid; ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; TBIL, total bilirubin; DBIL, direct bilirubin; IBIL, indirect bilirubin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MoCA, Montreal Cognitive Assessment Scale; ADS, Alcohol dependence scale; CIWA-Ar, Clinical Institute Alcohol Withdrawal Syndrome Scale; GAD-7, Generalized anxiety disorder-7; PHQ-9, Patient Health Questionnaire-9 items; VAS, Visual Analogue Scale; OCDS, Obsessive Compulsive Drinking Scale; PSQI, Pittsburgh Sleep Quality Index.

between the groups were considered statistically significant at $P < 0.05$.

# Results

## Clinical characteristics

A total of 297 subjects were included in this study, of which 34 were excluded according to the experimental termination criteria, and 263 subjects were finally included in the analysis. There were included in sham rTMS + C0 group ($n$ = 50), sham rTMS + C1 group ($n$ = 37), right rTMS + C0 group ($n$ = 45), right rTMS + C1 group ($n$ = 42), left rTMS + C0 group ($n$ = 49), left rTMS + C1 group ($n$ = 40). Table 1 shows the comparison of the baseline data between the six groups. Regarding demographic characteristics, laboratory tests scale, and assessment at baseline, there was no statistically significant difference.

## One-way ANOVA models for relapse rate between the six groups

The sham rTMS + C0 group relapse rate was significantly higher than the right rTMS + C1 group ($P$ = 0.006), the left rTMS + C0 group ($P$ = 0.031), the left rTMS + C1 group ($P$ = 0.043); the right rTMS + C0 group relapse rate was significantly higher than the right rTMS + C1 group ($P$ = 0.046) (Table 2). There was no significant difference in relapse rates between other groups.

## Repeated measures ANOVA for the scale score reduction rate in the six groups of patients after 2 weeks, 2 months, 3 months, and 6 months of follow-up

For the reduction rates of GAD, MoCA, OCDS, and PSQI scores among the six groups of alcohol dependent patients, repeated measures ANOVA showed no main effect on the group but a significant main effect of time (Table 3). Also, there was a significant interaction effect between group and time in the rate of PHQ-9 scale score reduction rate ($F$ = 3.001, $P$ = 0.020), and both the main effect of group and the main effect of time were significant ($F$ = 2.492, $P$ = 0.032; $F$ = 2.918, $P$ = 0.037). Further simple effect analysis revealed that, at week 2 of follow-up, the right rTMS + C0 group had a significantly higher PHQ-9 scale score reduction rate than the sham rTMS + C1 group ($P$ = 0.039); at week 2 of follow-up, the left rTMS + C0 group had a significantly higher PHQ-9 scale score reduction rate than the right rTMS + C0 group ($P$ = 0.011); the right rTMS + C0 group had a significantly higher PHQ-9 scale score reduction rate at week 12 of follow-up than week 2 of follow-up ($P$ = 0.046).

TABLE 2 One-way ANOVA models for relapse rate between the six groups.

| Groups | Mean ± SD | Groups | Mean ± SD | *P*-value |
|---|---|---|---|---|
| Sham rTMS + C0 | 0.450 ± 0.5038 | Right rTMS + C1 | 0.143 ± 0.3563 | 0.006 |
| | | Left rTMS + C0 | 0.219 ± 0.4200 | 0.031 |
| | | Left rTMS + C1 | 0.222 ± 0.4237 | 0.043 |
| Right rTMS + C0 | 0.371 ± 0.4902 | Right rTMS + C1 | 0.143 ± 0.3563 | 0.046 |

C1, cognitive behavioral therapy with a fixed schedule; C0, cognitive behavioral therapy without a fixed plan.

## Correlation and Binary logistic regression models for relapse

Relapse was positively correlated with alcohol consumption ($r$ = 0.186, $P$ = 0.011), white blood cell ($r$ = 0.182, $P$ = 0.013), hemoglobin ($r$ = 0.176, $P$ = 0.017), current smoking ($r$ = 0.170, $P$ = 0.021), CBT ($r$ = −0.169, $P$ = 0.022). Binary logistic analysis indicated that current smoking ($P$ = 0.038) and alcohol consumption ($P$ = 0.009) was independent determinant of relapse (Table 4).

## Total cholesterol, total bilirubin level, and current smoking were risk factors for relapse

At 24 weeks of follow-up, Kaplan−Meier survival analysis reveals a statistically significant relapse rate between six groups ($P$ = 0.025), left rTMS + C1 group has the best treatment effect for alcohol dependent patients (Supplementary Figure 2). Cox regression analysis showed that current smoking (β = 0.835, hazard ratio = 2.306, $P$ = 0.045), total cholesterol (β = 0.006, hazard ratio = 1.006, $P$ = 0.034), and TBIL (β = 0.025, hazard ratio = 1.025, $P$ = 0.026) level were risk factors of relapse (Table 5).

# Discussion

Most importantly, let's talk about the combination of rTMS and CBT. The effectiveness of CBT for AD has been demonstrated in an extensive review of psychosocial therapies (52, 53). The number of days of heavy drinking dropped significantly after CBT, according to new research (54). The combination of rTMS and CBT has been shown to be more effective than treatment strategies alone in patients with major depression (55), and a shorter course of treatment can achieve

TABLE 3 Repeated measures ANOVA for the rate of scale score reduction in the six groups of patients after 2 weeks, 2 months, 3 months, and 6 months of follow-up.

| Scales | Groups | 2 weeks | 2 months | 3 months | 6 months | Group main effect | Time main effect | Time × Group interaction effect |
|---|---|---|---|---|---|---|---|---|
| ADS | Sham rTMS + C0 | | | 0.192 ± 0.530 | 0.321 ± 0.991 | $F = 0.857$, $P = 0.511$ | $F = 0.339$, $P = 0.799$ | $F = 1.276$, $P = 0.279$ |
| | Sham rTMS + C1 | | | 0.055 ± 1.096 | 0.045 ± 0.434 | | | |
| | Right rTMS + C0 | | | 0.030 ± 0.520 | 0.364 ± 0.780 | | | |
| | right rTMS + C1 | | | 0.083 ± 0.527 | −0.198 ± 1.873 | | | |
| | Left rTMS + C0 | | | 0.077 ± 0.354 | 0.153 ± 0.365 | | | |
| | Left rTMS + C1 | | | 0.139 ± 0.357 | 0.009 ± 0.511 | | | |
| GAD-7 | Sham rTMS + C0 | 0.129 ± 0.807 | 0.150 ± 0.366 | 0.034 ± 0.994 | 0.124 ± 0.416 | $F = 1.046$, $P = 0.391$ | $F = 3.954$, $P = 0.047$ | $F = 1.185$, $P = 0.377$ |
| | Sham rTMS + C1 | 0.057 ± 0.667 | 0.136 ± 0.475 | −0.008 ± 0.520 | 0.166 ± 0.490 | | | |
| | Right rTMS + C0 | 0.215 ± 1.440 | −0.048 ± 0.895 | 0.136 ± 0.556 | 0.042 ± 0.647 | | | |
| | Right rTMS + C1 | 0.028 ± 0.833 | −0.0783 ± 1.379 | 0.159 ± 0.436 | 0.005 ± 0.893 | | | |
| | Left rTMS + C0 | 0.048 ± 0.565 | 0.144 ± 0.683 | 0.047 ± 0.595 | 0.123 ± 0.591 | | | |
| | Left rTMS + C1 | 0.036 ± 0.919 | 0.016 ± 1.364 | 0.177 ± 0.384 | 0.110 ± 0.604 | | | |
| MoCA | Sham rTMS + C0 | | −1.693 ± 5.168 | 0.038 ± 0.439 | −0.115 ± 0.559 | $F = 0.906$, $P = 0.477$ | $F = 8.533$, $P = 0.001$ | $F = 1.477$, $P = 0.126$ |
| | Sham rTMS + C1 | | −0.810 ± 2.262 | −0.184 ± 0.994 | −0.032 ± 0.182 | | | |
| | Right rTMS + C0 | | −0.861 ± 2.696 | −0.023 ± 0.241 | −0.054 ± 0.345 | | | |
| | Right rTMS + C1 | | −0.079 ± 2.467 | −0.028 ± 0.174 | −0.013 ± 0.161 | | | |
| | Left rTMS + C0 | | −0.505 ± 2.042 | −0.020 ± 0.083 | −0.014 ± 0.130 | | | |
| | Left rTMS + C1 | | −0.889 ± 3.690 | −0.215 ± 1.006 | −0.050 ± 0.147 | | | |
| OCDS | Sham rTMS + C0 | 0.008 ± 0.608 | 0.117 ± 0.846 | −0.006 ± 0.780 | 0.118 ± 0.820 | $F = 0.345$, $P = 0.885$ | $F = 3.543$, $P = 0.005$ | $F = 1.199$, $P = 0.386$ |
| | Sham rTMS + C1 | 0.006 ± 0.865 | 0.255 ± 0.385 | 0.078 ± 0.448 | −0.087 ± 1.111 | | | |
| | Right rTMS + C0 | 0.080 ± 0.408 | 0.151 ± 0.425 | −0.010 ± 0.568 | −0.172 ± 0.822 | | | |
| | Right rTMS + C1 | 0.163 ± 0.394 | 0.187 ± 0.388 | 0.132 ± 0.490 | −0.085 ± 1.080 | | | |
| | Left rTMS + C0 | 0.159 ± 0.419 | 0.204 ± 0.436 | 0.138 ± 0.317 | −0.088 ± 0.737 | | | |
| | Left rTMS + C1 | 0.047 ± 0.634 | 0.184 ± 0.413 | −0.141 ± 1.986 | 0.037 ± 0.519 | | | |
| PHQ-9 | Sham rTMS + C0 | 0.008 ± 0.678 | 0.077 ± 0.698 | 0.226 ± 0.514 | 0.079 ± 0.504 | $F = 2.492$, $P = 0.032$ | $F = 2.918$, $P = 0.037$ | $F = 3.001$, $P = 0.020$ |
| | Sham rTMS + C1 | 0.078 ± 0.457 | 0.209 ± 0.337 | 0.113 ± 0.421 | 0.060 ± 0.697 | | | |
| | Right rTMS + C0 | 0.135 ± 1.263 | −0.094 ± 1.141 | 0.182 ± 0.428 | −0.014 ± 0.757 | | | |
| | Right rTMS + C1 | 0.137 ± 0.385 | 0.103 ± 0.713 | 0.178 ± 0.492 | −0.047 ± 0.623 | | | |
| | Left rTMS + C0 | 0.251 ± 0.359 | 0.185 ± 0.507 | 0.123 ± 0.495 | −0.020 ± 0.508 | | | |
| | Left rTMS + C1 | 0.028 ± 0.701 | 0.087 ± 0.761 | 0.138 ± 0.216 | 0.124 ± 0.408 | | | |
| PSQI | Sham rTMS + C0 | 0.151 ± 0.884 | 0.008 ± 0.605 | 0.098 ± 0.951 | −0.060 ± 0.620 | $F = 0.788$, $P = 0.559$ | $F = 2.299$, $P = 0.004$ | $F = 0.731$, $P = 0.256$ |
| | Sham rTMS + C1 | 0.500 ± 2.207 | 0.188 ± 0.424 | 0.101 ± 0.367 | 0.004 ± 0.374 | | | |
| | Right rTMS + C0 | 0.059 ± 0.551 | 0.006 ± 0.521 | 0.047 ± 0.373 | 0.003 ± 0.537 | | | |
| | Right rTMS + C1 | 0.184 ± 1.068 | 0.142 ± 0.350 | 0.071 ± 0.457 | 0.090 ± 0.468 | | | |
| | Left rTMS + C0 | 0.036 ± 0.359 | 0.205 ± 0.484 | 0.045 ± 0.299 | −0.106 ± 0.813 | | | |
| | Left rTMS + C1 | 0.167 ± 1.144 | 0.103 ± 0.514 | −0.014 ± 0.445 | 0.019 ± 0.410 | | | |
| VAS | Sham rTMS + C0 | 0.112 ± 1.380 | 0.222 ± 0.407 | 0.216 ± 0.414 | 0.092 ± 0.516 | $F = 0.243$, $P = 0.943$ | $F = 1.406$, $P = 0.161$ | $F = 1.864$, $P = 0.154$ |
| | Sham rTMS + C1 | 0.133 ± 0.447 | 0.226 ± 0.278 | 0.193 ± 0.365 | 0.209 ± 0.686 | | | |
| | Right rTMS + C0 | 0.042 ± 0.585 | 0.202 ± 0.434 | 0.176 ± 0.326 | 0.087 ± 0.477 | | | |
| | Right rTMS + C1 | 0.193 ± 0.552 | 0.220 ± 0.591 | 0.148 ± 0.352 | 0.090 ± 0.518 | | | |
| | Left rTMS + C0 | 0.194 ± 0.430 | 0.221 ± 0.892 | 0.044 ± 0.448 | 0.094 ± 0.589 | | | |
| | Left rTMS + C1 | 0.085 ± 0.412 | 0.156 ± 0.383 | 0.148 ± 0.489 | 0.091 ± 0.593 | | | |

C1, cognitive behavioral therapy with a fixed schedule; C0, cognitive behavioral therapy without a fixed plan; MoCA, Montreal Cognitive Assessment Scale; ADS, Alcohol dependence scale; GAD-7, Generalized anxiety disorder-7; PHQ-9, Patient Health Questionnaire-9 items; VAS, Visual Analogue Scale; OCDS, Obsessive Compulsive Drinking Scale; PSQI, Pittsburgh Sleep Quality Index.

remission (56). To date, no studies have investigated the efficacy of this promising approach in AD. Our results are the first to show that rTMS combined with CBT is superior to rTMS alone in reducing the rate of relapse. At 24 weeks of follow-up, Kaplan−Meier survival analysis reveals a statistically significant relapse rate between six groups, left rTMS + C1 group has

TABLE 4 Statistically significant results in Binary logistic regression models for relapse.

| | B | S.E. | Sig. | OR | 95% CI | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| Current smoking | −1.329 | 0.642 | 0.038 | 0.265 | 0.075 | 0.931 |
| Alcohol consumption, ml | 0.000360 | 0.000150 | 0.009 | 1.000 | 1.000 | 1.001 |
| CBT | 0.528 | 0.456 | 0.246 | 1.696 | 0.694 | 4.143 |
| Constant | −0.075 | 1.649 | 0.964 | 0.927 | | |

CBT, cognitive behavioral therapy; CI, confidence ration; OR, odds ratio; SE, standard error.

TABLE 5 Statistically significant results in Cox regression analyses for predictors of relapse.

| Variable | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value |
| WBC | 1.133 | 0.033 | 1.077 | 0.267 |
| RBC | 1.977 | 0.006 | 1.260 | 0.462 |
| HGB | 1.019 | 0.010 | 1.010 | 0.306 |
| TBIL | 1.034 | 0.000 | 1.025 | 0.026 |
| Total cholesterol | 1.006 | 0.007 | 1.006 | 0.034 |
| Current smoking | 2.805 | 0.011 | 2.306 | 0.045 |

WBC, white blood cell; RBC, red-blood-cell; HGB, hemoglobin; TBIL, total bilirubin; CI, confidence interval; HR, hazard ratio.

the best treatment effect for alcohol dependent patients. CBT has been proposed to function at the neural level through DLPFC (57). Therefore, stimulation of left DLPFC by rTMS may synergistically enhance the effect of CBT, inducing neural plasticity and making neural circuits recover faster (58). It is also hypothesized that CBT may provide a "foundation" for treatment to improve treatment retention and adherence and address other ancillary issues. So it makes more sense to combine these two approaches, making it possible to have more powerful stacking effects and more prolonged-lasting effects.

Anxiety and depression of AD patients may be aggravated due to decreased self-control, poor social support system, and deteriorating quality of life. At the same time, AD patients will show withdrawal symptoms such as anxiety and depression when they reduce or stop drinking, which will affect their abstinence compliance. Negative emotional states will affect and induce craving (59). Negative emotions and subjective stress levels are clearly predictors of relapse after AD treatment (60). In our study, the PHQ-9 assessed patients' severity of depressive symptoms. Our study found that the PHQ-9 scale score reduction rate significantly affected treatment over time, as shown by the interaction effect. At week 2 of follow-up, the right rTMS + C0 group and the left rTMS + C0 group improved depressive symptoms are better. Previous studies have shown that high-frequency rTMS applied to left DLPFC and low-frequency rTMS applied to right DLPFC are an effective treatment for patients with major depression (61, 62). The above theories suggest that rTMS treatment of AD patients may reduce drinking cravings by improving depression, thereby reducing relapse to drinking.

Our study showed significant reductions in GAD, MoCA, OCDS, PSQI scales score reduction rate, improvements in anxiety, cognition, drinking cravings, and sleep in both the sham rTMS + C0 group, sham rTMS + C1 group, right rTMS + C0 group, right rTMS + C1 group, left rTMS + C0 group, and left rTMS + C1 group. There was continuous improvement at 2 weeks, 2 months, 3 months, and 6 months during the follow-up. However, there was no difference in treatment effect between these groups. In addition, we found an interesting finding that the sham rTMS group also improved sleep, anxiety and depression, cognition, drinking desire, and other aspects during 2 weeks, 2 months, 3 months, and 6 months follow-up. Drinking cravings are known to be sensitive to placebo (63), so it was first considered that sham rTMS might have a placebo effect. Second, neuroplasticity may be the most important mechanism in cognitive recovery (64), abstinence alone can restore cognitive impairment and brain abnormalities in some AD patients. Third, AD is seen as a symptom of a dysfunctional family system in which the alcohol dependent individual interacts with other family members. Family members and/or friends play a supportive and motivational role in AD, improve patients' adherence to therapy, can prevent relapse, and are important in resolving conflicts caused by alcohol abuse (3).

Our research found that smoking was an independent factor influencing alcohol dependent relapse. Many studies support our results. Nearly half of alcohol dependent patients also smoked, and nicotine dependence was associated with a tremendous urge to drink, an increased risk of relapse after treatment, and more alcohol consumption at the time of relapse (65). Alcohol use disorder patients who actively smoke and quit smoking for fewer days before treatment have a significantly higher chance of relapse within 6 months. Implementing smoking cessation could reduce the risk of alcohol use disorder relapse (66). Our finding result may be that both alcohol and nicotine activate the opioid system in reward-related brain regions, leading to adaptive changes in opioid signaling after prolonged exposure. A previous finding suggests that nicotine can increase drinking activity by modulating μ receptor activity in the ventral tegmental area (67). Our study also showed that alcohol consumption was a risk factor for drinking again. A recent domestic survey showed that the daily alcohol consumption of patients in the relapse group was significantly higher than that of patients in the non-relapse group before withdrawal treatment and that high daily alcohol consumption was an independent risk factor for alcohol dependence on relapse (68). The reason may be that everyday heavy drinking increases the patient's tolerance to alcohol and damages multiple body organs and systems. They were causing severe physical

and psychological damage to the patient, leading to more pronounced withdrawal effects and increased psychological addiction, making the patient more susceptible to alcohol-related stimuli and relapse into drinking after withdrawal (69).

## Conclusion

This study is the first to suggest that the combination of rTMS and CBT may be a potentially effective treatment for reducing relapse. Future research should focus on refining phenotypes to achieve personalized treatment approaches: Alcohol use disorders are complex and multifaceted disorders, and personalized treatment approaches may be the most effective to address this complexity. Given the role of individual differences in neuroregulatory effects and the high degree of heterogeneity in the AD population, the identification of phenotypes (including impaired cognitive function, craving, depressive and anxious mood, alcohol consumption, number of relapses, etc.) and individualized treatment options may be critical in the development of treatment for AD. It's clear that the recovery process is not linear. In order to avoid relapse, much attention should be paid to the interplay between the aspects according to the bio-psycho-social model in the treatment for AD, as well as to increasing patients' motivation to quit drinking. However, the present study has several limitations. Caution must be used in interpreting the current results, as the sample size for each AD group is not large and is an initial observation. Further studies with a larger sample are needed to replicate our results. In addition, given that one of the distinguishing features of CBT is its relative duration of effect, further follow-up can be extended to assess efficacy. Clinicians should also assess the lifestyle and family structure of the alcohol dependent patient and their role in the treatment process. Finally, although self-assessment diaries in reporting alcohol consumption are generally considered valid under certain conditions, self-assessment diaries are unreliable and inaccurate. In the future, we will further investigate sensitive and specific biological indicators of recent alcohol consumption as a secondary outcome measure to complement the self-reports obtained from patients.

## Data availability statement

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

## Ethics statement

The studies involving human participants were reviewed and approved by the First Affiliated Hospital of Harbin Medical University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

XH, LL, TZ, HM, XHZ, HXW, YP, and YJ contributed to the study conception and design. XH performed the statistical analysis and wrote the manuscript. All authors collected the data, commented on previous versions of the manuscript, and read and approved the final manuscript.

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## Conflict of interest

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

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.935491/full#supplementary-material

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# Clinical differences between men and women in a Swedish treatment-seeking population with gambling disorder

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**Introduction:** The purpose of this study was to explore clinical differences in Swedish treatment-seeking men and women with gambling disorder (GD). As the prevalence of GD is increasing among women, even though men are still highly overrepresented, the characteristic differences between men and women seeking treatment become increasingly important.

**Method:** A sample of 204 patients with GD (26.5% women and 73.5% men) at an outpatient clinic were diagnosed using the SCI-GD, screened for comorbid diagnoses using the MINI, and further completed a range of self-report questionnaires measuring demographics, GD, alcohol and other drug problems, symptoms of depression and anxiety, and pathways into gambling problems.

**Results:** Several characteristics differed between treatment-seeking men and women in our sample. Examples of differences between genders included age, onset age, living situation, duration, alcohol and drug problems, comorbidity, and pathways leading to gambling problems.

**Discussion:** The most evident difference was that women, in addition to GD, showed more symptoms of anxiety and depression than men, while men had a higher degree of substance use problems compared to women. The differences in clinical features between men and women are important to consider in treatment planning and possibly for future gender-based interventions.

KEYWORDS

**comorbidity, treatment-seekers, pathways, gambling disorder, gender**

# Introduction

The prevalence of gambling disorder (GD) has globally changed from a range of 0.5–7.6% to 0.3–10.9% in the last 10 years, with an overrepresentation of men (1, 2). In Sweden, prevalence continues to increase. The Swedish Health Authorities report that approximately 0.6% of the population suffers from gambling disorder (3). Gambling disorder is also associated with a high lifetime prevalence of having a comorbid psychiatric disorder, typically depression and substance use disorders (4, 5). In a Swedish nationwide register-based study, it was found that 73% of all patients diagnosed with GD had a co-occurring psychiatric diagnosis and that mortality due to suicide increased 15-fold (6).

Today about 20% of individuals with GD seek treatment for their gambling problems within healthcare services (7). This is an increase from the last report where 9.9% of patients with GD seek treatment (8, 9) and women present a lower chance of being in treatment (10). Considering this, the different clinical characteristics in men and women seeking treatment are still unknown, and knowledge needs to be updated. Even though women have increased their gambling habits and also show a increased prevalence of GD within the last decade (11, 12) men still gamble more frequently, for more money and they show a higher prevalence of gambling related problems than women do (13). In Sweden, it has been estimated that 0.2% of women and 0.8% of men have a severe gambling disorder and that more women than men proportionally stand for new cases i.e., number of individuals progressing from no problems or low risk to gambling problems or gambling disorder (3, 11).

Studies specifically comparing treatment-seeking men with women are limited [for review, refer to Gartner et al. (1)]. When only taking such studies into account, considerably more men than women seek treatment for their gambling disorder (14–19). The largest differences were observed in treatment-seekers from Britain, where 92.5% were men and 7.5% were women (20). This is comparable to a study in a treatment-seeking population in Sweden in where 80% were men and 20% were women (19).

Moreover, it has been reported that woman are older than men when they enter treatment (15, 17, 18, 20–22), that they tend to progress to gambling disorder faster and that they seek treatment earlier than men (14, 15, 21–29). However, in a sample of 2,256 gamblers seeking treatment, gender contribution to problem progression did not differ when age at onset and age of gambling initiation were taken into account (30).

Treatment-seeking women also have more comorbidity than men. Women report a higher prevalence of both affective and anxiety disorders (18–21, 24, 26, 29, 31–34) and have more general psychopathology (16). In contrast, men report more alcohol and other drug problems compared to women (14, 18–21, 32, 33, 35, 36). Interestingly, women tend to experience comorbid disorders before the onset of gambling, while men tend to experience other disorders after the first onset of problem gambling (28, 37).

Most studies also report that women often live alone, i.e., are likely to be divorced or widowed (21). They report that feelings of loneliness can trigger gambling initiation (35); and they are more likely to be retired, unemployed, or outside the workforce (20, 22, 36) or have problems with their professional life (34). However, the opposite has also been observed, with treatment-seeking women more likely to be married, living with family, and having dependent children (17).

Furthermore, treatment-seeking women engage more in casino gambling and bingo than men (18, 21, 29, 38) and are more likely to use electronic gaming machines (17, 26), with a preference for non-strategic forms of gambling (22, 24). Treatment-seeking men more often engage in sports betting (19–21). In treatment-seeking individuals, it has also been reported that female gamblers often report being victims of family violence (21, 34, 39) and that they, to a larger extent than men, had been exposed to childhood maltreatment (40).

Men and women also seem to differ in their pathways into GD. Using the Blaszczynski model (41), which presents three potential pathways into a GD, it has been suggested that women more likely than men start to gamble through the "emotionally vulnerable" pathway, i.e., they start to gamble primarily to escape aversive mood states. More so than women, men start to gamble through the "antisocial impulsivists" pathway, i.e., because of factors such as heightened impulsivity, antisocial personality traits, and comorbid substance use (42, 43). No gender differences have been found for the third pathway, the "behaviorally conditioned," which is described as a pathway with the absence of psychopathology, where it is theorized that gambling is initiated for recreation or socialization reasons.

Based on the increasing prevalence of GD in women (11, 12), even though men are still overrepresented, and more women than men proportionally stand for new cases of problem gamblers in Sweden (11, 44), we aim to explore sociodemographic characteristics, clinical correlates, co-morbidity, and the pathways into gambling problems (according to the Blaszczynski and Nower pathway model). We will study a sample of men and women seeking treatment at Sweden's largest outpatient clinic for gambling disorders.

# Materials and methods

## Study design

Our data were collected from individuals seeking treatment at the Clinic for Gambling Addiction and Screen Health between the first day of the opening of the clinic in May 2018 and May 2022. The demography, gambling severity, and prevalence of other psychiatric diagnoses were assessed. We also mapped other clinically relevant outcomes such as additional addictive behaviors, quality of life, and gambling-related cognitive distortions among these individuals. The information was obtained from several semi-structured interviews and standardized questionnaires.

## Participants

The participants ($n$ = 208) were recruited from the Clinic for Gambling Addiction and Screen Health at Sahlgrenska University Hospital in Gothenburg, Sweden, the largest public health outpatient facility offering treatment for pathological gambling in Region Västra Götaland in Sweden. Region Västra Götaland has 1.6 million inhabitants, with the clinic located in Gothenburg with its population of approximately 1 million. The clinic welcomes both patients with GD and gaming disorder from 16 years of age, and the treatment is based on cognitive behavioral therapy. Patients were either self-referred or referred by a physician or other healthcare professional to the clinic. No specific inclusion criteria were set. All patients that attended their first assessment at the clinic were asked to participate in the study. Patients were excluded if they did not fulfill the criteria for GD.

## Procedure

On the first visit to the clinic, all patients were assessed with a semi-structured anamnestic interview and a semi-structured diagnostic interview for diagnosing GD. Additionally, sociodemographic data and several questionnaires were given to measure, e.g., various aspects of mental health and quality of life. Patients were also assessed with a psychiatric structured diagnostic interview. This was only done for patients that did not have another psychiatric contact outside the clinic. On their first visit to the clinic, the patients were informed about the study and approved participation by signing an informed consent form in connection with their visit. The study was approved by the Swedish Ethical Review Authority, dnr 764-18, and was conducted according to the 1964 declaration of Helsinki.

## Measures

### Clinical interviews

*Structured Clinical Interview for Gambling Disorder (SCI-GD)* is a semi-structured guide for interviewing patients with suspected GD. It is based on the diagnostic criteria for GD in the latest version of the DSM-5 (45). If four or more of the criteria were met then the patient was diagnosed with GD. Fulfilling four to five criteria counts as mild GD, 6–7 as moderate GD, and 8–9 as severe GD (46).

*The Mini-International Neuropsychiatric Interview (M.I.N.I.)* is a brief structured interview based on diagnostic criteria in DSM-5 and ICD-10. The therapist asks specific questions and the patient answers all questions with "yes" or "no." The instrument is validated against other psychiatric measurements with good results (47). The M.I.N.I. has also been studied in a Swedish context (48) and is recommended by Swedish health authorities for use in addictive care (49).

*Anamnestic interviews* assess tobacco use, drug use, and other psychiatric diagnoses besides gambling. Drug use and psychiatric diagnoses were assessed using the MINI-psychiatric interview (47, 48), AUDIT (50), and DUDIT (51) questionnaires. Information related to gambling was also collected; age of gambling onset, how many years since gambling became a problem, the function of gambling (e.g., economic reasons), and the dominating type of gambling (e.g., sports betting).

### Self-report questionnaires

*The NORC Diagnostic Screen for Gambling Problems (NODS latest 30 days)* is a self-report questionnaire measuring the severity of the gambling problem based on the diagnostic criteria in DSM-5. The instrument consists of 17 questions with response alternatives "yes" or "no." The severity of gambling problems is classified into three categories based on the number of questions answered "yes": risk gambling (1–2 yes), problem gambling (3–4 yes), and pathological gambling (5–10 yes) (52). Three out of 17 questions do not give any points, and one yes in three specific groups of questions (e.g., questions 14, 15, or 16) gives one point. This explains the inclusion of 17 questions but only 10 points ("yes") maximum. It is considered to have good internal validity and clinical applicability (53).

*The Patient Health Questionnaire (PHQ-9)* consists of nine items screening for symptoms of depression during the last 2 weeks. PHQ-9 is developed according to diagnostic criteria in DSM-IV, and the total score can be used to assess the severity of depressive symptoms. Based on the total score, the level of severity is classified as none (0–4), mild (5–9), moderate (10–14), moderately severe (15–19), or severe (20–27). PHQ-9 has good validity for the detection of the severity of depression (54).

*Generalized Anxiety Disorder Assessment (GAD-7)* was developed as an instrument to measure the presence and grade of the symptoms of anxiety. It is a seven-item questionnaire screening for symptoms during the last 2 weeks. The total score is 21, with cut-off points at 5, 10, and 15, indicating minimal (0–4), mild (5–9), moderate (10–14), and severe (15–21) levels of anxiety (55).

*Gambler's beliefs questionnaire (GBQ)* is a measure of cognitive distortions in individuals with problematic gambling. The questionnaire consists of 20 gambling-related statements regarding thoughts connected to gambling. Higher scores indicate more irrational cognitions related to gambling (56). The GBQ has demonstrated reliability through its excellent internal consistency (56–58).

*Alcohol Use Disorders Identification Test (AUDIT)* screens for alcohol-related problems and identifies individuals with harmful use of alcohol. It consists of 10 items, divided into three areas: alcohol consumption, symptoms of dependence, and negative consequences of alcohol consumption. The maximum

score is 40, with a cut-off score of 6 for women and 8 for men, indicating hazardous or harmful drinking (50).

*Drug Use Disorders Identification Test (DUDIT)* screens for use of illicit drugs and events of drug-related consequences. Similar to AUDIT, it is a 10-item instrument with a maximum score of 40. The questions are categorized into three areas: drug use, dependence symptoms, and negative consequences of drug use. DUDIT scores of one or more for women and three or more for men indicate problematic drug use (51).

*Brunnsviken Brief Quality of life scale (BBQ)* measures an individual's subjective quality of life in a clinical setting. It is divided into six different life areas such as "view on life," "creativity," and "friends and friendship." A total score is 96 with higher scores indicating a higher perceived quality of life, and a score of 52 or lower is considered a cut-off indicating poorer quality of life (59).

*Difficulties in Emotion Regulation Scale (DERS-16)* measures difficulties in the regulation of emotions. It consists of 16 statements concerning reactions to emotional discomfort. Response alternatives are graded from 1 (almost never) to 5 (almost always). The scoring ranges from 16 to 80, with higher scores representing larger difficulties in emotion regulation. DERS-16 is divided into five subscales: clarity, goals, impulse, strategies, and non-acceptance (60).

*The Gambling Pathways Questionnaire (GPQ)* proposes three pathways for identifying etiological subtypes of problem gamblers. It consists of 48 statements and the response alternatives are graded from 1–6 points (strongly disagree 1 point to strongly agree 6 points).

The 48 responses allocate to one of three sub-scales which defines a specific pathway. The pathways are described as "behaviorall conditioned gamblers," "emotionally vulnerable gamblers," and "antisocial/impulsivist gamblers" (61).

*The World Health Organization adult ADHD self-report scale (ASRS-V1.1 screener)* is a screening tool, identifying adult individuals with symptoms of ADHD. Part A contains six items that are the most predictive symptoms of ADHD and are based on symptoms that are described in the DSM-IV with a 5-point response scale ranging from "never" to "very often" (62). Four or more responses at a specific severity level are considered indicative of a possible ADHD diagnosis. Part B contains 12 additional questions, which were not used here.

*The demographic data questionnaire* acquires several demographic aspects from the participants including age, sex, educational level, civil status, living situation, and current occupation.

## Missing data

Informed consent to participate in the study was received from a total of 208 patients during the study period. Of the 208 participants, one had a missing result on the SCI-GD and was excluded as it was not possible to confirm a diagnosis of GD. Similarly, another three were excluded as their SCI-GD score was $< 4$ and thus did not fulfill the criteria for GD. This left a total of $n = 204$ participants for analysis. Due to clinical considerations, the battery of measurements was changed during the course of the study. As such, the GPQ ($n = 93$) and ASRS ($n = 86$) were not administered to all participants. The MINI ($n = 161$) was also not administered to all participants due to clinical considerations. Frequencies of unanswered questionnaires for all other measures were between 5 and 11%.

## Data analysis

All analyses were performed using IBM SPSS Statistics version 28. To test the normality of continuous variables, a series of Shapiro–Wilk tests (63, 64) were performed. These indicated non-normality for all variables except the GBQ. Further analysis of histograms showed that AUDIT, DUDIT, duration of problems, years from onset to problems, and NODS were severely skewed and, thus, violated assumptions for parametric statistics. All other variables were close to normally distributed and deemed to not violate assumptions. Participants could give multiple answers regarding which gambling types they engaged in, and their reasons for gambling. These answers were clustered into five categories. For gambling types: online slots/casino, sports betting (online and offline), gambling in a physical store (bingo, slots, poker, horses), day trading, and others. For gambling reasons: financial, escape, excitement, habit, and self-harm. Frequencies for each gambling type and reason were reported in percentages. A Pearson Chi-square test was used to test possible differences between genders for categorical demographic variables and categorical gambling behaviors except in cases where $> 20\%$ of cells had an expected count less than five (reason: self-harm, gambling type: physical store, gambling type: day trading, occupation), where Fisher's exact test was used instead (65). Possible gender differences in the level of alcohol and other drug problems were evaluated by comparing frequencies of categorized problem levels using Chi-square tests and also by comparing raw scores on AUDIT and DUDIT using Mann–Whitney tests (66). The Mann–Whitney test was also used to test for differences between the duration of problems, years from onset to problems, and the NODS. To examine possible gender differences regarding age and age of gambling onset, an independent $t$-test was used. When assessing whether there were any gender differences between different clinical measures (PHQ-9, GAD-7, DERS-16, GBQ, and BBQ), age and possible ADHD were decided to be possible confounders based on a review of the literature (67–71). To assess possible differences and also control for confounders, Analysis of Covariance (ANCOVA) was used. Participants were coded as having possible ADHD if they

either had screened positively for ADHD on ASRS or the MINI or had an ADHD diagnosis in their medical records. No correction was made due to multiple testing, as the study is of exploratory nature and does not include any confirmative hypotheses.

# Results

## Sociodemographic characteristics

Sociodemographic characteristics of the total participants, as well as for women and men separately, together with test statistics, *p*-values, effect sizes, and odds ratios are reported in Table 1. Notably, the sample consisted of fewer women ($n = 54$) than men ($n = 150$). The women were older than the men, were more often single parents, and less often lived together with a partner without children. There was no difference between genders regarding the prevalence of possible ADHD.

The majority of the participants used nicotine in some form and harmful alcohol based on the AUDIT scale cut-offs was also common. There was no difference between genders in the frequency of harmful use, but when comparing raw scores on the AUDIT men had a higher score than women. Regarding problematic use of other drugs, men more often had a problematic use and scored higher on the DUDIT.

## Gambling behaviors

Gambling behaviors of the total participants, as well as women and men separately, together with test statistics, *p*-values, effect sizes, and odds ratios are reported in Table 2. Men and women had the same degree of gambling problems according to the SCI-GD and the NODS. Among all participants, a severe form of GD was the most common. The most common dominant gambling type for both men and women was an online casino. The opposite was true for online sports betting, which none of the women stated as their dominant gambling type. It was also more common for men to fall into the "other" category.

The most stated reason for gambling in all participants was economic reasons, followed by escape, excitement, habit, and self-harm. Women and men did not differ on any of the reasons for gambling, although there was a trend approaching significance regarding excitement. Women had a later gambling onset, a shorter duration of gambling problems, and fewer years between their gambling onset and the time when gambling became a problem.

Pathways to gambling were measured by the GPQ in a smaller subset of the sample, women ($n = 29$) and men ($n = 64$). There was a significant difference between gambling pathways between genders. The most common type for both genders was "behaviorally conditioned gamblers." The most notable difference was that women were much more likely to be categorized as "emotionally vulnerable gamblers" than men. Men were also slightly more likely to be categorized as "antisocial/impulsivist gamblers" than women.

## Clinical measures

Results from the ANCOVAs assessing the differences in clinical measures between women and men, together with unadjusted and adjusted means, *F*-values, *p*-values, and effect sizes are reported in Table 3. The level of depressive symptoms in the total sample, as measured by the PHQ-9, was $M = 13.8$ ($SD = 7.0$), which can be considered a moderate level. Women had more depressive symptoms than men. Covariates included in this analysis were age ($F = 0.0$, $p = 0.963$) and ADHD ($F = 16.8$, $p < 0.001$).

Regarding anxiety symptoms, as measured by the GAD-7, the total sample mean was $M = 10.8$ ($SD = 6.0$) which is also a moderate symptom level. As revealed by an ANCOVA, the women also had more anxiety symptoms than the men. Covariates included in this analysis were age ($F = 0.0$, $p = 0.858$) and ADHD ($F = 20.4$, $p < 0.001$).

The mean value for emotional dysregulation, as measured by the DERS-16, in the total sample, was $M = 43.2$ ($SD = 17.0$). There was no difference between men and women. Covariates included in this analysis were age ($F = 1.1$, $p = 0.299$) and ADHD ($F = 15.3$, $p < 0.001$).

There was also no difference between genders regarding the level of cognitive distortions related to gambling, as measured by the GBQ. Covariates included in this analysis were age ($F = 0.0$, $p = 0.961$) and ADHD ($F = 5.8$, $p = 0.017$). The mean for the total sample was $M = 71.8$ ($SD = 21.9$).

Finally, the total sample on average showed a clinical level of life dissatisfaction according to the BBQ, $M = 37.2$ ($SD = 21.2$). Frequencies of participants with a clinical level of life dissatisfaction (below the cut-off score) were 81.0% for the total group, 85.4% for women, and 79.4% for men. There was no difference between men and women on mean BBQ scores. Covariates included in this analysis was age ($F = 0.0$, $p = 0.938$) and ADHD ($F = 4.3$, $p = 0.039$).

# Discussion

The present study analyzed sociodemographic characteristics, comorbidity, and pathways in 204 treatment-seeking men and women with GD. On one hand, men seeking treatment at our clinic were around 5 years younger than the women; they started gambling about 10 years earlier and also had problematic gambling behavior for about 2 years longer. Women, on the other hand, developed a gambling

TABLE 1 Demographics of total sample, women, and men.

| | Total sample ($n$ = 204) | Women ($n$ = 54) | Men ($n$ = 150) | Test-statistic[5] | $p$-value | Effect size (odds ratio/Cohen's $d$)[6] |
|---|---|---|---|---|---|---|
| Age $M$ ($SD$) | 36.1 (10.2) | 40.5 (10.0) | 34.5 (9.8) | $t$ = 3.9 | < 0.001* | $d$ = 0.61 |
| Education % | | | | $X^2$ = 4.4 | =0.22 | – |
| Less than high school | 18.6 | 17.6 | 18.9 | | | |
| High school | 57.7 | 51.0 | 60.1 | | | |
| Occupational training | 3.6 | 7.8 | 2.1 | | | |
| University | 20.1 | 23.5 | 18.9 | | | |
| Occupational status % | | | | – | =0.335 | – |
| Working | 70.8 | 69.8 | 71.1 | | | |
| Sick-leave | 14.4 | 13.2 | 14.8 | | | |
| Unemployed | 6.9 | 3.8 | 8.1 | | | |
| Other | 7.9 | 13.2 | 6.0 | | | |
| Living situation % | | | | $X^2$ = 22.1 | < 0.001* | |
| Alone | 28.4 | 28.3 | 28.4 | | | OR = 1.0 |
| With partner | 20.4 | 3.8 | 26.4 | | | OR = 0.1 |
| With relatives/friends | 11.9 | 13.2 | 11.5 | | | OR = 1.2 |
| Single parent | 10.9 | 24.5 | 6.1 | | | OR = 5.0 |
| With partner and children | 26.9 | 28.3 | 26.4 | | | OR = 1.1 |
| Other | 1.5 | 1.9 | 1.4 | | | OR = 1.4 |
| Possible ADHD % | | | | $X^2$ = 0.1 | = 0.702 | – |
| Yes | 24.0 | 25.9 | 23.3 | | | |
| No | 76.0 | 74.1 | 76.7 | | | |
| Nicotine use % | | | | $X^2$ = 0.4 | =0.524 | – |
| Yes | 65.1 | 68.6 | 63.9 | | | |
| No | 34.9 | 31.4 | 36.1 | | | |
| AUDIT $M$ ($SD$)[1] | 6.2 (6.2) | 4.0 (4.4) | 6.9 (6.6) | $U$ = 4617.0 | < 0.001* | $d$ = 0.47 |
| Harmful alcohol use %[2] | | | | $X^2$ = 0.02 | = 0.902 | – |
| Yes | 29.3 | 30.0 | 29.1 | | | |
| No | 70.7 | 70.0 | 70.9 | | | |
| DUDIT $M$ ($SD$)[3] | 2.7 (7.5) | 0.9 (3.3) | 3.3 (8.4) | $U$ = 3915.0 | = 0.042* | $d$ = 0.32 |
| Problematic drug use %[4] | | | | $X^2$ = 4.3 | = 0.038* | OR = 0.02 |
| Yes | 17.6 | 8.0 | 21.0 | | | |
| No | 82.4 | 92.0 | 79.0 | | | |

Data is presented as means and standard deviations $M$ ($SD$) and in percent (%).
[1]Alcohol use disorders identification test.
[2]AUDIT scores ≥ 6 for women and ≥ 8 for men indicate potential harmful alcohol consumption.
[3]Drug use disorders identification test.
[4]DUDIT scores ≥ 1 for women and ≥ 3 for men indicate problematic drug use.
[5]Test statistics are either $X^2$, $t$, or $U$, depending on statistical test. For Fisher's exact test there is no test statistic.
[6]Effect size is reported as odds ratios for categorical variables and Cohen's $d$ for continuous variables. Odds ratios are reported for women to men. Effect size is only reported for significant effects. *Statistically significant.

problem faster than men even though they had gambled for a shorter duration and had a gambling problem for less time. This pattern has been seen in previous studies of clinical populations. The Ronzitti et al. (20) study found very similar results demonstrating that treatment-seeking men were about 6 years younger than women, they started gambling around 8 years earlier and had a problematic gambling behavior for about 3 years longer than the women. Similar age characteristics

TABLE 2 Gambling behaviors and pathways for total sample, women, and men.

| | Total sample ($n$ = 204) | Women ($n$ = 54) | Men ($n$ = 150) | Test-statistic[4] | $p$-value | Effect size (odds ratio/Cohen's $d$)[5] |
|---|---|---|---|---|---|---|
| Dominant gambling type[1] % | | | | | | |
| Online slots/casino | 66.2 | 94.4 | 56.0 | $X^2 = 26.2$ | < 0.001* | OR = 13.4 |
| Online sports betting | 24.0 | – | 32.7 | $X^2 = 23.2$ | < 0.001* | –[6] |
| Physical store | 6.9 | 3.7 | 8.0 | – | = 0.363 | – |
| Day trading | 4.9 | – | 6.7 | – | = 0.066 | – |
| Other | 9.3 | 1.9 | 12.0 | $X^2 = 4.8$ | = 0.028* | OR = 0.1 |
| Reasons for gambling[1] % | | | | | | |
| Economic | 63.2 | 57.4 | 65.3 | $X^2 = 1.1$ | = 0.300 | – |
| Escape | 58.8 | 63.0 | 57.3 | $X^2 = 0.5$ | = 0.471 | – |
| Excitement | 38.7 | 27.8 | 42.7 | $X^2 = 3.7$ | = 0.054 | – |
| Habit | 10.8 | 9.3 | 11.3 | $X^2 = 0.2$ | = 0.674 | – |
| Self-harm | 4.4 | 7.4 | 3.3 | – | = 0.249 | – |
| Age of gambling onset $M$ ($SD$) | 21.0 (10.4) | 27.2 (12.9) | 18.8 (8.2) | $t = 4.5$ | < 0.001* | $d = 0.87$ |
| Duration of problem $M$ ($SD$) | 7.9 (7.5) | 6.5 (7.1) | 8.4 (7.5) | $U = 4803.5$ | = 0.028* | $d = 0.26$ |
| Years onset to problem $M$ ($SD$) | 7.3 (8.1) | 6.9 (9.9) | 7.4 (7.3) | $U = 4739.5$ | = 0.028* | $d = 0.07$ |
| NODS-30[2] $M$ ($SD$) | 6.0 (3.0) | 6.1 (3.1) | 6.0 (2.9) | $U = 3418.0$ | = 0.551 | – |
| Gambling disorder severity % | | | | $X^2 = 0.1$ | = 0.936 | – |
| Mild | 13.7 | 13.0 | 14.0 | | | |
| Moderate | 38.7 | 40.7 | 38.0 | | | |
| Severe | 47.5 | 46.3 | 48.0 | | | |
| Gambling pathway %[3] | ($n$ = 93) | ($n$ = 29) | ($n$ = 64) | $X^2 = 11.1$ | = 0.004* | |
| Behavioral conditioned | 50.5 | 44.8 | 53.1 | | | OR = 0.7 |
| Emotional vulnerable | 16.1 | 34.5 | 7.8 | | | OR = 6.2 |
| Antisocial/impulsivist | 33.3 | 20.7 | 39.1 | | | OR = 0.6 |

Data is presented as means and standard deviations $M$ ($SD$) and in percent (%).
[1]Total percentages exceed 100% for dominant gambling type and reasons for gambling as participants could give several answers.
[2]The NORC diagnostic screen for gambling problems (NODS) (latest 30 days).
[3]As the gambling pathways questionnaire was only administered to a limited number of the participants the number of participants were lower for this analysis.
[4]Test statistics are either $X^2$, $t$, or $U$, depending on the statistical test. For Fisher's exact test there is no test statistic.
[5]Effect size is reported as odds ratios for categorical variables and Cohen's $d$ for continuous variables. Odds ratios are reported for women to men. Effect size is only reported for significant effects.
[6]Odds ratio could not be calculated as the number of women stating sports betting were zero.
*Statistically significant.

were also seen in the studies cited in the introduction (14, 15, 17, 18, 21, 22) finding altogether an average that the men were 9 years younger, started gambling 10 years earlier, and had gambling problems 6 years longer than the women. The men in our study started to gamble 10 years earlier than the women. This needs to be taken into consideration when looking at the pathway into GD. Early initiation of gambling behavior, in men specifically, is a well-known factor for GD, and specific awareness for prevention efforts is warranted.

The faster progression of women into a GD than men is called a telescoping effect and is well documented in previous research (18, 25, 30, 72, 73), although men have also been found to be "telescoped" (74). The same telescoping effect has previously also been seen to differ between men and women in several treatment-seeking populations (15, 20–24, 26–29, 38) except for one study in which both ages of onset and gambling initiation was taken into consideration (30). This is also interesting in light of the increase in GD prevalence seen in women (3, 11, 13) and that concomitantly fewer women seek treatment for GD than men (14–19). However, a small percentage increase is noted between a previous study from Sweden in where 20% were treatment-seeking women (19) compared to our finding that 26.5% women sought treatment in 2022. It has yet to be investigated whether this finding is due to the increased prevalence of GD or other factors, such as lessened stigmatization around the disorder.

TABLE 3 ANCOVA results between women and men for depression (PHQ-9), anxiety (GAD-7), emotional instability (DERS), gambling related cognitive distortions, (GBQ-SE), and quality of life (BBQ): *p*-values, means, and adjusted means with 95% confidence intervals.

| Measure | | Women | Men | *F*-value | *p*-value | Effect[6] size |
|---|---|---|---|---|---|---|
| | Unadjusted | 15.6 | 13.2 | | | |
| | 95% CI | (13.8–17.4) | (12.014.3) | | | |
| PHQ-9[1] | | | | 4.7 | = 0.036* | d = 0.36 |
| | Adjusted | 15.6 | 13.2 | | | |
| | 95% CI | (13.7–17.5) | (12.1–14.3) | | | |
| | Unadjusted | 12.2 | 10.3 | | | |
| | 95% CI | (10.5–14.0) | (9.4–11.3) | | | |
| GAD-7[2] | | | | 4.3 | = 0.039* | d = 0.33 |
| | Adjusted | 12.3 | 10.3 | | | |
| | 95% CI | (10.7–13.9) | (9.4–11.3) | | | |
| | Unadjusted | 45.6 | 42.4 | | | |
| | 95% CI | (40.8–50.3) | (39.5–45.3) | | | |
| DERS[3] | | | | 2.0 | = 0.155 | – |
| | Adjusted | 46.2 | 42.1 | | | |
| | 95% CI | (41.4–51.0) | (39.3–45.0) | | | |
| | Unadjusted | 71.8 | 71.8 | | | |
| | 95% CI | (66.1–77.7) | (68.0–75.6) | | | |
| GBQ[4] | | | | 0.0 | = 0.958 | – |
| | Adjusted | 72.0 | 71.8 | | | |
| | 95% CI | (65.7–78.3) | (68.1–75.5) | | | |
| | Unadjusted | 34.9 | 38.0 | | | |
| | 95% CI | (28.8–41.0) | (34.4–41.5) | | | |
| BBQ[5] | | | | 0.7 | = 0.414 | – |
| | Adjusted | 34.9 | 37.9 | | | |
| | 95% CI | (28.8–41.1) | (34.3–41.5) | | | |

[1]Patient health questionnaire.
[2]Generalised anxiety disorder assessment.
[3]Difficulties in emotion regulation scale.
[4]Gamblers' beliefs questionnaire.
[5]Brunnsviken brief quality of life scale.
[6]Cohen's *d*, calculated with differences between adjusted means and raw score standard deviations.
*Statistically significant.

Furthermore, our study found that more women than men lived without a partner and that women were more likely to be single parents than men. Other studies have found similar results. Echeburúa et al. (21) found in their clinical population that women more often lived alone and were more likely to be divorced or widowed. It has also been reported that loneliness is the main trigger of gambling initiation for women (38, 75). On the contrary, the opposite has been seen in a study from Australia comparing 1,520 problem gamblers seeking treatment where the women were more likely to be married than the men (17). Nevertheless, most studies report no differences in marital status between men and women seeking treatment for GD (14–16, 76). However, the majority of single-parent households are headed by mothers (77), and, in line with this, more treatment-seeking women than men were single parents in our study. In Sweden, it is estimated that 36.2% of the Swedish population lives in single households, with more women than men living alone (78). This hypothetically may indicate that women need a specific treatment plan directed toward single-parent households.

We further found that the dominant style of gambling for women was online slot machines. Gambling has previously been known to be a more social activity for men than for women (17), and this may influence the context in which men and women choose to gamble. Treatment-seeking women choose to gamble online while men, in addition to online gambling, also gamble in

person (17). The choice of online gambling for women may be a result of the stigmatization women still experience over their gambling (12).

Albeit lately, both men and women have been found to gamble online (79), treatment-seeking women specifically choose this method (19). This is in line with our results showing that even though the most common dominant gambling type for both men and women is online gambling, online gambling was more common among women (94.4%) than men (56.0%). Since online gambling has increasingly become a greater and more substantial problem, specifically in individuals with gambling problems in the last 2 years, as a consequence of COVID-19 (80) clinicians should assess and pay extra attention to this gambling type in treatment.

We further found that women showed significantly more depressive and anxiety symptoms than men. In a meta-analysis of the treatment-seeking problem and pathological gamblers, depression was one of thirteen predictors of gambling problems (81). However, the meta-analysis did not make any gender-specific associations. When comparing men and women seeking treatment for GD and their different comorbid symptoms women are more affected by depressive symptoms, they are more anxious, and they have poorer self-esteem than men (18–21, 24, 26, 29, 31–34).

Moreover, also in line with previous studies (18–21, 32, 33, 35, 36), the men in our study were found to have more problematic use of both alcohol and other drugs than women. Interestingly, it has been seen that treatment-seeking women tend to experience comorbid disorders, such as the experience of anxiety or depression before the onset of gambling problems (37), while men tend to experience other disorders after the first onset of problem gambling (28). This was, however, not investigated in our study.

It has been established that patients with concurrent depression present with greater severity of GD and have a higher anxiety level and more cognitive impairments (82, 83). It has also been seen that depression predicts GD severity (84) and that individuals who gamble to moderate their mood have a higher incidence of depression than others (85). Nevertheless, we cannot know from our data if comorbidity with depression/anxiety/substance use is a consequence rather than a cause.

Even though we only looked at pathways in a smaller subset of the patients, we saw a gender difference in the Blaszczynski and Nower gambling pathway model (41). First, the majority of both men (53.1%) and women (44.8%) were "behavioral conditioned gamblers." This is the most common pathway, in which one initiates gambling activities for social or entertainment reasons and develops a problem as a result of behavioral conditioning. Second, 34.5% of the women fall into the pathway of "emotional vulnerable gamblers" compared to only 7.8% of the men. People falling into this pathway are described as having higher levels of comorbidity with anxiety, depression, and substance use/abuse and with the escape of negative mood states as the motive to gamble. Third, 20.7% of the women were categorized as "antisocial/impulsivist gamblers" compared to 39.1% of the men.

This pathway is a subgroup of the "emotional vulnerable gamblers" that also exhibit impairments in neuropsychological functioning, attention deficit disorders, and impulsivity problems, which may be the reason why they show gambling problems [for review, refer to Dowling et al. (81)]. In the revised pathway model, anxiety, depression, childhood maltreatment, impulsivity, risk taking, and antisocial traits presided gambling problems for those categorized as "antisocial/impulsivist gamblers" (42). In a study looking at non-treatment-seeking problem gamblers, it was found that women were significantly overrepresented in both the "behaviorally conditioned gamblers" (36.2%) and "emotional vulnerable gamblers" (62.3%) pathways. No female overrepresentation was found in the "antisocial/impulsivist gamblers" pathway (86). Furthermore, in an earlier study, it was found that among 2,670 problem gamblers participating in a self-excluding program significantly more women were found in the "emotionally vulnerable gamblers" pathway compared to the other two pathways and significantly more men were found in the "antisocial/impulsivist gamblers" pathway (22). These studies all support our findings that more women than men were described as "emotional vulnerable gamblers" and more men were described as "antisocial/impulsivist gamblers." Assessing the GPQ in treatment planning may identify men and women that benefit from different strategies in treatment, i.e., women with more stress-relieving coping strategies and men with more impulse control strategies.

Besides the Blaszczynski model, other aspects of differences between men and women have been recognized in the literature. Sancho et al. (69) found in a treatment-seeking population that more men than women had emotion regulation deficits such as non-acceptance of emotions and impulse control. These deficits could explain why close to twice as many men than women (39.1 vs. 20.7%) in our patient sample fell into the category "antisocial/impulsivist gamblers" from the Blaszczynski model, although emotion regulation was not studied here.

This study has several strengths but also limitations. The first strength is that this study deepens the understanding and supports previous literature on gender differences in a clinical population. Furthermore, our patient group represents a true treatment-seeking population in specialized outpatient care. All patients were recruited to the study when they attended their first visit to the clinic after either self-referral or referral by a physician or other healthcare professional. All patients were diagnosed with gambling disorder using gold standard clinical interviews (SCI-GD). All self-report questionnaires were taken during their first visit before patients entered treatment at the clinic, and therefore, no measures are affected by treatment. A limitation of the study is that we only had 204 participants. A greater number would have given a better-powered study. Still, our results are in many ways supported by previous

literature, therefore, we believe that we had a significant number in our patients' group that was included in the analysis. Mainly, we were interested in a clinical population, but based on earlier studies, our results can be generalized to men and women with GD. Some were born in countries other than Sweden. Participants were all residing in Sweden, and the literature describes some differences between, for example, Asian countries and cultural perspectives (87, 88). Therefore, it is not possible to generalize all groups or cultures. Finally, the study is exploratory in nature with an open-ended hypothesis, and numerous statistical tests were performed. This increases the risk of potential type 1 error. Our findings, therefore, need to be confirmed in further studies.

In conclusion, we found in this study that men started to gamble about 10 years earlier than women. We also found that more women than men were single parents. The women were also significantly more depressed and anxious than men, and more often categorized as "emotional vulnerable gamblers" in the Blaszczynski gambling pathway model (41). This might indicate that depression and anxiety are pathways to gambling disorder and a risk factor for GD for women but not for men. Furthermore, men had significantly more alcohol and other drug problems than women and fit into the pathway category "antisocial/impulsivist gamblers." This suggests that a problematic intake of alcohol and other drugs is a risk factor for GD specifically in men.

Gender-specific associations in a treatment-seeking population are hard to characterize due to the limited number of studies in the field (1). Our findings are important not only considering the increased GD rates in women but also in relation to the specific understanding needed for both men and women seeking treatment for GD. In Sweden, men and women with GD are often treated in clinics specialized in gambling, but they can also be treated in support groups or within social healthcare. We advise caregivers to consider specific treatment plans for a problem and pathological gambling for men and women, with considerations of psychiatric comorbidity such as depression, anxiety, alcohol, and other use of drugs and sociodemographic factors such as single parenthood.

## 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 Regional Ethical Review Authority in Gothenburg 764-18. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

LM had the main responsibility of the writing of the manuscript, contributed to the specific knowledge in gender differences and main idea for the manuscript. MM has made all the statistical analyses and responsible for the section "Results." EA has been responsible for all of the 208 patients, from the informed consent form to collecting and keeps track of the data. AS was principal investigator for this research and supervised the writing of the whole manuscript throughout the research process. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

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

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# Prefrontal activity during the emotional go/no-go task and computational markers of risk-based decision-making predict future relapse in alcohol use disorder

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**Aim:** To longitudinally examine if the results of cognitive tasks or brain function during emotional or cognitive tasks can predict relapse in alcohol use disorder.

**Methods:** We selected 41 patients with alcohol use disorder during hospitalization. Functional near-infrared spectroscopy (fNIRS) measured the relative change in oxygenated hemoglobin in the frontotemporal areas during an emotional go/no-go task and verbal fluency task (VFT). They performed the N-back and risk-based decision-making tasks for determining working memory or risk-based decision-making. The presence of relapse 6 months following discharge was the primary outcome.

**Results:** Twenty-four patients (21 men, three women) remained abstinent, whereas 17 (14 men, three women) relapsed. Compared with the abstinent group, those with relapse displayed significantly decreased activation in the right frontotemporal region during the emotional go/no-go task, significantly shorter reaction time to non-emotional stimuli, and greater risk preference in the risk-based decision-making task. In the abstinent group, we observed a negative correlation between oxygenated hemoglobin and the craving scale. A logistic regression analysis demonstrated that the risk of relapse increased with smaller oxygenated hemoglobin in the right frontotemporal region (odds ratio = 0.161, $p = 0.013$) and with greater gambling thoughts (odds ratio = 7.04, $p = 0.033$).

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**Conclusion:** Decreased activation in the right frontotemporal region in response to an emotional stimulus and risk preference could predict relapse in alcohol use disorder.

KEYWORDS

alcohol use disorder, decision-making task, emotional go/no-go task, functional near-infrared spectroscopy (fNIRS), relapse, predictors

## Introduction

In 2016, the harmful use of alcohol caused approximately 3 million deaths (5.3% of all deaths) and 132.6 million disability-adjusted life years worldwide, and the mortality from alcohol consumption was higher than that from tuberculosis (2.3%), human immunodeficiency virus infection/acquired immune deficiency syndrome (1.8%), diabetes (2.8%), and hypertension (1). Alcohol use disorders (AUD) require early treatment because of the extensive impairment of daily functioning due to physical disabilities, such as liver damage and pancreatitis caused by drinking, and behavioral symptoms, including withdrawal, tolerance, and craving. However, the high relapse rate of AUD is challenging in the treatment of alcohol-related disorders. Neto et al. demonstrated that 39.2% of the patients with AUD remained abstinent 6 months following discharge (2). In addition, during the year after treatment, about 25% of the patients with AUD remained continuously abstinent, thus suggesting the difficulty of continuing abstinence (3). These findings suggest the difficulty of continuing abstinence. Biological markers are required to predict future relapse following discharge, identify high-risk inpatients, and provide effective interventions.

Cognitive dysfunction is one of the leading characteristics on psychiatric disorders including AUD. Actually, patients with AUD report impaired impulse control (4, 5), executive dysfunction (6, 7) and impaired risk-based decision-making (8), compared with controls. Moreover, the group that relapsed after 3 months displayed greater impulsivity than the group that remained abstinent (9). A recent review demonstrated a correlation between impulsivity and relapse in AUD (10). Noël et al. reported on a significantly stronger impairment of working memory in the drinking group than that in the abstinent group (11). Previous reports using the Iowa Gambling Task (IGT, (12, 13), which measures risk-based decision-making, demonstrated that lower performance on the test at the beginning of observation was positively correlated with alcohol consumption in a 2-year prospective study of low drinkers (14), whereas a 6-month prospective study did not observe a difference in the Iowa Gambling Test performance between the relapse and abstinent groups (15). The reason of this conflicting results with IGT may be due to the fact that IGT involves multiple cognitive processes and poor performance on the IGT can result from greater risk seeking, lower loss aversion, or compromised reinforcement learning of the reward/loss contingencies. That is, the task does not allow reliable evaluation of each cognitive process and to predict the prognosis of AUD, more precise economic theory-based tasks are required.

Despite these results suggesting that the mentioned impairments may be biological predictors of relapse in patients with AUD, they seldom included longitudinal studies. Therefore, we aimed to examine if these three factors can be used to predict the prognosis of patients with AUD 6 months following discharge from the hospital. Importantly, a recent meta-analysis of fMRI showed that patients with AUD demonstrated hyperactivation of the prefrontal cortex to alcohol cues compared to controls (16), suggesting impaired top-down emotional regulation. Thus, we intended to use functional near-infrared spectroscopy (fNIRS) to measure brain activation in the frontotemporal regions during the emotional go/no-go task and verbal fluency task (VFT) to assess neurocognitive foundations during cognitive and emotional regulation tasks. The emotional go/no-go task, which requires participants to discriminate stimuli of different emotional valence as well as to inhibit a prepotent response, measures inhibitory control that is supported by the prefrontal cortex. VFT requires participants to generate as many as possible words according to certain rules and has been shown to involve executive functions and the prefrontal cortex. Previous studies have reported poor performance of patients with AUD in the emotional go/no-go task, indicating impaired impulse control (4, 5). Also, patients with AUD also produce less words in the VFT, indicating compromised executive function (7). Based on these evidence, we hypothesized that patients with relapse would display compromised impulse control (specifically, shorter reaction time), accompanied by decreased brain activation response to emotional stimuli during the emotional go/no-go task or to VFT.

Furthermore, to evaluate working memory performance, we used the commonly employed n-back task and hypothesized that patients with AUD would demonstrate decreased working memory. For the evaluation of risk-based decision-making, rather than IGT, we used a risk-based decision-making task that allow economic theory-based computational modeling of

the underlying cognitive process. Specifically, following our previous study (17), we dissected risk preference into two parameters, utility sensitivity and probability weighting that allows more precise evaluation of risk seeking behaviors. Utility sensitivity represents general risk preference while probability weighting focuses on potentially different risk preference at small vs. large probabilities. Based on previous reports indicating that greater risk seeking may be associated with AUD, we hypothesized that patients with relapse would show altered utility sensitivity and probability weighting that indicate enhanced risk seeking.

# Materials and methods

## Design

This longitudinal study was conducted at the Koryo Hospital and Yamaguchi University Hospital. **Figure 1** illustrates the flow of the study. Following admission, the patients underwent detoxification treatment. The detoxification period was 1 week. We administered infusions once daily for 7 days, diazepam 15 mg 3 days and diazepam 7.5 mg 4 days for a total of 7 days. After detoxification, psychological tests including self-reports was performed. Subsequently, we performed the N-back task and risk-based decision-making task on the participants using a computer. Eventually, we measured their brain activity using fNIRS with the emotional go/no-go task and VFT during hospitalization. We performed the task in the first month after admission and the fNIRS measurements in the first month and a half. Relapse, the outcome of this study, was defined as self-reported or reported by a relative or close friend at the Koryo Hospital outpatient clinic 6 months following discharge, with $\geq$60 and $\geq$40 g alcohol consumption for men and women, respectively, during the follow-up (6 months) according to Beck et al. (18).

## Participants

All participants were recruited from the patients admitted to the Koryo Hospital, which specializes in the treatment of AUD. This study was approved by the institutional review boards of the Koryo Hospital and Yamaguchi University Hospital. It was conducted in accordance with the ethical standards of the Declaration of Helsinki. The age of the participants ranged from 20 to 70 years, and all met the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (19) for alcohol dependence. Written informed consent was obtained from all participants. The exclusion criteria were as follows: (1) a history of the loss of consciousness for more than 1 h owing to severe head injury or brain tumor; (2) a history of or current treatment for a neurodegenerative disease; (3) alcohol withdrawal syndrome with impaired consciousness; and (4) dementia or suspected dementia with a score $\geq$24 on the Mini-Mental State Examination (20, 21) of cognitive function. As a standard of care, all participants participated in a treatment program based on 12 STEP meetings during hospitalization. During the follow-up after discharge, the participants were encouraged, but not required, to participate in the hospital's standard treatment program, including outpatient visits and participation in day care. Moreover, they were encouraged to join self-help groups. Following enrollment, they completed an interview to assess alcohol dependence and comorbid psychiatric disorders. Furthermore, we performed interviews to determine the average number of drinking days per week and the average amount of alcohol consumed per day during the year prior to hospitalization. We assessed the severity of AUD prior to admission using the Alcohol Use Disorders Identification Test (AUDIT) (22), vulnerability to alcohol, or craving using the Stimulus-Induced Vulnerability subscale of the Alcohol Relapse Risk Scale (ARRS-SV) (23). We assessed depression with the Beck Depression Inventory-II (BDI-II) (24) and Structured Interview Guide for the Hamilton Depression Rating Scale-17 (25). Moreover, impulsivity was assessed with the Barratt Impulsiveness Scale 11th (BIS-11) (26). The dominant arm was evaluated using the Edinburgh Handedness Inventory (27).

## fNIRS instrument

Functional near-infrared spectroscopy is a device that uses near-infrared light to measure blood dynamics on the surface of the prefrontal cortex in real time. It offers the advantages of no radiation exposure, lower cost, smaller size than fMRI, and the ability to measure while sitting (28, 29). We used a continuous-wave fNIRS system (ETG-4,000; Hitachi Medical Corporation, Tokyo, Japan) to measure brain function. Relative changes in oxygenated hemoglobin concentrations (oxy-Hb) were monitored. The time resolution was 0.1 s. We used multichannel probe holders (3 $\times$ 11), each consisting of 17 eliminating and 16 detecting probes alternately arranged at an inter-probe distance of 3 cm, thus resulting in 52 channels per set. The channels were placed in accordance with the international 10–20 system. The lowest probes were positioned along the Fp1–Fp2 line. We corrected for motion artifacts using the moving average method according to a previous study (30), which removed short-term motion artifacts from the analyzed data to smooth out these concentration change (moving average windows: 5 s), and the algorithm method to exclude channels contaminated with rhythmic signals that indicated noise and motion artifacts. We measured physiological noise in this study, such as heart rate. There was no significant difference in heart rate between the two groups ($p = 0.30$). In addition, channels with remarkable motion artifacts were deleted following blinded assessment by the first author (JS) and a co-author (TM).

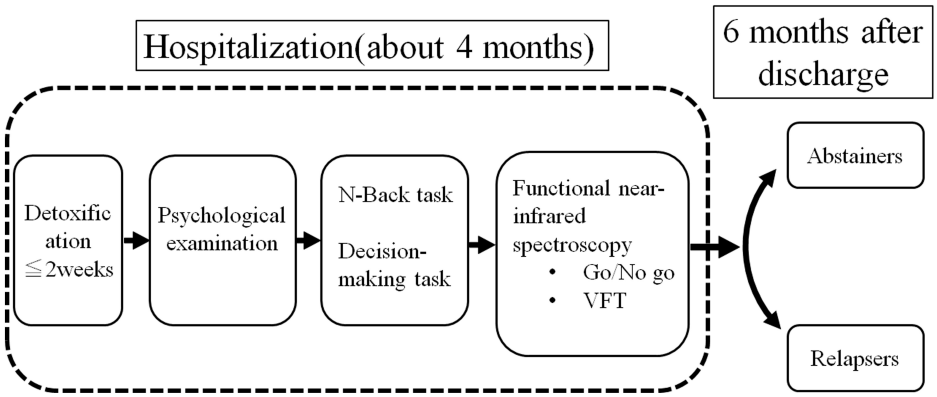


FIGURE 1
Study design.

Data were analyzed using the integral mode, in which the pre-task baseline during the control block was determined as the mean (oxy-Hb) of the last 10 s in the post-task period. The data between the two baselines were fitted linearly. Based on previous studies (28, 29), we measured the frontal and temporal areas using 31 channels (channels #22–52). We anatomically identified the areas using a virtual registration method with an automated anatomical labeling that enabled the registration of fNIRS channel positions in the standard brain space (31). These channels were classified into the following three areas according to previous fNIRS studies: the frontopolar area (channels #25–28, 36–38, and 46–49, corresponding to the superior and middle frontal gyri), left frontotemporal area (#29–31, 39–42, and 50–52, corresponding to the anterior portion of the superior and middle temporal gyri), and right frontotemporal area (#22–24, 32–35, and 43–45, corresponding to the inferior and middle frontal gyri) (**Figure 2**). For analyzing the fNIRS data, we used (oxy-Hb) during the task as an outcome measure for statistical analyses because it reflected the activation of gray matter in the brain. We used the integral value of (oxy-Hb), the change in (oxy-Hb) over the period of the targeted task, for the analysis (28, 29, 32–34).

## Stimuli and experimental procedure

According to our previous study (34), the emotional go/no-go task consisted of five blocks as follows: one emotional block with emotional faces of anger or fear, one non-emotional block with neutral faces, and three control blocks with geometric shapes (**Figure 3**). There were 32 trials in each run. We selected facial photographs from the Japanese and Caucasian Facial Expressions of Emotion and Neutral Faces (35). We used presentation soft (Neurobehavioral System, Inc) to show the photographs. For the go trials, the participants responded by rapidly pressing a button on a keypad with the index finger of their preferred hand upon the appearance of a target stimulus (e.g., angry face). By contrast, they were instructed to withhold pressing a button in the no-go trials (e.g., fearful faces). The go and no-go trials comprised 50% of the task. In the non-emotional block, the participants were required to identify the sex of the neutral face picture, and the block consisted of two types of non-emotional tasks (go-man and no-go-woman, or go-woman, and no-go-man). We recorded their accuracy rates and reaction times in the emotional and non-emotional go/no-go tasks. The control block comprised a sensorimotor go/no-go task with similar instructions, in which the participants responded to geometric shapes (square or circle). We assessed the task performance using the false alarm error rate (the number of incorrect response/all correct withholding to no-go trials), omission error rate (the number of incorrect no response/all correct responses to go trials), and reaction time (for correct hits) for each block condition. For different performance parameters, reaction time and false alarm indicate impulsivity while omission error rate indicates maintenance of attention.

We measured the participants' performance in a VFT, which consisted of a 30-s pre-task baseline period, 60-s word production period comprising three 20-s blocks, and 70-s post-task baseline period (33). During the baseline period, we instructed the participants to repeatedly vocalize the five Japanese vowels sequentially. During the word production period, we instructed them to generate the maximum words possible for a particular Japanese mora (rhythmic phonetic unit in the Japanese language). The words were recorded on a digital recorder, and repeats as well as words inflected for the tense or number based on an earlier word were excluded while calculating the total number of words as the measure of the task performance.

We used a computer-based N-back task to measure their working memory performance, as described in our previous study (36). In this task, the participants were displayed a

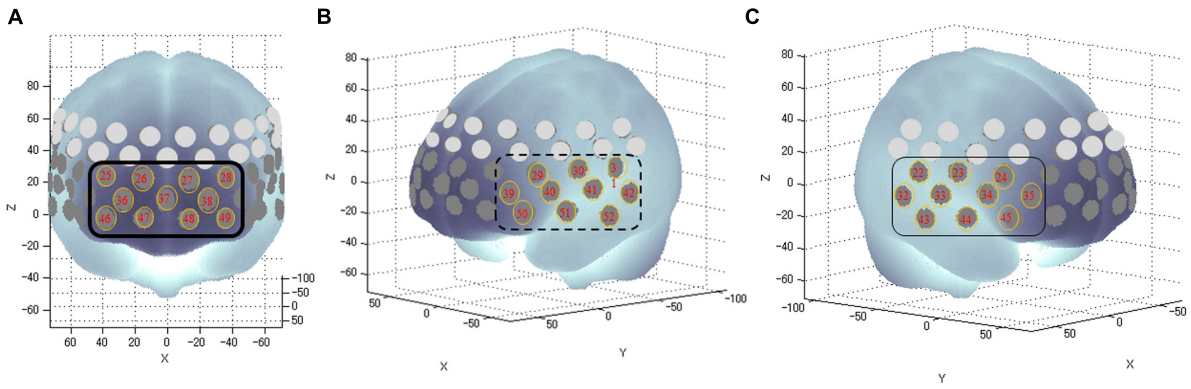


FIGURE 2
Anatomical areas of the brain measured by fNIRS. The numbers in tangerine-colored circles represent the channels of measurement in the anatomical area **(A)**: The frontopolar area (channel #25–28, 36–38, and 46–49) corresponding to the superior and middle frontal gyri; **(B)**: Left frontotemporal areas (channel #29–31, 39–42, and 50–52) corresponding to the inferior and middle frontal gyri; and **(C)**: Right frontotemporal areas (channel #22–24, 32–35, and 43–45) corresponding to the anterior portion of the superior and middle temporal gyri.

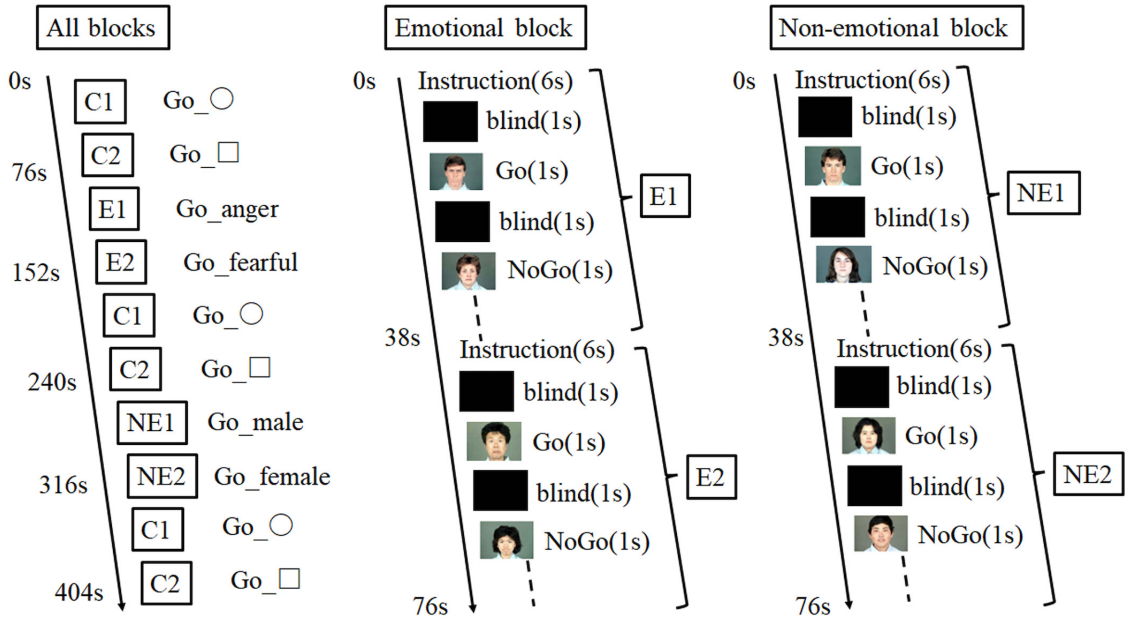


FIGURE 3
Experimental design of the emotional go/no-go task.

sequence of visual stimuli (random shapes) and had to judge if the current stimulus was identical to the one presented in n positions in the sequence. The shapes were displayed in black and centrally presented on a gray background for 500-ms each, followed by a 2, 500-ms interstimulus interval. We instructed them to rapidly press a predefined key for the targets, and no response was required for the non-targets. The percentages of correct responses and response times (ms) were used for the data analysis.

To identify the risk preferences of the patients with AUD, we used a computer-based risk-based decision-making task (**Figure 4**), as described in our previous study (17). This task consisted of 120 trials conducted in three sessions, each separated by a short break. In each trial, the participants were instructed to select between two gambling options to maximize their rewards. Each option consisted of a reward magnitude (in JPY, the lower number) and the probability of receiving the magnitude of the reward (the upper number). To ensure that the participants were focusing on the task, we inserted a test trial (a total of eight) with a correct answer (e.g., 30%, 5,000 vs. 50%, 5,000) after a randomly selected trial every 15 trials. Following a 1.5-s fixation phase (or inter-trial interval),

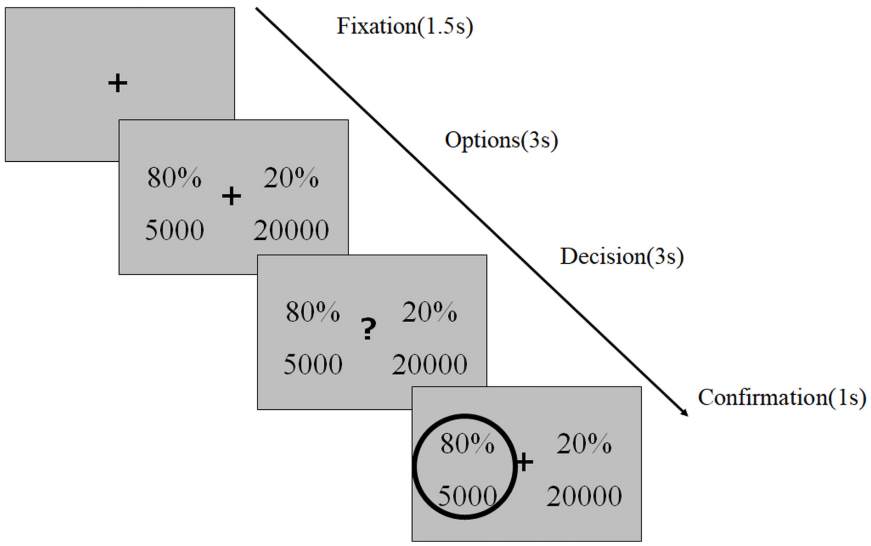


FIGURE 4
Experimental design of the risk-based decision-making task.

the stimuli were displayed on the screen for 3 s (option phase), following which a question mark appeared and the participants rapidly indicated their choice by pressing one of the two arrow keys within 3 s and decided which option to select (decision phase). The selected option was highlighted by a gray frame (confirmation phase). We informed the participants that failure to respond within the decision phase would be considered as having no response, and would lead to no reward in the trial. We performed computational modeling to simulate the risk-based decision-making process, in which we estimated a utility function parameter λ and probability weighting parameter (i.e., the one-parameter Prelec weighting function). The utility function parameter (λ) of 1, < 1, and > 1 represented risk-neutrality, risk-aversion, and risk-seeking, respectively. For the probability weighting function parameter (γ), 1, < 1, and > 1 indicated rational probability weighting, the overweighting of small probabilities and underweighting of large probabilities, and the opposite, respectively. The most common maximum likelihood estimation method was used for the model fitting.

## Statistical analyses

We used the geometric shapes task as a control task in addition to the target task (emotional or non-emotional task) in fNIRS. To measure the effect of emotional stimuli on specific brain responses, we extract the results of brain responses during the neutral face task from that of brain responses during the emotional face task. We compared the demographic data or all outcomes of behaviors or brain activations between the two groups using the Mann–Whitney *U*-test or the Student's *t*-test. Sex distribution was compared using the chi-squared test. Spearman's rho method was used to perform a correlation analysis of clinical variables and the integral value of (oxy-Hb) in the three brain areas. We performed a binomial logistic regression analysis following the standardization of variables to predict prognosis 6 months following discharge from the hospital.

All statistical analyses were performed using the R ver. 4, Jamovi ver. 2.0, and MATLAB 2018b. Statistical significance was set at $P < 0.05$.

# Results

## Demographic and clinical variables

We recruited 67 patients with AUD. Of these patients, there were 26 dropouts, including two deaths, eight uncontrollable diseases, and 16 who were unable to perform the test.

Forty-one participants (men = 35, 85.4%) completed the 6-month follow-up and were included in the analysis. Of them, 24 (58.6%, men = 21) were sober, and 17 (41.4%, men = 14) relapsed within the first half year of discharge. **Table 1** summarizes the characteristics of the abstainer and relapse groups. There were no significant differences (all *p*s > 0.05) between the groups in the background factors and psychiatric symptom rating scales. Ten out of 41 patients with AUD had comorbid illnesses. Of the 24 abstainers, eight had comorbid psychiatric disorders (5 with major depressive disorder, two with dysthymia, and one with major depressive disorder and anxiety disorder). Two relapsers had major depressive disorder. Of the 41 patients, 10 (24.4%) patients each were under antidepressants

TABLE 1 Sociodemographic data of the participants.

| | Abstainers ($n = 24$) | Relapsers ($n = 17$) | *P*-value |
|---|---|---|---|
| Age | 55.0 ± 8.7 | 51.6 ± 9.3 | 0.24 |
| Sex (male/female) | 21/3 | 14/3 | 0.49 |
| Age at first drinking (years) | 20.0 (18.0–20.3) | 18.0 (16.0–20.0) | 0.077 |
| The age of onset (years) | 47 (34.8–56.5) | 40.0 (35.0–50.0) | 0.33 |
| The duration of illness (years) | 7.5 (2.8–13.3) | 6.0 (3.0–15.0) | 0.92 |
| The number of drinking days (per week) | 7.0 (6.0–7.0) | 7.0 (5.0–7.0) | 0.91 |
| The daily intake of alcohol (g) | 103.8 ± 34.9 | 140.0 ± 74.0 | 0.074 |
| HAND | 100.0 (80.0–100.0) | 100.0 (80.0–100.0) | 0.76 |
| The duration of education (years) | 12.0 (12.0–14.3) | 12.0 (12.0–14.0) | 0.56 |
| SIGH-D 17 | 3.5 (2.0–6.0) | 6.0 (1.0–8.0) | 0.55 |
| BDI-II | 11.5 (9.0–9.3) | 12 (7.0–18.0) | 0.68 |
| ARRS-SV | 14.8 ± 4.5 | 14.9 ± 4.1 | 0.92 |
| BIS-11 | 62.0 ± 9.8 | 63.6 ± 14.0 | 0.67 |
| AUDIT | 21.3 ± 7.0 | 23.2 ± 6.8 | 0.39 |
| Comorbid illness | 8 | 2 | 0.11 |

Date represent median [inter-quartile range (25–75%)] or mean ± standard deviation. HAND: Edinburgh handedness inventory. SIGH-D 17, structured interview guide for the Hamilton depression rating scale-17; BDI-II, beck depression inventory-II; ARRS-SV, alcohol relapse risk scale-stimulus-induced vulnerability; BIS-11, Barratt impulsiveness scale 11th; AUDIT, alcohol use disorders identification test.

and sleeping pills, and seven (17.1%) patients each were under antipsychotics and anxiolytics.

## fNIRS

Compared with the abstinent group, the patients with relapse displayed significantly decreased (oxy-Hb) changes in the right frontotemporal region during the emotional go/no-go task [relapse group: −33.6 (−88.4 to 12.7) vs. abstinent group: 30.5 (−35.8 to 68.3), $U = 121$, $p = 0.028$] (Figure 5). In contrast, there were no significant (oxy-Hb) changes during the VFT between the groups in three regions (all $p > 0.05$).

In the behavior performance, the reaction time to non-emotional stimuli in patients with a relapse was significantly shorter than that in the abstinent group ($U = 96.0$, $p = 0.004$) (Table 2). There was no significant difference in the reaction time to emotional stimuli between the groups. The VFT results did not reveal a significant difference in the number of words generated between the groups ($p = 0.473$) (Table 2).

## Computer-based cognitive tasks

In the 1- and 2-back trials, there were no significant differences between the groups, with respect to the reaction time and the percentage of correct responses (all $p > 0.05$).

Figure 6 depicts the results of the risk-based decision-making task. The relapse group displayed significantly higher λ than the abstainer group [relapser: 0.530 (0.422–0.996) vs. abstainer: 0.241 (0.114 to 0.525), $p < 0.01$] (Figure 6A). There were no significant differences in γ between the groups (all $p > 0.05$) (Figure 6B).

## Associations between brain activation and clinical variables

We examined the correlations between (oxy-Hb) in the right frontotemporal region during the emotional go/no-go task and clinical measures in each group. There were no significant correlations between (oxy-Hb) and the age of onset, the daily intake of alcohol, BDI-II, BIS-11, or AUDIT in the relapse group ($\rho = 0.38$, $p = 0.13$; $\rho = -0.12$, $p = 0.65$; $\rho = -0.24$, $p = 0.36$; $\rho = 0.18$, $p = 0.50$; and $\rho = -0027$, $p = 0.92$, respectively) or the abstinent group ($\rho = -024$, $p = 0.25$; $\rho = -0.28$, $p = 0.18$; $\rho = -0.18$, $p = 0.41$; $\rho = 0.23$, $p = 0.29$; and $\rho = 0.16$, $p = 0.45$, respectively). In the abstinent group, we observed a negative correlation between (oxy-Hb) and ARRS-SV ($\rho = -0.439$, $p = 0.032$); however, there was no correlation between similar measures in the relapse groups ($\rho = -0.067$, $p = 0.80$) (Figure 7).

## Associated factors for predicting prognosis 6 months following discharge

To predict the prognosis 6 months following discharge, we used the drinking status (relapse or abstainer) as a dependent variable. We used age, the AUDIT scores and the age at AUD onset as the independent variables, which have been previously

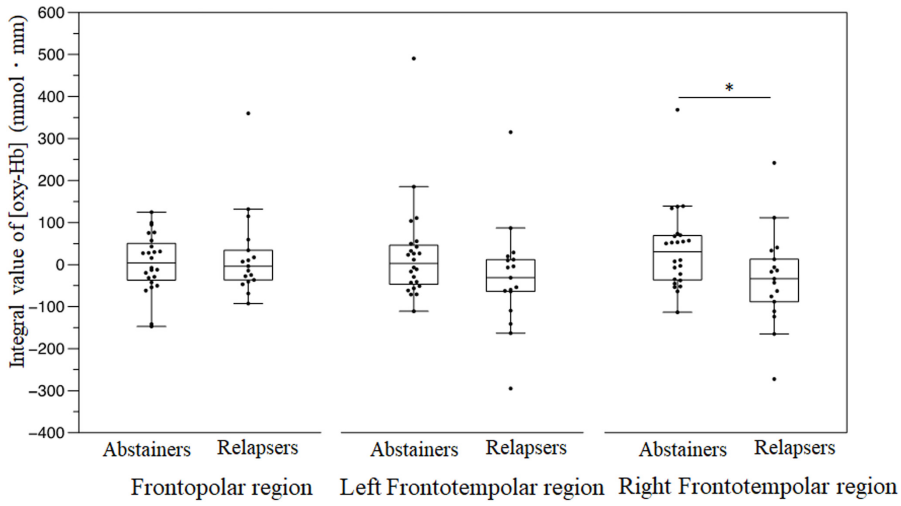


FIGURE 5
Brain activation displayed as the integral value of (oxy−Hb) in the frontopolar, left frontotemporal, and right frontotemporal regions during the emotional go/no-go task. *$P < 0.05$.

TABLE 2 Behavioral data of the participants.

| | Abstainers ($n = 24$) | Relapsers ($n = 17$) | $P$-value |
|---|---|---|---|
| False alarm error (%) (emotional go/no-go task) | 3.13 (0.00–9.38) | 3.13 (0.00–9.38) | 0.848 |
| Omission error rate (%) (emotional go/no-go task) | 6.25 (2.34–10.16) | 3.13 (3.13–9.38) | 0.627 |
| Reaction time (ms) (emotional stimulus) | 724.81 (673.99–794.98) | 659.81 (621.25–775.79) | 0.186 |
| Reaction time (ms) (non-emotional stimulus) | 600.29 (555.06–656.26) | 528.73 (468.98–568.33) | 0.004* |
| Generated words (verbal fluency task) | 14.5 (9.75–17.3) | 14 (9.00–16.0) | 0.473 |

*$P < 0.05$. Date represent the median [inter-quartile range (25–75%)].

reported as factors contributing to relapse (23, 37). In addition, (oxy-Hb) changes in the right frontotemporal region by fNIRS and λ, which displayed significant differences between the groups, were added as independent variables. We tested linearity in the logit using the Box-Tidwell transformation in SPSS before performing the logistic regression analysis. The interaction terms of all covariate showed linearity (all $ps > 0.05$). Table 3 presents the results of the regression analysis. The sensitivity and specificity were 68.8 and 87.0%, respectively. Lesser the (oxy-Hb) change in the right frontotemporal region, greater the gambling thoughts were likely to relapse (odds ratio = 0.161; odds ratio = 7.037, respectively).

## Discussion

This longitudinal study examined the factors predicting the prognosis of patients with AUD, 6 months following their discharge from the hospital. Patients with a relapse displayed significantly decreased activation in the right frontotemporal region during the emotional go/no-go task, significantly shorter reaction times to non-emotional stimuli, and greater risk preference in the risk-based decision-making task, compared with the abstinent group. Moreover, we observed a negative correlation between (oxy-Hb) and the craving scales. The logistic regression analysis revealed that the risk of relapse increased with smaller (oxy-Hb) in the right frontotemporal region. There were no significant differences in brain activation during the VFT and N-back tasks between the groups.

In the present study, the relapse group demonstrated significantly decreased (oxy-Hb) changes in the right frontotemporal region, compared with the abstinent group. Several previous studies have demonstrated an association between brain response to emotional stimulation and prognosis prediction in AUD. Brislin et al. observed a negative correlation between activation and subsequent alcohol consumption in the left inferior frontal cortex, which was less activated by negative emotional word stimuli than neutral word stimuli in controls (38). Cservenka et al. mentioned that during positive facial expression stimuli, first-degree relatives of patients with AUD displayed reduced activation in the left superior temporal cortex, compared with non-first-degree relatives (39). In a cross-sectional study using the stop signal task, which examined the response inhibition of the frontal lobe as well

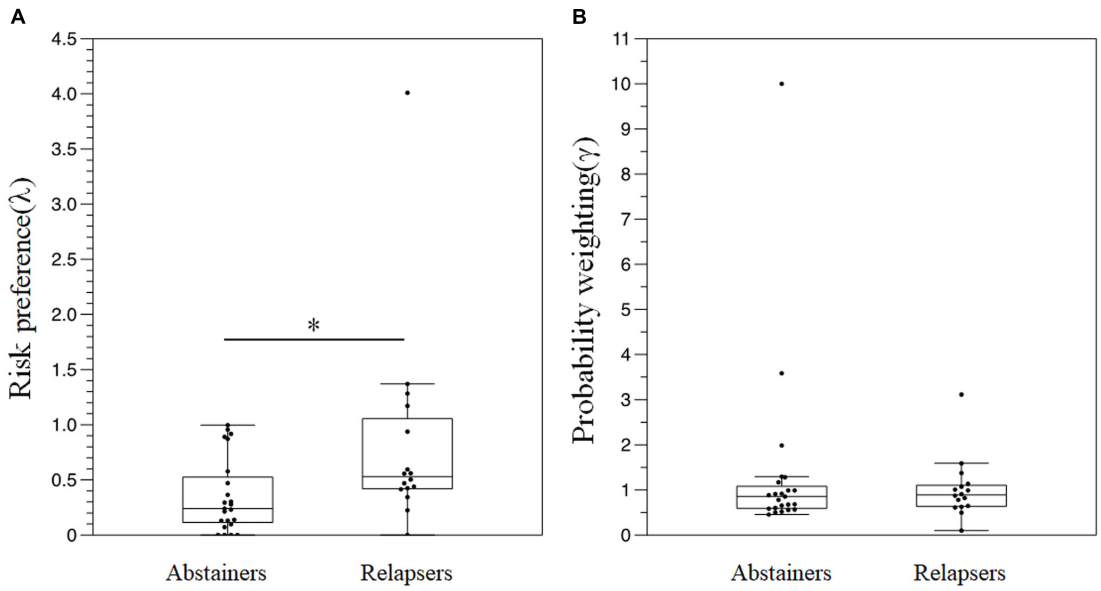


FIGURE 6
A comparison of the results in the risk-based decision-making task between the groups. **(A)** λ. **(B)** γ. *$P < 0.05$.

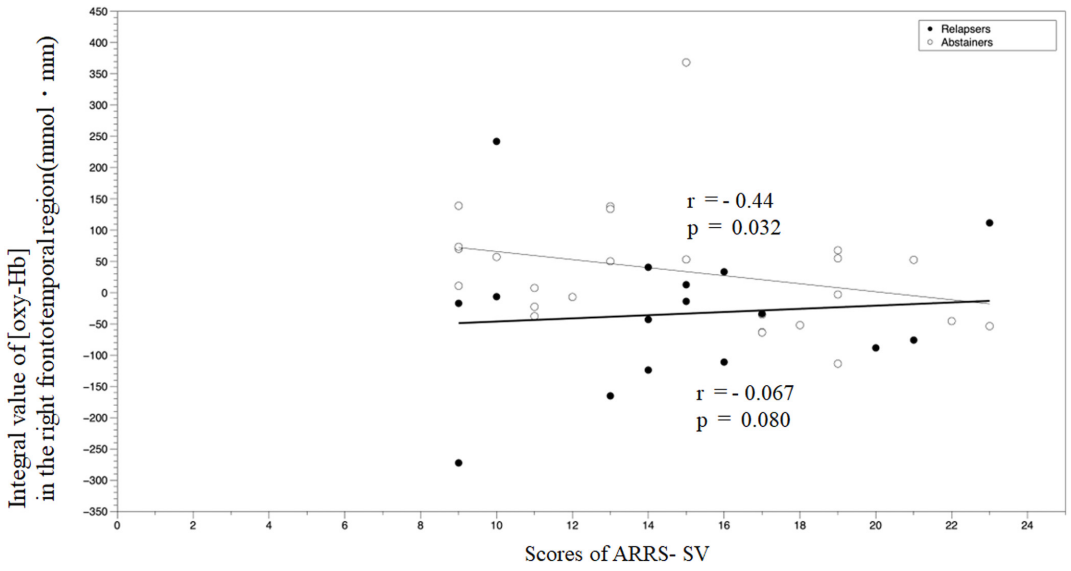


FIGURE 7
A correlation analysis of the integral value of (oxy−Hb) in the right frontotemporal region during the emotional go/no-go task and ARRS-SV. ARRS-SV, alcohol relapse risk scale-stimulus-induced vulnerability.

as the go/no-go task, heavy drinkers displayed significantly lower activation in the right superior frontal cortex than moderate to lower drinkers (40). In other words, the relapse group could display decreased frontal activation to emotional stimuli which may be associated with increased alcohol use. The prefrontal cortex is responsible for various functions, including emotional regulation (41–44). Neural substrates, including emotional dysregulation, are considered the basis for the onset or susceptibility to relapse in AUD (45). In addition, we observed a negative correlation between brain activity and ARRS-SV in the abstinent group, but not in the relapse group, thereby suggesting craving may not activate brain activity in the right frontotemporal cortex in the relapse group. Craving is a core concept in AUD, and refers to strong demand for drinking. An fMRI study reported that the right dorsolateral prefrontal cortex is one of the regions activated in outpatients

TABLE 3 A logistic analysis of the factors associated with a relapse.

| Presense of relapse | | | |
|---|---|---|---|
| | **OR** | **95% CI** | ***P*-value** |
| (oxy-Hb) change in the right frontotemporal region | 0.161 | 0.038–0.685 | 0.013* |
| λ | 7.037 | 1.17–42.42 | 0.033* |
| Age of onset | 0.918 | 0.313–2.70 | 0.877 |
| AUDIT | 1.072 | 0.436–2.635 | 0.880 |
| ARRS-SV | 1.010 | 0.410–2.489 | 0.982 |
| Age | 0.669 | 0.222–2.014 | 0.474 |

*$P < 0.05$. AUDIT, alcohol use disorders identification test; ARRS-SV, alcohol relapse risk scale; stimulus-induced vulnerability; OR, odds ratio; CI, confidence interval.

with AUD during craving regulation tasks (46), consistent with our findings, thus suggesting a correlation between craving and prefrontal cortex activity. Therefore, our findings suggested that right frontal region dysfunction may be a part of the pathophysiology of relapse. A recent meta-analysis of fMRI showed that patients with AUD demonstrated hyperactivation to alcohol cues compared to controls in prefrontal cortex (16). Interestingly, they showed reduced activity in prefrontal cortex after AUD treatment, suggesting that prefrontal activation may be related to craving suppression. Our results also support that prefrontal activity associated with craving suppression may be an indicator of relapse of AUD. Other biological candidates for relapse in AUD include increased impulsivity due to frontal dysfunction. The relapse group displayed significantly shorter reaction time in the non-emotional go/no-go task than the abstinent group in this study. Impulsivity may represent as a result of impaired inhibitory control. Rupp et al. reported that poor response inhibition in the go/no-go task could be a risk factor for early prognostic detection in AUD (4), consistent with our findings. Therefore, the lack of response inhibition may be one of the characteristics of the prospective relapse group. A recent study showed that GMV reductions in the prefrontal cortex were associated with scores of AUDIT (harmful drinking) and increased impulsivity (47). These findings suggest that frontal dysfunction may be one of the mechanisms of recurrence in AUD.

The parameter λ in the risk-based decision-making task was significantly higher in the relapse group than that in the abstinent group. The result suggested that the relapse group was less averse to risks or in other words, more risk-seeking compared to the abstainer group. Risk-based decision-making encompasses the selection of an action from a set of available alternatives (48), and consists of an aspect of executive function related to the ability to adjust the perception of reward and punishment to make a favorable choice (49). The prefrontal cortex reportedly plays an important role in risk-based decision-making (50), and the impairment of risk-based decision-making is considered one of the characteristics of AUD (51). However, the Iowa Gambling Task, a cognitive task commonly used to explore risk-based decision-making deficits, includes multiple risk-based decision-making components, such as reinforcement learning, the loss of aversion, and risk preference. The risk-based decision-making task developed in our previous study was based on a combination of a utility function and probability-weighted function to capture only risk preferences (17). In this study, the task suggested that the abstainers were more averse to risks.

In the present study, there were no significant differences in behavioral and (oxy-Hb) changes during the VFT, which reflected the executive function between the groups. There are a few studies measuring brain function during VFT in patients with AUD. Patients with AUD after detoxification displayed an identical degree of behavioral performance and (oxy-Hb) changes in the frontotemporal region during the VFT as controls (52). In a cross-sectional study, there was no difference in (oxy-Hb) changes in the frontal activity between the pre- and post-detoxified patients with AUD during the VFT, while brain activity was significantly lower in the pre-detoxified patients with AUD compared to controls (53). These findings indicate the possibility of recovery of brain function in patients with AUD after acute intoxication.

In this study, there was no significant difference between the groups in the N-back task, thereby indicating both groups had comparable working memory capacity. Working memory refers the ability to process information in response to external stimuli, which is necessary for several cognitive abilities, such as reasoning, language comprehension, planning, and spatial processing (54). In a 7-month longitudinal study, Cha. did not observe differences in the results of the N-back task between the relapse and abstinent groups, consistent with our findings (55). A meta-analysis demonstrated that patients with AUD who had been abstainers for <1 year displayed cognitive impairment, including working memory, compared with controls (7), suggesting that cognitive function in patients within up to 1 year of abstinence may be as impaired as that of relapsers.

Our study had some limitations. First, the sample size was small. Second, this study utilized fNIRS, in which the measurement area was limited to 3 mm from the brain's surface. We could not assess the basal ganglia involved in the reward system, which is associated in the pathology of AUD. Third, it was impossible to determine if our findings were attributed to the original traits of patients with AUD or to the effects of alcohol consumption on the brain. Adolescent rats display higher risk preference 3 months following the consumption of a large dose of alcohol (56). Forth, in the emotional go/no-go task, there was no difference in behavioral performance to emotional stimuli in the two groups despite difference in brain response to emotional stimuli. Fifth, about a quarter of the participants in this study had psychiatric comorbidities, which may influence the results. Sixth, we did not have a control group in this study, and we did not know whether the blood flow changes by using

fNIRS in the two groups were similar to the control group or not. Seventh, with only 32 trials per run in the emotional go/no-go task, the signal to noise was very low. Despite these limitations, the strength of this study was that it was a longitudinal study that identified the prognostic factors based on the neural basis or pathophysiology of AUD.

In summary, decreased activation in the right frontotemporal region in response to negative emotional stimuli and risk preference in AUD could predict the relapse of AUD 6 months following discharge.

## Data availability statement

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

## Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Boards of Koryo Hospital and Yamaguchi University Hospital. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

JS, TM, CC, TH, and SN: conceptualization. TM, CC, and SN: funding acquisition. JS, TM, CC, KE, YoF, YuF, MN, KN, and SN: methodology. JS, TM, YoF, YuF, MN, and KN: investigation. JS, TM, CC, and KE: data analysis. TH and SN: supervision. JS: writing – original draft. TM, CC, TH, and SN: writing – review and editing. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

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

## Publisher's note



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# Caudate gray matter volumes and risk of relapse in Type A alcohol-dependent patients: A 7-year MRI follow-up study

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**Background:** Whether alteration in regional brain volumes can be detected in Type A alcoholics both at baseline and after a long follow-up remains to be confirmed. Therefore, we examined volume alterations at baseline, and longitudinal changes in a small follow-up subsample.

**Methods:** In total of 26 patients and 24 healthy controls were assessed at baseline using magnetic resonance imaging and voxel-based morphometry, among which 17 patients and 6 controls were re-evaluated 7 years later. At baseline, regional cerebral volumes of patients were compared to controls. At follow-up, three groups were compared: abstainers ($n = 11$, more than 2 years of abstinence), relapsers ($n = 6$, $<2$ years of abstinence), and controls ($n = 6$).

**Results:** The cross-sectional analyses detected, at both times, higher caudate nuclei volumes bilaterally in relapsers compared to abstainers. In abstainers, the longitudinal analysis indicated recovery of normal gray matter volumes in the middle and inferior frontal gyrus, and in the middle cingulate, while white matter volumes recovery was detected in the corpus callosum and in anterior and superior white matter specific regions.

**Conclusions:** Overall, the present investigation revealed larger caudate nuclei in the relapser AUD patient group both at baseline and at follow-up in the cross-sectional analyses. This finding suggest that a higher caudate volume could be a candidate risk factor of relapse. In patients with specific type A alcohol-dependence, we showed that long-term recovery in fronto-striato-limbic GM and WM volumes occurs during long-term abstinence. These results support the crucial role of frontal circuitry in AUD.

KEYWORDS

**caudate nuclei, alcohol use disorder, relapsers, abstainers, structural magnetic resonance imaging, longitudinal analysis**

# 1. Introduction

Alcohol use disorder (AUD) causes extensive cortical and subcortical Gray Matter (GM) and White Matter (WM) brain damage (1–3), characterized by lower regional volumes. There might be a change in key-brain regions modulated by treatments available for AUD, as it is a multidimensional disorder which includes several subtypes with different neurobiological underpinnings (4, 5).

Previous studies have not exclusively included individuals without neurological complications (i.e., type A alcohol-dependent individuals). There are scarce studies examining AUD's patients with Type A alcohol-dependence, as designated by Chanraud et al. (6) with no neurological, somatic or psychiatric complications, and for whom the onset of dependence occurred late in life (6–8). Compared to 24 controls, Chanraud et al. (6) showed decreases in gray matter volumes that were detected bilaterally in 26 Type A alcohol-dependent individuals in the dorsolateral frontal cortex (up to 20% lower), and in the temporal cortex, insula, thalamus, and cerebellum. Decreases in white matter volumes were widespread, reaching 10% in the corpus callosum (6). Fein et al. analyzed 24 young to middle-aged treatment-naïve Type A alcohol-dependent individuals who showed reduced whole brain, prefrontal, and parietal cortical gray matter volumes compared to 17 controls. These structural brain changes were negatively associated with age and lifetime duration of alcohol use, which were highly intricated. Temporal cortex and white matter did not differ between the two groups (7). Finally, Pfefferbaum et al. showed that 16 Type A alcohol-dependent patients had a cortical gray matter loss over time in the prefrontal cortex and the anterior superior temporal lobe and enlarged ventricles, compared to 28 controls who drank low amounts of alcohol (8).

Several longitudinal MRI studies investigated the short-term reversibility (up to 24 months) of these structural alterations. They compared AUDs vs. controls as well as abstainers vs. relapsers after a period of abstinence ranging from 1 to 24 months (9–22) (see for review Supplementary Table 1). In patients maintaining abstinence for over 3 months, regional GM volumes partially recovered in the cingulate cortex, the orbito-frontal cortex and the insula (15). In patients maintaining abstinence over 8 months a regional GM volumes recovery was shown in the frontal and parietal regions after 1 month (14, 16).

Furthermore, there are scarce reports on structural predictors of relapse between relapsers and abstainers. These studies highlight initial hypovolumetry, in the fronto-ponto-cerebellar and mesocorticolimbic regions (12, 14), in the bilateral frontal cortex (21), the frontal cortical thickness (16), as well as in the right orbito-frontal cortex, medial prefrontal cortex, and right anterior cingulate cortex regions (17), the amygdala (23) and the striatum and the thalamus (24).

However, the follow-up duration in all these longitudinal studies varied from 1 month to 2 years.

Thus, to our knowledge, no studies have investigated the brain structure damage in AUD between abstainers and relapsers after more than 24 months.

Besides most of the longitudinal studies conducted evaluated AUD patients with somatic and psychiatric comorbidities (12–16, 20, 21, 25) (see Supplementary Table 1). Few studies (11, 15, 17, 26) have explored uncomplicated AUD men and women, i.e., Type A, as designated by Babor et al. (27).

Therefore, our study aimed to detect whether there are brain damage differences beyond 24 months between relapsers and abstainers, particularly in Type A AUD patients, and identify regional volumes as potential predictors of outcome at baseline, or as predictors of reversibility at follow-up.

Therefore, we first compared WM and GM volumetry between all healthy controls and AUD patients at baseline.

The groups were formed according to the maintenance or not of abstinence at 7 years of follow-up; afterwards, at follow-up, we compared relapsers, abstainers, and controls groups.

Secondly, we aimed to investigate the long-term changes in regional volumes at follow-up, by comparing cross-sectionally and longitudinally the followed-up subgroups of abstainers, relapsers, and controls.

In line with the literature, we hypothesized that long-term abstinence would lead to, at least partial, recovery of the prefrontal cortex, cingulate cortex, and WM volume reductions.

# 2. Materials and methods

## 2.1. Participants

At baseline (BL) twenty-nine AUD patients detoxified for at least 3 weeks (mean age 47.4 ± 7.7 years), and meeting DSM-IV criteria for alcohol-dependence were recruited from consecutive admission to addiction disorders wards of addiction departments at Paul Brousse and Emile Roux Hospitals (AP-HP).

Twenty-nine healthy controls with neither past nor current substance abuse, matched to AUD patients for age, sex, Body Mass Index (BMI) and education were recruited from the neighboring community. Body Mass Index (BMI; $kg/m^2$) was calculated as the ratio of patient collected data on weight and height and is defined as the weight divided by the square of the body height. Because some studies have reported sex-differences regarding alcohol-dependence (28), we chose to include only men in our study, in order to limit the impact of gender and heterogeneity in our limited sample size.

At baseline (BL), twenty-nine patients and twenty-nine healthy controls were recruited.

All patients and controls were males, Caucasian and right-handed as determined by the Annett Hand Preference Questionnaire (29).

Finally, due to motion artifacts and other technical difficulties, 3 AUD and 5 controls were excluded. Thus, 26 AUD and 24 controls were finally included in analyses at baseline [see Chanraud et al. (6) and the flow chart in Supplementary Figure 1].

The inclusion criteria for the control group were a consumption of less than two standard units of alcohol per week (20 g) during the previous year and a score of ≤5 on the Alcohol Use Disorders Identification Test (AUDIT) (30).

Exclusion criteria for both groups included being under 25 or over 65 years of age, in order to avoid age-related increased brain vulnerability to alcohol abuse (31–33). Other exclusion criteria were left- handedness, non-fluency in French, history of substance abuse or dependence other than caffeine and tobacco, sedative treatment for at least 1 week, axis I disorder (particularly mood and/or anxiety disorders, psychosis), high scores (>5) on the Hamilton Anxiety and Hamilton Depression Rating Scale (HARS and HDRS) (34, 35), malnutrition, hepatic pathology revealed by a ratio of liver enzymes aspartate aminotransferase/alanine aminotransferase (AST/ALT) greater than 2 (36), neurological and somatic diseases including a history of head injury with loss of consciousness, stroke, or other major brain abnormalities observed on MRI scans.

TABLE 1 Characteristics of the three participant groups and whole brain volumes at baseline and follow-up.

| | At baseline | | | | | At follow-up | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Relapsers ($n = 6$) | Abstainers ($n = 11$) | Controls ($n = 24$) | Kruskal-Wallis /Wilcoxon | | Relapsers ($n = 6$) | Abstainers ($n = 11$) | Controls ($n = 6$) | Kruskal-Wallis /Wilcoxon | |
| | Means (SD) | Means (SD) | Means (SD) | Chi2/Z | P-value | Means (SD) | Means (SD) | Means (SD) | Chi2/Z | P-value |
| Age (years) | 44.17 (6.1) | 47.73 (7.52) | 44.25 (7.4) | 2.09 | 0.35 | 50.83 (5.52) | 54.91 (5.8) | 54.33 (4.41) | 1.39 | 0.5 |
| Education (years) | 13.16 (3.54) | 12 (2.19) | 13.54 (3.25) | 1.45 | 0.48 | 13.16 (3.54) | 12 (2.19) | 14.16 (2.56) | 2.10 | 0.34 |
| BMI | 22.16 (1.48) | 23.94 (3.44) | 24.66 (3.1) | 3.81 | 0.15 | 23.31 (1.91) | 24.74 (3.57) | 24.37 (3.57) | 1.03 | 0.59 |
| Age of first drinking (years) | 18.83 (5.53) | 22.18 (10.07) | / | 0.75 | 0.38 | | | | | |
| Age of alcohol dependence onset (years) | 41.75 (7.82) | 49.5 (8.14) | / | 2.28 | 0.13 | | | | | |
| Total years of alcohol dependence | 10.08 (7.26) | 6.9 (5.56) | | 0.65 | 0.42 | 14.94 (7.88) | 7.15 (5.13) | | 0.04 | 0.84 |
| Alcohol family history (yes/no) | 2y/4n | 9y/2n | | Fisher test | 0.11 | | | | | |
| Consumption (SDU) | 27.50 (20.57) | 32.91 (17.54) | | 0.65 | 0.42 | 20 (16.91) | 5.18 (17.18) | | 11.76 | **0.0006** |
| Prior detoxification treatments No | 0.5 (0.54) | 1 (1) | | 0.94 | 0.33 | 3.16 (1.47) | 1.36 (1.63) | | 4.44 | **0.04** |
| Length of abstinence (years) | 0.43 (0.45) | 1.18 (2.58) | | 0.45 | 0.5 | 0.36 (0.77) | 6.02 (0.87) | | 11.19 | **<0.001** |
| Pack-years of active smoking | 32.25 (18.30) | 28.29 (19.31) | 3.04 (8.34) | 22.77 | **<0.0001** | 39.83 (19.36) | 31.80 (20.16) | 2, 62 (6,41) | 10.08 | **0.006** |
| AST (U/l) | 33.83 (20.97) | 24.27 (6.77) | | 0.16 | 0.68 | 21.16 (4.11) | 19.91 (6.36) | | 1.02 | 0.31 |
| ALT (U/l) | 31.66 (19.83) | 23.81 (11.34) | | 1.12 | 0.29 | 19.66 (9.43) | 24.63 (19.96) | | 0.16 | 0.68 |
| Gamma GT | 71.16 (95.41) | 39.63 (43.81) | | 1.58 | 0.21 | 39.5(79.63) | 29.82 (29.4) | | 3.13 | 0.07 |
| HDRS | 1 (1.55) | 0.73 (1.01) | | 6.18 | 0.01 | 1 (0.83) | 0.73 (1.01) | | 0.08 | 0.77 |
| HARS | 1.83 (1.17) | 2.09 (1.51) | | 0.02 | 0.87 | 1.5 (2.35) | 1.09 (1.04) | | 0.04 | 0.83 |
| AUDIT | 31 (4.98) | 35.09 (4.15) | | 2.2 | 0.14 | 13.5 (15.1) | / | | | - |
| MMSE | 28.16 (3.6) | 29.63 (0.67) | 29 (1.21) | 3.1 | 0.21 | 29.17 (0.98) | 29.36 (0.81) | 29.16 (1.6) | 0.27 | 0.87 |
| SAS-SR | 2.80 (0.46) | 2.47 (0.52) | | 1.71 | 0.19 | | | | | |
| CSF volume | 367.67 (40.42) | 376 (65.51) | 306.7 (44.68) | 12.1 | **0.002** | 426 (65.76) | 380, 18 (61.1) | 313 (35.83) | 7.05 | **0.03** |
| GM volumes | 652 (37.9) | 617.27 (52.22) | 653.1 (42.1) | 2.57 | 0.09 | 631 (34.1) | 616, 73 (58.4) | 611.16 (35.7) | 0.39 | 0.82 |
| WM volume | 532.33 (45.46) | 521.27 (39.37) | 543 (50.68) | 3.72 | 0.15 | 505.67 (49.5) | 519, 09 (44.47) | 506.16 (36.36) | 0.20 | 0.9 |
| TIV | 1,551.8 (74.1) | 1,514.9 (123.1) | 1,502.6 (95.7) | 1.4 | 0.5 | 1,562.8 (77.1) | 1,516 (121, 84) | 1,430.8 (97.5) | 5.43 | 0.07 |

R, relapsers; A, abstainers; C, controls. BMI, body mass index; alcohol consumption in Standard Drinking Unit. Drinking Unit. Unity Laboratory norms. AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl-transferase; Tests: AUDIT, Alcohol Use Disorders Identification Test (range 0–40); MMSE, Mini-Mental State Examination; SAS-SR, Social Adjustment Scale Self Report; TIV, Total intracranial volume; GM, Gray Matter; WM, White Matter; CSF, Cerebrospinal fluid. Between-group comparisons were performed using Kruskal-Wallis and Wilcoxon tests. Bold P-values indicate a significant difference between groups ($p < 0.05$).





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The characteristics of the participants' groups are provided in Table 1. The Bicêtre Ethics Committee (CPP-IDF 7) approved the study protocol. All participants received verbal and written protocol information, signed a consent form and received monetary compensation for their participation.

## 2.2. Clinical assessment

Trained psychiatrists (CM, EA, HJA, and JLM) performed a clinical evaluation of all the participants, examined their medical records and biological data at BL and follow up (FU). The presence of an axis I disorder (particularly mood and/or anxiety disorders, psychosis) was evaluated by a clinical interview. Trained psychiatrists (CM, EA, HJA, and JLM) interviewed and clinically evaluated patients, as well as examined their medical records and biological data. The diagnosis was determined after the clinical interview, by consensus of at least two interviewers and according to DSM-IV criteria.

Alcohol-dependence was assessed using the AUDIT and nicotine dependence by the Fagerström test (FTND) (38). Social functioning was evaluated using the Social Adjustment Scale Self Report (SAS-SR) (39), a self-report questionnaire, that evaluates daily functioning, and includes questions on leisure and social activities, relationships, economic status, marital status, children and extended family. Intellectual deterioration was assessed by the Mini-Mental State Examination (MMSE) (40), intellectual efficiency was assessed by the Information Subtest of the Weschsler Adult Intelligence Scale III Third Revision (41), and anxiety and depression were assessed using the Hamilton Anxiety Rating Scale and Hamilton Depression Rating Scale respectively (34, 35).

Moreover, we asked participants to rate among their first- and second-degree family members, the number of problematic alcohol drinkers.

Biological blood tests were performed for all subjects on both BL and FU. On the day of testing, fasting blood samples were drawn to investigate the somatic complications of chronic alcoholism. The panel of tests included liver function tests: aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl-transferase (GGT), carbohydrate-deficient transferrin (CDT), bilirubin, hemoglobin, hematocrit and mean blood volume (MCV). Abstinence was ascertained by normal blood levels of carbohydrate-deficient transferrin (CDT), of gamma-glutamyl-transferase (GGT), and of mean blood volume (MCV).

At FU, the AUDIT and the alcohol consumption self-report since BL were used to retrospectively estimate the quantity and the frequency of their alcohol consumption. Participants were also asked to report the duration and number of relapses and related-detoxifications during the follow-up period (from 0 to 3 detoxifications). Furthermore, we verified these data by reviewing their medical records.

Sub-group's characteristics: sub-groups were formed according to patients self-reported alcohol consumption during the 2 years before follow-up evaluation and confirmed by medical reports and blood alcohol tests [normal blood levels of gamma-glutamyl-transferase (GGT), carbohydrate-deficient transferrin (CDT) and mean blood volume (MCV)].

Abstainers self-reported no alcohol consumption for at least 2 years at FU that was confirmed by available medical records and available laboratory indicators of alcohol consumption [e.g., gamma glutamyltransferase (GGT)], which were within normal limits at follow-up. Relapsers self-reported alcohol consumption in the 2 years before FU, and this was confirmed by available medical records.

The two-year threshold is in line with the literature on long-term abstinent alcoholics, which commonly uses a duration of abstinence of more than 18 months (18, 37, 42) or more than 2 years (11, 43, 44).

All controls remained abstinent: three did not drink at all, one drank one drink per week, one consumed 2 drinks by month and one consumed 2 drinks by year. At 6-year follow-up, all AUD patients and controls were called by phone. The average duration between the baseline and follow-up MRI acquisitions was $77 \pm 5$ months and ranged from 68 to 85 months. Among the initial twenty-six AUD patients, eighteen were still followed in detoxification centers. Of those lost to follow up, two died between BL and FU. An additional research subject was excluded because of an incidental leukemia diagnosis. Five patients were unreachable. Among the twenty-four control subjects, seventeen were unreachable. At FU, a technical problem was encountered during the MRI acquisition of one patient and one control subject.

Overall, 17 AUD (11 abstainers and 6 relapsers) patients and 6 controls were included in the final analyses.

## 2.3. Imaging methods

### 2.3.1. Magnetic resonance imaging acquisition

MRI data was acquired at BL and at FU on the same Signa 1.5 Tesla Whole Body system from General Electrics (Milwaukee, Wisconsin) at SHFJ (CEA, Orsay, France), with a standard 3D T1-weighted inversion recovery fast-spoiled gradient-recalled sequence with identical parameters: axial orientation, matrix = 256 × 192 interpolated to 256 × 256, 124 slice locations, 0.9375 × 0.9375 $mm^2$ in-plane resolution, slice thickness = 1.3 mm, TE = 2 ms, TR = 10 ms, TI = 600 ms, flip angle = 10°, and read bandwidth = 12.5 kHz.

### 2.3.2. Magnetic resonance image preprocessing

Spatial normalization and tissue segmentation in gray and white matter probability maps were performed for all images using the Cat12 toolbox (http://www.neuro.uni-jena.de/cat/), in SPM12 (Statistical Parametric Mapping, https://www.fil.ion.ucl.ac.uk/spm/) implemented in Matlab (https://fr.mathworks.com/help/matlab/ref/edit.html). Gray and white matter segmented images were modulated to compensate for deformations and finally smoothed with a 8-mm FWHM Gaussian filter. Total intracranial volume (TIV) was also estimated using the Cat12 toolbox. Visual quality control was performed for each raw image by one author (RM) and verified by another (CM). Cat12 quality rating was examined, and all preprocessed images were used.

Thus, participants underwent brain scanning both at BL and FU, using the same scanner, head coil, and volumetric MRI sequence parameters.

## 2.4. Statistical analyses

### 2.4.1. Sociodemographic, clinical, and biological analyses

At BL and at FU, socio demographic, clinical and biological data, brain volumes of the three groups (relapsers, abstainers and controls) were compared, with the Jmp 14 software (https://www.jmp.com/fr_fr/home.html) using non-parametric tests such as Wilcoxon and Kruskal-Wallis.

All neuroimaging analyses were performed with SPM12, in whole brain. All scans were free from abnormalities.

### 2.4.2. Cross-sectional voxel-based morphometry analyses

Cross-sectional voxel-based morphometry (VBM) analyses were performed on whole-brain GM and WM images (45) at both BL and FU.

A one-way ANOVA model in SPM was used, with group (relapsers, abstainers, controls) as the between-subject factor and age, years of education and TIV as confounding covariates.

At baseline, analyses were performed with all included controls ($n = 24$), and all AUD patients. Thereafter, we compared the baseline groups from participants included at both times (abstainers $n = 11$, relapsers $n = 6$, controls $n = 6$). At FU, analyses were conducted with all subjects included at both times (abstainers $n = 11$, relapsers $n = 6$, controls $n = 6$).

Statistical height threshold was set at $p < 0.001$ uncorrected, and extent threshold at $p < 0.05$ uncorrected (k = 300 voxels) (46). The get_totals SPM function was used to extract volumes from all significant clusters at BL (http://www0.cs.ucl.ac.uk/staff/g.ridgway/vbm/get_totals.m.).

### 2.4.3. Longitudinal analyses

Longitudinal analyses were conducted using a flexible factorial design (one-way ANOVA for repeated measures) with time (BL and FU) as within-subject factor and group (relapsers, abstainers, controls) as between-subject factor.

As tobacco consumption may have confounding effects (20, 47), we conducted supplementary analyses with the number of cigarette packs smoked per year, entered as covariate.

In the longitudinal analyses, the height threshold was set at $p < 0.001$ uncorrected and the extent threshold at $p < 0.05$ uncorrected (respectively k = 150 voxels and k = 210 voxels for the GM and the WM analysis).

We used the AAL atlas (48) within the xjview toolbox (https://www.alivelearn.net/xjview/) and the JHU toolbox in MRIcron software to locate regions in all VBM analyses (49).

# 3. Results

## 3.1. Participant's characteristics

The three participant groups did not significantly differ in most socio-demographic data, biological variables, rating scales scores and whole brain tissues volumes except for CSF at BL and at FU, as described in Table 1. The duration of alcohol abstinence ($p < 0.0001$), alcohol consumption ($p = 0.0006$) and the number of withdrawals ($p = 0.04$) differed between the two subgroups of AUDs (abstainers vs. relapsers) at FU whereas no difference was found at BL. In addition, AUD patients smoked more than controls at both time points (BL: RvC Z = 4.08; $p < 0.0001$; AvC Z = 3.23; $p < 0.0001$; RvA Z = 0.15; $p = 0.88$; FU: RvC Z = 2.9; $p = 0.004$; AvC Z=2.65; $p = 0.008$; RvA Z=0.45; $p = 0.65$). All patients had good social functioning based on the SAS-SR scale: SAS-SR scale AUD subgroups scores were not different at BL (Table 1).

Thus, AUD patients were split into two groups: relapsers, who had been abstinent for <2 years ($n = 6$; mean 0.36 ± 0.77 years), and abstainers, whose duration of abstinence was >2 years ($n = 11$; 6.02 ± 0.87 years).

It is worth noting that no significant difference in education level, age, or BMI was found between the unreachable ($n = 6$) and the reachable ($n = 17$) controls (Supplementary Table 2).

## 3.2. MRI results

### 3.2.1. Cross-sectional GM analyses at baseline

At BL, the comparison between controls and all AUD patients (controls $n = 24$; AUDs $n = 17$) revealed significant regional gray matter volume reductions in AUDs in bilateral hippocampus and para-hippocampus, left amygdala, bilateral medial frontal, right precentral, left temporal middle gyri and right thalamus (Supplementary Table 3). No larger GM volumes were found in AUD patients compared to controls.

The cross-sectional BL differences between subgroups (controls $n = 24$; relapsers $n = 6$; abstainers $n = 11$) with voxel-wise two-sample t-tests showed that the relapsers had a higher volume than the abstainers in the head of the caudate nucleus (CN) bilaterally (PFWE-corrected <0.05 at cluster and peak levels) (Table 2, Figure 1A). Individual plots of the bilateral heads of the caudate nuclei cluster volumes (in $cm^3$), at baseline, in controls, relapsers and abstainers are represented in Figure 1B to illustrate this result. No significant difference was found among relapsers < abstainer's contrast.

With respect to controls, the relapsers only had a higher volume in the right caudate head ($p < 0.001$ uncorrected at peak level) (Supplementary Table 3).

Compared to controls, the abstainers had lower volumes in the right precentral gyrus, left hippocampus, left medial frontal gyrus, right para-hippocampus and bilateral thalamus ($p < 0$, 001 uncorrected at cluster and peak level) (Supplementary Table 3).

### 3.2.2. Cross-sectional GM analyses at follow-up

At FU, the comparison between the reassessed controls and all AUD patients (AUDs $n = 17$; controls $n = 6$) revealed no significant regional GM volume reduction in all AUDs vs. controls contrasts.

The cross-sectional GM differences between subgroups (relapsers $n = 6$, abstainers $n = 11$, controls $n = 6$) with voxel-wise two-sample $t$-tests still showed higher volumes in the head of the CN bilaterally in relapsers compared to abstainers (see Table 2, Figure 1C). No significant difference was found in the relapsers < abstainers' comparison.

No significant GM volume difference was found between controls and both patient sub-groups (Supplementary Table 3).

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TABLE 2 Gray Matter (GM) cross-sectional analyses: comparisons between relapsers and abstainers: Relapsers > Abstainers.

| | Regions | Cluster level | | Peak level | | MNI coordinates | | |
|---|---|---|---|---|---|---|---|---|
| | | k | p (FWE)-corr | t | p (FWE)-corr | x | y | z |
| **Baseline** | R Caudate Head | 1,091 | 0.007 | 6.21 | 0.01 | 10 | 18 | 4 |
| | L Caudate Head | 899 | 0.016 | 5.58 | 0.049 | −12 | 16 | 0 |
| **Follow-up** | L Caudate Head | 987 | 0.011 | 8.09 | 0.009 | −14 | 16 | 2 |
| | R Caudate Head | 1,055 | 0.008 | 6.09 | 0.161 | 10 | 16 | 0 |

P(FWE)-corr = P Family-Wise Error corrected; BA, Brodmann's area; L, left; R, right. No significant difference for WM cross-sectional relapsers vs. abstainers comparisons, at baseline and at follow-up.

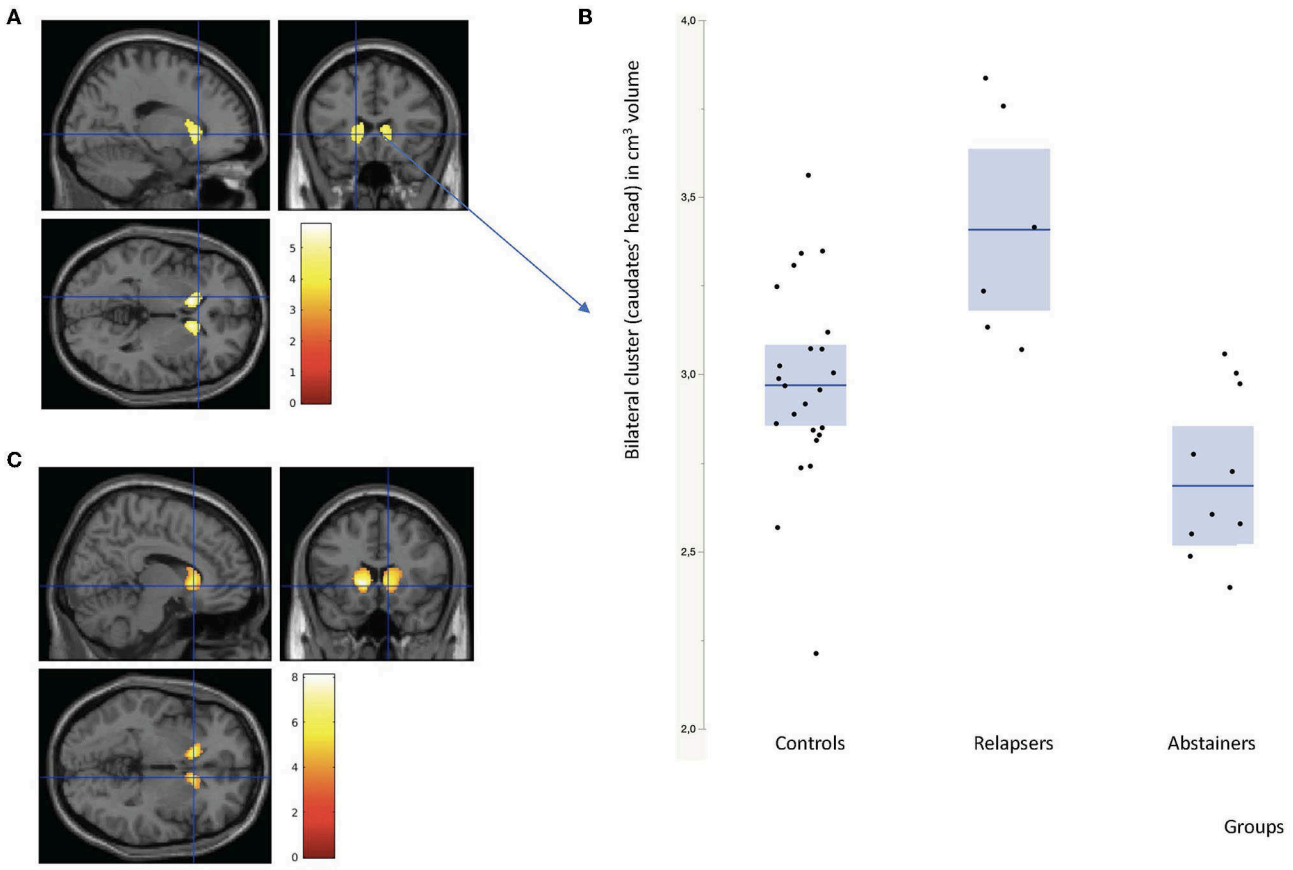


FIGURE 1
**(A)** Gray matter volumes: cross-sectional bilateral caudate nuclei increases in relapsers compared to abstainers Alcohol Use Disorders (AUD) patients, at baseline (height and extent threshold $p < 0.05$ FWE corrected). **(B)** Individual plots: bilateral heads of the caudate nuclei cluster volumes (in $cm^3$) at baseline in controls on the left, relapsers on the middle and abstainers on the right. **(C)** Idem at follow-up (height threshold $p < 0.001$ uncorrected and extent threshold $p < 0.05$ FWE corrected).

### 3.2.3. Cross-sectional WM analyses at baseline

At BL, the comparison between controls and all AUD patients (controls $n = 24$; AUDs $n = 17$) revealed widespread reductions of the regional WM volume in patients in the midbrain, left cerebral peduncle, right retrolenticular part of the internal capsule, superior and inferior longitudinal and inferior fronto-occipital fasciculi, right superior corona radiata and left corpus callosum. Reductions were also detected in the bilateral parietal and left middle occipital, superior temporal, cingulate, middle frontal, left medial and left superior frontal (Supplementary Table 3). No significant WM volume reduction was found in controls compared to AUD patients.

The cross-sectional BL comparisons between subgroups for volumes of WM (controls $n = 24$; relapsers $n = 6$; abstainers $n = 11$) showed no difference between relapsers and abstainers. However, compared to controls, relapsers had significant WM reduction adjacent to the bilateral thalamus, lingual, inferior frontal, and inferior parietal regions, as well as in the left cerebral peduncle, midbrain, and right superior longitudinal fasciculus (Supplementary Table 3). Also, compared to controls, abstainers had lower WM volume in the superior longitudinal fasciculus, left superior corona radiata, left anterior limb of internal capsule (ALIC), right external capsule, sagittal stratum and regions adjacent to the left

putamen and bilateral frontal regions. No WM volume reduction was found in controls compared to abstainers (Supplementary Table 3).

### 3.2.4. Cross-sectional WM analyses at follow-up

At FU, the comparison between the reachable controls and all AUD patients (controls $n = 6$; AUDs $n = 17$) revealed no significant regional WM volume differences, and none were found between subgroups (Supplementary Table 3).

The cross-sectional analysis results are maintained after control by tobacco consumption (pack/year).

### 3.2.5. CSF at both BL and FU

AUD patients had significantly more CSF than controls at both BL and FU (BL: RvC Z = 2.70; $p = 0.007$; AvC Z = 2.79; $p = 0.005$; RvA Z = 0.45; $p = 0.65$; FU: RvC Z = 2.80; $p = 0.005$; AvC Z = 1.66; $p < 0.1$; RvA Z = 0.75; $p = 0.45$).

### 3.2.6. Longitudinal gray matter analysis

For relapsers vs. abstainers, significant time (BL and FU) x group interactions were found in the frontal cortex bilaterally: middle frontal gyrus (BA 9, BA 10, and BA 46), inferior frontal gyrus, pars opercularis (BA 44), and the left precuneus. Other significant clusters include the bilateral middle cingulate (BA 24 and BA 32) (see Table 3, Figure 2A).

GM volume decreased in relapsers over the course of 7 years in all listed regions, while abstainers displayed GM volume increase. An example is given for the middle frontal region in Figure 2B.

For controls vs. relapsers, significant time (BL and FU) x group interactions were found in the pars triangularis of the inferior frontal gyrus bilaterally. *Post-hoc* analyses indicated that relapsers had lost GM volume in this region while it had increased in controls over time.

For controls vs. abstainers, no significant time (BL, FU) x group interactions were found. Supplementary Table 4 reports all time (BL and FU) x group (relapsers, abstainers, and controls) GM volume interactions.

### 3.2.7. Longitudinal white matter analysis

For the relapsers vs. abstainers, significant time (BL, FU) x group interactions were found in all parts of the corpus callosum. The same interactions were found in left anterior limb of internal capsule, bilateral corona radiata, external capsule, in the regions adjacent to caudate nuclei and the cingulate gyrus (all cluster-level PFWE-corrected $\leq 0.05$). Interactions were also found in the left inferior and superior longitudinal fasciculi, inferior fronto-occipital fasciculus, and regions adjacent to the inferior frontal gyrus, pars opercularis (see Table 3, Figure 2C).

For all listed regions, WM volume decreased in relapsers and increased in abstainers over the course of 7 years. An example is given for the left ALIC region in Figure 2D.

For the controls vs. relapsers, significant time (BL, FU) x group interactions were found in regions adjacent to the insula, as well as in the right external capsule, right anterior corona radiata and right ALIC (see Supplementary Table 4).

For the controls vs. abstainers, no significant time (BL, FU) x group interactions were found. The Supplementary Table 4 reports the time (baseline and follow-up) × group (relapsers, abstainers, and controls) WM volume interactions.

## 4. Discussion

Regional tissue volume was different during long-term (7-year) recovery in a Type A alcohol-dependent sample compared with a control group. Yet, the final numbers of participants in each group (primarily abstainers and relapsers and controls) were small and due to the small patient sample, the present findings have to be considered as exploratory. Future studies are therefore necessary to confirm these findings in larger groups. It is however noteworthy that the finding of larger caudate nuclei appears to dissociate specifically relapsers from abstainers both at BL and FU. This main finding is supported by other ones in the present study, which are in agreement with previous literature concerning shorter follow-ups (generally up to 2 years).

In line with the literature, at BL, AUD patients relative to healthy controls showed smaller gray matter volume in limbic structures (hippocampus, para-hippocampus, amygdala) as well as the medial frontal and temporal regions, the precentral gyrus, and thalamus (12, 18, 23, 47, 48). In this same comparison, a significant decrease in the volume of WM is extensive in the brainstem, in the cerebral peduncle, in the anterior regions (the right internal capsule, the superior, and anterior right corona radiata), in the cingulum middle bilaterally and the right inferior and superior longitudinal bundle, in the right fronto-occipital inferior bundle, and in the commissural fibers of the corpus callosum (genu). Volume reductions were also detected in the right superior temporal WM, the bilateral sub gyral and middle frontal WM, in the left median and superior frontal WM, the right parietal WM and in the left occipital WM (49–52). These decreases in volumes of both WM and GM correspond to the parallel increase in the volume of CSF (12, 48, 53, 54) and further confirm our results.

Both at BL and at FU, relapsers had larger heads of caudate nuclei (CN) than abstainers bilaterally.

Longitudinal analyses showed recovery of normal GM volumes in the bilateral middle and inferior frontal, left precuneus and the bilateral mid-cingulate after long-term abstinence. Findings pointed to potential recovery of WM volume in adjacent regions, as well as in commissural tracts, the corona radiata bilaterally, left ALIC, the external capsule and the left superior and left inferior longitudinal fasciculus and the inferior fronto occipital fasciculus.

### 4.1. Cross-sectional gray matter analysis: The caudate nuclei

The finding of larger heads of CN in relapsers compared to abstainers was bilateral and symmetrical at both BL and FU, indicative of its robustness. The longitudinal analysis did not detect any significant change in this region, confirming the stability over time of the larger CN volumes in relapsers. This suggests that the pre-existing CN volume difference at baseline might be associated with a risk of relapse and thus could be a candidate vulnerability factor. It is strikingly consistent with a recent IMAGEN consortium study reporting higher GM volume in bilateral CN at age 14, as a

TABLE 3 Grey Matter (GM) and White Matter (WM) longitudinal analyses: comparisons between relapsers and abstainers.

| Interaction between times (BL–FU) and groups (abstainers vs. relapsers): GM longitudinal comparison | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Regions | BA | Cluster level | | Peak level | | MNI coordinates | | |
| | | k | p uncorr. | t | p uncorr | x | y | z |
| R middle frontal gyrus | 46 | 448 | 0.002* | 5.55 | $1.43 \times 10^{-5}$ | 46 | 40 | 14 |
| L middle frontal gyrus | 10 | 194 | 0.031* | 5.01 | $4.54 \times 10^{-5}$ | −39 | 44 | 14 |
| L inferior frontal gyrus, opercular part | 44 | 166 | 0.044 | 5.01 | $4.58 \times 10^{-5}$ | −52 | 20 | 12 |
| L precuneus/cingulate gyrus | | 437 | 0.003* | 4.96 | $5 \times 10^{-5}$ | −4 | −56 | 27 |
| L precuneus/parietal lobe | | | | 4.78 | $7.41 \times 10^{-5}$ | −6 | −64 | 33 |
| R inferior frontal gyrus, opercular part | 44 | 227 | 0.021 | 4.89 | $5.9 \times 10^{-5}$ | 46 | 10 | 28 |
| R middle frontal gyrus | 9 | | | 4.52 | $1.31 \times 10^{-4}$ | 42 | 3 | 38 |
| L middle cingulate/supplementary motor aera | 32 | 256 | 0.016 | 4.44 | $1.58 \times 10^{-4}$ | −4 | 9 | 45 |
| L middle cingulate | 24 | | | 4.34 | $1.99 \times 10^{-4}$ | −2 | 3 | 44 |
| R middle cingulate | 32 | | | 4.32 | $2.06 \times 10^{-4}$ | 8 | 3 | 46 |
| L middle cingulate | 24 | | | 4.10 | $3.22 \times 10^{-4}$ | −6 | −6 | 39 |
| Interaction between times (BL – FU) and groups (relapsers > abstainers): GM longitudinal comparison: no significative difference. | | | | | | | | |
| Interaction between times (BL–FU) and groups (abstainers vs. relapsers): WM longitudinal comparison. | | | | | | | | |
| Regions | Cluster level | | Peak level | | MNI coordinates | | | |
| | k | p uncorr | t | p uncorr. | x | y | z | |
| L anterior limb of internal capsule/caudate nuclei | 2,511 | $2.52 \times 10^{-7*}$ | 6.81 | $1.12 \times 10^{-5*}$ | −18 | 20 | 8 | |
| Body of corpus callosum/sub gyral frontal lobe | | | 5.33 | $2.27 \times 10^{-5}$ | −16 | 12 | 26 | |
| L cingulum | | | 4, 92 | $5.54 \times 10^{-5}$ | −8 | 21 | 27 | |
| L anterior corona radiata | | | 4, 84 | $6.6 \times 10^{-5}$ | −28 | 22 | 6 | |
| L external capsule | | | 4, 53 | $1.30 \times 10^{-4}$ | −28 | 16 | 6 | |
| R anterior corona radiata | 1,173 | $1.06 \times 10^{-4*}$ | 5.33 | $2.28 \times 10^{-5}$ | 20 | 30 | 0 | |
| Genu of corpus callosum | | | 4, 39 | $1.76 \times 10^{-4}$ | 12 | 26 | 0 | |
| L inferior frontal gyrus, opercular part | 215 | 0.05 | 5.22 | $3.23 \times 10^{-5}$ | −48 | 8 | 8 | |
| WM near R median cingulate gyrus | 214 | 0.05 | 4.71 | $3.22 \times 10^{-4}$ | 9 | −42 | 33 | |
| WM near R posterior cingulate gyrus | | | 3.37 | $3.7 \times 10^{-4}$ | 8 | −42 | 28 | |
| Splenium of corpus callosum | | | 3, 28 | $5.24 \times 10^{-4}$ | 4 | −36 | 16 | |
| L inferior longitudinal fasciculus and inferior fronto occipital fasciculus | 437 | 0.009* | 4.64 | $1.02 \times 10^{-4}$ | −44 | −20 | −14 | |
| L superior longitudinal fasciculus/sub-gyral frontal lobe | 280 | 0.03 | 4.56 | $1.22 \times 10^{-4}$ | −32 | 0 | 28 | |

*Height or extend threshold <0.05 FWE corrected. The height threshold was set at $p < 0.001$ uncorrected and the extent threshold at $p < 0.05$ uncorrected; L, left; R, right. Interaction between times (BL–FU) and groups (relapsers > abstainers): WM longitudinal comparison: no significative difference.

structural brain predictor of a larger increase in alcohol use scores over 5 years, between age 14 and 19 (55). While both studies used voxel-wise analyses methods over the whole-brain volume (Supplementary Figure 2), the present findings in AUD relapsers confirm the location of their CN findings. This is consistent with the hypothesis that larger CN may indirectly denote vulnerability to poor alcohol use outcome.

Several reports below are of note to support this suggestion.

For instance, enlarged CN volume was reported in binge drinkers (56), in cocaine dependence (57, 58) and in methamphetamine dependence (59, 60). Moreover, only a few studies in AUD patients report a longitudinal exploration of the CN volume, notably in Type A alcohol-dependent subjects, and their follow-up durations were much shorter, ranging from 3 weeks to 18 months. Among eleven longitudinal and cross-sectional studies comparing abstinent AUD patients vs. controls, seven did not explore the caudate nuclei volumes (8, 19, 61–65) three did not find any significant difference (24, 66, 67) and one reported a reduction in CN volume (68). Two previous studies comparing AUD patients abstinent for 6 years to controls, but without any longitudinal design, and did not find any

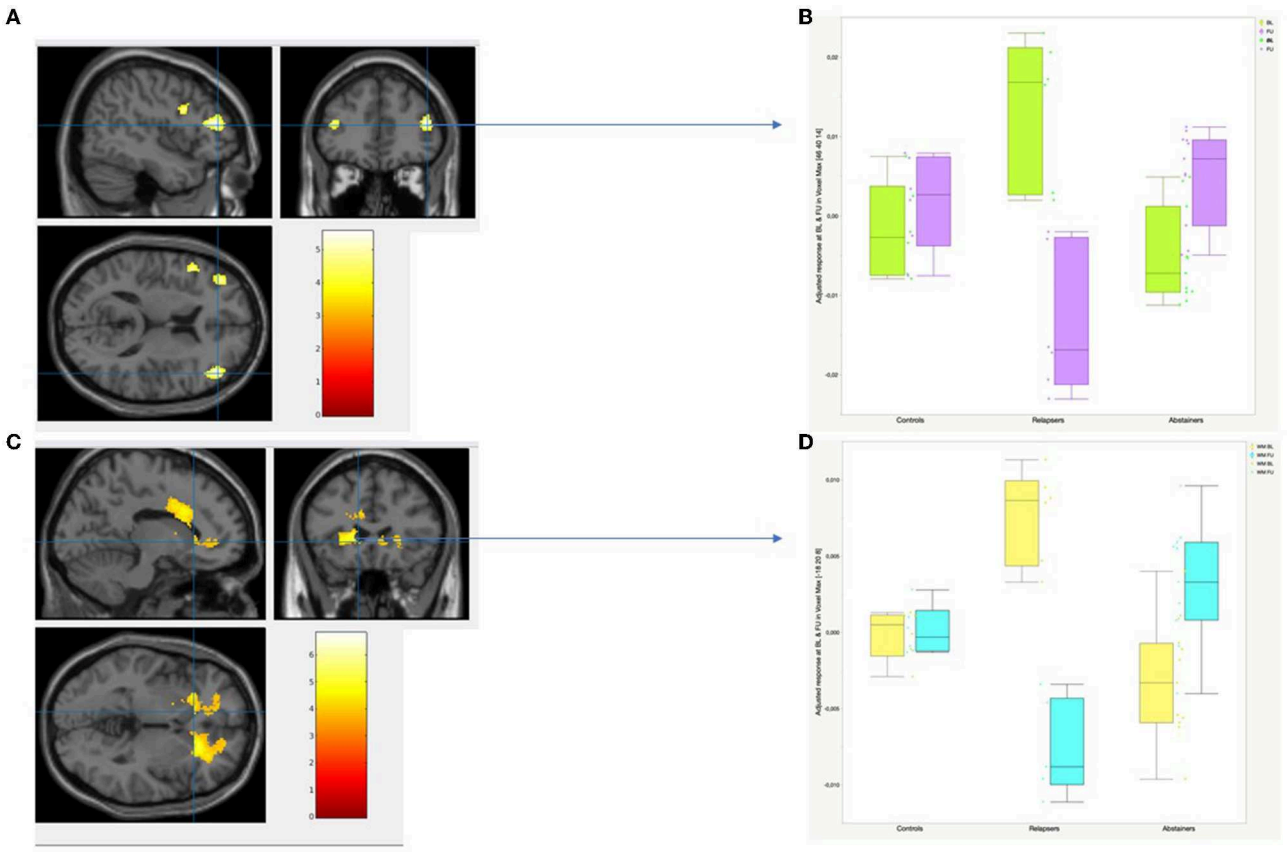


FIGURE 2
Longitudinal gray matter and white matter analysis: Time by Group Interaction. **(A)** 2D views of GM regions showing significant time x group interaction. The height threshold was set at $p < 0.001$ uncorrected and the extent threshold at $p < 0.05$ uncorrected. **(B)** Individual plots and adjusted voxel values at baseline (boxplots in green) and at follow-up (boxplots in purple) in control, relapser and abstainer groups at the highest peak-voxel detected by the Time by Group Interaction in GM (right middle frontal gyrus, BA 46: MNI coordinates: x = 46, y = 40, Z = 14). **(C)** 2D views of WM regions showing significant time x group interaction. The height threshold was set at $p < 0.001$ uncorrected and the extent threshold at $p < 0.05$ uncorrected. **(D)** Individual plots and adjusted voxel values at baseline (boxplots in yellow) and at follow- up (boxplots in blue) in control, relapser and abstainer groups at the highest peak-voxel detected by the Time by Group Interaction in WM (Anterior Limb of Internal Capsule: MNI coordinates: x = −18 y = 20, Z = 8).

difference in CN volume either (42, 69) (see Supplementary Table 1 for a review).

Among twelve longitudinal studies comparing abstainers vs. relapsers, one reported a tendency toward CN volume increase in abstainers (12) at 7-months follow- up, one noted CN volume heterogeneity (20), and five did not find any differences in CN volume between groups (13, 14, 18, 20, 21).

The remaining studies did not explore potential differences in CN volume (9, 11, 15, 17, 22, 26).

Critically, most of these studies used data from patients with comorbidity (addictions and mental health disorders) (see Supplementary Table 1). This variety of subjects contrasts with the homogeneity of our own AUD patient sample, which might account for the detection of higher CN volume in relapsers. The filter used to smooth Jacobian maps could contribute to a difficulty in accurate detection of brain matter volume differences (12). Moreover, we can note other differences in the methodology used in the only longitudinal report over 18-months in abstainers vs. relapsers, which did not find any difference in CN volume, which included the manual delineation of brain regions, with no voxel-based analysis, and a mixed-gender sample (70).

The caudate nucleus mediates higher cognitive functions, including the executive functions and cognitive control (71–73), and is highly connected with the prefrontal cortex (74).

Moreover, the CN is implicated in the reward system (75, 76). The dorsal striatum, including CN and putamen, has been strongly linked to the development and expression of habituation behaviors (72, 77, 78). A link was made between enlarged striatal volumes and higher dopamine synthesis capacity, with an increase in dopamine level in the dorsal striatum, including the caudate and putamen (79, 80). In an fMRI study, when presented with alcohol-associated stimuli, dependent AUD patients showed hyper-activation of the caudate nuclei (81).

These data and the present exploratory results may suggest that individuals who recruit more often or more strongly motivational or reward circuits have larger CNs and are more likely to feel alcohol craving and thus relapse. Replication of our findings in a larger sample could allow further confirmation of this potential risk factor for alcohol consumption relapse. Therefore, supplementary investigations are needed to test the hypothesis of an enlargement of the CN, as an appetitive region, and a risk factor of relapse through automatic behavior.

## 4.2. Cortical gray matter longitudinal analysis

In line with the literature and with our hypotheses, abstainers compared to relapsers showed an increase in GM volume in a number of frontal regions, including the bilateral middle (BA 9, BA 10, and BA 46) and inferior (BA 44) frontal cortex, left precuneus and bilateral mid-cingulate (BA 24, 32). Consistently, previous longitudinal comparisons among abstainers and relapsers mentioned similar results, with a frontal GM volume increase already detected after 4 weeks of abstinence (22). After 3 months (15), then 8 months of abstinence (12), GM volume recovery was reported in the cingulate cortex. After 12 months of abstinence, a GM volume increase was also detected in various frontal regions in abstainers, in the superior frontal gyrus and orbitofrontal cortex (14–16), middle frontal cortex (16), middle and anterior frontal cortices (12), anterior mesial and prefrontal cortices (9), dorsolateral frontal cortex (13), and inferior frontal cortex (26).

We can also note that the consistency of the present findings with the previous literature supports that such volumetric changes can be detected using longitudinal voxel- and pair- wise methods in small and homogeneous groups of abstainers and relapsers followed-up during a longer time.

Herein, no longitudinal difference was detected between abstainers and controls in GM volume. This may indicate a recovery of the cortical GM volume. Previous longitudinal studies comparing AUD patients and controls found smaller volumes in the medial frontal and lateral prefrontal cortices (66). After 7 months of abstinence, a volume increase was reported in the dorsolateral and orbitofrontal cortices (65).

Overall, our results are mostly in line with the literature, showing general frontal hypovolumetry in relapsers compared to abstainers, the latter having possibly recovered GM volumes at long-term (7 years).

## 4.3. White matter longitudinal analysis

In line with the literature and with our hypotheses, relapsers compared to abstainers showed a widespread WM volume increase along with long-term abstinence in the cingulum, inferior frontal and temporal regions and adjacent to the bilateral CN. WM volume increase was also detected in the commissural tracts (genu, body and splenium of the corpus callosum), the corona radiata bilaterally, left ALIC, the external capsule and the left superior and left inferior longitudinal fasciculi, and finally the inferior fronto occipital fasciculus.

This is in line with previous longitudinal reports stating that relapsers compared to abstainers have smaller WM volume after 24 months (11), after 13 months (9) and after as early as 8 months of abstinence, in the brainstem, corpus callosum, cerebellum, bilateral temporal, anterior, and middle frontal WM connected to the bilateral orbitofrontal cortex (12), and in the WM in close proximity to the right frontal cortex and adjacent to anterior cingulate (14). Thus, WM volume starts to increase in a linear manner in AUD patients after at least 7.5 months of abstinence (20, 21) and the present results support that this effect remains on the long-term.

No significant difference in WM volume was found, after 7 6? years, between controls and abstainers, in line with reports of recovered WM assessed by Diffusion Tensor Imaging (20, 21) in abstainers, although with shorter abstinence duration.

On a speculative note, we provide evidence of volume recovery with abstinence in cortical regions and WM, while volumes in appetitive (sub-cortical CN) regions did not vary. Imbalance between the "appetitive" network including the CN, and the "executive" network including the cingulate and prefrontal cortex (82), might therefore lead to a failure to optimize the regulation of relevant functions (follow-up of recent actions, anticipation of results and action choice) that could *a fortiori* increase vulnerability to relapse.

## 4.4. Limitations

Due to our stringent exclusion criteria and the rigorous quality control processes, eligible patient profiles (only male Caucasian subjects, characterized by good social functioning, and preserved executive functions) were rare in a hospital setting. As we included subjects with Babor's Type A alcohol addiction, our results cannot be generalized to all AUD patients. Our sample was homogeneous but small, making our findings mostly exploratory and further studies are needed to extend our results to all alcohol-dependent patients.

Indeed, from the 26 patients and 24 controls recruited at baseline, we were only able to re-include 17 patients and 6 controls at follow-up. Most control participants were difficult to reach and were lost at follow-up due to the long duration of the study. This could explain that we did not find any difference between groups in the cross-sectional analysis, at follow-up.

As we already mentioned, many participants were lost at follow-up due to the long duration of the study but also to technical difficulties (cf Flow chart in Supplementary Figure 1). Consequently, our small sample limited our possibilities to highlight correlations between neuroimaging and neuropsychology.

A technical limitation in long-term longitudinal studies is linked to evolving MRI methods. At baseline, and then at follow-up, we had access to a 1.5 Tesla MRI, but, at follow-up, the acquisition settings had been slightly updated twice. However, the same machine was used for both evaluations. We could have used another MRI machine at high field strengths at follow-up, but this would have created another bias.

Further studies should continue to investigate other typologies of alcohol-dependence, such as Type B alcoholism, which is often associated with family history of alcoholism and related genetic data (*BDNF* gene). Some studies showed that among AUD patients and after 7 months of abstinence, BDNF gene Val/Val homozygotes displayed an increase in hippocampal volume compared to Val/Met heterozygotes (19). Another study showed a caudate nuclei volume decrease among Val/Val after 5 weeks of abstinence, but not among Val/Met (68). Mon et al. (68), showed that caudate nuclei volume recovery in abstinent Type A alcohol-dependent individuals was dependent on *BDNF* genotype. Indeed, among 41 middle-aged alcohol-dependent subjects (including 5 women), who started their heavy drinking around 27 years old and without biomedical or psychiatric disorders, Val/Val genotype patients had a caudate nuclei volume decrease after 5 weeks of abstinence, whereas Val/Met did not. The BDNF Val66Met (rs6265) polymorphism was significantly related to the recovery of regional GM tissue volumes within the first 5 weeks of sobriety, suggesting genetic influences on brain tissue changes during abstinence from alcohol in this Type A alcohol-dependent cohort. The BDNF is associated with neuronal survival, neuronal growth and synaptic plasticity in the adult brain (83). The

allelic association of the A1 allele of the *DRD2* gene with alcohol-dependence was found in males but not in females. This discrepancy could be explained by the gender difference in dopamine D2-like receptor affinity and levels (84). Moreover, it has been shown that the presence of this A1 allele of the *DRD2* gene is correlated with a lower density of the D2 receptor in the striatum, including the caudate nucleus (85).

Overall, these results suggest that caudate volume in males with type A alcoholism could be associated with *BDNF* genotype. In our study, we did not perform genetic analyses due to our small sample and due to the scarcity of genetic assays.

## 5. Conclusions

The present findings raise the hypothesis of higher caudate GM volume to be a candidate risk factor of relapse. In patients with specific type A alcohol-dependence, we showed that long-term recovery in fronto-striato-limbic GM and WM volumes occurs during long-term abstinence. These results support the crucial role of frontal circuitry in AUD.

## 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.

## Ethics statement

The studies involving human participants were reviewed and approved by the Bicêtre Ethics Committee (CPP-IDF 7) had approved the study protocol. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

J-LM obtained funding for the study. J-LM, AB, and CM designed the study and wrote the protocol. EA, J-LM, and CM conducted literature searches and analyses. SC, CM, and H-JA recruited participants. CM, EA, and J-LM conducted their clinical assessments. SC, CM, J-LM, and EA assisted the MR image acquisition in patients and controls. EA conceptualized and designed longitudinal analyses. CM and RM conducted cross-sectional and longitudinal image data processing as well as all statistical analyses. CM, EA, and J-LM interpreted the data, prepared the manuscript and wrote and edited the manuscript. RM, BR, AP, H-JA, AA, SC, and AB critically reviewed the manuscript for intellectual content and edited of final draft. All authors agree for all aspects of this work. All authors approved the final version of the manuscript for publication.

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## Conflict of interest

H-JA is a member of advisory boards or DSMB for Bioprojet, and Ethypharm, and has received sponsorship to attend scientific meetings, speaker honoraria or consultancy fees from Bioprojet, D&A Pharma, Ethypharm, Kinnov Pharmaceuticals, and Lundbeck. He is also a member of the American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initiative (ACTIVE), which was supported in the last 3 years by Alkermes, Amygdala Neurosciences, Arbor Pharmaceuticals, Ethypharm, Indivior, Lundbeck, Mitsubishi, and Otsuka. AB has given talks for Lundbeck, Mylan, Merck-Serono, Bristol-Myers Squibb, and Ethypharm and is a member of the Indivior board.

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.

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1067326/full#supplementary-material

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# Challenges and future trends in wearable closed-loop neuromodulation to efficiently treat methamphetamine addiction

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Achieving abstinence from drugs is a long journey and can be particularly challenging in the case of methamphetamine, which has a higher relapse rate than other drugs. Therefore, real-time monitoring of patients' physiological conditions before and when cravings arise to reduce the chance of relapse might help to improve clinical outcomes. Conventional treatments, such as behavior therapy and peer support, often cannot provide timely intervention, reducing the efficiency of these therapies. To more effectively treat methamphetamine addiction in real-time, we propose an intelligent closed-loop transcranial magnetic stimulation (TMS) neuromodulation system based on multimodal electroencephalogram–functional near-infrared spectroscopy (EEG-fNIRS) measurements. This review summarizes the essential modules required for a wearable system to treat addiction efficiently. First, the advantages of neuroimaging over conventional techniques such as analysis of sweat, saliva, or urine for addiction detection are discussed. The knowledge to implement wearable, compact, and user-friendly closed-loop systems with EEG and fNIRS are reviewed. The features of EEG and fNIRS signals in patients with methamphetamine use disorder are summarized. EEG biomarkers are categorized into frequency and time domain and topography-related parameters, whereas for fNIRS, hemoglobin concentration variation and functional connectivity of cortices are described. Following this, the applications of two commonly used neuromodulation technologies, transcranial direct current stimulation and TMS, in patients with methamphetamine use disorder are introduced. The

challenges of implementing intelligent closed-loop TMS modulation based on multimodal EEG-fNIRS are summarized, followed by a discussion of potential research directions and the promising future of this approach, including potential applications to other substance use disorders.

KEYWORDS

**closed-loop neuromodulation, wearable devices, methamphetamine addiction, EEG-fNIRS, multimodal, neuroimaging biomarkers, TMS technique**

## 1. Introduction

Addiction is defined as a strong need to use a particular substance or engage in a specific behavior, often in spite of harmful consequences. Addiction not only causes personal health problems but can have severe social impacts (1, 2). The most common addictions involve alcohol, drugs, gambling, and smoking; and during the COVID-19 pandemic, the incidence of internet addiction increased owing in part to the limited availability of alternative activities allowed during quarantine (3). However, drug addiction or substance use disorder is perhaps the most severe example, and laws have been established internationally to ban the use, sale, transport, and promotion of specific drugs, including heroin, cocaine, methamphetamine (METH), amphetamine, and cannabis. When an individual first experiences the rewarding effects of drugs, the habit of drug-seeking develops (4). Thus, more of the substance is needed to maintain satisfaction, and the individual experiences an impulse to use the drug even though doing so is harmful to health (5). Followed by increased drug cravings and further resulting in executive dysfunction. These disrupted reward-related processes in the brain cause physical and mental problems. Physically, the immune, digestion, respiration, cardiovascular, and, in particular, neurological systems are often damaged by addiction to drugs (6, 7). Mental health problems include depression, anxiety, psychosis, violence, suicide, etc. (8). Addictions might be a multidimensional disorder that includes several subtypes with different neurobiological underpinnings. This might lead to emotional and behavioral dysregulation (9–11). The effects of dysregulation often associated with increased risk of suicide (9, 12). Moreover, disordered behavior resulting from addiction creates a severe economic burden on families and society (13). Long-term use and dependence typically results in a variety of maladaptive behaviors and negative outcomes, and the current efficacy of existing interventions is limited.

Methamphetamine (METH) has been among the most frequently misused drugs for the past two decades in Southeast and East Asia (14). This is largely because of the geographical proximity to production and trafficking resources (15). To treat and prevent misuse of METH, clinicians and researchers have studied the mechanisms of addiction (16, 17). There are various approaches to treatment, including detox, behavior therapy, and peer support (18), and behavior therapy administered *via* a series of cognitive behavior tasks is currently considered to be the most effective approach to METH use disorder (17). In terms of medical therapy, the search for effective medicines to treat METH dependence and addiction is a hot research topic in the pharmaceutical field (19, 20). However, no promising results have been found. During the treatment process and the follow-up stages after abstinence has been achieved, the most serious challenge in treating METH addiction is relapse. Once relapse occurs, abstinence becomes more difficult.

Conventional approaches to detect METH usage include analysis of sweat, saliva, or urine (21–23). In addition, hair analysis may be used (24). During abstinence, questionnaires are used to evaluate the results of treatment or the risk of relapse (25, 26). However, detection of METH usage *via* these conventional methods is too slow to prevent relapse. Moreover, interpreting the outcomes of abstinence using questionnaires is subjective and can be inaccurate. One mechanism to reduce rates of relapse would be to reduce the preoccupation with and perseverance on METH before these maladaptive thoughts lead to actions. Therefore, real-time monitoring of patients' physiological signals during abstinence before or when cravings arise is an important goal (27, 28). Use of METH and other drugs results in long-lasting brain changes, which can manifest in changes in brain signals when later exposed to cues, drugs, and/or stressors (17). Desires and cravings for METH also cause unique activity patterns in the brain, which can be observed using neuroimaging techniques (29–31). Analysis of brain signals can thus be used to determine whether an individual is or will be experiencing strong desire for METH. Once these biomarkers for METH cravings have been detected, corresponding actions can be implemented to reduce the potential for relapse.

Various neuroimaging techniques have been used to study the influence of METH use on cognitive functions (32). Functional magnetic resonance imaging (fMRI) is a commonly used tool to investigate the changes caused by METH and the recovery process of brain structures during rehabilitations (33). However, the temporal resolution of fMRI is relatively low, and its accessibility is limited. Other non-wearable neuroimaging techniques, such as positron emission tomography (PET) and magnetic resonance spectroscopy (MRS), are also not suitable for real-time monitoring. To achieve a timely response to the onset of craving when an individual is exposed to an environment where the desire for METH is triggered and to increase the efficacy of treatment, real-time monitoring techniques to record neural signal variations continuously are needed.

Electroencephalogram (EEG) and functional near-infrared spectroscopy (fNIRS) are promising tools for brain signal monitoring. Biomarkers in EEG signals have been explored in patients with METH addiction (33). Biomarkers specifically found in fNIRS signals recorded from METH-addicted participants have also been reported (34). Applying a multimodal EEG-fNIRS

neuroimaging technique has many benefits, including enabling better understanding of neural coupling mechanisms compared with analysis of both signals recorded simultaneously. However, few studies have investigated the use of concurrent EEG and fNIRS signals (35). Monitoring such biomarkers not only can confirm the effect of the drug on an individual but also can be used to quantify METH cravings and thus inform treatment (36).

Various intervention approaches are used to help individuals with drug addictions. The conventional treatments are psychological counseling, family support, and legal restriction. These interventions are often planned according to a regular schedule with a set frequency. Family and social support often depend on the willingness and availability of others. Legal restrictions are often applied too late, when drug compulsive use is already established. Achieving abstinence from drug use is a long journey with a need for high self-motivation as well as external influences and legal constraints. Therefore, successful abstinence is a challenge. In contrast to the passive methods mentioned above, neurostimulation has the potential to alter brain activity to reduce cravings for drug use (37). Neuromodulation involves providing electrical, magnetic, optical, or ultrasound stimulation to the specific cerebral locations to interfere with neuron activity (38). Various modulation approaches have been shown to help with the management of neurological disorders such as addictions, resulting in alleviation or improvement in the clinical symptoms of the disorder (39).

Neuromodulations exists as both invasive and non-invasive types. Deep brain stimulation (DBS) is the most frequently reported invasive neuromodulation solution for drug addiction (40). However, invasive devices can cause inflammation, limiting the feasibility of their long-term use. Therefore, non-invasive types are preferred owing to their wearability and accessibility. Commonly employed non-invasive neuromodulations for METH addiction include transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) (41, 42). tDCS changes the excitation states of neurons using low-dose direct currents (43). TMS modulates neuronal activity *via* a local current generated by magnetic fields of coils placed close to the scalp (44). Compared with tDCS, TMS has been shown in one study to achieve a longer and more stable effect against relapse in METH addiction, likely owing to the deeper stimulation depth and more precise targeting area (45). More important, TMS has been approved by the US Food and Drug Administration as an approved therapy for neurological diseases. However, at present, most commercially available TMS devices are bulky, reducing the accessibility of the treatment. Fortunately, applying TMS treatment remotely can increase the impact on the outcome. Therefore, miniaturization of TMS is an important goal. eNeura proposed a handheld TMS device to treat migraine (46). REMED introduced the first compact repetitive TMS (rTMS; using a train of repetitive magnetic pulses) device to initially treat major depressive disorder (47). However, compared with other wearable neurosignal-monitoring devices, such as EEG and fNIRS, portable TMS devices are not user-friendly because of their size and weight. Moreover, the current protocols for TMS therapy for METH addiction are based on the results of previous studies, and the protocol assigned to a patient may not be appropriate for that specific person. In addition, the therapy is often carried out on a regular schedule owing to the limited availability of the devices and device operators. To increase the success rate of TMS therapy for drug addiction, a wearable and compact closed-loop system to accurately provide a timely and appropriate treatment protocol to each person according to their needs is required (**Figure 1**) (48). Conventional open-loop neuromodulation validates the effects by comparing the related parameters before and after the interventions. No timely adjusted neuromodulation protocols can be applied based on the comparison results. In contrast, a closed-loop neuromodulation system can launch a new round of treatment with the optimal protocols for instant abnormal neurological disorders. The closed-loop system can help to determine the time when the treatment might can end.

To achieve effective treatment for METH addiction, three key elements are required for an intelligent closed-loop TMS neuromodulation system based on multimodal EEG-fNIRS measurements: (1) an appropriate measurement protocol for multimodal EEG-fNIRS monitoring, (2) intelligent signal-processing strategies, and (3) customized, user-friendly, wearable TMS devices. Section "2. Materials and methods" introduces the materials and methods of conducting the literatures collection for this review. Section "3. Detection and monitoring techniques for METH addiction" of this manuscript reviews the available techniques for physiological monitoring to detect drug use and addiction, with a particular focus is on wearable EEG and fNIRS neuroimaging approaches. In section "4. Biomarkers of neuroimaging techniques," biomarkers in EEG and fNIRS recordings to identify METH addiction and the progression of recovery during abstinence are discussed. In section "5. Neuromodulation treatments for METH addiction," the most common neuromodulation treatments for METH, tDCS, and TMS are introduced, and research supporting the efficacy of these treatments is summarized. The promising future of the application of intelligent closed-loop TMS modulation based on multimodal EEG-fNIRS for METH addiction is summarized in section "6. Challenges and future trends in treatment of METH addiction," and the challenges to be overcome to achieve an optimized closed-loop system are discussed.

## 2. Materials and methods

We did not conduct a systematic review since this type of review is less common in engineering than in the medical and public health fields. This review aims to summarize the challenges and propose a future trend of a wearable closed-loop neuromodulation system for METH addiction treatment from an engineering point of view based on the available evidence. Our review provides insights into combing the three key elements, biomarkers, real-time signal analysis approach and neuromodulations, of the proposed closed-loop system. We do not aim to find a fixed answer to a specific question or an optimal medical therapy as a standard systematic review does. Neither needs all available evidence to support the concept of the wearable closed-loop system. In addition, the need to reduce the total bias and quantify (statistical analysis) the available results is not the top priority. For building a biomedical system, interdisciplinary knowledge is needed. Therefore, a systematic review might not be the best approach to convey our perspectives.

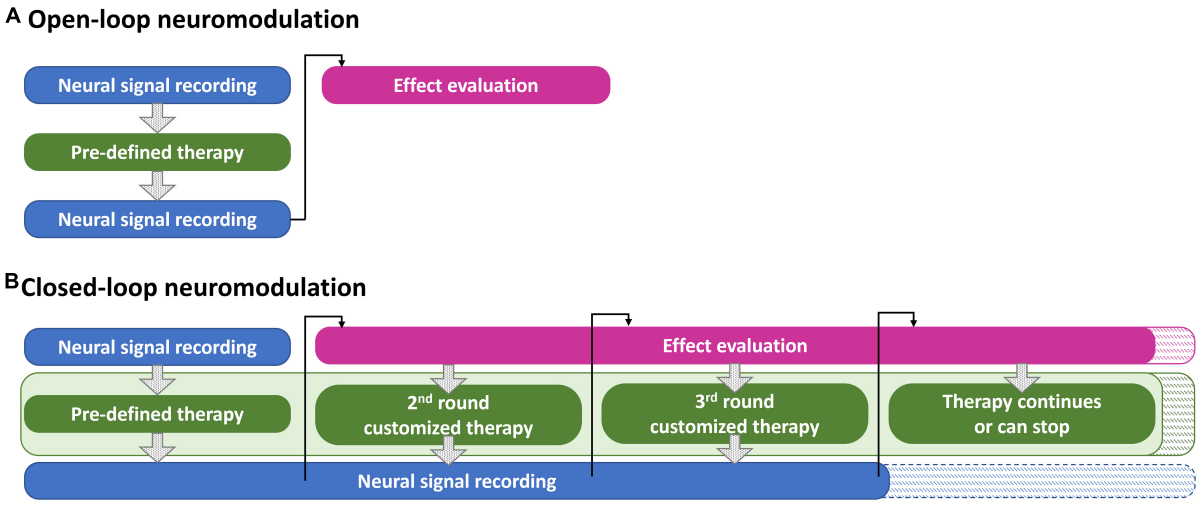


FIGURE 1
The workflow examples of **(A)** an open-loop neuromodulation system and **(B)** a closed-loop neuromodulation system for METH addiction treatment.

Since this review contains a wide subtopic, the key words used for searching the published journal papers are introduced in this section. The databases "Web of Science" and "Google" were used. For section "4.2. Biomarkers of EEG and fNIRS in METH addiction," key words used to search the EEG biomarkers in METH addiction were EEG or Electroencephalography or Electroencephalographic and Methamphetamine or Meth. The keywords used to search fNIRS biomarkers in METH addiction are functional near-infrared spectroscopy, fNIRS, NIRS, and Methamphetamine or Meth. The validated papers suggest potential EEG or fNIRS biomarkers to distinguish the subjects with METH use disorder from healthy ones. In addition, articles that provide biomarker information to classify the subjects of METH use disorder receiving different treatments or at a different phase of abstinence are included in this review article. For section "5.1. tDCS for methamphetamine addiction," key words applied for searching are transcranial direct current stimulation or tDCS and Methamphetamine or Meth. For section "5.2. TMS for methamphetamine addiction," keywords used to explore the related studies are transcranial magnetic stimulation or TMS or theta burst stimulation and Methamphetamine or Meth. Only the studies with solid conclusions that certain tDCS or TMS protocols are helpful to treat patients with METH use disorder are included in this review article. No matter the validation approaches for the outcomes of neuromodulation. The techniques include self-rating scales, questionnaires, cognitive tasks, physiological signals, or neuroimaging. For all the found literature, only those that conducted the experiments on humans are reported in this review article.

# 3. Detection and monitoring techniques for METH addiction

Several approaches can be used to determine if an individual meets the criteria for diagnosis of a dependence or addiction. Subjectively, questionnaires are highly accessible and easily administered to evaluate the condition of drug addiction. Also, various methods are available to quantitatively detect physiological parameters of patients who use illicit drugs or suffer from drug addiction. Some methods detect drugs in biological fluids, while others detect neurological signals. These approaches are discussed in detail in the following sections.

## 3.1. Questionnaires

Various questionnaires have been developed for use before a person becomes addicted to drugs and during abstinence to predict the likelihood of relapse. The Inventory of Drug-Taking Situations is a questionnaire to judge the risk of drug addiction based on everyday situations. Abuse of drugs can be screened for using the assessment tools suggested by the National Institute on Drug Abuse (49). Among the suggested questionnaires, the most popular choice to examine an individual's involvement with a variety of drugs is the Drug Use Questionnaire or Drug Abuse Screening Test (50, 51). To evaluate drug addiction over time, the Desire for Drug Questionnaire can be used to rate instances of cravings for drugs, whereas the Obsessive Compulsive Drug Use Scale evaluates cravings over a period of time (52). Regarding the effects of the drugs, the Visual Analog Scale (VAS), a visualization scale, is helpful for quantifying levels of craving for drugs. In addition, the Addiction Severity Index is used to evaluate overall issues, from personal to family and society, in the context of drug addiction (53).

As drug addiction affects has both physical and psychosocial effects, scales that characterize anxiety, depression, or impulsivity resulting from drug abuse are often used to obtain a broad view dependence and substance abuse. These scales include the 21-item Beck Anxiety Inventory, 21-item Beck Depression Inventory, and 30-item Barratt Impulsiveness Scale-11 (54). For the assessment of drug abstinence, the Drug Abstinence Self-Efficacy Scale is available (55). During the withdrawal period from drug use, the Subjective

Opioid Withdrawal Scale, for example, can be used to check the symptoms of withdrawal (56), and the Methamphetamine Withdrawal Questionnaire was developed to specifically evaluate METH withdrawal-related symptoms (57). The Risk of Relapse Assessment Scale can be used to determine the possibility of relapse (26), while another option is the Stimulant Relapse Risk Scale (58). Furthermore, the Time to Relapse Questionnaire has been proposed to distinguish two types of relapses, with or without forewarning, to enable better treatment (59, 60).

Although questionnaires are the most convenient and broadly accessible approach for a variety of drug addiction-related applications, the results of the scales have limited reliability and accuracy. As the results of these scales are based on the answers of the respondents, the results exhibit individual variations and are influenced by the attitudes and conditions of the participants (61). Moreover, clinicians are often needed to draw conclusions about the severity of addiction based on the results of the scales and consultations. These limitations restrict the scope of application. Therefore, questionnaires often need to be combined with physiological tests to strengthen their conclusions about addiction, withdrawal, abstinence, or relapse.

## 3.2. Conventional detection techniques and emerging wearable techniques

In addition to questionnaires, saliva, urine, and blood tests are conventional ways to quantitatively detect drug use (22). Nail and hair also contain evidence of drug use with a detection window lasting from weeks to months (62, 63). Moreover, breath analyzers can be used to detect the drug in the breath (64). However, the time windows of the above conventional methods are limited. Moreover, they cannot provide real-time results owing to the time-consuming nature of the required examination and analysis procedures. Emerging wearables are promising options to detect biomarkers in real-time (27, 65), most commonly using sweat to screen for drugs using electrochemical techniques (66). Other body fluids containing drugs are saliva and tears. However, it is sometimes difficult to obtain sufficient body fluids for accurate sensing. In addition to electrochemical sensing of body fluids, wearables can detect other physiological parameters to predict or determine addiction to drugs: these include electrocardiographic (ECG) parameters, heart rate variability (HRV), breath rate, and skin conductance response/galvanic skin response (SCR/GSR). Both heart rate (HR), determined by the R-R interval of ECG signals recorded from a chest band and breath rate increase with increasing dosages of cocaine (67). Other parameters available in ECG waveforms for drug addiction evaluation are the QT, PR, QRS, and QTc intervals and the height of T waves, as summarized in previous work (67). Regarding the morphology of the breathing waveform, the time and depth of inhalation and exhalation, and respiration duration are features used to predict drug-seeking and craving for drugs. Furthermore, a wristband is another option to identify the use of cocaine based on recorded skin temperature, heartbeat, motion, and SCR (28, 68). HRV can be used to evaluate stimulation in individuals with METH addiction *via* virtual reality (VR) (69) and SCR increases in patients with METH addiction when receiving specific cues (70); importantly, longer use of METH results in a stronger physiological reaction to the cues. Owing to the ease of access and user friendliness of wristband devices for ECG recording, the effects of aerobic exercise on the HRV parameters of patients with METH addiction have been investigated (71). HRV can be further separated into high-frequency HRV and low-frequency HRV. In addition to the frequency domain, parameters can be derived from the recorded time domain of HR, including the standard deviation of normal-to-normal intervals, root mean square difference of the standard deviation, and percentage of beats that change by more than 50 ms compared with the previous beat.

In addition to ECG and HR, drug abuse has effects on pupil size (72). The features of ECG, GSP, and eye tracking that can indicate METH addiction are summarized in Tsai et al. (73). Wearables can be used not only to monitor physiological signals but also to track the psychological impact of drug addiction. For example, the information obtained from accelerometry and GPS location is useful in characterizing the cravings resulting from the addiction (74, 75). Owing to the large variety of the features available to diagnose drug addiction or the resulting psychological changes, machine learning (ML) has been introduced to increase the precision of the analyzed results; more information will be provided in section "6.1.2. Analysis of recorded neural signals."

The wearable techniques presented in this section are used to measure the physiological reactions of the autonomic nervous system caused by drug usage. However, drug addiction also affects the central nervous system (7). We believe that the development of a closed-loop system for overall management of drug addiction would provide substantial value, regardless of whether patients are still using drugs, in the abstinence stage, or aim to reduce the rate of relapse rate. Application of this closed-loop system would rely on neuroimaging techniques, being the most straightforward approaches for brain studies, to identify and characterize the brain signatures of drug addictions.

## 3.3. Neuroimaging techniques

Whereas the wearable technologies discussed in the previous section can be used to monitor physiological changes in the body as relates to drug use and withdrawal, clinicians and researchers are also keen to learn how drug use influences the control center of the body, the brain. The process of developing an addiction includes several phases, including drug intoxication, craving, binging, and withdrawal with loss of self-control (76–78). A series of complex changes occur, including modification of brain structures as well as mental and physiological changes, resulting in various symptoms such as depression, impulsiveness, anxiety, aggression, and many other psychological problems (11). Consequently, a tool to monitor the response/effect of a neuromodulation treatment is a need for a closed-loop system. Neuroimaging techniques provide opportunities to monitor the overall process of the functional modifications of the central nerve system in various conditions (79). Therefore, they are suitable to study the mechanisms of neurological disorders (76, 80).

Neuroimaging approaches can be separated into two categories: those that can be used to examine the structural changes at different stages of drug dependence and addiction to understand the physiological mechanisms of addiction (30), and those that

monitor the functional brain changes that occur as a consequence of addiction (77). MRI, MRS, and single photon emission computed tomography are used to inspect structures in patients with METH addiction (31, 32, 81). PET is used to study the impact of drug addiction on the brain at a molecular level, in order to find the optimal brain location for treatments (82). fMRI is a powerful tool to evaluate hemodynamic conditions after the neurons have been activated by specific tasks (83, 84). The studies investigating the relationship between METH use and cognitive function using neuroimaging techniques have been summarized elsewhere (32).

Although these neuroimaging techniques provide high spatial resolution, they have limitations. For instance, the devices required are costly and bulky, with low accessibility, and trained operators are needed to conduct the examinations. Moreover, MRI may not be suitable for patients with metallic implants, and the use of radioactive agents in PET limits the frequency of examinations. Furthermore, those with claustrophobia may find it difficult to participate the examinations owing to the spatially confined test environment that is needed. Low temporal resolution also restricts the application of real-time monitoring.

Wearable devices, being compact and easy to access, are appropriate for real-time monitoring of neural activity. Owing to their user-friendly implementation, wearable neuroimaging devices have been widely used to study the outcomes of various treatments, including the effects of exercise on parameters of drug addiction (85). Another example is the evaluation of cravings to predict the risk of relapse during abstinence. Real-time signals recorded in a natural environment provide more reliable information than could be obtained under stressful conditions using bulky equipment.

Electroencephalogram can be used to record brain cortical electrical activity *via* electrodes attached to the individual's head. It is popular in research and clinical studies owing to the high temporal resolution of afforded by this approach. This benefit enables EEG to be used to record variations in neural activity when patients receive drug-related stimuli or experience the desire for drug taking.

When neurons change their activity patterns, such as during different phases of addiction, the local hemodynamic conditions in the brain change, resulting in neurovascular coupling (86). Whereas EEG can monitor electrical signals in the brain, fNIRS is a popular wearable device for monitoring the hemodynamic conditions of the brain, enabling these two to be used in combination. For example, the prefrontal, dorsolateral prefrontal, and orbitofrontal cortices are responsible for decision-making (30). When patients with drug addiction use the drug or receive cues related to it, this can change the activity patterns of these brain regions. This results in alternations in oxygenated and deoxygenated hemoglobin concentrations, which can be recorded using fNIRS at the corresponding cortices (87). Studies have shown that changes in these concentrations in patients with drug addictions are different from those in healthy controls (88). In addition, with its advantages of being light, compact, wearable, highly accessible, and user-friendly, fNIRS is becoming a popular tool to study the effects of exercise on drug addictions. For instance, fNIRS has been used to evaluate the effects of spin training and strength training on those with a METH addiction (89). Another study used fNIRS to evaluate the effects of dancing and exercise on aspects of meth addiction (90). As well as its applications in analysis of the hemodynamic variations influenced by exercise, fNIRS has been used to investigate the relative hemodynamic changes at different cortical regions in the brain (91). For example, a classification algorithm based on the fNIRS signals at various brain cortices was used to distinguish addictions to different drugs.

Neurovascular coupling indicates that electrical neuron signals are closely related to hemodynamic conditions. In neurovascular coupling, when neuronal activity is elevated, more oxygen is delivered to the activated brain regions, resulting in a local increase in oxygenated hemoglobin. As EEG measures neural electrical activity whereas fNIRS monitors hemodynamic activity, multimodal EEG-fNIRS recording provides a more holistic measurement, enabling a more comprehensive understanding of the effects of drug use and withdrawal on the brain (86). This dual approach has recently been used in several studies, for example, multimodal EEG-fNIRS has been used to study the brain activity of those with a METH addiction under visual stimulation (92, 93), whereas another study used multimodal EEG-fNIRS for those with an opioid addiction (94).

A further benefit of wearable systems is that they can be applied without the limitations of time and location, with a minimal influence on social activity. Consequently, multimodal EEG-fNIRS systems are suitable for evaluation of the efficacy of treatment and rehabilitation. An important goal during treatment and rehabilitation is the reduction of the incidence of relapse. Craving is a key symptom that promotes relapse to drug use; thus, identifying brain activity patterns during, immediately before, and immediately following cravings could help to optimize treatment and rehabilitation programs. For example, if we could identify the neuronal signatures of craving, we could trigger a closed-loop stimulation protocol to combat these activity patterns, or provide alternative interventions. In addition, brain signal monitoring can provide more information on changes in psychological and physiological conditions than the wearables measuring ECG, HR, and GSR mentioned in section "3.2. Conventional detection techniques and emerging wearable techniques." Notably, including as many modalities as possible in the wearables would increase their diagnostic precision.

It has been suggested that wearables could be used to track the efficacy of treatment of those with a drug addiction (65). However, the propensity for interventions based on this approach alone is limited. To more effectively reduce rates of drug use and relapse, a closed-loop system to provide real-time treatment that is customizable to each specific case is needed (95). Such a closed-loop system would consist of three parts. The first part is neuroimaging, which can be achieved using multimodal EEG-fNIRS devices. The second involves computational algorithms to identify the neuronal and/or hemodynamic activity biomarkers of addiction. Finally, the loop is closed by neuromodulation approaches that provide stimulation of targeted brain areas to combat pathological activity changes related to addiction.

## 4. Biomarkers of neuroimaging techniques

In a closed-loop system, the treatment protocol can be optimized according to the real-time signals from the neuroimaging recording. Approaches to stimulate cues to further

evaluate the level of desire for the drug are introduced in section "4.1. Stimulation cues." The EEG and fNIRS biomarkers used to identify drug addiction are presented in section "4.2. Biomarkers of EEG and fNIRS in METH addiction."

## 4.1. Stimulation cues

Approaches to investigating brain signal changes influenced by drug addiction include comparing recorded signals from those suffering from addictions with control populations, or comparing the signals of those suffering from an addiction across the addiction cycle. One approach to minimize the acute and long-lasting effects of drug intake on the participants during attempts to identify brain signal biomarkers, drug-related cues can be applied as alternatives to drugs. This approach is used because the variations in autonomic nervous system and brain signals occur not only after the presentation of drug use but also after cues. To identify useful biomarkers to distinguish addiction and control groups, protocols including various stimulations to provoke cue reactivity have been proposed (96). Cues can be videos, photos, audios, or VR of the drugs or individuals using the drugs. This approach has been done before using MRI and EEG. In these studies, it was found that VR induced more cravings than other stimulation types (97, 98). Natural cues are included as important controls to identify drug-specific cue responses (99). Natural cues can be categorized into those with limited connections to drugs and those that share some features with drug-related cues. The former types may include natural scenes such as trees and flowers, while the latter types could be, for example, a person holding a screwdriver close to the face. This may trigger thoughts of METH use because a screwdriver may appear similar to the use of a long tube typically used for METH consumption. Therefore, placing a different tool of a similar shape close to the face can induce desire for the drug. Another example of the latter type is a light bulb, which may look similar to a METH pipe. It has been demonstrated that these natural cues have common features with the drug-related ones that in turn induce higher levels of craving and desire (100).

As drug-paired cues are highly salient, emotional responses are influenced when an individual receives cues (101). Therefore, when neuroimaging signals are recorded, scales are applied to evaluate changes in emotions, such as valence, arousal, and craving (100). Measuring both the neural signals and the score on emotional scales provide more comprehensive information for over multiple physiological and behavioral dimensions.

Although cues provide an opportunity to distinguish those suffering from an addiction from healthy controls, experiments in which drug-related cues are provided to the participants have potential ethical issues. For example, the risk of relapse may increase after stimulation by drug-related cues. One alternative approach has been recorded, brain signals when participants are involved in cognitive tasks, to differentiate those suffering from an addiction from healthy controls (32); for example, in one study, EEG signals were analyzed when patients with METH addiction performed cognitive tasks, including the N-back task to assess working memory and Stroop task to assess attention (102).

Furthermore, it has been reported that without cue stimulation and cognitive testing, the resting state brain of those suffering from an addiction and healthy individuals exhibit differences (94, 103). Monitoring the brain signals altered by the METH addiction and tracking the recovery process at resting state is an attractive approach because no additional efforts are needed to implement the drug-related cues and synchronize the cues and recorded signals or to arrange a supervisor to conduct cognitive assessments.

## 4.2. Biomarkers of EEG and fNIRS in METH addiction

Biomarkers of neuroimaging techniques are not only used to distinguish those suffering from drug addiction from healthy controls, but they are also widely used to evaluate the efficacy of abstinence, exercise, and medical interventions. The biomarkers of EEG signals that have been shown to characterize the brain activity of those suffering from METH addiction are listed in **Tables 1**, **2**. The biomarkers were determined by comparing the recorded EEG signals from patients with a METH addiction with those of healthy controls. The brain signals were recorded when participants received various METH-related cues (see section "4.1. Stimulation cues"), after conducting cognitive tasks, or during resting states. The EEG biomarkers that can identify the patients with a METH addiction can be categorized into three types based on the analysis approaches used. First, the time-domain EEG signals can be converted to frequency-domain signals to reveal the spectral information of EEG sub-bands. The sub-bands of each frequency range represent different conditions affected by METH (54, 85, 104–110) of **Table 1**. The entropy of the EEG signals at a specific frequency range can be derived from the spectrum of that frequency range (104). The second type of biomarkers are based on time-domain signals. As EEG records neural activity on a millisecond timescale, the neural signals triggered by stimuli (visual, audio, etc.) show specific wave forms, namely the event-related potential (ERP) (111, 112).

The third type of EEG biomarker can be visualized by the topography of the data (**Table 2**). The advantage of plotting brain signals topographically is that signal variations throughout the cortex can be evaluated. Brain activity is typically not localized to one specific region, but rather observed as coordinated activity throughout multiple connected regions. Functional connectivity (FC) in this case refers to the level of connectivity of each channel and the connectivity between cortical regions (54, 113–117). FC can be analyzed by processing an EEG signal using various approaches. Some studies have considered the coherence of the EEG sub-bands of electrode pairs (113, 116). However, coherence neglects the non-linear relationship between the channels. Therefore, another study used visibility graph similarity as a non-linear approach (113). Later, the weighted phase lag index (WPLI), a modification of the phase lag index (PLI), was used for FC analysis. Compared with coherence, PLI (117) and WPLI can better indicate the delays in signals between channels (54, 114, 115). Parameters of such graph theory analyses include node strength, characteristic path length (L), clustering coefficient (CC), and small-world index (SWI), which is derived as the ratio of CC to L. Moreover, the network hub(s) can be identified by the node strength, betweenness centrality, and eigenvalue centrality. These parameters can be used

TABLE 1 Biomarkers of EEG signals in frequency and time domains on patients with methamphetamine addiction.

| References | Comparison conditions | Groups for comparison | Number of the electrodes and their locations | Biomarkers | Main limitations |
|---|---|---|---|---|---|
| Newton et al. (104) | Eye-closed resting state during abstinence | METH (with 4 days of abstinence) versus HC | 35 electrodes distributed across the scalp | Increases: delta and theta bands across the scalp | Patients with another period of abstinence can be investigated. |
| Newton et al. (105) | Eye-closed and cognitive tasks | METH (with 4 days of abstinence) versus HC | 35 electrodes distributed across the scalp | Increases: theta band increases with the increasing of the reaction time of cognitive tasks | Difficult to identify that the EEG biomarkers have resulted from METH use disorder or other health issues. |
| Yun et al. (106) | METH users at abstinence stage. Eye-closed resting state. | METH versus HC | 16 electrodes distributed across the scalp | Decreases: approximate entropy | Patients are separated in to high- and low-dose of METH groups by their duration of METH use, not by the cumulated dose. |
| Kalechstein et al. (107) | 2.5 h of neurocognitive assessment tests | METH versus HC | 35 electrodes distributed across the scalp | Increases: theta band correlation with poor performances on cognitive tasks | The changes of biomarkers along with varies abstinence time can be further studied. |
| Howells et al. (108) | Resting eyes closed, eyes-open and a cognitive task | METH versus HC | 6 channels (F3, F4, C3, C4, P4, and P4) | Increases: delta/alpha ratio | Future studies are needed, including a wider variety of mental disorders in METH patients. |
| Ding et al. (109) | Drug-related and neutral VR | (1) METH versus HC<br>(2) METH versus neutral cues | 5 channels (Fpz, AF7, AF8, TP9, and TP10) | (1) Increases: beta and gamma<br>Decrease: delta and alpha<br>(2) Decrease: delta, theta, and alpha | Be cautious when applying the machine learning modal built from male-only patients on female patients. |
| Lu et al. (85) | METH users received anaerobic resistance treatment (RT) and aerobic cycling treatment (CT).<br>Test conditions are eyes closed (EC), eyes open (EO), and drug-related and neutral cues | (1) METH with exercise (RT or CT) versus METH without any exercise<br>(2) Before and after exercises | 64 electrodes distributed across the scalp | (1) Increases: absolute power of theta, alpha, and beta bands on RT group during EC; the alpha block rate on RT group during EO and drug cues<br>Decreases: mean frequency on RT group during drug cues<br>(2) Decreases: brain lateralization index on RT group during EC | Lack of a healthy control group. |
| Minnerly et al. (110) | Eye-closed resting state | METH versus HC | 19 electrodes distributed across the scalp | Increases: delta and theta bands across scalp<br>Decrease: alpha | Did not apply AI algorithm to reduce the analysis workload of extensive data. |
| Zhao et al. (54) | Visual stimuli (video) then eyes-closed resting state | METH users in abstinence for 1–3 months versus other abstinence lengths | 128 electrodes distributed across the scalp | Increases: beta across scalp<br>Decreases: theta and alpha | No comparison with healthy control and no longitudinal measurements on the same patient. |
| Shahmohammadi et al. (111) | METH users at abstinence stage. Visual stimuli (drug-related, drugs and neutral images). | METH versus HC | 32 electrodes distributed across the scalp | Increases: P300 peaks of the event-related potentials (ERP) | All METH patients had history of cigarette smoking and no healthy subject had the history. This might influence to results. |
| Khajehpour et al. (112) | Visual stimuli (drugs and neutral images) after tDCS | Biomarkers mean the difference of the biomarkers of watching drug related cues and neutral cues. METE users before versus after treated with tDCS. | 62 electrodes distributed across the scalp | Increases: P3-related late positive potential (LPP) component of the ERP<br>Decrease: P3 component | Repetitive tDCS was not applied, only a single session tDCS is conducted. |

GSR, galvanic skin response; HC, healthy control; tDCS, transcranial direct current stimulation; METH, methamphetamine.





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TABLE 2 Biomarkers of EEG signals in functional connectivity (FC) network and network topological properties on patients with METH addiction.

| References | Comparison conditions | Groups for comparison | Number of electrodes and their locations | Biomarkers* | Main limitations |
|---|---|---|---|---|---|
| Ahmadlou et al. (113) | Resting state | METH (with 1–3 weeks of abstinence) versus HC | 31 channels distributed across the scalp | Increases: CC and the CC/L of gamma band in the small world network (SWN)<br>Decreases: L of the gamma band in the SWN | The backgrounds of the METH and HC groups may not be similar. |
| Khajehpour et al. (114) | Resting state | METH (during 1–6 months of abstinence) versus HC | 62 electrodes distributed across the scalp | Increases: CC and SWI in delta and gamma frequency bands<br>Decreases: L in delta and gamma frequency bands<br>Abnormal changes: inter-regional connectivity and network hubs in all the frequency bands | HC can have a smoking, drinking, or caffeine history, which may affect the results. |
| Khajehpour et al. (115) | Resting state | METH versus HC | 64 channels on the overall scalp | Decreases: WPLI of beta bends | Only male patients were included. |
| Shafiee-Kandjani et al. (116) | Resting eyes closed and eyes open | METH versus HC | 19 channels on occipital, temporal, frontal, and parietal lobes | Decreases: coherences of the delta and theta band on the left frontoparietal cortices (F3Fz and C3Cz) | Coherences were used to study the linear relationship of the signals. However, brain signals seem to have more non-linearity properties. |
| Zhao et al. (54) | Visual stimuli (video) then eyes-closed resting state | METH users abstinent for 1–3 months versus other abstinence lengths | 128 channels distributed across the scalp | Increases: WPLI between medial prefrontal cortex and bilateral orbital gyrus in the beta band | No comparison with healthy control and no longitudinal measurements on the same patient. |
| Qi et al. (117) | Resting state with eyes open. METH users in control group, dancing group, and bicycling group | METH with exercises versus control group | 64 channels distributed across the scalp | Increase: brain flexibility and network connectivity entropy<br>Decrease: mean frequency and beta relative power | Lack of data from healthy subjects. |
| Chen et al. (102) | Resting state | METH versus HC | 64 channels distributed across the scalp | Increases: GEV of 1 microstate (customized microstate C)<br>Decreases: MMD of 2 microstates (customized microstates A and B); GEV of 1 microstate (microstate B) | Simultaneously MRI recording will be helpful to compare with the microstates data. |
| Lin et al. (118) | Resting state with eyes open; then visual stimuli of METH cues with VR | (1) METH under cues versus resting;<br>(2) METH versus HC | 32 channels on the overall scalp | (1) Increases: coverage and occurrence of microstate B, transitions of microstates B → D and D→ B pairs<br>Decreases: coverage, duration, and occurrence of microstate A, occurrence of microstate C, transitions of microstates A → C and C → A pairs<br>(2) Increases: coverage of microstate A<br>Decreases: coverage and occurrence of microstate B | The number of microstates was limited to 4 during the analysis. Results might change with other numbers of microstates. |

CC, clustering coefficient; GEV, global explained variance; HC, healthy control; L, characteristic path length; METH, methamphetamine; MMD, mean microstate duration; SWI, small-world index; WPLI, weighted phase lag index. *The microstates discussed in this table were derived based on individual EEG recordings (102, 118). In other words, microstates with the same names may have different topographies in different studies.





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as features of ML models to classify and differentiate those with METH addiction from healthy subjects (115).

Other EEG biomarkers represented by topography include EEG microstates that show the spatial distribution of electrical signals recorded by the electrodes over the scalp (102, 118). The dynamic changes of these electric potential states can be validated by examining a consecutive set of topographies. EEG microstates represent an emerging technique for analysis of EEG signals, especially at resting states. The parameters used to investigate microstates are the mean states duration, total time covered/coverage ratio, global explained variance (GEV), occurrence, and transition probability. Studies to date have been limited because the number and type of microstates are optimized differently, depending on the database used. Fortunately, most microstates derived from the resting state of healthy subjects of different studies comprise four representative states, where each state corresponds to specific neural activity patterns, such as visual or audio responses. However, microstates of people with neurological diseases or actively engaged in task-related states (e.g., receiving cues or being involved in a cognitive task) vary across studies (118). Therefore, interpretation of results is not always straightforward, and comparisons between different studies can be challenging.

In the EEG spectrum analyses summarized in **Table 1**, one approach is that an individual electrode is inspected only when the number of electrodes is small (108). Alternatively, the spectrum of individual electrodes is calculated, then representative channels are selected for further investigation (111). In studies with larger numbers of electrodes, the average EEG spectrum of all electrodes is often investigated (54, 85, 104–107, 109, 112). Lu et al. and Minnerly et al. studied changes in the EEG spectrum of different brain regions (85, 110). The former separated the brain into four areas, whereas the latter separated the cortices using five different approaches. A lower number of EEG channels reduces the preparation time when the region of interest is well known. However, increasing the number of electrodes allows for studying FC across various brain regions.

Some studies had explored EEG biomarkers when subjects had their eyes closed but were not asleep; this is done to reduce the disturbance due to non-task related visual stimuli (104–106, 108, 110). Other studies report the identification of biomarkers specifically when the subjects had received cues (85, 109, 111, 112). Some studies included cognitive tasks in the experiment protocols. However, most of these studies only analyzed the correlation of the level of cognitive impairment (e.g., the reaction time and the response accuracy) and the EEG spectrum (105, 107). Few studies have monitored the variation in the EEG spectrum during cognitive tasks (108). For future applications in closed-loop neuromodulation systems, the biomarkers found when the participants were simultaneously receiving cues may be more helpful than, e.g., at a resting state, as the use of cues can more accurately simulate the conditions of having a desire for a drug.

In addition to the EEG signal, FC is often studied in the resting state as well. In the task state, the connectivity needs to be analyzed in every pair of channels at every point of interest, resulting in a heavy computational load. This is because the brain is engaged in various tasks at different stages along with the task. Only the data of a selected resting time period is calculated in the resting state. For this reason, in the task state, only the channels of interest are often analyzed to reduce computational load (54). Only one study has evaluated the effects of exercise on those with METH addiction using EEG signals (116). In this study, the EEG signals were not recorded simultaneously during the exercise, but rather before and after the acute and long-term period of exercise.

An fNIRS device is easy to wear without time-consuming preparation such as is required for EEG gel electrodes. Therefore, fNIRS devices have been widely used to study the effects of exercise on patients with METH addiction during abstinence. Optodes of fNIRS are often mounted on the prefrontal cortex and the motor cortex to study the influence of METH on decision-making as well as on cognition and motion abilities. The biomarkers of fNIRS signals are listed in **Table 3**. These biomarkers include a variation of hemoglobin concentration (34, 87, 89, 90, 119–122) and parameters of functional connectivity (34, 88, 121, 122). The most used hemodynamic parameter is the concentration variation of oxygenated hemoglobin, △[OxyHb]. Deoxygenated hemoglobin concentration variation and regional cerebral oxygen saturation were not found to have been used in METH-related applications. To calculate the FC of channel pairs, Pearson's correlation is the most frequently used approach (34, 121, 122). Some studies have used the coherence of the channel pairs (88, 89). In this case, the fNIRS signals must first be converted to various frequency ranges. One study calculated the coherence of four frequency ranges (89), whereas another used only one (88). Optimization of the frequency of coherence evaluation needs further study. The fNIRS parameters include global efficiency and local efficiency, in addition to the graph theory parameters of path length and clustering coefficients (122).

The fNIRS studies in individual with METH addiction were all conducted in the past 3–4 years. Interestingly, all these studies were carried out in China, specifically by the groups of Dong (34, 88, 89, 122), Chen, and Zhou (90, 119, 121). This might be because of an increasing focus in mainland China on treating drug addiction *via* scientific approaches that can quantify the efficacy in treatment outcomes (123).

Most of the experimental groups in the studies summarized in **Tables 1–3** consisted of those with a METH addiction before or during abstinence. This was likely because rehabilitation centers are the most convenient places to recruit participants for those studies. However, limited studies have reported how long that those in recovery from METH addiction had been abstinent, and the amount of METH taken has been seldom reported in a systematic fashion. It has been demonstrated that brain activity changes with abstinence duration (54), and that the propensity for relapse varies as a function of abstinence duration. Thus, more detailed research on a wider variety of METH user groups using fNIRS needs to be performed, and long-term follow-up of users after withdrawal may yield important insights toward development more efficacious treatments.

## 5. Neuromodulation treatments for METH addiction

Advances in neurophysiology together with the neuroimaging technologies discussed here have led to the identification of some mechanisms underlying METH addiction disorders. Many studies

TABLE 3 Biomarkers of fNIRS signals recorded on patients with methamphetamine addiction. The biomarkers include variation of hemoglobin concentration and functional connectivity (FC).

| References | Comparison conditions | Groups for comparison | Locations* and number of the channels | Biomarkers | Main limitations |
|---|---|---|---|---|---|
| Bu et al. (89) | METH users during resting and exercise: spinning training and strength training | (1) After exercises versus resting;<br>(2) Strength versus spin training | Prefrontal cortex: 8,<br>motor cortex: 16 | (1) Increase: △[OxyHb], wavelet phase coherence (WPCO) at frequency intervals II and IV†<br>Decrease: WPCO at frequency interval I<br>(2) Increase: △[OxyHb], WPCO at frequency intervals III and IV<br>Decrease: WPCO at frequency intervals II | Longitudinal recordings can be carried out to explore the changes in the biomarkers. |
| Bu et al. (88) | METH users during resting and exercise: kick boxing | (1) METH group versus HC at resting and training states;<br>(2) METH group during training versus resting | Prefrontal cortex: 8,<br>motor cortex: 16 | (1) Decrease: effective connectivity (EC) of some pair of channels<br>(2) Decrease: EC of some pair of channels | Only signals when eyes closed were analyzed. |
| Wang et al. (119) | METH users exercising; then visual stimuli of images with food | After exercises versus control group (no exercise) when receiving cues with high-calorie food | OFC: 4,<br>VLFPC: 4,<br>DLFPC: 7,<br>PPA: 5 | Increase: △[OxyHb] of some channels at OFC | No measurements on healthy subjects for comparison. |
| Zhou et al. (90) | METH users exercising: dancing or treadmill; then visual stimuli of images with food | After versus before treadmill training when receiving cues with high-calorie food | OFC: 4,<br>VLFPC: 4,<br>DLFPC: 7,<br>PPA: 5 | Decrease: △[OxyHb] of one channel at left DLFPC | fNIRS cannot provide hemodynamic information in the deep brain. |
| Tao et al. (120) | METH users exercising: dancing or cycling, then visual stimuli of images which caused negative emotions | After versus before dancing, when receiving cues with negative images | OFC: 4,<br>VLFPC: 4,<br>DLFPC: 7,<br>PPA: 5 | Decrease: △[OxyHb] of one channel at DLFPC | No measurements on healthy subjects for comparison. |
| Gao et al. (121) | METH users exercising: cycle ergometer with moderate or high intensity | METH with high intensity versus moderate intensity of exercises | OFC: 4,<br>VLFPC: 4,<br>DLFPC: 7,<br>PPA: 5 | Increase: △[OxyHb] at PFC and DLFPC, FC of left DLPFC and OFC | No measurements on healthy subjects for comparison. |
| Qi et al. (34) | METH users exercising: VR cycling, then visual stimuli of images with drug-related and neutral cues | (1) Drug-related versus neutral cues;<br>(2) After versus before exercise when seeing drug-related cues | DLPFC: 8,<br>VLPFC: 8,<br>PM and SMA: 6,<br>M1: 4<br>S1: 6,<br>FPA: 2,<br>OFC: 4,<br>FEF: 4 | (1) Increase: △[OxyHb] at OFC and DLPFC;<br>(2) Increase: FC between PFC and motor cortex, between VLPFC and other cortices;<br>Decreases: △[OxyHb] at OFC and DLPFC | No measurements on healthy subjects for comparison. |

*(Continued)*





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TABLE 3 (Continued)

| References | Comparison conditions | Groups for comparison | Locations* and number of the channels | Biomarkers | Main limitations |
|---|---|---|---|---|---|
| Qi et al. (122) | METH users exercising: VR cycling. Before and after the exercise session, a cognitive task (Stroop task) was carried out | (1) After versus before exercise during cognitive task;<br>(2) After versus before exercise during resting | DLPFC: 8,<br>VLPFC: 8,<br>PM and SMA: 6,<br>M1: 4<br>S1: 6,<br>FPA: 2,<br>OFC: 4,<br>FEF: 4 | (1) Increase:<br>• Cortical activation at DLPFC;<br>• $C_p$, $E_{local}$, $E_{global}$, and $E_{nodal}$ [‡];<br>• Decrease: $L_p$<br>(2) FC between prefrontal cortex and motor cortex | No measurements on healthy subjects for comparison. |
| Gu et al. (87) | Patients with various drug addiction drug-related cues | METH group versus heroin group and mixed group | DLPFC: 16,<br>VLPFC: 6,<br>FPA: 16,<br>OFC: 10 | Increase: activation of OFC | Limited number of subjects. |

FC, functional connectivity; Δ [OxyHb], concentration variation of oxygenated hemoglobin. *DLPFC, dorsolateral prefrontal cortex; FEF, frontal eye field; FPA, frontopolar cortex; M1, primary motor cortex; OFC, orbitofrontal cortex; PM, pre-motor cortex; S1, primary somatosensory cortex; SMA, supplementary motor cortex; VLPFC, ventrolateral prefrontal cortex. †Frequency intervals of fNIRS signals: interval I: 0.6–2 Hz, interval II: 0.145–0.6 Hz, interval III: 0.052–0.145 Hz, and interval IV: 0.021–0.052 Hz. ‡Network efficiency metrics of the small world properties: clustering coefficient ($C_p$), characteristic path length ($L_p$), nodal efficiency ($E_{nodal}$), network global efficiency ($E_{global}$), and local efficiency ($E_{local}$).

have suggested that impaired self-control, irritability, compulsive consumption, etc., are caused by dysregulation and malfunction of specific brain circuits. Traditional pharmacotherapy, one of the most commonly applied interventions, can be viewed as a type of neural circuit modulation. However, traditional interventions lack spatial and temporal specificity of action. Neuromodulation, a novel approach that can modulate brain activity with spatiotemporal precision, has shown efficacy and is a promising treatment for addiction disorders (38) (**Figure 2**). Invasive neuromodulation techniques such as DBS, vagus nerve stimulation, etc., require surgery to implant a device and are usually used in severe and otherwise intractable brain disorders such as Alzheimer's disease and epilepsy (124), with some promising results. However, the safety and long-term biocompatibility are still challenging issues to be overcome for invasive neuromodulation. In contrast, non-invasive techniques such as TMS, tDCS, and transcranial ultrasound stimulation are widely used as research tools to probe affected circuits and also as therapeutic interventions for a variety of neurological and psychiatric disorders, with encouraging results (125). In the remainder of this section, we focus on non-invasive neuromodulation devices for treatment of METH addiction.

## 5.1. tDCS for methamphetamine addiction

Transcranial direct current stimulation uses a constant low-intensity current that passes through two electrodes attached to the scalp of the participant to modulate neural activity. During tDCS modulation, a current flows between the electrodes and passes through the brain. A positive anodal current is generally considered to depolarize the neurons, thereby increasing cortical excitability and behaviors associated with the cortical region under the electrode. On the other hand, a negative cathodal current hyperpolarizes neurons, thereby inhibiting action potentials and behaviors in the corresponding cortical region.

A standard apparatus for tDCS stimulation, as shown in **Figure 2C**, includes a target electrode, used to stimulate the region of interest as determined by the modulation task. A reference electrode is commonly placed opposite the target electrode. Modeling studies have shown that the shorter the distance between the two electrodes, the more susceptible the current is to shunting effects. Generally, large distances between the scalp electrodes are expected to increase cortical modulation, allowing the current to be drawn through the cortex rather than shunted across the scalp (126). As the advisable safety threshold for human studies is 2 mA (127), most tDCS stimulation studies use currents between 0.5 and 2 mA with a duration between 5 and 30 min.

The dorsolateral prefrontal cortex (DLPFC) is the area most selected for tDCS stimulation of subjects with METH addiction, as dysfunction in this area has been reported frequently among these individuals. Moreover, DLPFC can also be easily targeted in a non-invasive fashion. **Table 4** summarizes recent studies that have used tDCS for the treatment of addiction. Shahbabaie et al. conducted three 20-min sessions with 30 participants in a double-blinded sham-controlled trial (128). They found that the anodal tDCS of the right DLPFC decreased immediate craving at

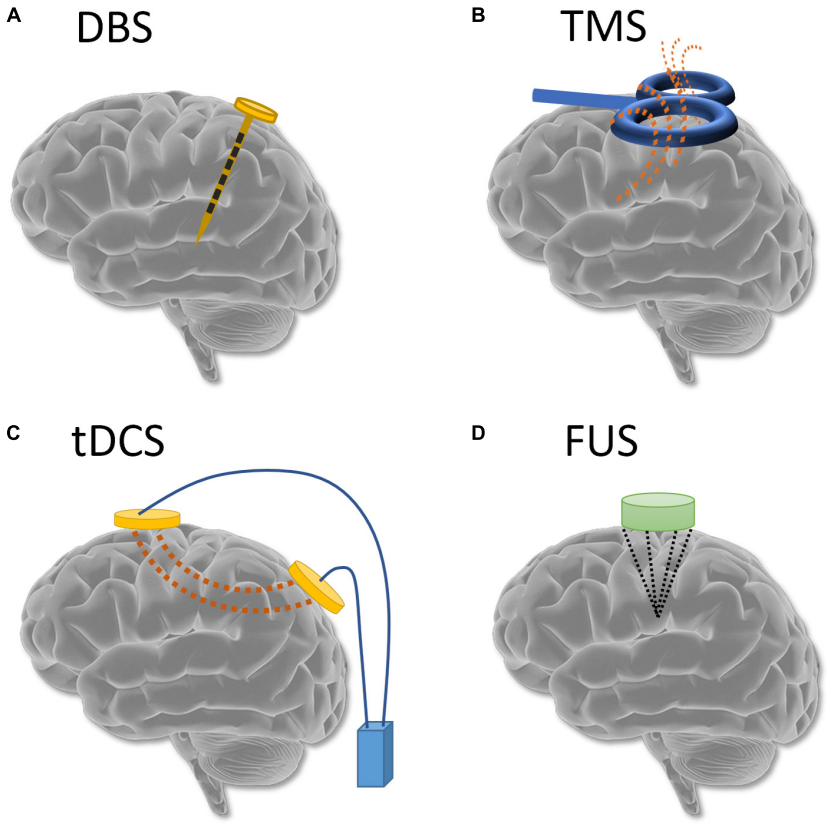


FIGURE 2
Common neuromodulation techniques: **(A)** deep brain stimulation; **(B)** transcranial magnetic stimulation; **(C)** transcranial direct current stimulation; and **(D)** transcranial ultrasound stimulation.

rest; however, cue-induced METH cravings could increase under active online stimulation of the right DLPFC. In another study, tDCS experiments lasting for half a year were conducted. After 20 sessions (1 month), the subject reported a significant reduction in craving and was able to control their cravings. Four booster tDCS sessions were given in the following 5 months as symptom-triggered therapy (129). These booster tDCS treatments were shown to be helpful in controlling psychological stress and drug cravings. Shahbabaie et al. conducted a double-blinded sham-controlled crossover study with 15 males with METH addiction (130). For each anticipant, 20 min sessions of real or sham 2-mA tDCS were applied over the DLPFC on two separate days in a random order. Participants receiving the real tDCS stimulation showed significant decreases in cravings. However, another clinical trial reported that cue-induced craving was reduced significantly but there were no significant effects on spontaneous cravings (131). More recently, a randomized controlled trial investigated the effects of tDCS on cue-induced craving; consistent with the findings of other studies, the results showed that tDCS could significantly reduce cravings (132). Jiang et al. applied tDCS and used two-choice oddball tasks to evaluate behavioral impulsivity prior to and after the treatment. However, they found that their protocol was not optimized to reduce symptoms associated with METH addiction (42). Khajehpour et al. conducted a sham-controlled tDCS stimulation experiment with 42 male participants with METH addiction (112). The results showed that tDCS could mitigate initial attention bias to METH stimuli. Overall, the findings summarized in Table 4 indicate that tDCS stimulation of DLPFC likely can play an active role in suppressing cravings.

The most common electrode locations in these studies are F4 (right DLPFC) for the anodal and F3 (left DLPFC) for the cathode electrodes. In these other studies, only two of the studies listed in Table 4 placed the cathode at other locations. One placed the cathode electrode on the left supraorbital area (128), and the other placed it over the right arm (129). Regarding the current used for stimulation, most studies used 2 mA, while one used 1.5 mA (132). For the evaluation of treatment effects, Shahbabaie et al. used EEG, Khajehpour et al. used fMRI, and the others used VAS or performance on cognitive tasks.

## 5.2. TMS for methamphetamine addiction

Transcranial magnetic stimulation techniques use a strong electrical current through an electromagnetic coil to generate magnetic pulses (Figure 2B). The magnetic pulse-induced electrical activity in the targeted brain area serves the purpose of neuromodulation. In practice, rTMS is used to elicit neuromodulation and neuroplasticity. Unlike tDCS, where the excitation and inhibition are controlled by anodal and cathodal

TABLE 4 Examples of tDCS treatments in patients with methamphetamine addiction.

| References | Number of subjects METH patients | Treatment sessions | Stimulation parameters (current, duration, and location) | Effects | Main limitations |
|---|---|---|---|---|---|
| Shahbabaie et al. (128) | 30 males | 3 sessions. At least 72 h between two sessions. | 2 mA, 20 min. Anode: F4 (right); cathode: contralateral supraorbital area. | Reduced craving at resting state. Increased craving during meth-related cue exposure. | The effects might be transient. Long-term effects need to be explored. |
| Shariatirad et al. (129) | 1 male | 5 sessions a week, for 4 weeks. During 6-month follow-up, booster tDCS on days 67, 70, 72, and 88. | 2 mA, 20 min. Anode: right DLPFC; cathode: over right arm. | Reduced drug cravings as measured by DDQ and LDQ. | This is a case report. |
| Shahbabaie et al. (130) | 15 males | Two separate days, one-week washout period. | 2 mA, 20 min. Anode: F4 (right); cathode: F3 (left). | Significant decrease of craving after tDCS, modulation of DMN, ECN, and SN. | A limited number of subjects. |
| Anaraki et al. (131) | 30 males | 5 sessions. | 2 mA, 20 min. Anode: F4 (right); cathode: F3 (left). | Cue-induced cravings reduced significantly, no significant change in instant cravings. | Lack of longitudinal recordings to analyze the long-term effect of tDCS. |
| Xu et al. (132) | 75 females | CCAT + tDCS, 5 sessions per week, for 4 weeks. | 1.5 mA, 20 min. Anode: F4 (right); cathode: F3 (left). | Reduced cue-induced cravings. | Lack of longitudinal recordings to analyze the long-term effect of tDCS. |
| Jiang et al. (42) | 45 males | 5 days daily. | 2 mA, 20 min. Anodal: F4 (right); cathode: F3 (left). | Counterproductively increased impulsivity. | No simultaneous neuroimaging signals to provide the real-time effect of tDCS. |
| Khajehpour et al. (112) | 42 males | 1 | 2 mA, 20 min. Anode: F4 (right); cathode: F3 (left). | Mitigated initial attention bias but not sustained motivated attention to METH related stimuli. | Repetitive tDCS was not applied. Only a single-session tDCS is conducted. |

CCAT, computerized cognitive addiction therapy; DDQ, Desire for Drug Questionnaire; DLPFC, dorsolateral prefrontal cortex; DMN, default mode network; ECN, executive control network; LDQ, Leeds Dependence Questionnaire; METH patients, patients who were addicted to methamphetamine; SN, salience network.



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stimulations, respectively, in rTMS the frequency drives the direction of neuromodulation (133). Frequencies over 5 Hz have been shown to increase cortical excitability, whereas low frequency rTMS, such as 1 Hz, decreases cortical excitability. Still another type of rTMS is the theta burst stimulation (TBS, a variation of high frequency rTMS) has also been applied to evaluate the effects on withdrawal of METH (134–137). TBS can be further separated into continuous TBS (cTBS) and intermittent TBS (iTBS), depending on the existence of intertrain intervals. The TBS consists of 3 pulses at 50 Hz forming 1 burst, and the bursts are repeated at 5 Hz. In cTBS the bursts are applied continuously while in iTBS, the bursts are applied with 2 s on and 8 s off, continuing for a designed number of cycles. TMS treatments have been reported to not only reduce feelings of craving in patients with METH addiction, but also to reduce negative emotions (such as depression and anxiety) and improve cognitive function (138–140). TMS stimulation on DLPFC also an FDA-approved treatment for depression (FDA approval K061053). Therefore, like tDCS, DLPFC is also the most commonly targeted stimulation area to modulate METH addiction (**Table 5**). A pilot study by Li et al. reported that low-frequency rTMS increased cravings of METH patients receiving drug-related cues (141). Liang et al. developed a protocol with 2 days rest between two 5-day treatments (142). Chen et al. designed a TMS protocol to stimulate not only the DLPFC but also the ventromedial prefrontal cortex (vmPFC) and reported an improved effect of this combined protocol (125). Zhao et al. showed that high-frequency rTMS over the DLPFC and low-frequency rTMS over the right DLPFC could reduce cravings for METH (135). Other studies have shown that TMS of the left DLPFC is effective to reduce METH addiction (142, 143). Wen et al. reported a decrease in theta/beta ratio after participants had received TMS treatment (144). Liu et al. showed that iTBS, which is a more time-efficient protocol, had similar effects to those of rTMS at 10 Hz (145). Besides the studies discussed in **Table 5**, some ongoing protocols have been proposed to investigate the effects of TMS treatment on METH addiction. One protocol proposes to analyze the power spectrum of EEG sub-bands when individuals receive METH-related VR cues before and after the cTBS treatment (137). Another protocol is designed to examine the effects of various stimulation parameters (146). Protocols are not listed in **Table 5** since no experimental data are reported yet.

All studies in **Table 5** apply self-rated VAS scores to assess the effects of TMS. Only one study uses EEG signals together with VAS scores to assess the effects (144). Some studies use images (125, 141, 143, 145), some use videos (135) and still others use VR as the cues (144). One study asks the participants to actively interact with the tools used for METH consumption (142). Since the FDA has approved TMS to treat depression, effects on emotions are compared before and after the treatments. The most common assessment is self-rating questionnaires regarding depression, anxiety, and withdrawal symptom. Results have indicated that the VAS, depression, anxiety, and withdrawal symptoms all decrease after TMS treatment (145). iTBS has become a more popular treatment approach because it takes less time to achieve the same therapeutic effect as rTMS (145). However, comparing the long-term effects of various protocols is challenging because the results reported after TMS treatments are not over the same time frame. For example, the VAS scores are measured either immediately or 4 weeks after the TMS (**Figure 3**). In addition, stimulation intensity is often non-consistent across studies: the published intensity has varied from 70% resting motor threshold (rMT) to 110% rMT. In the future, more data regarding the stimulation intensities and long-term effects will be needed.

Another potential confound of the studies being discussed is that the patients population within a given study is either all male, or all female. This is because of a single-gender policy that applies at the rehabilitation centers. With the wearable closed-loop system we propose in the following section, assessing potential effects of TMS in both males and females would be easier to implement without these limitations.

## 6. Challenges and future trends in treatment of METH addiction

In section "4. Biomarkers of neuroimaging techniques," we summarized the evidence that neuroimaging biomarkers can be used to distinguish patients with METH addiction from healthy individuals and evaluated the efficacy of various types of treatment, such as exercise training and neuromodulations. Furthermore, in section "5. Neuromodulation treatments for METH addiction," we discussed the results of studies that have used TMS on the DLPFC to reduce cravings resulting from drug-related cues in METH user groups. However, these results were based on offline signal processing, which does not the variations of brain activity during treatment in real time, which is essential for closed-loop therapeutics. In addition, bulky TMS systems hinder wider applications to increase the efficacy of the therapy. We propose a wearable closed-loop neuromodulation to efficiently treat METH addiction (147).

### 6.1. The modules of the proposed wearable closed-loop neuromodulation system

This system consists of multimodal EEG-fNIRS combined with TMS (**Figure 4**), a combination that could potentially overcome the limitations of current detection and treatment approaches. The advantages of individual module in the proposed closed-loop system are described in this section. Furthermore, an example of the scenario of applying the closed-loop system is explained in section "6.2. Apply our closed-loop system to treat METH addiction."

#### 6.1.1. Multimodal EEG-fNIRS neuroimaging

Limited studies have combined multimodal EEG and fNIRS for METH-related applications. Chen et al. used concurrent EEG-fNIRS monitoring to evaluate the influence of aerobic exercise on patients with METH addiction during cognitive tasks (35). In the studies presented in section "4.2. Biomarkers of EEG and fNIRS in METH addiction," most fNIRS measurements carried out on patients with METH addiction focused on signals from frontal cortices, whereas they recorded EEG signals from several channels covering a larger area of the scalp. Recording fNIRS signals from cortical regions other than the frontal cortices could be interesting, as this would both enable analysis of multimodal signals

TABLE 5 Examples of TMS treatments for methamphetamine addiction.

| References | Groups for comparison | Treatment sessions | Brain area, coil type, and stimulation parameters (frequency, intensity, total number of pulses, and duration of treatment) | Effects | Main limitation |
|---|---|---|---|---|---|
| Li et al. (141) | 10 METH* versus 8 HC. Real versus sham TMS. | One session: 15 min of sham and real TMS separated by 1 h. | Left DLPFC, figure-of-eight, 1 Hz rTMS, 100% rMT, 900 pulses, 15 min. | Increase: cue-induced craving in METH. | The first studies to explore the TMS effect on METH addiction. Many stimulation parameters can be further optimized. |
| Liang et al. (142) | 50 males (1–15 days of abstinence). Real versus sham TMS. | 5 days treatments, then 2 days of rest, followed by another 5 days of treatments. | Left DLPFC, 10 Hz rTMS (5 s on and 10 s off), 100% rMT, 2,000 pulses, 10 min. | Decrease: craving and withdrawal symptoms. | The long-term effect of rTMS needs to be further explored. |
| Chen et al. (125) | 74 METH, separated into 3 real (A, B, and C) and 1 sham TMS. | One session/day and 5 days/week, in total 10 sessions over 2 weeks. | (A) Left DLPFC, figure-of-eight, 2 s on and 8 s off iTBS, 100% rMT, 900 pulses, 5 min;<br>(B) Left vmPFC, butterfly coil, 900 pulses cTBS, 110% rMT, 60 s;<br>(C) A combination of the above two protocols. | Decrease: cue-induced craving for all three groups. Group 3 was most effective. | The long-term effect of treatment needs to be further explored. |
| Zhao et al. (135) | 83 METH, separated into 3 TMS groups (A, B, and C) | Twice daily over 5 days for a total of 10 sessions. | (A) Left DLPFC, figure-of-eight, 2 s on and 8 s off iTBS, 70% rMT, 600 pulses, 3 min;<br>(B) Right DLPFC, round-shaped, 600 pulses cTBS, 70% rMT, 40 s;<br>(C) Left DLPFC, figure-of-eight, 600 pulses cTBS, 70% rMT, 40 s. | Decrease: cue-induced cravings for groups (A) and (B). | The long-term effect of treatment needs to be further explored. |
| Wang et al. (143) | 66 METH (within 3 months of detoxification). Real and sham TMS. | 5 days/week, 20 sessions. | Left DLPFC, figure-of-eight, 2 s on and 8 s off iTBS, 100% rMT, 600 pulses, 3 min. | Decrease: cue-induced cravings. | The long-term effect of treatment needs to be further explored. |
| Liu et al. (145) | 20 male METH, separated into 2 TMS groups. | First 10 days daily, then on days 15 and 20. | (A) Left DLPFC, circular, 10 Hz rTMS (5 s on and 10 s off), 100% rMT, 2,000 pulses, 10 min;<br>(B) Left DLPFC, 2 s on and 8 s off iTBS, 100% rMT, 600 pulses, 190 s. | Decrease: cue-induced craving for both groups. | iTBS had a much shorter stimulation time compared to rTMS, which might affect the results. |
| Wen et al. (144) | 15 female METH. Real versus sham TMS. | Two separate sessions within 1 week | Left DLPFC, figure-of-eight, 2 s on and 8 s off iTBS, 80% rMT, 1,800 pulses, 10 min. | Decrease: frontal EEG theta/beta ratio during cue-related VR scenes. | The long-term effect of treatment needs to be further explored. |

cTBS, continuous theta burst stimulation; HC, healthy control; iTBS, intermittent theta burst stimulation; METH, individuals with methamphetamine addiction; rMT, resting motor threshold; vmPFC, ventromedial prefrontal cortex; VR, virtual reality. *Individuals with current methamphetamine dependence and non-treatment seeking.





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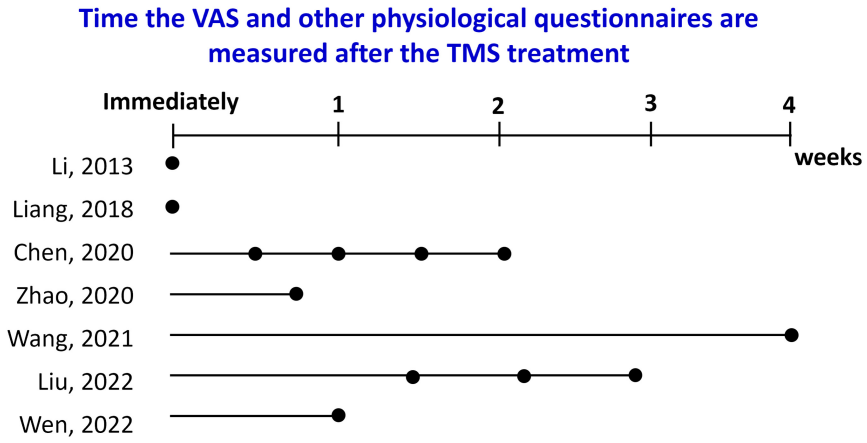


FIGURE 3
The time when the VAS and other physiological questionnaires (if available) were measured after TMS treatment for the studies is listed in Table 5.

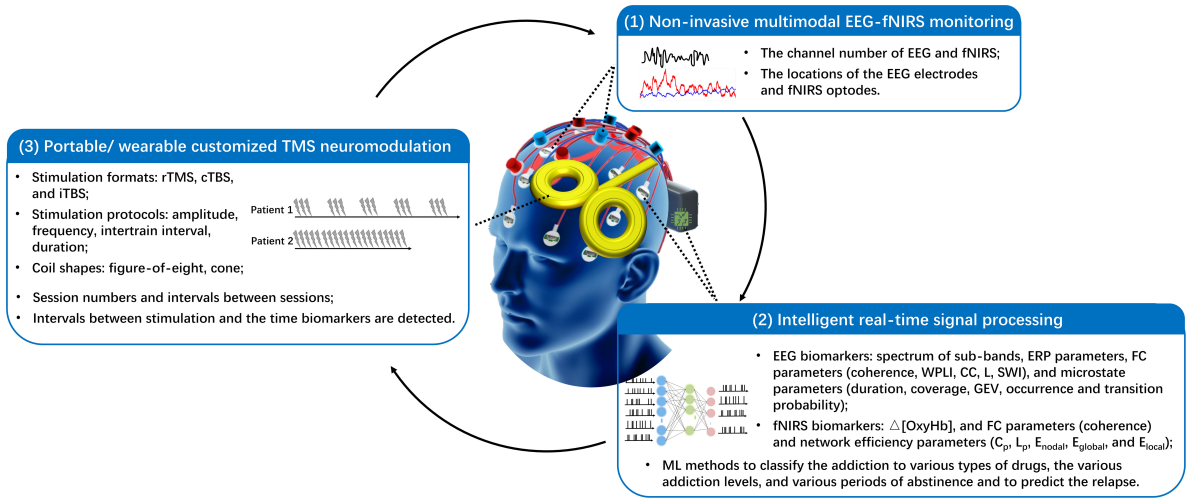


FIGURE 4
Proposed intelligent closed-loop TMS neuromodulation to treat methamphetamine addiction. It uses EEG-fNIRS measurements and is composed of three main parts: a real-time brain signal monitoring interface, an artificial intelligence signal processing block, and a customized neuromodulation system. $C_p$ and CC, clustering coefficient; cTBS, continuous theta burst stimulation; $E_{global}$, network global efficiency; $E_{local}$, local efficiency; $E_{nodal}$, nodal efficiency; ERP, event-related potential; FC, functional connectivity; GEV, global explained variance; iTBS, intermittent theta burst stimulation; $L_p$ and L, characteristic path length; rTMS, repetitive TMS; ML, machine learning; Δ[OxyHb], concentration variation of oxygenated hemoglobin; SWI, small-world index; WPLI, weighted phase lag index.

of nearby EEG and fNIRS signals to study the effects of addiction on neurovascular coupling mechanisms, and could also increase the data from which to extract useful biomarkers to identify phases of addiction, withdrawal, and relapse in METH users. Many commercially available systems support multimodal EEG and fNIRS measurements simultaneously, and other multimodal EEG-fNIRS systems are under development because of research to achieve more compact and user-friendly systems.

### 6.1.2. Analysis of recorded neural signals

To demonstrate the efficacy of TMS treatment, neural signal analyses are carried out offline. Thus, the alternations in brain signals resulting from the stimulation cannot be identified in real time. Given the functionality of microchips for use in small systems, algorithms to detect biomarkers in real time can be embedded in a custom chip of a wearable system (148). Moreover, with embedded ML algorithms, multimodal EEG, fNIRS, and other related physiological recordings can be analyzed to identify signs of addiction more accurately. A support vector machine (SVM) algorithm has been implemented to stratify METH-user and healthy groups using FC network features of EEG signals (115). Concerning the relative frequency-specific power change ratio of EEG signals, SVM, logistic regression (LR), decision tree (DT), random forest (RF), multilayer perceptron, radial basis function networks, AdaBoost and gradian boost are implemented to compare the accuracy of classifying the METH and healthy groups (149). A convolutional neural network (CNN) model has been applied to EEG-fNIRS signals to classify METH addiction into light, moderate, and severe (93). Another CNN was used to classify the fNIRS signals of METH users and mixed users (150). The same

research group compared the performances of linear discriminant analysis, SVM, and CNN of fNIRS signals to distinguish METH users and mixed users (87). When applying the EEG and GSR data, the accuracy of distinguishing the METH and the healthy group determined by random forest, logistic regression, and SVM have been compared (109).

Another limitation is that when ML models are designed for METH addiction applications, the performance of classification for different types of drugs or different periods of METH use is the focus, rather than the features used in stratification and the links between neurological systems. This limits our understanding of how these algorithms work, and thus, makes it hard to improve upon them. A more detailed interpretation of ML models would increase the confidence of clinical professionals in the classification results. Yet other limitation of existing EEG or fNIRS biomarkers is that they cannot be used to determine the stage or severity of addiction; therefore, they cannot be used to evaluate treatment effects during the therapy or as features to predict the possibility of relapse. Until now, the most used approach for stratifying the severity of addiction has been questionnaires, although the scores are based on subjective answers. Using body fluidic tests, the amount of drug in one's system can be quantified. It has been shown that the longer a person uses METH, the stronger their ΔSCR reactions are to drug-related cues (70). As neuroimaging techniques are more complex than the above-mentioned methods, there have been limited studies on the correlations of the severity of addiction with the EEG or fNIRS biomarkers discussed in section "4.2. Biomarkers of EEG and fNIRS in METH addiction." Conversely, the severity level (degree) of addiction during abstinence is also an issue that interests not only academics but also the judicial community (54). There is no solid evaluation system available to treatment centers to assess whether a patient has been rehabilitated when the scheduled therapy period is completed. With real-time signal-processing chips, various experimental protocols could be implemented to quantify the recorded biomarkers, providing information about the severity of addiction, amount of successful recovery, and correlations of these factors with cognitive functions.

### 6.1.3. Portable/wearable TMS for customized treatments

The TMS protocol has not been extensively customized; previous studies have reported the effect of treatments in a fixed time frame owing to a pre-scheduled treatment protocol. To ensure a significant effect when comparing experimental and the controlled groups, which require analysis of performance over a fixed and limited time period, the protocols are often prescribed for a period from a few weeks to months (**Table 5**). Moreover, few studies have investigated the long-term effects of the treatment after the prescribed TMS treatment had been completed. These limitations of the published research are also due to the low accessibility of the commercially available bulky TMS devices and a lack of professional operators to conduct the treatment.

With the proposed wearable closed-loop system, treatment could be conducted at any time when it is needed. First, the parameters of the stimulation protocol (amplitude, frequency, intertrain interval, and duration) and numbers of treatment sessions can be customized depending on the real-time-monitored neural signals. Ideally, the potential customized protocol would increase the efficiency of the TMS devices and the work of clinical professionals. Second, the efficacy of TMS treatment could be further improved by the use of a wearable TMS system. A wearable TMS device could provide the required stimulations without constraints of time and location. However, the wearability of the TMS system depends strongly on miniaturization of the magnetic coil and the control module. Achieving sufficient stimulation voltage for neuromodulation applications is an important issue to be addressed in the development of a compact wearable TMS system (48).

## 6.2. Apply our closed-loop system to treat METH addiction

The treatment often has a predefined protocol in a rehabilitation center for drug abstinence. Patients receive a fixed amount of therapy in a fixed period. In addition, the effect of the treatment is difficult to quantify. This condition limits the flexibility of customizing the treatment protocol based on the latest conditions. One scenario of applying the closed-loop system in proposed.

### 6.2.1. Baseline brain signal recording

The patients are recruited using EEG-fNIRS measurements to record the baseline brain signals. During the recording, the patients will be guided to watch the cues, such as drug-related pictures and videos, on a screen and rate the level of craving after seeing the cues. The differences of the various parameters of EEG and fNIRS signals from METH disorder users and healthy participants are analyzed. Moreover, various recorded signals when receiving neutral or drug-related cues are investigated. Brain signals' features, found explicitly in patients receiving drug-related cues, are defined as biomarkers. During biomarker identification, no real addictive stimulus (drug) is required to arouse the thoughts of craving.

### 6.2.2. Biomarkers identification to predict the desire of METH

During daily life, no matter in the rehabilitation centers or not, patients wear the EEG-fNIRS cap as frequently as possible. Twenty-four hours per day would be optimal. Theoretically, when the users receive anything related to their previous experiences of METH use, the brain signals alter, and specific signals containing biomarkers can be detected. The potential cues can be a wide variety, such as the environment similar to where the users used METH, the people who look identical to who the users had METH with, and the items with similar shapes or functions as the tools used for METH. The advantages of the real-time signal processing chips are that the biomarkers can be extracted and compared with baseline biomarkers at every moment. As soon as the results of biomarkers comparison can reveal the increasing of craving, an alarm will be sent to the TMS module to active a treatment. Moreover, with the low-power and high-performance real-time processing chips, multimodal biomarkers can be analyzed without delay.

### 6.2.3. TMS protocol customization

If this is the first time the TMS is activated, the protocol applied by previous publications can be used. During the TMS

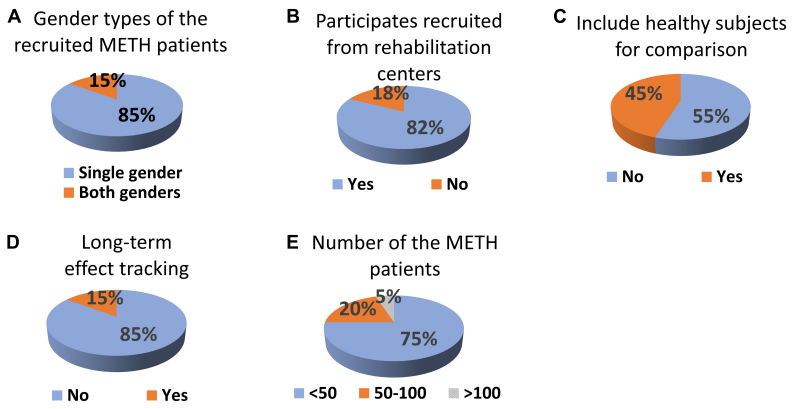


FIGURE 5
The summary of the limitations of literatures listed in Tables 1–4. **(A)** Gender types of the recruited subjects with METH addiction; **(B)** whether the participants are recruited from rehabilitation centers; **(C)** whether healthy subjects are included as comparison; **(D)** whether long-term effects are tracked; and **(E)** number of the subject with METH addiction in each study.

planned period, the biomarker changes are identified when being exposed to the cues which bring more craving, seeing real drug, for example. If a second round of TMS can be conducted after the planned stimulation period and the variance of the biomarkers before and after the treatment is not apparent, this can be a sign to reduce the TMS treatment intensity or even stop the stimulation (Figure 1B). Thanks to the flexibility of the wearable TMS module, the optimal stimulation onset time when biomarkers are detected can be explored. Moreover, how long the TMS therapy last can be studied.

### 6.2.4. Contributions to clinical practice and medicine

With this wearable closed-loop system, many research questions which were listed in the limitations of previous published work (Tables 1–4) can be more feasible to conduct. Figure 5 summarizes the main limitations of the literature reviewed in Tables 1–4 of this review article. In total, there are 40 pieces of literature included. As shown in Figure 5A, 34 papers have single genders, and 7 are females. Single-gender dominates because most experiments are conducted in rehabilitation centers where single-gender is allowed in most places. Figure 5B, only the studies that recruited participants from society have a chance to include both genders. Figure 5C, not all studies include healthy subjects as a comparison. When validating the effect of neuromodulation techniques, often, the stimulations are not conducted on healthy subjects due to ethical concerns. Excluding the literature aimed to explore the biomarkers of METH and healthy group, others implemented neuromodulations or therapies, such as exercise training. However, only 4 of the 27 studies performed the track monitoring to evaluate the long-term effect of the treatments (Figure 5D). For clinical studies, more subjects can lead to a more solid conclusion. Among the 40 pieces of literature in the tables of this review, 30 studies contain less than 50 METH patients, eight studies contain 50–100 METH patients, and two studies have over 100 METH patients. It is noted that even though some literature uses the same group of participants, they are still considered individual studies in Figure 5. These limitations and challenges to obtaining an optimal experiment are due to limited devices and manpower to conduct a large-scale investigation and later analyze the massive data.

The wearable closed-loop system we propose is highly accessible and user-friendly, and can be easily applied to a broader range of subjects. This means measurements on both genders and on both healthy and used disordered. Moreover, longitudinal recordings to track the long-term effect of the TMS treatment can be investigated. This system can provide a quantitative evaluation of the craving level in real-time. This is helpful for clinical doctors to adjust the therapy plan in the rehabilitation centers. Further quantitatively support the decision to leave the rehabilitation centers in advance or extend the stay. Furthermore, subjects not in the rehabilitation center, meaning those still using METH and those leaving the rehabilitation center, can be easily monitored. All scenarios, besides the rehabilitation centers, exit real METH. Therefore, the risk of relapse can be higher, which might result in more effective treatment of the system. With chips that can powerfully analyze the signals using ML algorithms in real-time, multimodal biomarkers can be analyzed efficiently.

We intend this review to provide a foundation for our current understanding of the potential for wearable closed-loop neuromodulation for treating methamphetamine addiction, which hopefully could be used for other addictive disorders. Here we detail wearable technologies and how those could be interfaced with neuroimaging techniques to understand how brain signals may relate to and influence biological signatures identified using the wearables. This information would be required to design closed-loop stimulation parameters that could be applied to patients. Our goal is that this review will provide a state of the field and a clear set of questions and next steps, including barriers that need to be overcome, to design such systems, which we believe hold great promise.

## 7. Conclusion

To boost the effectiveness of TMS treatment for METH addiction, we propose the concept of a wearable closed-loop

neuromodulation with three main parts: a real-time brain signal monitoring system, an artificial intelligence signal processing system, and a customized neuromodulation system. In this review, we have summarized the research findings relevant to the essential modules required to achieve a wearable system that can be used to efficiently treat addiction, including biomarkers of EEG and fNIRS signals in patients with METH addiction, ML algorithms that can identify METH addiction, and applied TMS protocols to treat the addiction. Moreover, various cues that can be used to induce the desire for METH in validation experiments have been introduced. This novel approach currently focuses on METH but could be applied to other substance addictions in the future.

## Author contributions

Y-HC, JY, HW, and MS: conceptualization and writing—review and editing. Y-HC and JY: data curation. Y-HC, JY, and KB: writing—original draft preparation. Y-HC: visualization. MS: supervision, project administration, and funding acquisition. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

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

## Publisher's note



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# Drinking alcohol to cope with hyperactive ADHD? Self-reports vs. continuous performance test in patients with ADHD and/or alcohol use disorder

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**Rationale:** Attention deficit/hyperactivity disorder (ADHD) is common in alcohol use disorder (AUD). Continuous performance tests (CPTs) allow to measure ADHD related deficits in a laboratory setting. Most studies on this topic focused on CPTs measuring inattention or impulsivity, disregarding hyperactivity as one of the core symptoms of ADHD.

**Methods:** We examined $N = 47$ in three groups (ADHD $N = 19$; AUD $N = 16$; ADHD + AUD $N = 12$) with questionnaires on ADHD core symptoms, executive functioning (EF), mind wandering, and quality of life (QoL). $N = 46$ (ADHD $N = 16$; AUD $N = 16$; ADHD + AUD $N = 14$) were examined with a CPT (QbTest®) that also measures motor activity objectively.

**Results:** Inattention and impulsivity were significantly increased in AUD vs. ADHD and in AUD vs. ADHD + AUD. Hyperactivity was significantly higher in ADHD + AUD vs. ADHD and ADHD + AUD vs. AUD, but not in ADHD vs. AUD. EF was lower in both ADHD groups vs. AUD. Mind wandering was increased in both ADHD groups vs. AUD. QoL was significantly lower in ADHD + AUD compared to AUD. In contrast, results of the QbTest were not significantly different between groups.

**Conclusion:** Questionnaires are more useful in assessing ADHD core symptoms than the QbTest®. Hyperactivity appears to be a relevant symptom in ADHD + AUD, suggesting a possible pathway from ADHD to AUD. The lower QoL in ADHD + AUD emphasizes the need for routine screening, diagnostic procedures and treatment strategies for this patient group.

KEYWORDS

**attention deficit/hyperactivity disorder (ADHD), alcohol use disorder (AUD), quality of life, continuous performance test, motor activity (MA), mind wandering**

# 1. Introduction

Attention deficit/hyperactivity disorder (ADHD) has a prevalence rate of 7.1% in children and adolescents (1) and leads to ongoing symptoms and impairment at least until young adulthood in about 90% of cases (2). Adolescents with ADHD are at increased risk for early initiation and quick escalation of substance use (3–5).

In adults with alcohol use disorder (AUD), comorbid ADHD is common with prevalence rates between 16 and 21% (5–7). However, ADHD is often under-diagnosed in AUD despite its negative effect on adherence and outcome (5).

International expert consensus recommends routine screening for ADHD in patients with substance use disorders (SUDs) (8), although ADHD screening questionnaires show decreased validity in AUD (9). In any case, additional diagnostic assessment is needed to verify ADHD diagnosis, while so far only one diagnostic interview for ADHD has been validated in AUD (5).

The high prevalence of ADHD in AUD (5–7) and low detection rate (5) affect the outcome for the individual patient but also the results of basic human and clinical research. AUD studies most likely included an uncertain number of undetected ADHD cases (10).

Sensitive methods objectively measuring ADHD symptoms could therefore aid in clinical and scientific settings.

Continuous performance tests (CPTs) to measure ADHD symptoms have not been studied extensively in the comorbidity of SUD with ADHD (11), but hyperactivity has been suggested as a relevant parameter for ADHD in SUD (12).

Our study aimed to investigate whether objective measurements or self-rating scales on inattention, impulsivity, and hyperactivity would show differences between patients with ADHD, AUD, and ADHD + AUD.

# 2. Materials and methods

Participants were 18–64 years old and patients in treatment at the Central Institute of Mental Health (Mannheim, Germany).

## 2.1. Inclusion criteria

Alcohol use disorder was diagnosed by trained masters- or medical-degreed personnel according to ICD-10 alcohol dependence (13); participants had to be abstinent for at least 5 days prior to study inclusion (completed detoxification).

Attention deficit/hyperactivity disorder was diagnosed by trained masters- or medical-degreed personnel according to clinical guidelines (14), based on DSM-5 criteria for adult ADHD (15). If available, structured interviews, school records and informants' ratings were used for the diagnostic assessment.

## 2.2. Exclusion criteria

For the groups AUD or ADHD, individuals with a diagnosis of a mental disorder within the last year or intake of psychotropic medication within the last 3 days were excluded. Stable medication with fluoxetine was considered acceptable in one participant in the ADHD group (self-reports only). Participants in the ADHD group were allowed to take prescribed stimulants, but not the day when the QbTest was conducted.

Psychiatric comorbidity did not lead to an exclusion for the ADHD + AUD group, as psychiatric comorbidity in individuals with ADHD and SUD is remarkably high (10, 16–18).

### 2.2.1. AUD group

Participants in the AUD group had to screen negative for ADHD in three different questionnaires: Wender Utah Rating Scale (19), ADHD self-report scale (20), Adult ADHD Self-Report Scale (21).

### 2.2.2. ADHD group

Participants in the ADHD group had to screen negative (cut-off <8) for AUD in the Alcohol Use Disorder Identification Test (22).

### 2.2.3. Exclusion criteria for all groups

- Cocaine/amphetamine/opioid dependence lifetime
- Lifetime diagnosis of delusional disorders, schizophrenia, or bipolar disorder
- Severe physical illness

The Ethics Committee of the Medical Faculty Mannheim, Heidelberg University, Germany approved the study beforehand (approval number 2013-530 N-MA). All participants provided written informed consent and the study was in accordance with the Declaration of Helsinki.

## 2.3. QbTest®

This commercially available CPT comprises of a 1-back task while measuring head movements with an infrared camera and a reflector attached to a headband. The QbTest® provides raw scores for motor activity, inattention and impulsivity. From these raw scores, the cardinal parameters Qb-activity, Qb-inattention, and Qb-impulsivity are derived by performing a principal component analysis. These parameters are transformed into normally distributed Q-scores implicating information about the difference between the individual raw score compared to scores of a gender- and age-controlled group (23).

## 2.4. Self-report scales

### 2.4.1. ADHD Self-Rating Scale

ADHD Self-Rating Scale (ADHD-SR) consists of 18 items (DSM criteria for ADHD). A total score as well as sub-scores on hyperactivity, impulsivity, and inattention can be calculated (20, 24).

### 2.4.2. Barratt Impulsivity Scale

The 30 items of the Barratt Impulsivity Scale (BIS-11) assess trait impulsivity [attentional (e.g., distraction), motor, and non-planning] (25).

### 2.4.3. Quality of Life Enjoyment and Satisfaction Questionnaire

The 16 items of the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) measure quality of life (QoL) as the degree of enjoyment and satisfaction experienced in various areas of daily functioning (26).

### 2.4.4. Behavior Rating Inventory of Executive Function – Adult Version

Executive functioning (EF) summarizes a set of advanced cognitive abilities that allow cognitive, emotional, and motor control to create goals, create plans to achieve the goals and stick to the plan until the goals are achieved. Higher scores in the 75 items Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A) mean more EF deficits (27).

### 2.4.5. Mind Excessively Wandering Scale

Unintentional mind wandering is common in ADHD and higher frequency of mind wandering is associated with increased functional impairment and related to lower EF (28). The Mind Excessively Wandering Scale (MEWS) consists of 15 items (29, 30).

## 2.5. Statistical analysis

Data were analyzed with IBM SPSS Statistics for Windows, Version 27.0. The distribution of gender was compared using Fisher's exact test. An analysis of variance (ANOVA) was calculated to compare the mean age between groups. Since cardinal Qb-parameters were already controlled for sex and age, we applied an ANOVA, using Bonferroni correction for multiple testing. A one-way analysis of covariance (ANCOVA) was conducted on the questionnaire scores controlling for age and gender, using a Bonferroni correction for multiple testing. A $p$-value $< 0.05$ was used as significance level for all calculations.

# 3. Results

Complete data on the self-report scales were available for $N = 47$ participants (ADHD $N = 19$; AUD $N = 16$; ADHD + AUD $N = 12$) and were included in this analysis. For the QbTest®, we included $N = 46$ (ADHD $N = 16$; AUD $N = 16$; ADHD + AUD $N = 14$).

Age and gender were significantly different between groups, see Table 1.

## 3.1. QbTest®

One-way ANOVA with Bonferroni *post-hoc* correction showed no statistically significant differences between groups for all QbTest results (see Table 2 and Figure 1B).

## 3.2. Questionnaires

One-way analysis of covariance with Bonferroni *post-hoc* correction showed statistically significant differences between groups: inattention, impulsivity (both measured with BIS-11 and ADHD-SR), mind wandering, and EF were significantly different in ADHD vs. AUD and in ADHD + AUD vs. AUD, but not in ADHD + AUD vs. ADHD.

In contrast, hyperactivity was significantly increased in ADHD + AUD vs. ADHD, and in ADHD + AUD vs. AUD (Figure 1A), while the numerical difference in ADHD vs. AUD did not reach significance. QoL was significantly lower in ADHD + AUD vs. AUD, but no further statistically significant group differences emerged (Table 3).

# 4. Discussion

To our knowledge, this is the first study directly comparing individuals with AUD and/or ADHD objectively measuring hyperactivity and other core ADHD symptoms (inattention, impulsivity).

ADHD + AUD showed increased hyperactivity in self-reports. Other ADHD related deficits also showed differences for ADHD groups (ADHD + AUD or ADHD) vs. AUD. However, we found no group differences for the QbTest parameters.

Substance use disorder and ADHD show comparable inattentive and impulsive behavior in CPTs, but hyperactivity was identified as a promising parameter to distinguish ADHD from SUD (11). One study used certain measures of motor impulsivity (e.g., pressing buttons too quickly or randomly) as a proxy for hyperactivity, and found a significant difference between ADHD (with or without SUD) and SUD, although the effect size was small (31).

Attention deficit/hyperactivity disorder and healthy controls significantly differ in all ADHD core symptoms as measured by the QbTest® (32). Although sensitivity and specificity for the QbTest® were decreased in clinical samples, most studies still

TABLE 1 Basic characteristics.

| | | AUD | ADHD | ADHD + AUD | *p*-Value | | |
|---|---|---|---|---|---|---|---|
| | | | | | AUD vs. ADHD | AUD vs. ADHD + AUD | ADHD vs. ADHD + AUD |
| QbTest | % male | 94% | 75% | 50% | 0.333[a] | 0.012[a] | 0.257[a] |
| | Age | 44.4 (12.1) | 29.4 (7.8) | 40.0 (11.7) | <0.001[b] | 0.269[b] | 0.009[b] |
| Self-report scales | % male | 94% | 68% | 50% | 0.092[a] | 0.011[a] | 0.452[a] |
| | Age | 44.0 (12.5) | 30.4 (9.7) | 39.7 (11.7) | 0.001[b] | 0.314[b] | 0.030[b] |

[a]Fisher's exact test.
[b]ANOVA with *a priori* contrasts between groups.

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TABLE 2 QbTest.

| | AUD | ADHD | ADHD + AUD | *F* | df | *p*-Value | | | |
|---|---|---|---|---|---|---|---|---|---|
| | *N* = 16 | *N* = 16 | *N* = 14 | | | Overall model | AUD vs. ADHD | AUD vs. ADHD + AUD | ADHD vs. ADHD + AUD |
| Hyperactivity | −0.69 (1.57) | 1.09 (1.32) | 0.44 (1.77) | 2.224 | 2 | 0.120 | 0.124 | 1.0 | 0.775 |
| Impulsivity | 0.19 (1.52) | 0.79 (1.09) | 0.58 (1.18) | 0.897 | 2 | 0.415 | 0.581 | 1.0 | 1.0 |
| Inattention | 0.21 (1.01) | 0.83 (0.75) | 0.34 (1.5) | 1.359 | 2 | 0.268 | 0.370 | 0.716 | 1.0 |

Means of QbTest cardinal parameters (ANOVA, Bonferroni *post-hoc* correction); standard deviation in brackets.

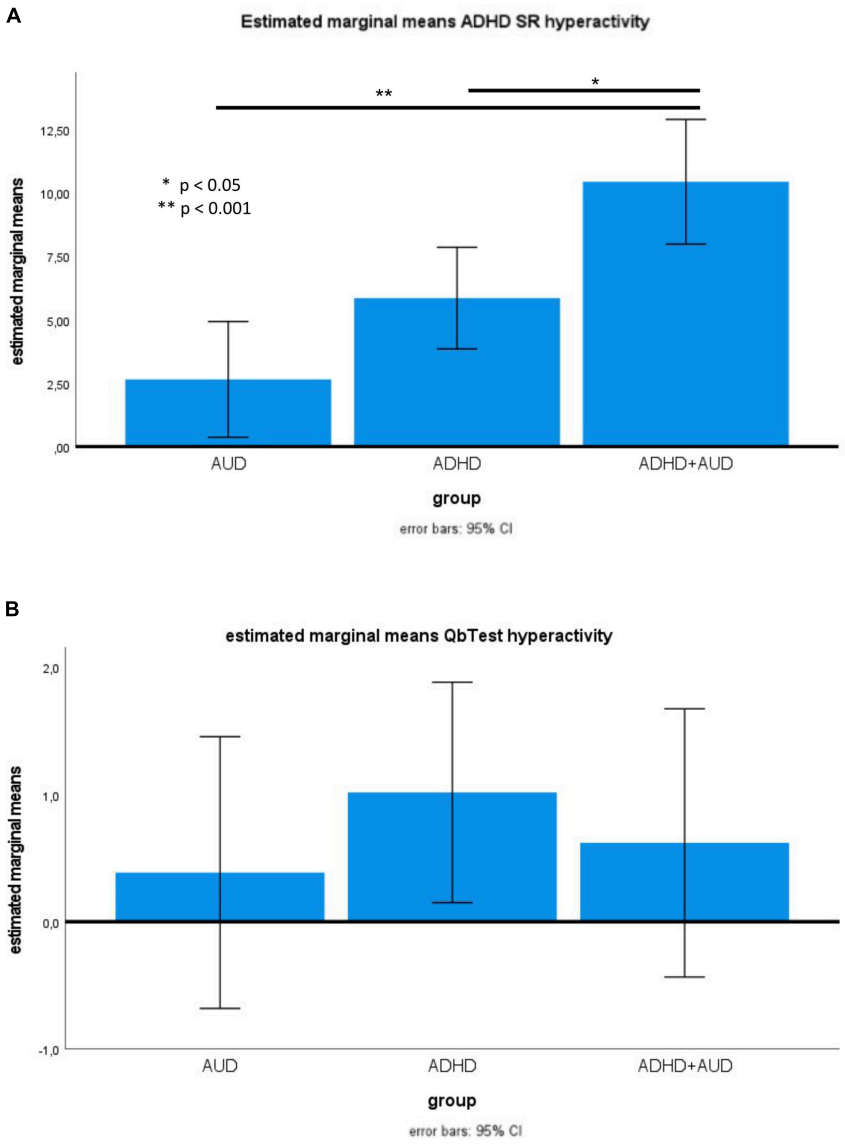


FIGURE 1
**(A)** Estimated marginal means of ADHD-SR hyperactivity. **(B)** Means of Qb activity.

found differences on a group level (33–36), especially regarding hyperactivity (36). Thus, ADHD remains a clinical diagnosis (14).

This contrasts with the results of our study. Here, the QbTest® did not show any differences between groups regarding objectively measured ADHD core symptoms.

In ADHD, new and interesting situations with low distraction – as in (laboratory) research – often lead to a temporary decrease in symptoms including hyperactivity (37). Functional imaging studies on AUD and ADHD showed similar impulsivity and resting state brain networks (38), but brain activation during inhibition tasks depended on ADHD and AUD severity (39). These findings, together with our results, suggest that in ADHD a less effective brain network compensates impulsivity, which might be more vulnerable to distractors or a general increased level of stress in real

TABLE 3 Self-report scales.

| | AUD | ADHD | ADHD + AUD | *F* | df | Partial $\eta^2$ | *p*-Value | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *N* = 17 | *N* = 19 | *N* = 12 | | | | Overall model | AUD vs. ADHD | AUD vs. ADHD + AUD | ADHD vs. ADHD + AUD |
| ADHD-SR hyperactivity | 2.6 (1.1) | 5.8 (1.0) | 10.5 (1.1) | 11.997 | 2 | 0.358 | <0.001 | 0.111 | <0.001 | 0.015 |
| ADHD-SR inattention | 3.1 (1.1) | 17.9 (1.0) | 16.3 (1.3) | 47.082 | 2 | 0.687 | <0.001 | <0.001 | <0.001 | 1.0 |
| ADHD-SR impulsivity | 1.3 (0.8) | 5.8 (0.8) | 6.2 (0.9) | 9.582 | 2 | 0.308 | <0.001 | 0.002 | 0.001 | 1.0 |
| BIS-11 impulsivity | 63.5 (2.8) | 75.8 (2.6) | 76.1 (3.1) | 5.801 | 2 | 0.216 | 0.006 | 0.013 | 0.017 | 1.0 |
| MEWS mind wandering | 10.9 (2.1) | 26.6 (1.9) | 27.4 (2.3) | 18.177 | 2 | 0.458 | <0.001 | <0.001 | <0.001 | 1.0 |
| BRIEF executive functioning | 103.2 (5.0) | 148.3 (4.6) | 148.9 (5.6) | 24.589 | 2 | 0.534 | <0.001 | <0.001 | <0.001 | 1.0 |
| Q-LES-Q quality of life | 50.4 (1.8) | 45.5 (1.6) | 39.4 (2.0) | 8.198 | 2 | 0.276 | <0.001 | 0.196 | 0.001 | 0.071 |

Estimated marginal means of self-report scales adjusted for gender and age (ANCOVA, Bonferroni *post-hoc* correction); standard deviation in brackets.

life (40), but not in a controlled laboratory setting. This might also apply to other ADHD symptoms.

Larger samples might be needed to detect group differences in ADHD related deficits (11, 31) due to a large overlap of affected domains in ADHD and AUD (41). However, larger samples often lead to more heterogeneous groups (31). This might affect study results, as for example heavy cannabis use has been associated with more ADHD related deficits during a CPT (42). In our study, we investigated a more homogenous sample (e.g., exclusion of other SUDs).

Of note, self-report questionnaires already showed significant and group specific differences at the given sample size.

Hyperactivity decreases during adolescence (43). In adults, a feeling of inner restlessness can be the main hyperactive symptom (44) and thus can only be assessed by self-report. However, persisting hyperactivity has been associated with severe comorbidity such as SUD (45). This is confirmed by our study, as ADHD + AUD reported higher hyperactivity than AUD or ADHD alone. Adolescents with ADHD and comparably high hyperactivity might be more prone to drink alcohol to cope with their hyperactivity and develop an AUD subsequently. ADHD did not differ from AUD regarding self-reported hyperactivity, implicating that increased hyperactivity is a possible pathway from childhood ADHD to development of AUD later in adolescence or early adulthood, probably to reduce unpleasant hyperactivity or restlessness (46). As we did not assess comorbidity, hyperactivity could also be driven by co-occurring mental health problems such as emotional dysregulation (10), traumatic experiences (17, 47) or trauma-related disorders (16, 17).

Our results show that individuals with ADHD (with or without AUD) are more impulsive than individuals with AUD only. Decades of research have linked AUD to increased impulsivity (48). Impulsivity is either increased in AUD (but even more in ADHD + AUD) or only increased in AUD + ADHD. Supporting the latter, impulsivity is mainly increased in individuals with "early onset" AUD (49). Since the age of onset of AUD is almost 10 years earlier in patients with ADHD (5), many ADHD cases might be hidden in the term "early onset" AUD.

Although impulsivity and alcohol consumption in adolescence negatively affect each other leading to early AUD (10, 50, 51), we did not find differences in impulsivity between ADHD and ADHD + AUD. This is probably due to a ceiling effect, as the impulsivity scores in both ADHD groups corresponded to the scores of in-patients in a forensic setting (52).

Attention deficit/hyperactivity disorder or ADHD + AUD had more deficits in EF compared to AUD, which is in line with recent findings (53). EF deficits are associated with an increased risk for treatment drop-out in AUD (54) and SUD + ADHD (55) and lower QoL in ADHD (56).

Mind wandering (MW) was increased in ADHD (with or without AUD) compared to AUD. MW is associated with lower EF, lower QoL and more severe ADHD (28, 57), and an increased risk for traffic accidents (58, 59). Alcohol consumption increases MW but decreases individual awareness for MW (28). Since individuals with ADHD are at increased risk for traffic accidents, especially with co-occurring substance use (40), reducing MW might be relevant especially in ADHD + AUD.

Attention deficit/hyperactivity disorder or AUD is associated with low QoL (60, 61) but successful treatment improves QoL (62, 63). In our study, ADHD + AUD had lower QoL vs. AUD, while ADHD did not differ from AUD. We conclude that co-occurrence of AUD and ADHD has a significant impact on QoL in AUD. QoL is an important outcome parameter in AUD (64) and studies on interventions in ADHD + AUD might also address improvement of QoL.

## 5. Conclusion

In conclusion, self-report scales on core symptoms of ADHD as well as on ADHD related deficits showed significant and specific

group differences between ADHD, AUD, and ADHD + AUD, while a CPT did not show any differences between groups.

Hyperactivity was confirmed to be a relevant symptom in ADHD + AUD, suggesting a possible pathway from ADHD to AUD. The lower QoL in ADHD + AUD compared to AUD emphasizes the need for routine ADHD screening, diagnostic procedures and treatment strategies in patients with AUD.

## Data availability statement

The datasets presented in this article are not readily available because the data contain information that would compromise research participant consent. We will provide data upon direct request by research colleagues following current data protection guidelines. Requests to access the datasets should be directed to ML, mathias.luderer@kgu.de.

## Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Medical Faculty Mannheim, Heidelberg University, Heidelberg, Germany. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

ML and ES designed the study. ML, JS, and SG collected the sample. ML performed the literature review, conducted the analyses together with JS, and wrote the initial version of this manuscript. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

ML has received honoraria as a speaker and/or for participation in advisory boards from Medice, Shire/Takeda, and Recordati. ES has received honoraria for participation in advisory board from Takeda. AR has received a research grant from Medice and served on advisory boards and/or speaker's bureau for Medice, Shire/Takeda, Janssen, Servier, and Neuraxpharm.

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.

## Publisher's note



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# Methadone maintenance treatment alters couplings of default mode and salience networks in individuals with heroin use disorder: A longitudinal self-controlled resting-state fMRI study

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**Background:** Methadone maintenance treatment (MMT) is a common treatment for heroin use disorder (HUD). Although individuals with HUD have been reported to show impaired coupling among the salience network (SN), executive control network (ECN), and default mode network (DMN), the effects of MMT on the coupling among three large-scale networks in individuals with HUD remains unclear.

**Methods:** Thirty-seven individuals with HUD undergoing MMT and 57 healthy controls were recruited. The longitudinal one-year follow-up study aimed to evaluate the effects of methadone on anxiety, depression, withdrawal symptoms and craving and number of relapse, and brain function (SN, DMN and bilateral ECN) in relation to heroin dependence. The changes in psychological characteristics and the coupling among large-scale networks after 1year of MMT were analyzed. The associations between the changes in coupling among large-scale networks and psychological characteristics and the methadone dose were also examined.

**Results:** After 1year of MMT, individuals with HUD showed a reduction in the withdrawal symptom score. The number of relapses was negatively correlated with the methadone dose over 1year. The functional connectivity between the medial prefrontal cortex (mPFC) and the left middle temporal gyrus (MTG; both key nodes of the DMN) was increased, and the connectivities between the mPFC and the anterior insular and middle frontal gyrus (key nodes of the SN) were also increased. The mPFC-left MTG connectivity was negatively correlated with the withdrawal symptom score.

**Conclusion:** Long-term MMT enhanced the connectivity within the DMN which might be related to reduced withdrawal symptoms, and that between the DMN and SN which might be related to increase in salience values of heroin cues in individuals with HUD. Long-term MMT may be a double-edged sword in treatment for HUD.

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KEYWORDS

methadone maintenance treatment, large-scale networks, withdrawal symptoms, heroin, addiction, functional magnetic resonance imaging

# Introduction

Heroin use disorder (HUD) is characterized by excessive heroin-seeking and heroin-consumption behaviors despite patients' knowledge that these behaviors are harmful for their physical and mental health (1). Individuals with HUD often show a chronically relapsing cycle of withdrawal and craving despite the substantial adverse consequences. Approximately 24 to 43% of individuals with HUD had anxiety symptoms (2), and heroin also may contribute to major depressive disorder in HUDs (3). The methadone maintenance treatment (MMT) program is one of the most effective treatments for heroin dependence. Behavioral studies have demonstrated that MMT effectively alleviates heroin dependence, reduces overdose fatality, improves the abstinence rate, and yields a better quality of life in individuals with HUD (4). Nevertheless, up to 53% of individuals with HUD do not maintain stable abstinence (5). Some studies have reported a gradual increase in the drop-out rate and relapse rate during MMT. The drop-out rate was 14% during the first year, 17% during the second year, and 22% during the third year (6). Relapse rates were even higher with 60% after 1 year (7). Moreover, MMT increases anxiety symptom among HUDs (8), which may lead to high suicide rate (9) and increased relapse rate (8). For individuals with HUD, the effect of MMT on the functional connectivity of brain is largely unknown, and neuroimaging methods may help characterize the mechanisms underlying the effects of MMT on the brain.

Numerous studies have shown different effects of MMT. Long-term MMT could increase the local activity in right dorsolateral frontal cortex and bilateral parietal cortex and might help restore executive control function toward that of healthy controls for individuals with HUD (10). However, some studies have implied that long-term MMT program might lead to impaired structure and function of parts of brain for individuals with HUD. A longitudinal study found that individuals with HUD show a smaller gray matter volume in insula, cingulate cortex, caudate nucleus after 1 year of MMT (11). Heroin relapsers undergoing MMT program showed lower white matter integrity in the right retrolenticular part, left anterior and posterior limb of internal capsule, bilateral anterior corona radiata relative to abstainers (12). Compared with healthy controls, the individuals with HUD undergoing MMT program had a lower interhemispheric insular functional connectivity (13). Furthermore, a higher methadone dose was associated with a smaller globus pallidus in the MMT group (14). However, these studies were cross-sectional, and the diversity of results could have been attributed to the presence of many variable and complex factors related to the research participants. Thus, a longitudinal self-controlled study may yield objective conclusions. However, few self-controlled longitudinal functional neuroimaging studies have focused on the effect of MMT on the functional connectivity characteristics of the brain in individuals with HUD.

The increased interest in understanding the mechanisms underlying intrinsic fluctuations in the ongoing resting activity among large-scale brain functional networks is relevant to cognitive dysfunctions during MMT in individuals with HUD. In this regard, a triple-network model composed of the salience network (SN), executive control network (ECN), and default mode network (DMN) has received the most attention. The current view suggests that the ECN and DMN show anticorrelation at rest, and the SN performs the critical role of adjusting brain activity between the DMN and ECN, driving attention resources into internal or external stimuli (15). One study on HUD suggested that the number of relapses are positive associated with enhanced SN-DMN coupling and negative associated with decreased left ECN-DMN coupling (16). Our previous findings preliminarily suggest that MMT could increase the coupling of the SN and the bilateral ECN in individuals with HUD compared to healthy controls and untreated HUDs (17). However, this study is cross-sectional and lacks longitudinal in-depth exploration. Up to now, little is known about the mechanisms underlying the influence of long-term MMT on coupling among the SN, DMN, and ECN in individuals with HUD.

In the current study, we recruited a cohort of individuals with HUD who were undergoing stable MMT as a part of a longitudinal self-controlled resting-state fMRI study. We also recruited a cohort of healthy individuals as controls. We hypothesized that (1) after 1 year of MMT, individuals with HUD would show lower functional connectivity between the SN and DMN and stronger functional connectivity between the SN and ECN compared with baseline; (2) longer-term MMT is helpful in decreasing the craving for heroin and relieving negative symptoms such as withdrawal symptoms; (3) the changes in connectivity would be associated with changes in negative symptoms and craving for heroin.

# Materials and methods

## Study design

This observational, prospective, longitudinal one-year follow-up study aimed to evaluate the effects of methadone on anxiety, depression, withdrawal symptoms and craving and relapse behavior, and brain function in relation to HUD. Individuals with HUD taking stable doses of methadone were recruited for this study, and their psychological characteristics and resting-state fMRI data were collected at baseline and 1 year later, respectively. During this one-year follow-up period, all individuals with HUD underwent monthly random urine testing. Urine tests were considered positive if the concentration of drugs in the urine exceeded the cut-off threshold of 300 ng/ml for morphine, 1,000 ng/ml for methamphetamine and 1,000 ng/ml for ketamine. This was done to detect the presence of relapse behavior in individuals with HUDs during MMT program. Individuals in the healthy control group were measured only once and were not followed up. The study was approved by the Ethics

Committee of Tangdu hospital. All participants provided informed consent prior to the study.

## Participants

Patients undergoing MMT who met the following criteria were enrolled from a heroin treatment program in Baqiao District, Xi 'an: (1) diagnosed as showing HUD (for at least 6 months) based on the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition), (2) receiving a stable dosage of methadone for at least 3 months, and (3) right-handed. Healthy volunteers from the nearby community around Tangdu Hospital were recruited as the healthy control (HC) group. All participants who showed any of the following findings were excluded: (1) a history of substance use disorder except heroin and nicotine, (2) a diagnosis of past or current brain disease, especially brain injury and neurological disorders, (3) inability to complete psychological and behavioral measurements and MRI examinations, and (4) contraindications for MRI scanning (such as claustrophobia, hyperpyrexia, and metal implants). Seventy-four patients undergoing MMT and 60 HCs were initially enrolled in the study. Part of the data came from our previous study (17).

## Measures

Demographic characteristics included sex, age, years of education, history of smoking, and history of heroin and methadone usage. Psychological scores are assessed by self-report. Psychological assessments were taken twice for individuals with HUDs, at the time of enrollment and 1 year after MMT program. Psychological assessments for healthy controls were taken only once at enrollment and were not followed up. Psychological characteristics included anxiety (measured with Hamilton Anxiety Scale-14, HAMA-14) (18), depression (evaluated with Beck Depression Inventory II, BDI-II) (19), and withdrawal symptoms (assessed with a published scale for heroin dependent individuals) (20) as well as pre-cue and post-cue craving scores. The pre-cue craving assessment was completed prior to MRI data acquisition. After resting-state functional MRI data acquisition, the drug cue-induced craving task was administered, and the post-cue craving score was evaluated again. Individuals with HUD underwent urine testing for morphine, methamphetamine and ketamine once a month during the one-year follow-up study.

The craving scores for heroin was assessed using an event-related picture cue craving paradigm (20–22). This task included 24 heroin-related (drug scenes, drug paraphernalia, etc.) and 24 neutral control (bus, tree, etc.) cue pictures. Each picture was showed for 2 s with an interval of 4–12 s in pseudorandom mode through a computer. Each subject self-reported a score (0–10) for heroin craving before and after the task on a visual analog scale (VAS), within which "0" for no craving and "10" for very severe craving.

## Magnetic resonance imaging

All participants were required to have a negative urine test for morphine, ketamine, and methamphetamine on the day of the MRI scan, and individuals with HUD took methadone after the MRI scan. A General Electric Signa Excite HD 3.0 T MRI scanner equipped with a standard eight-channel head coil at Tangdu Hospital was used for functional magnetic resonance imaging (fMRI). All participants were instructed to relax and quietly view a white cross in the background through a mirror mounted on the head coil during the resting-state fMRI scan. To help participants acclimatize to the MRI scanning environment, mock scanning was conducted for 1 min without data collection. Subsequently, resting-state images were collected during the formal scan for 5 min.

Resting-state fMRI was performed by a gradient-echo echo-planar imaging sequence with the following parameters: repetition time = 2000 ms, echo time = 30 ms, flip angle = 90°, thickness = 4 mm, spacing = 0 mm, number of slices = 32, field of view = 256 mm × 256 mm, matrix = 64 × 64, number of excitation = 1, and 150 volumes. 3D high-resolution anatomical images (T1-weighted sequence) were acquired for the resting-state imaging registration by a fast spoiled phase gradient-echo sequence. Its parameters are as follow: repetition time = 7.8 ms, echo time = 3.0 ms, flip angle = 20°, inversion time = 450 ms, thickness = 1 mm, number of slices = 166, spacing = 0 mm, FOV = 256 mm × 256 mm, matrix = 256 × 256, number of excitation = 1. The detailed scanning parameters were the same as in a previous study (17). All images were evaluated by two neuroradiologists to eliminate cases showing structural abnormalities. However, no participant was excluded on the basis of this criterion.

## Image data processing

### Preprocessing

The preprocessing was performed using DPABI,[1] SPM12,[2] and MATLAB 8.1[3] for neuroimaging. The resting-state fMRI dates for each participant were corrected for slice timing to eliminate time differences caused by multi-slice interval imaging. For each participant, images were then spatially realigned to the first scan of the series. Motion artifacts of all participants were monitored through a realignment parameter. Subjects with the maximum head motion exceeding 3 mm in translation or 3.0° in rotation were removed. To accurately locate the functional brain area, the functional image was co-registered to the respective high-resolution anatomical image (T1 weighted sequence). The brain tissue is divided into gray matter, white matter, and cerebrospinal fluid with a new segmentation method in structural image. Subsequently, the nuisance covariates, namely, 24 head motion parameters and white matter and cerebrospinal fluid signals, were regressed out. The original space of functional brain was registered to the standard anatomical space (Montreal Neurological Institute, MNI) and resample to 3 × 3 × 3 mm, addressing differences in brain morphology among subjects. Dates are spatially smoothed using a Gaussian filter with a 6-mm full-width at half maximum kernel to improve the signal-to-noise ratio (SNR) after normalization. At the end of preprocessing, linear detrend and band-pass filtering (0.01–0.1 Hz) was applied to the images.

1 http://rfmri.org/dpabi
2 https://www.fil.ion.ucl.ac.uk/spm/software/spm12/
3 www.mathworks.com

### Identification of the DMN, ECN, and SN

Independent component analysis (ICA) was performed on the smoothed data of all participants by using the GIFT 4.0 toolbox.[4] Most parameters and procedures were set to the default values. First, the GIFT software was used to estimate the number of independent components and the number of ICA components were set as 25. Second, Principal Component Analysis (PCA) was used to reduce the dimensionality in two steps (individual level and group level). At the individual level, the dimensionality of a single subject was used to reduce by PCA, and 38 principal components were retained. At the group level, 25 principal components of all subjects were dimensionally reduced. Then, based on the independent components obtained at the group level, a back reconstruction of the data to individual subject-independent components was also conducted to examine the reproducibility of the components detected. All components were identified through the back reconstruction. ICA was repeated 40 times by running randinit and bootstrap mode in the ICASSO toolbox to ensure repeatable and stable results. Referring to the resting state network reported in previous studies, the components were defined based on structural and functional properties. The spatial z-map of reconstructed components was used to calculate range of brain regions within each independent network. The SN, bilateral ECN, and DMN were identified by one-sample *t*-test [Gaussian Random Field (GRF) correction, voxel-$p < 0.001$, cluster-$p < 0.05$].

The SN included the dorsal anterior cingulate cortex (dACC), bilateral anterior insula (AI), and middle frontal gyrus (MFG) (23). The DMN included the medial prefrontal cortex (mPFC), precuneus/posterior cingulate cortex (PCC), and bilateral middle temporal gyrus (MTG). The left ECN consisted of the left dorsolateral prefrontal cortex (dlPFC) and posterior parietal cortex (PPC). The right ECN included the right dlPFC and PPC (Table 1 and Figure 1). We performed principal components analysis on all individuals, including HC and MMT individuals, and determined DMN, SN, and ECN by within-group one-sample t-test. The identified map served as a mask for functional connectivity of the brain networks.

### Definition of regions of interest and functional connectivity

To analyze the group differences in connectivity among the SN, bilateral ECN, and DMN, we selected the peak voxel of each key region in the identified large brain network as the centers of spherical regions of interest (ROIs; radius = 6 mm). The voxel-wise functional connectivity analyses were performed on band pass-filtered data based on each ROI within all the defined SN, bilateral ECN, and DMN. Pearson correlation coefficients were used to estimate the functional connectivity among the SN, bilateral ECN, and DMN [16; 17] with the DPABI software. The paired *t*-test was performed to test differences in functional connectivity based on each ROI of the SN, bilateral ECN, and DMN between the Baseline and one-year follow-up groups with the DPABI software (GRF correction, voxel-$p < 0.001$, and cluster-$p < 0.05$).

4 http://icatb.sourceforge.net

### Correlation analysis

Pearson correlation analyses were performed between the functional connectivity strength of differential regions and psychological characteristics (such as depression, anxiety, withdrawal symptoms, pre-cue-induced craving scores and post-cue-induced craving scores) at the baseline and 1 year later. The correlation between the change in functional connectivity strength of differential regions and the total methadone dose during the year was analyzed. The correlation between the psychological characteristics and number of relapses were also analyzed 1 year later. The correlation results were corrected for multiple comparisons with the Bonferroni correction method.

## Results

### Demographics

For this longitudinal study, 74 patients receiving MMT were initially enrolled, of which 33 patients were lost to follow-up after 1 year. The resting-state fMRI data of four participants were excluded because of head movements. Thus, 37 patients receiving MMT were eventually enrolled in the study. Among the 60 HCs that were initially recruited, three were ruled out due to head movements or incomplete brain scans. Finally, 57 healthy controls were included in this study.

Table 2 summarizes the demographic and clinical characteristics of the MMT and HC groups. The MMT patients and HCs were well-matched for sex, age, education, history of smoking, anxiety symptom, and depression symptom ($p > 0.05$). The groups did not differ in mean head motion during the resting fMRI scan ($p > 0.05$).

### Psychological characteristics

In the self-assessment of opioid withdrawal symptom score, 31 individuals with HUD completed the evaluation for the first time. One year later, only 27 individuals with HUD completed the evaluation for the second time. During the one-year follow-up period, the opioid withdrawal symptom scores (mean ± standard error) of 27 individuals with HUD at the Baseline and 1 year later were 20.62 ± 3.54 and 13.12 ± 2.50, respectively. The individuals with HUD showed a significantly lower withdrawal symptom level ($n = 27$, $t_{(26)} = 3.11$, $p = 0.005$ Cohen's dz. = 0.60) 1 year later (Figure 2).

The pre-cue-induced craving scores (mean ± standard error) of the baseline and 1 year later were 0.97 ± 0.25 and 1.19 ± 0.26, respectively, while the post-cue-induced craving scores (mean ± standard error) were 1.03 ± 0.28 and 1.73 ± 0.40, respectively. The pre- and post-cue-induced craving scores showed no significant changes during one-year follow-up ($t_{(36)} = -0.85$, $p = 0.4$; $t_{(36)} = -1.5$, $p = 0.14$; Figure 2). The anxiety symptom scores (mean ± standard error) at baseline and 1 year later were 9.27 ± 1.77 and 10.24 ± 1.54, respectively. The depression symptom scores (mean ± standard error) of Baseline and 1 year later were 9.97 ± 1.44 and 8.78 ± 1.21, respectively. The individuals with HUD showed no significant changes in the anxiety and depression symptom scores after one-year follow-up ($t_{(36)} = 1.14$, $p = 0.26$; $t_{(36)} = -0.94$, $p = 0.35$; Figure 2).

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TABLE 1 Large-scale networks from the group independent component analysis.

| Network | Brain area | Side of the brain (R/L) | *X* | *Y* | *Z* | Peak intensity | Cluster size ($mm^3$) | Cluster size (voxels) |
|---|---|---|---|---|---|---|---|---|
| DMN | MPFC | | 0 | 55 | 19 | 28.79 | 50,355 | 1865 |
| | PCC | | 0 | −70 | 30 | 33.06 | 45,063 | 1,669 |
| | MTG | R | 57 | −51 | 15 | 7.55 | 1971 | 73 |
| | MTG | L | −39 | −63 | 42 | 11.13 | 11,421 | 423 |
| LECN | dlPFC | L | −51 | 21 | 21 | 28.63 | 48,033 | 1779 |
| | PPC | L | −54 | −54 | 27 | 14.33 | 14,904 | 552 |
| RECN | dlPFC | R | 48 | 18 | 39 | 16.14 | 35,316 | 1,308 |
| | PPC | R | 48 | −54 | 42 | 25.69 | 20,088 | 744 |
| SN | ACC | | 0 | 35 | 29 | 26.09 | 24,273 | 899 |
| | MFG | L | −30 | 39 | 36 | 26.71 | 19,143 | 709 |
| | AI | L | −39 | 12 | 0 | 16.46 | 9,504 | 352 |
| | MFG | R | 33 | 42 | 33 | 22.47 | 9,450 | 350 |
| | AI | R | 39 | 15 | 0 | 10.5 | 3,213 | 119 |

SN, salience network; DMN, default mode network; ECN, executive control network; dACC, dorsal anterior cingulate cortex; mPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; AI, anterior insula; MTG, middle temporal gyrus; MFG, middle frontal gyrus.

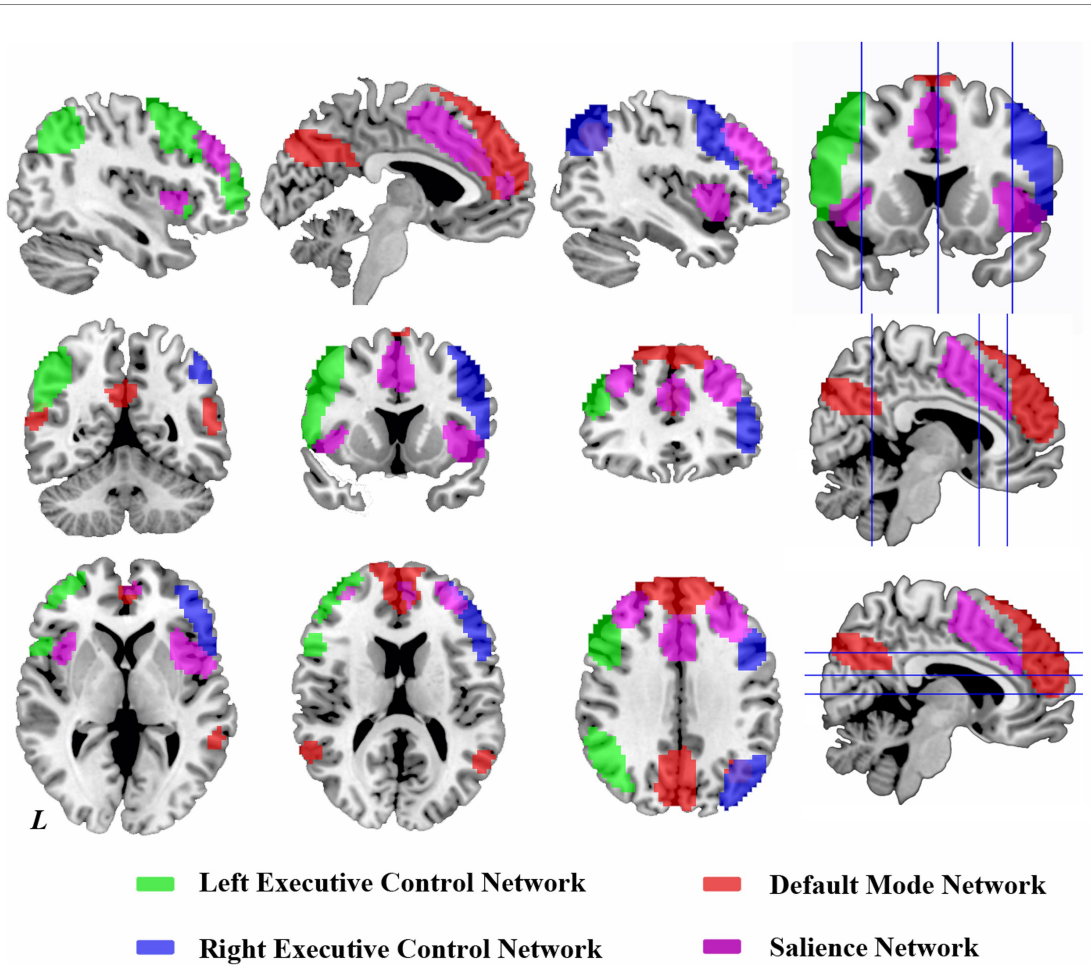


FIGURE 1
Brain networks revealed by the group-level independent component analysis.

## Relapse

During the one-year follow-up period, 19 of the 37 patients undergoing MMT (51.35%) relapsed. The number of occurrences of relapse within a year was 5.25 ± 2.83 (range, 1–11). The number of relapses was negatively related to the total methadone dose in 1 year ($r = -0.515$, $p = 0.001$, Bonferroni corrected $p = 0.05/5 = 0.01$; Figure 3).

TABLE 2 Demographic, heroin usage, and methadone usage characteristics of the Methadone maintenance treatment (MMT) and healthy control (HC) groups (mean±standard deviation).

| Participant characteristics | MMT (*N*=37) | HC (*N*=57) | $t/\chi^2$ | *P* |
|---|---|---|---|---|
| Sex (male/female)[a] | 33/4 | 52/5 | −0.11 | 0.74 |
| Age (years) | 37.57 ± 7.50 | 35.63 ± 6.91 | 1.28 | 0.2 |
| Years of education | 9.43 ± 2.46 | 10.37 ± 2.35 | −1.85 | 0.07 |
| Years of smoking cigarettes | 18.92 ± 8.11 | 16.14 ± 8.01 | 1.64 | 0.11 |
| Cigarettes per day | 18.89 ± 8.89 | 16.46 ± 9.47 | 1.25 | 0.22 |
| Anxiety (HAMA) | 9.27 ± 10.77 | 6.59 ± 3.29 | 1.47 | 0.15 |
| Depression (BDI) | 9.97 ± 8.78 | 7.25 ± 5.34 | 1.70 | 0.10 |
| Mean FD_Power | 0.16 ± 0.08 | 0.15 ± 0.10 | 0.62 | 0.54 |
| Mean FD_Jenkinson | 0.1 ± 0.04 | 0.09 ± 0.06 | 1.67 | 0.1 |
| Duration of heroin usage (months) | 113.94 ± 85.78 | - | - | - |
| Amount of heroin used per day (g) | 0.38 ± 0.4 | - | - | - |
| Duration of methadone usage (months) | 39.54 ± 19.38 | - | - | - |
| Amount of methadone used per day (ml) | 41.38 ± 19.87 | - | - | - |

HAMA, Hamilton Anxiety Scale; BDI, Beck Depression Inventory; FD, frame wise displacement. a: $x^2$ The degree of freedom of the two-sample *t*-test is 92. The degree of freedom of the chi-square test is one.

## Brain network connectivity

The paired *t*-test results showed that only the change in connectivity based on the mPFC (a key node of DMN), which included the left MTG and PPC and the right MFG among the individuals with HUD between baseline and 1 year later (Figure 4), survived the GRF correction (*voxel-p* < 0.001, *cluster-p* < 0.05). This is a longitudinal self-controlled study to observe the effects of methadone on brain connectivity of individuals with HUD. Since it is a self-controlled, longitudinal, observational study, the HC group was only used as a reference control. Therefore, we did not conduct cross-sectional comparison in connectivity between HC and Baseline and one-year follow-up MMT groups.

### Within-DMN connectivity

In comparison with the baseline, the individuals with HUD under MMT showed significantly higher functional connectivity between the mPFC and the left MTG (key nodes of the DMN) 1 year later ($t_{(36)} = 7.18$, *voxel-p* < 0.001, *cluster-p* < 0.05, corrected with GRF, Cohen's dz. = 1.18; Table 3, Figure 5).

### DMN-SN connectivity

In comparison with the Baseline, the individuals with HUD under MMT showed significantly higher functional connectivity between the mPFC and the left AI and right MFG (nodes of the SN) 1 year later ($t_{(36)} = 7.13$, $t_{(36)} = 7.02$, *voxel-p* < 0.001, *cluster-p* < 0.05, corrected with GRF, Cohen's dz. = 1.17; Table 3, Figure 5).

## Correlation between brain connectivity and psychology

We analyzed the correlations between functional connectivity (between the mPFC and the left MTG, left AI, and right MFG) and psychological characteristics (withdrawal symptoms, anxiety symptoms, depression symptoms, and cravings) at the Baseline and 1 year later. Only the functional connectivity of the mPFC-left MTG was negatively correlated with withdrawal symptoms 1 year later

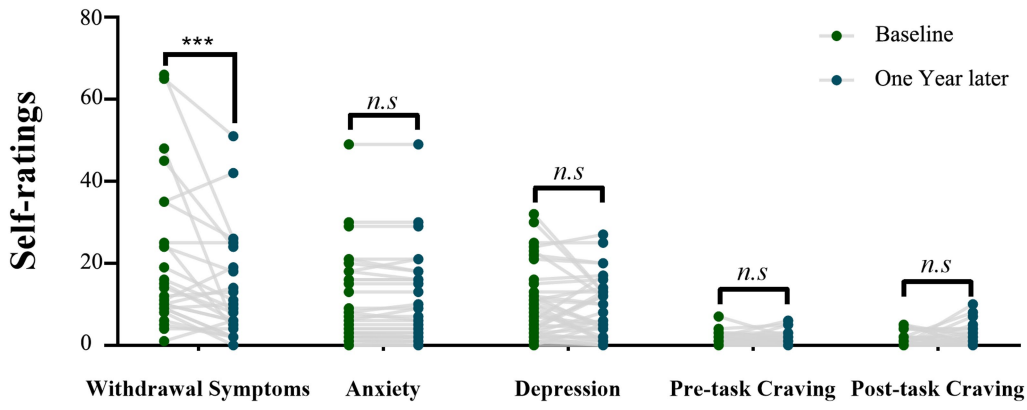


FIGURE 2
The scores of psychological variables of the individuals with HUD at the Baseline and 1year later. Comparison between the two time points by using the paired-sample *t*-test (***$p$=0.005).

($r = -0.58$. $p = 0.002$; Bonferroni corrected $p = 0.05/12 = 0.004$; Figure 6).

We did not find a significant correlation between the change in functional connectivity (between the mPFC and the left MTG, left AI, and right MFG) and the total methadone dose during the year (mPFC-left MTG: $r = -0.138$, $p = 0.517$; mPFC-left AI: $r = -0.037$, $p = 0.827$; mPFC-right MFG: $r = -0.138$, $p = 0.824$).

## Discussion

To the best of our knowledge, this is the first longitudinal self-controlled resting-state fMRI study of the effects of MMT on large-scale brain networks in individuals with HUD. The data showed that (1) MMT continuously reduced withdrawal symptoms in individuals with HUD over 1 year of follow-up and (2) the number of relapses were negatively related to the total methadone dose during the one-year period. We also found that (1) MMT enhanced functional connectivity between the mPFC and the left MTG, AI, and right MFG and (2) the mPFC-left MTG connectivity was negatively correlated with the withdrawal symptoms. In this study, the fMRI connectivity data of HC group were just used as referential control and not followed up. Our findings imply that MMT enhanced the internal functional connectivity within the DMN, which was associated with a reduction in withdrawal symptoms in individuals with HUD, and that it enhanced the coupling between the DMN and SN, which might be related to the risk of relapse.

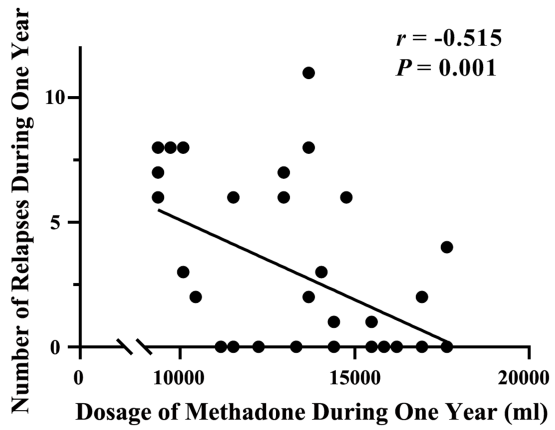


FIGURE 3
Correlation between the number of relapses and total methadone dose during the one-year follow-up period.

### Methadone dose is negatively associated with numbers of relapses

Our findings are consistent with the results of previous studies (6, 24) showing that higher dosages in MMT resulted in lower levels of relapse. Adequate methadone dosage is a key contributor to optimal treatment outcomes for HUD and is required to alleviate withdrawal symptoms, avoid opioid overdose, and even eliminate persistent illegal opioid use (24). One longitudinal study showed that measures of adequate methadone dose improved addiction severity parameters in opioid substitution treatment (25). These management strategies could optimize treatment outcomes, e.g., by relieving withdrawal symptoms and decreasing cravings for heroin.

### DMN connectivity increased for HUDs on MMT

The DMN (mainly including the mPFC, PCC, and MTG) has been linked to regulation of self-focused thoughts, particularly

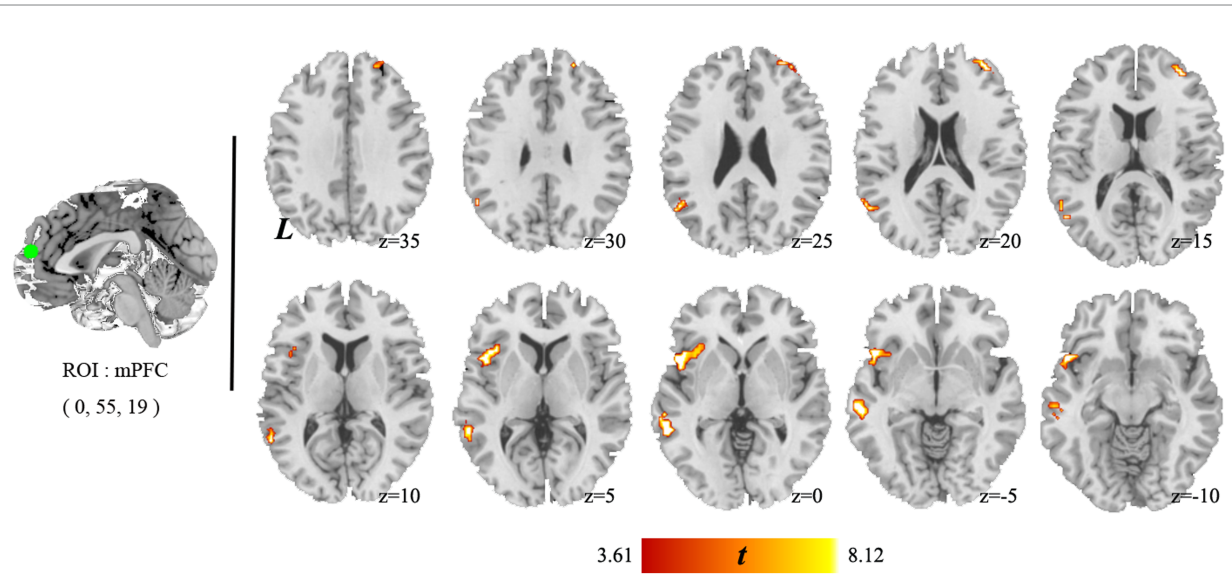


FIGURE 4
Brain areas showing significant changes in mPFC connectivity between baseline and 1year later. The individuals with HUD showed higher functional connectivity in the left middle temporal gyrus, left anterior insula, and right middle temporal gyrus after 1year follow-up.

monitoring psychological states and internal attention, and mediating a dynamic interplay between cognitive functions and emotional processing (26, 27). In addicted individuals, aberrant activation levels within this network have been correlated with a decreased ability, such as deficient tagging of self-relevance and impaired self-awareness (28). A meta-analysis of studies on internet gaming disorder (IGD) showed that individuals with IGD exhibited significant hypoconnectivity within the DMN (29). Low mPFC-MTG connectivity may bias decision-making in smokers, leading to risky behavior and further drug use (30). Internal connectivity within the DMN can influence recall for the best action, including emotional responses to specific events and circumstances from past experiences (31). The mPFC has been shown to be involved in constructing personal meaning from salient stimuli, such as self-reflection, emotion, and evaluation (32). We found that the connectivity between the mPFC and MTG was enhanced and negatively correlated with withdrawal symptoms in individuals with HUD during self-controlled one-year MMT, indicating that the internal connectivity of the DMN was more intense together with improvements in withdrawal symptoms in HUD patients during MMT. Our findings obtained with longitudinal self-controlled MMT provided evidence that MMT may improve monitoring of own psychological states and might benefit emotional regulation by modulating the interconnections of the DMN. The characteristics of connectivity within the DMN might be a feasible neuroimaging biomarker for predicting therapeutic outcomes in individuals with HUD during MMT (33).

TABLE 3 Changes in functional connectivity based on medial prefrontal cortex (mPFC) in the salience network (SN), executive control network (ECN), and default mode network (DMN) in individuals with heroin use disorder (HUD) after 1year follow-up.

| Brain area | Peak Coordinate | | | Peak Intensity (*t*-value) | Cluster size (voxels) | Cluster size ($mm^3$) |
|---|---|---|---|---|---|---|
| | *X* | *Y* | *Z* | | | |
| Right MTG | −51 | −57 | 24 | 7.13 | 112 | 3,024 |
| Left AI | −48 | 6 | 3 | 7.18 | 105 | 2,835 |
| Left MFG | 33 | 51 | 21 | 6.56 | 32 | 864 |

## Connectivity between the DMN and SN increased for HUDs on MMT

Different from our hypothesis, our data showed enhanced functional connectivity between the DMN (mPFC) and SN (AI and MFG), consistent with the results of a previous study in which relapsed heroin-dependent individuals showed greater connectivity between the SN and DMN during MMT (16). Similar results were also obtained in another study in which individuals with IGD exhibited significantly enhanced functional connectivity between the DMN and AI (29). The SN participates in processing salient external stimuli, negative coupling with the DMN, and modulating between networks to trigger executive control when a salient stimulation is monitored (29). The relevance of the increased connectivity between the DMN and SN to cognitive impulsivity has been reported previously (34). Given the role of the SN in switching between the DMN and ECN, the increased interaction between DMN and SN might be related to curbing of executive control driven to heightened sensitivity to addiction-related cues and weakened goal-directed behaviors (i.e., inhibitory control). These findings were supported by the results of a systematic review in which MMT was associated with impairments in cognitive functions such as attention, memory, decision-making and emotional interpretation (35). Taken together, the increased connectivity between the DMN and SN might underlie attentional bias to incentive triggers leading to enhanced salience values of heroin cues in individuals with HUD during long-term MMT which in turn could raise relapse risk.

Our previous study showed that (17) for individuals with HUD who did not receive any treatment, methadone can increase

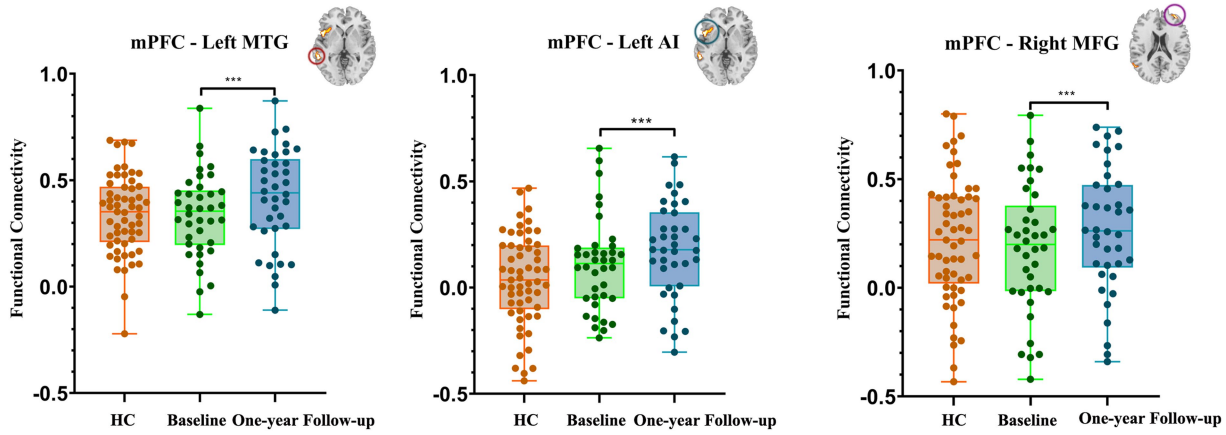


FIGURE 5
Bar chart of the post-hoc results related to the changes in functional connectivity based on mPFC after one-year follow-up. The data of the HC group is presented as control data (HC, healthy controls; mPFC, medial prefrontal cortex; MTG, middle temporal gyrus; AI, anterior insula; MFG, middle temporal gyrus. ***$p$<0.001).

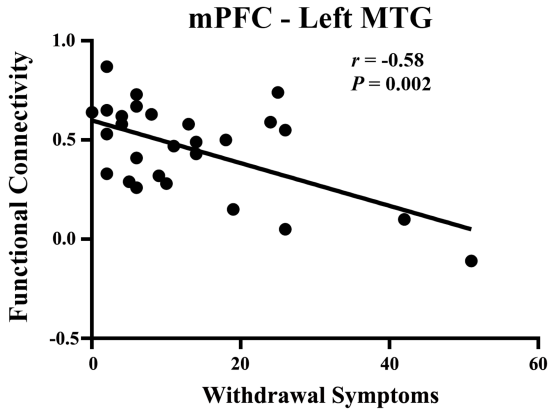


FIGURE 6
Correlation between withdrawal symptoms and functional connectivity of the mPFC-left MTG in the individuals with HUD after one-year follow-up.

functional connectivity between SN and ECNs. These results suggested that methadone might be beneficial to the recovery of the inhibitory control function for individuals with HUD. The present longitudinal self-control study showed that as time went on, long-term MMT program both enhanced the internal functional connectivity within the DMN and the connectivity between the SN and DMN. These results suggest that methadone may have both positive and negative effects on individuals with HUD.

This study had several limitations. First, the urine tests for HUD patients were performed once a month, rather than random multiple tests within a month. This limited our ability to accurately ascertain the number of relapses among patients undergoing MMT. Second, our sample mostly included men because of the difficulties in recruiting female individuals with HUD. Third, although we asked the participants to avoid thinking about anything specific during the resting-state fMRI scans, we could not ensure their compliance with this instruction. However, this may be a communal problem in resting-state fMRI studies. Fourth, we only studied the connectivity of the three core large networks. Other networks may also contribute to the effect of MMT on brain connectivity. Thus, future studies should aim to investigate the characteristics of changes in other large-scale networks. Fifth, we did not collect longitudinal follow-up data of healthy controls. It cannot be excluded that other factors may have an impact on the study results, such as aging of brain function with time, reduced heroin use, less anxiety during scanning, lifestyle changes, health changes, etc.

In conclusion, this longitudinal self-controlled study showed that MMT increased the internal connectivity of the DMN, which was associated with a reduction in withdrawal symptoms in individuals with HUD. MMT also increased the connectivity between the DMN and SN, which might be related to increase in salience values of heroin cues in individuals with HUD during long-term MMT. Our findings suggest that long-term MMT might be a double-edged sword in the treatment of HUD. Thus, more research is needed to identify a balance in guiding MMT protocols to achieve optimal internal and external DMN connectivity.

## Primary finding

(1) Long-term methadone maintenance treatment enhanced the connectivity within the default mode network and that between the default mode network and salience network.
(2) The connectivity within the default mode network was negatively correlated with the withdrawal symptom score.
(3) The number of relapses was negatively correlated to the total methadone dose used during in one-year follow-up.

## 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 Tangdu Hospital Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

JC analyzed the data and drafted the paper. WW, CJ, and QL designed the study and wrote the protocol. YoL, SW, WLi, YaL, LJ, ZL, JZ, FW, WLiu, JX, and HS collected the MRI data. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

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

## Publisher's note

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# Effects of a brief mindfulness meditation practice on Pavlovian-to-instrumental transfer in alcohol use disorder – a pilot study

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**Introduction:** Pavlovian conditioned contextual cues have been suggested to modulate instrumental action and might explain maladaptive behavior such as relapse in participants suffering from alcohol use disorder (AUD). Pavlovian-to-Instrumental transfer (PIT) experimentally assesses the magnitude of this context-dependent effect and studies have shown a larger PIT effect in AUD populations. Taken this into account, a reduction of the influence of cues on behavior seems warranted and one approach that could alter such cue reactivity is mindfulness. Mindfulness-based interventions have been shown to be efficient in the treatment of AUD, but underlying mechanisms are yet to be elucidated. Therefore, we aim at investigating the effect of a brief mindful body scan meditation on the magnitude of the PIT effect in AUD subjects and matched controls.

**Methods:** Using a randomized within-subjects design, we compared the effect of a short audio guided body scan meditation against a control condition (audio of nature sounds) on PIT in healthy ($n$ =35) and AUD ($n$ =27) participants.

**Results:** We found no differences in PIT effect between healthy and AUD participants as well as between conditions. However, a significant interaction effect points to a decreased PIT effect after body scan meditation in AUD subjects only.

**Discussion:** These pilot results suggest that AUD might be susceptible to mindfulness-induced changes in PIT, with these findings contributing to entangling the underlying mechanisms of the efficacy of mindfulness-based interventions in AUD. However, further investigation should confirm these preliminary results and the efficacy of mindfulness meditation practice in decreasing the PIT effect.

KEYWORDS

**mindfulness, alcohol use disorder (AUD), Pavlovian-to-instrumental transfer, cue, intervention**

## Introduction

Alcohol use disorder (AUD) is characterized by high relapse rates despite severe negative consequences (1). Multiple studies have indicated that alcohol-related cues can promote drug-seeking behavior in the context of AUD which has been termed cue reactivity (2). In particular, neural activation in response to alcohol cues has been associated with drinking outcomes (3–5).

Conditioning processes attribute incentive salience to cues in the course of AUD, which goes beyond the initial hedonic experience. Individuals with AUD experience craving and continue maladaptive consumption despite negative consequences, together with drug-related neurobiological adaptations and loss of cognitive control (6). The association of the reinforcing effect of stimuli and instrumental behavior has been experimentally modeled in various ways. One paradigm that has been established, is the so-called Pavlovian-to-instrumental transfer task (PIT) (7, 8). PIT tasks include an instrumental training phase aiming at linking behavioral responses to dispense of rewards. During a phase of Pavlovian conditioning, stimulus–outcome associations are established by linking formerly neutral stimuli to reward. Finally, the established instrumental behavior is assessed in the presence of the previously conditioned stimuli during Pavlovian conditioning (9). The enhancement or suppression of instrumental responses due to the value of Pavlovian conditioned stimuli is referred to as PIT effect (10). Various studies found AUD populations to be affected by an increased PIT effect, i.e., an increased impact of conditioned cues on behavior (11). In addition, the PIT effect has been associated with relapse propensity in detoxified AUD participants (12–14).

In AUD, stress is known to be an important factor that is associated with adverse disease outcomes (15, 16). It has been proposed that stress results in alterations in cognitive function as well as in a shift toward habitual decision-making (17). Stress also might potentially emphasize automatized cue-induced behavior (18). In this context, stress has been discussed as a potential moderator of the PIT effect by strengthening the impact of contextual cues on experimental behavior (14, 19, 20). Other studies however, did not find stress to affect the PIT effect (21, 22). One approach to reduce stress, are so-called mindfulness-based interventions (MBIs). In line with this, programs such as mindfulness-based relapse prevention (MBRP) or Mindfulness-Oriented Recovery Enhancement (MORE) have been specifically tailored to addictive disorders and have shown efficacy in increasing abstinence and decreasing measures of dependence severity (23). With regards to the underlying mechanisms of the efficacy of MBIs, a body of research suggests various underlying mechanisms. It has been proposed that these interventions reduce subjective and physiological stress, increase cognitive control and decrease the effect of addiction-related cues on behavior (24). With regard to cue-reactivity, in populations with opioid abuse, evidence for an effect of mindfulness on neurophysiological reactions to drug cues have been found (25). In addition, conditioned responses to drug cues, operationalized by salivation, were reduced after an MBI (26). In this context, in AUD participants, trait mindfulness as well as mindfulness training was associated with lower reactivity as well as increased physiological recovery toward stress-primed alcohol cues (27, 28). These findings suggest that MBIs may have an impact on the association between Pavlovian cues and instrumental behavior, as demonstrated by the PIT effect. This is supported by previous research demonstrating the influence of cues on instrumental behavior and their role in increasing susceptibility to relapse. In light of this, we wanted to investigate whether PIT effects can be modulated by mindfulness training. Therefore, a pilot sample of participants with AUD as well as healthy controls were subjected to a brief mindful audio-guided body scan meditation before completing the transfer phase of a newly developed single-lever PIT paradigm (29). We contrasted this meditation with the same subjects passively listening to a recording of nature sounds. We specifically hypothesized that the body scan would decrease the magnitude of the PIT effect. We furthermore expected the PIT effect to be increased in AUD compared to healthy controls according to previous research [e.g., (11)]. The findings of this study could be used to further inform the mechanistic investigation of formal MBI programs.

# Methods

## Participants

Thirty-five healthy controls and 27 participants with AUD were recruited via online advertisement in Berlin, Germany. A telephone screening to confirm eligibility was performed prior to assessment. Inclusion criteria were age between 18 and 70 years, sufficient German language skills and the ability to understand the study protocol and give informed consent. AUD participants had to fulfill at least two criteria for AUD according to the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) (DSM-5) (30) with no requirement of medically supervised alcohol detoxification or request for therapeutic intervention. Exclusion criteria were positive urine drug-screening for recreational drugs as well as use of psychoactive medication and substance use disorders other than alcohol, nicotine or cannabis (mild up to two criteria). Other criteria that led to exclusion were medical history of DSM-5 bipolar disorder, psychotic disorder, schizophrenia or schizophrenic spectrum disorder, medical history of severe head trauma or other severe central nervous system disorders as well as necessity of AUD treatment. Participants were compensated 80€ for study participation and gave written informed consent. The study adhered to the Declaration of Helsinki and was approved by the local ethics committee at Charité – University Medicine, Berlin.

## Procedure

Before the experiment, participants completed diagnostic interviews as well as questionnaire assessments. The experiment was executed as a within-subjects design and testing comprised of two consecutive sessions. Participants were assigned to the intervention conditions in randomized order which consisted of participants listening to a 25 min audio file of either nature sounds (NS) (European forest sounds, downloaded[1]) or a guided body scan meditation (BS) [adapted from Kabat-Zinn (31)], respectively. Upon completion of other cognitive tasks, the instrumental training and Pavlovian conditioning phases of the PIT paradigm were administered. Before the transfer phase and forced-choice task (i.e., query trials, where participants had to indicate which one out of two conditioned stimuli they prefer to test that the conditioning was successful), the participants were exposed to another 6 min in terms of a refresher of the assigned intervention condition (please see Figure 1 for details of the procedure).

1 http://stampede.it/

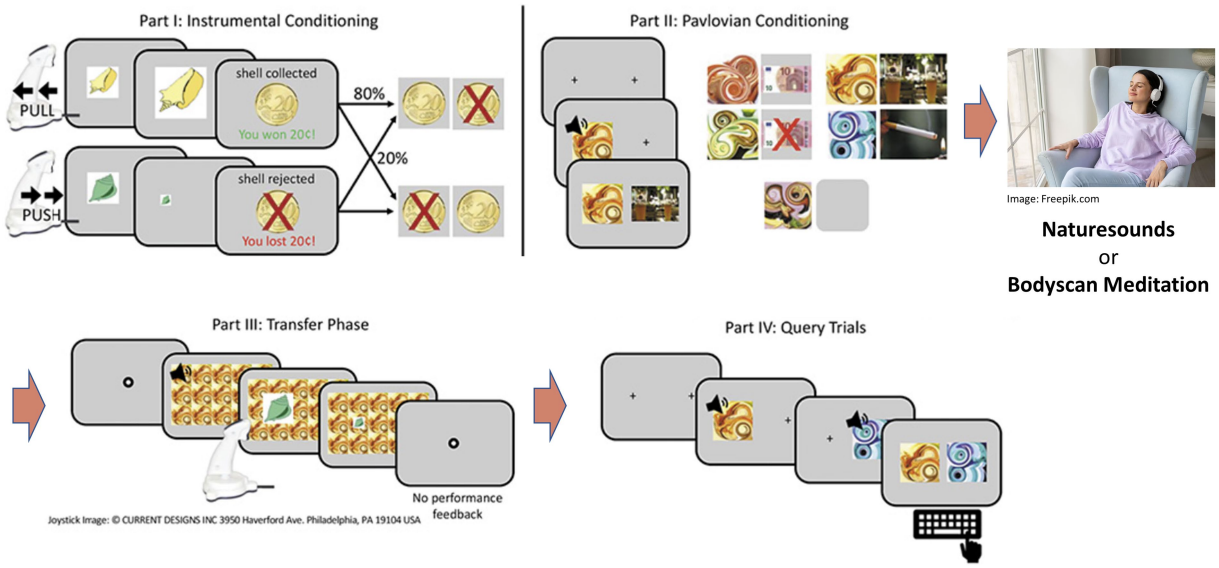


FIGURE 1
Schematic representation of the PIT procedure: In counterbalanced order, participants received a control intervention (nature sounds) or a mindfulness intervention (body scan) per experimental session. The intervention took place between Pavlovian conditioning and the actual transfer phase of the PIT task. Figure adapted from (29). The final, published version of this article is available at https://doi.org/10.1159/000526774.

## PIT paradigm

The task was programmed using Matlab 2019 (version 1.8.0_202; The MathWorks, Natick, MA) and the Psychophysics Toolbox Version 3 [PTB-3; (32)]. Due to the within-subjects design we used two versions that contained different stimuli in the instrumental conditioning part (shells/leaves) as well as in the Pavlovian conditioning part (different colored fractals) to prevent carry-over effects. For a detailed description of the paradigm, please see (29). The task consists of four parts (depicted in Figure 1):

(1) *Instrumental conditioning*: Participants collected or rejected shells or leaves by means of a pull or push joystick movement after which they received probabilistic feedback. In the "approach trials," collecting a shell was rewarded in 80% of the trials and penalized in 20% of the trials, and vice versa if it was rejected. For the "rejection trials," collecting a shell was penalized in 80% of the trials and rewarded in 20% of the trials, and vice versa if it was collected. For instrumental training, a learning criterion was set to ensure that participants performed comparably in the end of instrumental training (after at least 60 trials, 80% correct decisions in 16 consecutive trials) to avoid between group effects in instrumental performance that might influence the PIT effect. Instrumental conditioning lasted a maximum of 120 trials or until the learning criterion was reached. (2) *Pavlovian conditioning*: At the beginning of each trial, a picture of an abstract fractal accompanied by a tone (combined CS) was presented. After a 3 s delay, an unconditioned stimulus (US) (neutral: depicted by a fixation cross; positive: depicted by + 10€; negative: depicted by – 10€) was shown for an extra 3 s. Participants were instructed to pay attention to the CS-US pairs. Pavlovian conditioning ended after 80 trials. (3) *Transfer phase*: In each trial lasting on average 3 s (ranging from 2 to 6 s as determined by an exponential distribution), were tiled over the background while participants were instructed to reject or collect shells/leaves according to previously learned contingencies (part 1). While no feedback was provided, participants were told that their decisions would affect the final monetary outcome. Part 3 lasted for 180 trials. (4) *Query trials*: Over 30 trials, participants were presented with two combined CSs at a time with the instruction to choose one according to their subjective liking. All possible CS pairs were presented three times in a random order.

## Intervention conditions

During the mindfulness intervention, participants listened to a 25-min audio file that consisted of instructions to a body scan mediation. Participants were asked to close focus on various body parts and observe any sensation without judgment while staying in the moment and letting other thoughts recede. The control condition consisted of participants' listening to 25 min of nature sounds. During both conditions, participants remained seated in a comfortable chair with their eyes closed while being unaccompanied in a quiet room.

## Other measures

Next to diagnostic interviewing according to DSM-5 criteria of AUD, we administered a questionnaire commonly administered in clinical samples. The Alcohol Dependency Scale (ADS) is a measure of the severity of the participant's dependence on alcohol and comprises of factors such as loss of control over drinking, obsessive–compulsive drinking and withdrawal symptoms (33).

To assess a proxy of premorbid intelligence, we administered a multiple choice vocabulary test, MWT-B (Mehrfachwahl-Wortschatz-Test), that is broadly used in clinical and research context in Germany (34).

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Alcohol consumption was estimated by assessing quantity frequency of average consumption over the last 90 days. Participants retrospectively reported the average quantity per type of drink per occasion as well as the frequency in the given time interval in which that amount is consumed (35).

In addition, participants completed the Perceived Stress Scale (PSS) (36) widely used to measure subjectively perceived stress, as well as the Five Facets Mindfulness Questionnaire (FFMQ) (37) to assess trait mindfulness across five dimensions including nonjudging, describing, nonreacting, acting with awareness and observing.

Before and after the intervention condition, participants completed visual analog scales to assess vigilance, alertness and relaxation.

## Data analysis

Data were analyzed with MATLAB R2019b (MATLAB version 9.7, 2019; The MathWorks, Inc.) and the R System for Statistical Computing – version 4.2.2 (R Development Core Team, 2022). Demographic as well as questionnaire-based comparisons between AUD participants and HC were examined using chi-square and *t*-tests (Table 1). For examination of the effect of the interventions on self-reported vigilance, alertness and relaxation, we calculated a mixed ANOVA with time (pre and post) and intervention (body scan and nature sounds) as factors.

To analyze the motivational component of instrumental behavior during the transfer phase, the peak velocity (in degrees per second) of the collection and rejection movements of the joystick were examined. Here, the PIT effect is reflected by the interaction of the background stimulus' value and the peak velocity of the instrumental action. The aim of study was to assess the effect of the intervention condition as well as of group (AUD versus HC) on the PIT effect. Since we used a within-subjects design, we included session in the model to account for carry-over effects from session 1 to session 2, although administration of the intervention was done in randomized fashion.

A linear mixed-effect model (LMM) [R-package: lme4 (38)] was constructed to include the following fixed effects and their

TABLE 1 Sample characteristics of AUD and HC groups.

| | AUD (*N*=27) | HC (*N*=35) | Test statistics |
|---|---|---|---|
| | M (SD) | M (SD) | |
| *Demographic variables* | | | |
| Age | 39.85 (11.88) | 38.51 (14.26) | $t = -0.39$, $p = 0.70$ |
| Sex (% female) | 17% | 59% | $\chi^2 = 11.8$, $p < 0.001$ |
| AUD criteria | 4.36 (2.30) | 0.06 (0.24) | $t = -10.59$, $p < 0.001$ |
| *Questionnaires* | | | |
| ADS | 8.58 (4.04) | 2.60 (2.39) | $t = 6.48$, $p < 0.001$ |
| Average consumption per day | 2.89 (2.34) | 0.54 (0.83) | $t = 4.98$, $p < 0.001$ |
| FFMQ | 136.67 (18.53) | 135.35 (17.07) | $t = 0.279$, $p = 0.78$ |
| PSS | 17.42 (6.83) | 13.97 (5.13) | $t = 2.20$, $p = 0.032$ |
| MWT-B | 26.50 (10.60) | 31.09 (3.53) | $t = -2.04$, $p = 0.051$ |
| | N (%) | N (%) | |
| *Highest educational qualification* | | | $t = -0.746$, $p = 0.459$ |
| General certificate of secondary education (Realschulabschluss) | 2 (7.4) | 1 (2.9) | |
| Polytechnic secondary school (Polytechnische oberschule) | – | 1 (2.9) | |
| Advanced technical college certificate (Fachhochschulreife) | 5 (18.5) | 3 (8.6) | |
| General certificate of education | 20 (74.1) | 30 (85.7) | |
| *Cannabis consumption** | | | $t = 1.060$, $p = 0.293$ |
| Never | 20 (74.1) | 31 (88.6) | |
| 1–2 times | 3 (11.1) | 2 (5.7) | |
| Weekly | 3 (11.1) | 1 (2.9) | |
| Daily | 1 (3.7) | 1 (2.9) | |
| *Tobacco consumption** | | | $t = 2.94$, $p = 0.293$ |
| Never | 12 (44.4) | 27 (77.1) | |
| 1–2 times | 2 (7.4) | 3 (8.6) | |
| Weekly | 4 (14.8) | 1 (2.9) | |
| Daily | 9 (33.3) | 4 (11.4) | |

AUD, Alcohol use disorder; HC, Healthy controls; M, mean; SD, standard deviation; ADS, Alcohol Dependence Scale; FFMQ, Five Facets Mindfulness Scale; PSS, Perceived Stress Scale; MWT-B, Mehrfachwahl-Wortschatz-Test; *consumption frequency in the last 3 months.

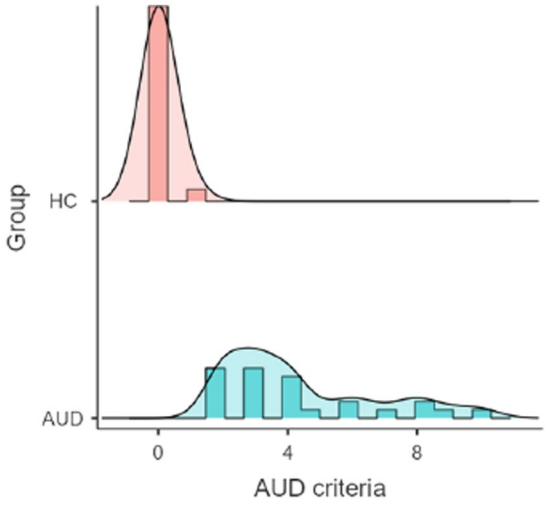


FIGURE 2
Density plot of the distribution of AUD criteria in the HC and AUD group.

**TABLE 2** Model comparisons between the full model and models that excluded fixed effects.

| Model | AIC | Log likelihood |
|---|---|---|
| 1. Full model | 176,728 | −88,271 |
| 2. No session | 176,914 | −88,422 |
| 3. No condition | 176,868 | −88,399 |
| 4. No group | 176,848 | −88,389 |

AIC, Akaike information criterion.

interactions: Pavlovian CS (dummy coded with 10€ as a reference), intervention condition (nature sounds or body scan, coded as 0.5 and −0.5 respectively), session (second and first session, coded as 0.5 and −0.5 respectively), group (AUD and HC, coded as 0.5 and −0.5 respectively) and instrumental response (reject and collect, coded as 0.5 and −0.5 respectively). For random effects, we included the effect of instrumental response as well as Pavlovian CS per subject as likelihood ratio tests (LRT) of random effects indicated the variance parameter of instrumental response (LRT = 2,231; $p < 0.001$) and Pavlovian CS (LRT = 734; $p < 0.001$) to be significantly different from zero.

In addition, we carried out a mediation analysis testing for an association of FFMQ, PSS and ADS (please see Supplementary material for details).

## Results

The groups did not differ in age, premorbid intelligence as well as trait mindfulness measured by MWT-B and FFMQ, respectively. Compared to the HC group, AUD participants displayed significantly higher ADS scores, average daily consumption, perceived stress (PSS) as well as AUD criteria (please see Figure 2 for distribution of AUD criteria). Finally, the AUD group contained more male participants than the HC group. All results are shown in Table 1.

The subjects' performance during query trials indicated that there was no difference between session and conditions. The results are reported in the Supplementary Table S1.

Regarding the transfer phase, prior to inspection of the fixed effects, we performed and compared several linear mixed models. We found the full model that contained session, group and condition to best fit our data (see Table 2 for details). In extension of this, omnibus F-tests of the fixed effects are reported in Supplementary Table S2. Here, all four-way interactions between fixed effects were not significantly contributing to the model (ranging from $p = 0.07$ – $p = 0.95$) and were therefore omitted.

In line with our hypotheses, there was an overall effect of Pavlovian CS on peak velocity (10€ –10€: estimate −116.45; $t = -4.65$; $p < 0.001$), specifically, the positive Pavlovian CS was approached faster (mean = 80.49; SE = 15.2) than the neutral CS (mean = 6.02; SE = 11.8) while the negative CS was avoided (mean = −35.97; SE = 15.9) (see Table 3). As expected, there was an effect of instrumental response (estimate −364.14; $t = -10.25$; $p < 0.001$). Moreover, we found condition to be significant (estimate 25.17; $t = 2.53$; $p = 0.011$), indicating a generally faster peak velocity after the nature sounds condition across all CS. Additionally, we found session to interact with instrumental response (estimate −62.85; $t = -3.44$; $p < 0.001$), indicating a higher contrast between collect and reject trials (session 1 estimate −367, SE = 37.1; session 2 estimate −407, SE = 37.4) that implies better accuracy in the second session concerning instrumental contingencies. However, instrumental response did not interact with group (estimate 33.92; $t = -0.47$; $p = 0.64$) or condition (estimate −32.24; $t = -1.77$; $p = 0.08$) which suggests that these factors do not impact the instrumental performance in the transfer phase. Furthermore, we found a significant interaction between Pavlovian CS and session (estimate 57.37; $t = 4.06$, $p < 0.001$), here the PIT effect was less pronounced in the second session (please see Table 4 for means and standard errors).

We did not find an interaction effect of condition*Pavlovian CS (estimate −18.92, $t = -1.34$, $p = 0.18$), nor group*Pavlovian CS (estimate 42.90, $t = 0.84$, $p = 0.41$). Interestingly, however the interaction between group * condition * Pavlovian CS (10€ –10€: estimate −115.43; $t = -4.09$; $p < 0.001$) indicates that after the body scan condition the PIT effect was reduced in the AUD group only (please see Figure 3 for an illustration of this interaction effect).

Simple effects analysis indicated that the effect of Pavlovian CS on peak velocity in the body scan condition was not significant in the AUD group ($F = 1.19$, $p = 0.31$). This contrast indicates the non-significance of the PIT effect in the AUD group after administration of the body scan. In turn, it was significant in HC across both conditions (body scan: $F = 12.28$, $p < 0.001$; nature sounds: $F = 6.58$, $p = 0.002$) as well as in the nature sounds condition in AUD ($F = 5.42$; $p = 0.006$).

The results of the mixed ANOVA indicated no effect of the intervention conditions on change in self-reported vigilance ($p = 0.5$), relaxation ($p = 0.51$) and alertness ($p = 0.68$). There was also no effect of group on the change in vigilance ($p = 0.95$), relaxation ($p = 0.63$) and alertness ($p = 0.30$).

In addition, testing for an association among of trait mindfulness, stress and ADS, we found that perceived stress assessed by the PSS was negatively correlated with trait mindfulness assessed by FFMQ in both groups (AUD $r = -0.7$, $p < 0.05$; HC $r = -0.51$, $p < 0.05$). In AUD participants, PSS score positively correlated to ADS scores ($r = -0.47$, $p < 0.05$) (Please see Supplementary Figures S1, S2). However, there was no association between ADS and FFMQ scores ($r = -0.19$, $p > 0.05$). Mediation analysis of the effect of FFMQ on ADS through PSS scores indicated a significant indirect effect (estimate = −0.10; 95% CI = −0.2169; −0.0205), meaning that FFMQ is negatively associated with ADS though reduction of PSS scores.

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TABLE 3 Fixed effects parameter estimates.

| 95% Confidence interval | | | | | | |
|---|---|---|---|---|---|---|
| Names | Estimate | SE | Lower | Upper | *t* | *p* |
| (Intercept) | 80.48 | 15.24 | 50.60 | 110.35 | 5.28 | <0.001 |
| Session (2) | −8.68 | 9.96 | −28.20 | 10.85 | −0.87 | 0.384 |
| Group (AUD) | −39.66 | 30.92 | −100.26 | 20.94 | −1.28 | 0.205 |
| Instrumental response (reject) | −364.14 | 35.51 | −433.74 | −294.54 | −10.25 | <0.001 |
| Pavlovian CS (−10€-10€) | −116.45 | 25.06 | −165.57 | −67.33 | −4.65 | <0.001 |
| Condition (nature sounds) | 25.17 | 9.95 | 5.66 | 44.67 | 2.53 | 0.011 |
| Session (2) * Group (AUD) | −10.44 | 19.92 | −49.49 | 28.60 | −0.52 | 0.600 |
| Session (2) * Instrumental response (reject) | −62.85 | 18.26 | −98.64 | −27.06 | −3.44 | <0.001 |
| Group (AUD) * Instrumental response (reject) | 33.92 | 72.50 | −108.18 | 176.03 | 0.47 | 0.641 |
| Session (2) * Pavlovian CS (−10€–10€) | 57.37 | 14.12 | 29.71 | 85.04 | 4.06 | <0.001 |
| Group (AUD) * Pavlovian CS (−10€–10€) | 42.90 | 51.22 | −57.51 | 143.29 | 0.84 | 0.406 |
| Instrumental response (reject) * Pavlovian CS (−10€-10€) | 1.95 | 12.30 | −22.16 | 26.05 | 0.16 | 0.874 |
| Session (2) * Condition (nature sounds) | 102.45 | 61.96 | −18.99 | 223.89 | 1.65 | 0.103 |
| Group (AUD) * Condition (nature sounds) | 35.03 | 19.91 | −3.98 | 74.05 | 1.76 | 0.078 |
| Instrumental response (reject) * Condition (nature sounds) | −32.24 | 18.22 | −67.94 | 3.46 | −1.77 | 0.077 |
| Pavlovian CS (−10€-10€) * Condition (nature sounds) | −18.92 | 14.09 | −46.55 | 8.70 | −1.34 | 0.179 |
| Session (2) *Group (AUD) * Instrumental response (reject) | 22.01 | 23.19 | −23.45 | 67.47 | 0.95 | 0.343 |
| Session (2) * Group (AUD) * Pavlovian CS (−10€–10€) | 40.89 | 28.23 | −14.44 | 96.21 | 1.45 | 0.147 |
| Session (2) * Instrumental response (reject) * Pavlovian CS (−10€-10€) | 23.54 | 24.43 | −24.34 | 71.42 | 0.96 | 0.335 |
| Group (AUD) * Instrumental response (reject) * Pavlovian CS (−10€-10€) | 8.43 | 24.63 | −39.84 | 56.71 | 0.34 | 0.732 |
| Session (2) * Group (AUD) * Condition (nature sounds) | 40.32 | 72.41 | −101.60 | 182.23 | 0.56 | 0.580 |
| Session (2) * Instrumental Response (reject) * Condition (nature sounds) | −14.37 | 142.79 | −294.24 | 265.50 | −0.10 | 0.920 |
| Group (AUD) * Instrumental Response (reject) * Condition (nature sounds) | 0.19 | 23.19 | −45.26 | 45.64 | 0.01 | 0.993 |
| Session (2) * Pavlovian CS (−10€-10€) * Condition (nature sounds) | −76.48 | 102.78 | −277.91 | 124.96 | −0.74 | 0.460 |
| Group (AUD) * Pavlovian CS (−10€-10€) * Condition (nature sounds) | −115.43 | 28.20 | −170.70 | −60.16 | −4.09 | <0.001 |
| Instrumental Response (reject) * Pavlovian CS (−10€-10€) * Condition (nature sounds) | −12.17 | 24.34 | −59.88 | 35.53 | −0.50 | 0.617 |

TABLE 4 Estimated marginal means.

| Pavlovian CS | Session | Mean | SE | df | 95% Confidence interval | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| 10€ | 1 | 84.8 | 15.8 | 70.6 | 53.3 | 116.34 |
| 0 | 1 | −28.8 | 12.6 | 77.6 | −53.8 | −3.77 |
| −10€ | 1 | −60.3 | 16.4 | 70.4 | −93.1 | −27.52 |
| 10€ | 2 | 76.1 | 16.3 | 78.7 | 43.8 | 108.51 |
| 0 | 2 | 40.8 | 13.1 | 89.9 | 14.9 | 66.74 |
| −10€ | 2 | −11.6 | 16.9 | 77.6 | −45.2 | 21.95 |

## Discussion

To examine the underlying mechanisms of the efficacy of MBIs in addictive disorders, we assessed the influence of a brief mindfulness meditation on the magnitude of the PIT effect in AUD participants and healthy controls. The preliminary results of our pilot study demonstrated a significant effect of the body scan intervention in reducing the PIT effect in the AUD cohort but not in healthy controls. Next to this, we could not find group differences in the slope of the PIT effect between our AUD and HC sample.

Using a newly developed PIT paradigm that utilizes a joystick response device, we detected a significant association between Pavlovian CSs and instrumental behavior in accordance with the related monetary reward. In contrast to neutral stimuli, the Pavlovian CS that were associated with monetary gain were approached faster. However, in contrast to findings by Belanger et al. (29), who observed a symmetrical effect of Pavlovian CS on approach and avoidance behavior, we found the negatively valanced Pavlovian CS to be avoided to a lesser extent than approach toward positive Pavlovian CS. Overall this finding corroborates the research on the influence of motivation on the magnitude of instrumental responding (39). The nature of the within-subjects design led to repeated administration of the PIT paradigm. While the order of the intervention conditions across sessions was randomized, we included session as a factor that indeed contributed to our model. In our sample, we found that the magnitude

of the PIT effect decreased in the second session relative to the first one. Assessing effects of therapeutic interventions warrants outcome measures with good psychometric properties (40); here it is worth mentioning that versions of the PIT paradigm have been ascribed a low test–retest reliability (41). In light of this, the temporal stability of a variation of the PIT task used in this study has been previously investigated (42). Here, a paradigm that consisted of the same stimuli but utilized a button-box response device, was administered on two consecutive days. Analysis of intra-class correlation coefficients (ICC) for subject-specific PIT effects revealed a moderate temporal and moderate to good internal consistency (42). So, in summary, the proficient psychometric properties of our PIT task in combination with randomized intervention administration render our results well-founded and reliable, although analysis of a larger sample is necessary to corroborate this reliability.

Surprisingly, we did not find the AUD and HC group to differ in magnitude of the PIT effect when averaging across both intervention conditions. This stands in contrast to previous research that demonstrated an enhanced PIT effect in a sample of males at risk for AUD compared to low-risk consumers (43). In extension of these findings, Chen et al. (44) also found participants with risky drinking patterns to be more prone to be influenced by monetary Pavlovian CS compared to low-risk drinkers. These behavioral results were accompanied by functional neuroimaging findings that associated the strength of the behavioral PIT effect to decreased prefrontal activation as well as decreased prefrontal-limbic connectivity (44). In various studies that included participants with AUD and compared them with HC, an increased PIT effect was found as well (11). However, one of those studies found this group effect to be driven by the negative Pavlovian CS condition (11, 14). In addition, the magnitude of the PIT effect could distinguish abstainers from prospective relapsing participants (13). Sommer et al. (13) specifically observed that appropriate inhibitory behavior was disrupted by positive Pavlovian CS. These results stand in contrast to the lack of group differences between our AUD and HC samples; however, the employed response devices render the paradigms' conditions dissimilar. In contrast to the button-box version used by the listed studies which requires the inhibition of a response (assessing Go versus Nogo instrumental behavior), the joystick version (assessing approach versus withdrawal behavior) demands an active avoidance of negative instrumental stimuli. Here, the active avoidance might not capture the dysfunctional inhibitory control that was previously found in prospectively relapsing AUD participants. Further, previous studies assessed patients included recently after detoxification, i.e., there were severely ill and abstinent at the time of inclusion while we here included less severely ill and non-abstinent subjects with AUD. Moreover, other studies also failed at detecting an increased PIT effect in populations with various substance use disorders (45–49). The mixed data situation has been proposed to result from discrepancies between the paradigms as well as systematic differences between AUD samples (42). Lastly, the preliminary nature of our data warrants further investigation in a larger sample.

It has been suggested that prolonged drug exposure over the course of addiction, renders environmental cues to exert higher motivational impact on drug consumption by activating positive associations in cost of distinctive drug-memories (50). Thus, in contrast to the notion that the PIT effect might predispose for development of AUD, its' magnitude might increase over the course of disease, providing an explanation why our non-treatment seeking sample might have not displayed a comparatively increased PIT effect.

Finally, in the AUD group, we found the body scan meditation to reduce the strength of the PIT effect. In fact, the effect of (negative) Pavlovian CS on instrumental behavior was rendered non-significant. In contrast, the HC group did not show any differences in PIT effect between conditions. This comparatively heightened susceptibility to the mindfulness intervention in the AUD group is difficult to interpret. Through a learning criterion in the instrumental learning phase, we ensured homogeneous accuracy during the transfer phase. Our results also showed no impact of group or condition on instrumental performance, which rules out the possibility of accuracy impacting the PIT effect. Additional analyses showed that the efficacy of the body scan intervention in AUD cannot be explained by

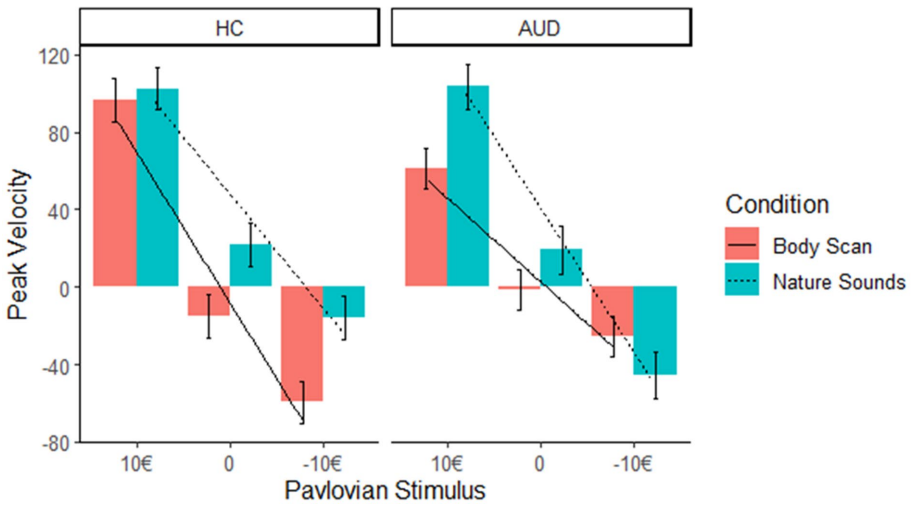


FIGURE 3
In AUD participants, the slope of peak velocity regressed on Pavlovian CS was not significant, indicating a decreased PIT effect after the body scan versus nature sounds condition in the AUD group only.

subjective ratings of intervention-induced vigilance and alertness. As intended, relaxation was affected by both conditions equally. As the body scan is meant to induce a mindful state, we wanted to capture this state specifically and control for relaxation effects. We therefore employed a very strict nature sounds control condition instead of a waiting condition. However, subjective ratings on a visual analog scale might have not captured the effects as well as, e.g., physiological measures such as heart rate variability (HRV). Past research has shown that mindfulness meditation induces changes in various measures of HRV [for a review, see (51)]. Furthermore, trait mindfulness did not differ between AUD and HC groups, ruling out a possible moderation effect of dispositional mindfulness on intervention effects that have been indicated by previous research (52). We could speculate that motivational aspects in the susceptibility to the mindfulness intervention might have played a role; in this case participants with AUD could have shown increased engagement during the mindfulness intervention compared to HC.

Furthermore, FFMQ-based trait mindfulness was negatively associated with perceived stress. Perceived stress in turn is positively correlated with dependence severity in AUD participants. Results of a mediation analysis indicated that mindfulness indirectly affects dependence severity through decreasing perceived stress. A body of research suggests a generally negative relationship between trait mindfulness and substance abuse and it has been suggested that this relationship is in part due to alterations in stress reactivity (53, 54). Synthesizing these findings with evidence for the role of stress as well as mindfulness in cue-reactivity processes, it is warranted that a thorough mindfulness training could reduce the effect of cues on maladaptive behavior.

Besides the described findings, our study has several limitations that we want to address. First, our groups contained unproportional gender distributions. The HC group is characterized by a high number of female subjects while the AUD sample contained mostly male participants. Concerning the AUD sample, our numbers reflect the epidemiological situation as men are diagnosed with AUD about four times as often as women (55). However, it has been repeatedly shown, that PIT effects are not affected by confounders such as age or gender (42). Another limitation is the comparatively small sample size that could have prevented us from detecting group differences in PIT effects as previous studies that noted positive results have used larger sample sizes (11–14, 43, 44). However, as this is a pilot study, we advocate further study in larger sample sizes to validate these findings. Future research should elaborate on the refinement of intervention administration as well as describe the mechanistic effects on an objective level such as heart rate or heart rate variability. Finally, although we detected an effect on the magnitude of the PIT effect in AUD using an ultra-brief body scan meditation, the influence of mindfulness interventions on addiction-relevant cue reactivity should be investigated in the context of a comprehensive mindfulness training such as MBRP.

In conclusion, our pilot study provides interesting results that show that Pavlovian CS exert effects on instrumental responding and that this effect can be decreased by application of a brief mindfulness intervention. This reduction in magnitude of the PIT effect was seen in AUD participants only. These results should however be interpreted with caution, as they are preliminary and based on a small sample size. In sum, our findings add to the knowledge of how MBIs may work in substance use disorders, and indicate that mindfulness training may be a potential intervention approach to mitigate the influence of environmental triggers being one important driver of problematic behavior in individuals with AUD.

## Data availability statement

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

## Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Charité – Universitätsmedizin Berlin. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

AB and NR-S designed and supervised the study. AB, NR-S, and AR implemented the study. MG has partly designed the task. AR has carried out analyses, wrote the first draft of the manuscript, and submitted the manuscript. All authors critically revised the manuscript.

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## Conflict of interest

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

## Publisher's note



## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1134458/full#supplementary-material

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# Resting state connectivity in people living with HIV before and after stopping heavy drinking

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**Background:** Heavy alcohol use in people living with HIV (PLWH) has widespread negative effects on neural functioning. It remains unclear whether experimentally-induced reduction in alcohol use could reverse these effects. We sought to determine the effects of 30-days drinking cessation/reduction on resting state functional connectivity in people with and without HIV.

**Methods:** Thirty-five participants (48.6% PLWH) demonstrating heavy alcohol use attempted to stop drinking for 30 days via contingency management (CM). MRI was acquired at baseline and after thirty days, and functional connectivity across five resting-state fMRI (rsfMRI) networks was calculated with the Conn toolbox for Matlab and examined in relation to transdermal alcohol concentration (TAC) recorded by the ankle-worn secure continuous remote alcohol monitor (SCRAM) and self-reported alcohol use (timeline follow-back; TLFB). Associations between alcohol use and reduction, HIV status, functional connectivity, and change in functional connectivity across five major rsfMRI networks were determined relative to the pre- and post-CM timepoints.

**Results:** Baseline resting-state functional connectivity was not significantly associated with average TAC-AUC during the pre-CM period, though higher self-reported alcohol use over the preceding 30 days was significantly associated with higher baseline connectivity within the Dorsal Attention Network (DAN; p-FDR<0.05). Baseline connectivity within the Salience network was significantly negatively related to objective drinking reduction after intervention (DAN; p-FDR<0.05), whereas baseline connectivity within the Limbic network was positively associated with self-reported drinking reduction (p-FDR<0.05). Change in between-networks functional connectivity after intervention was significantly positively associated with biosensor-confirmed drinking reduction such that higher reduction was associated with stronger connectivity between the limbic and fronto-parietal control networks (p-FDR<0.05). PLWH with lower DAN connectivity at baseline demonstrated poorer alcohol reduction than those with higher DAN connectivity at baseline.

**Discussion:** Lower resting-state functional connectivity of the Salience network significantly predicted stronger drinking reduction across all participants, suggesting a potential biomarker for reduced susceptibility to the environmental and social cues that often make alcohol use reduction attempts unsuccessful. Increased between-networks connectivity was observed in participants with higher alcohol reduction after CM, suggesting a positive benefit to brain

connectivity associated with reduced drinking. PLWH with lower baseline DAN connectivity may not benefit as greatly from CM for alcohol reduction.

KEYWORDS

human immunodeficiency virus, alcohol use, resting-state functional magnetic resonance imaging, contingency management, cessation

## Background

People living with human immunodeficiency virus (PLWH) demonstrate a 29.8% point-prevalence of alcohol use disorder (AUD) (1), which is considerably high given the implications heavy alcohol use has on the immune system (2) and on the metabolism of antiretroviral drugs (3) in this population. Not only has heavy alcohol use been associated with increased risk of all-cause mortality among PLWH compared to those without HIV (4), its impact is widespread across domains of health, social, cognitive, and brain functioning (5–11). In fact, heavy alcohol use has been shown to have more deleterious effects on cognitive and neural domains in PLWH when compared to people without HIV (12). Specifically of interest is the effect of these comorbid conditions on neural functioning, where our group has demonstrated a number of effects of heavy alcohol use in HIV including reduced frontal white matter integrity (13) and reduced functional connectivity of frontal and parietal attentional networks (14). Despite the risk factors associated with heavy drinking, studies of drinking cessation and its effects on brain function in PLWH are quite limited, thus necessitating further work to highlight the clinical relevance of functional connectivity changes in drinking cessation among people living with and without HIV.

## Introduction to neural networks under study

Neural networks in the brain are large-scale functional and structural networks composed of groups of interconnected neurons and brain regions that work together to process and integrate information. Some of the most commonly examined resting-state networks in the context of alcohol use and HIV include the default mode network (DMN), the dorsal attention network (DAN), the cingulo-opercular network (CON/Salience network), the limbic network, and the fronto-parietal control network (FPCN). The DMN comprises regions including the medial prefrontal cortex, posterior cingulate cortex, and the inferior parietal lobule and is active when an individual is at rest, suggesting involvement in intrinsic activity. The DMN is also thought to play a role in regulating attention and monitoring the external environment for salient information (15). The DAN includes several regions of the parietal and frontal cortices, including the superior parietal lobule, intraparietal sulcus, and frontal eye fields, and has been implicated in controlling attention and selecting relevant information from sensory input. It is primarily responsible for directing attention to visual and spatial information, and for the control of voluntary eye movements (16). The cingulo-opercular (e.g., salience) network is a neural network in the brain that is involved in detecting and filtering important or salient sensory and cognitive information from the environment or internal mental states. It includes the anterior insula, dorsal anterior cingulate cortex (dACC), and the fronto-insular cortex (17). The limbic network is a group of interconnected brain structures (e.g., the hippocampus, amygdala, hypothalamus, thalamus, and cingulate gyrus) that play a key role in emotional processing, motivation, learning, and memory (18). The FPCN is involved in cognitive control, attentional processing, working memory, planning, goal-directed behavior, and decision-making, and consists of regions in the prefrontal and parietal cortices that are interconnected by white matter tracts, enabling the rapid transmission of information between these regions (19). There is an abundance of evidence suggesting alterations in the resting-state functional connectivity (rsFC) of these neural circuits associated with AUD and HIV.

## Functional connectivity in AUD

AUD is thought to be caused by a compulsive "drive" toward alcohol consumption (20) as well as an inability to inhibit alcohol consumption, which correspond with increased activity in the appetitive drive networks (a subset of the limbic network associated with reward processing) and decreased activity in brain regions which mediate executive control compared to individuals without AUD (21–23). Resting-state fMRI research in alcohol use and disorders consistently implicates the DMN, the FPCN (also referred to as the Central Executive Network), and the salience network (20). For example, one group found that alcohol use disorder was associated with increased connectivity between fronto-parietal regions involved in cognitive control and decreased connectivity between nine regions of the Salience network involved in reward processing and emotional regulation (Kamarajan, 2022). Similarly, increased between-network rsFC among the executive control network, Salience network, and Limbic regions including the striatum and amygdala as well as increased within-network connectivity in the Salience network, DMN, executive control network, and Limbic network has been found in individuals with AUD (Le Berre et al. 2017). Additionally, rsfMRI studies have shown decreased synchronicity in the posterior cingulate and cerebellar regions (i.e., circuitry of the DMN and DAN) in people with AUD, indicating compromised functional connectivity (28). These rsFC differences may contribute to the cognitive and emotional deficits commonly observed in individuals with chronic alcohol use. However, these alterations in activation may be reversible after prolonged reduction in alcohol use.

## Connectivity changes after drinking reduction

Following drinking reduction and abstinence, individuals with AUD experience altered neural circuits of stress and reward

modulation (e.g., increased limbic network circuitry), making them highly sensitive to stress, anxiety, low mood, autonomic nervous system disruption, fatigue, and sleep problems (29, 30). Functional MRI (fMRI) studies have shown that participants with AUD who stop drinking demonstrate greater activity in limbic-striatal regions (e.g., the limbic network) associated with emotional processing and lower activity in the medial frontal and cingulate regions, particularly in the caudate and posterior cingulate regions associated with emotional regulation, self-control, and executive functioning (31–33). These findings either suggest negative implications of drinking reduction in this population, specifically increased emotional reactivity and decreased self-monitoring, which may make it more difficult to maintain abstinence, or indicate a lack of reversibility of functional connectivity changes associated with AUD. Interestingly, individuals with alcohol use disorders who successfully completed detoxification showed higher connectivity of the DMN, the FPCN, and the salience network compared to those who dropped out of treatment (34). However, several studies have identified evidence for compensatory mechanisms in the resting state networks of long-term abstinent individuals with AUD. One study found increased synchrony in the inhibitory control network (i.e., a subset of the FPCN) and reduced synchrony in the appetitive drive reward network in long-term abstinent persons with AUD when compared to controls without AUD (J. Camchong, Stenger, and Fein 2013), suggesting alterations in connectivity with prolonged drinking reduction. Similarly, Chanraud et al (2011) found resting state synchronicity in posterior cingulate and cerebellar regions (i.e., circuitry of the DMN and DAN) in abstinent persons with AUD compared to age-matched healthy controls who did not meet criteria for AUD connectivity that improved with longer durations of abstinence (Chanraud et al. 2011). Similarly, another study found increased synchrony in the inhibitory control network (i.e., a subset of the FPCN) and reduced synchrony in the appetitive drive reward network in long-term abstinent persons with AUD when compared to controls without AUD (35), suggesting alterations in connectivity with prolonged drinking reduction. While there is evidence for neurobiological changes following drinking reduction and abstinence in adults with AUD, the length of abstinence needed to achieve these changes is unknown. Similarly, there is a dearth of literature investigating these effects in PLWH.

## Connectivity in PLWH

fMRI techniques have been widely used to investigate the neural basis of HIV-associated neurocognitive disorders. In fact, previous fMRI studies have demonstrated marked functional connectivity differences in PLWH, independent of alcohol consumption. For example, a recent meta-analysis found consistent alterations in the fronto-striatal-parietal sub-networks (functionally related to the FPCN), including hyperactivation in the left inferior frontal gyrus and caudate nucleus, which are associated with cognitive impairment, disease progression, and treatment outcomes (36). Further, reduced within-network connectivity of the DMN, the FPCN, and the salience network is implicated in PLWH, in addition to inter-network differences in the DAN and the salience network (37). In studies utilizing diffusion tensor imaging (DTI), duration of HIV infection has been independently associated with white matter injury, especially in frontal projections of the corpus callosum and thalamus (38). Importantly, fronto-striatal and fronto-parietal circuits implicated in HIV progression are functionally involved in the inhibition and regulation of appetitive, attention, impulsive, and emotional responses and behaviors (39), and therefore may be altered by substance abuse. Indeed, in a prior rsfMRI study, our group has shown in a prior resting-state fMRI study lower fronto-parietal connectivity (e.g., FPCN) and increased connectivity between attention/working memory networks (i.e., the DAN) and mesolimbic regions (i.e., the limbic network) critical to addiction in PLWH with chronic alcohol abuse (14). Taken together, previous research indicates reduced white matter integrity in regions important for inhibition and regulation of alcohol consumption as well as increased connectivity between regions implicated in appetitive drive toward alcohol consumption, suggesting a compounding of effects in individuals with HIV and alcohol use disorder.

## Alcohol monitoring and interventions

Behavioral interventions focusing on reducing the frequency of harmful alcohol use are becoming increasingly common. Contingency management (CM) is one of the most effective evidence-based treatment approaches directly addressing substance use disorder that encourages drinkers to alter their drinking behavior to reduce the probability of alcohol-related consequences (40, 41). CM is a behavioral treatment based on operant conditioning principles that gives participants rewards in the form of cash, prizes, or vouchers to reinforce positive behaviors, such as alcohol abstinence (42). This operant conditioning approach is often preferred by patients and their clinicians (43, 44), and contingency management as a harm-reduction intervention produces similar health outcomes as those who abstain from alcohol (45, 46).

Technologies that allow continuous monitoring of alcohol use have been developed and combined with the CM approach to objectively monitor drinking reduction, such as transdermal alcohol detection. This method senses the 1% of ingested alcohol that is secreted through the skin via sweat glands and diffusion (47), allowing for the separation of heavy drinking episodes from lower and moderate drinking levels (48, 49). One device, the Secure Continuous Remote Alcohol Monitoring bracelet (SCRAM, Alcohol Monitoring Systems; AMS), which is regularly worn by court-referred offenders, has been established as valid in controlled laboratory and field trials (50, 51). This device contains three sensors that assess contact with the skin, skin temperature, and perspiration once every 30 min. As a noninvasive measurement approach, the SCRAM measures the concentration of alcohol in insensible perspiration, providing estimates of the frequency and quantity of alcohol consumption over extended periods of time within the participant's natural environment while avoiding the limitations of frequent testing and self-report.

Transdermal alcohol detection devices, such as the SCRAM, have shown a strong correlation ($r = 0.84$) between area under the curve (AUC) values and breath alcohol content (BrAC) (51). The SCRAM-CAM (Secure Continuous Remote Alcohol Monitor Continuous Alcohol Monitoring; Alcohol Monitoring Systems, Inc., Littleton, CO) anklet is the most commonly used and well-validated alcohol biosensor available (52–54). The SCRAM device can reflect blood alcohol concentration (BAC) within a drinking event continuously and in near real-time (55) by plotting the transdermal

alcohol content (TAC) curve, as well as the AUC value representing the geometric area beneath the TAC curve (56). Peak TAC represents the highest level of TAC reached during a drinking episode (48), while area under the curve (TAC-AUC) represents an individual's total exposure to alcohol during a drinking episode (57). Studies report that TAC is significantly associated with self-reported drinking with correlations ranging from 0.30 to 0.74 (58–61). In a laboratory setting, peak TAC and TAC-AUC have strong correlations to breath alcohol concentration (0.6–0.9) (51). However, SCRAM data, much like BrAC, cannot yet be directly equated into number of drinks consumed. Thus, the equivocation of SCRAM data to real-life drinking level in cross-sectional research is limited, and within-subjects, longitudinal data analysis may be more appropriate.

In the present study, we sought to determine: (1) the baseline associations between resting-state functional MRI (rsfMRI) connectivity, self-reported and objective alcohol use, and HIV, (2) changes in rsfMRI connectivity after 30 days of attempted abstinence from heavy alcohol use (including reduction of alcohol use), and (3) how rsfMRI connectivity alterations after 30 days attempted abstinence from heavy alcohol use differ between PLWH and people without HIV. We propose the examination of five resting-state networks (DMN, DAN, CON/Salience, limbic, and FPCN) in the present study examining the effects of alcohol reduction in individuals exhibiting current heavy alcohol use who may or may not carry a diagnosis of HIV. Prior to data analysis, we hypothesized that participants living with HIV will demonstrate lower rsfMRI connectivity within regions comprising frontal networks, including the Fronto-Parietal Control Network (FPCN), Default Mode Network (DMN), and Limbic, but will be equivalent to participants without HIV in remaining resting-state network (CON/Salience). Further, we hypothesized that resting-state connectivity will be negatively associated with self-reported drinking severity at baseline (prior to intervention), and that associations between resting-state connectivity and drinking severity will be enhanced in participants living with HIV compared to participants without HIV. With regard to changes after the intervention, we hypothesized that participants with stronger abstinence as measured by lower self-reported drinking and a lower TAC-AUC over the 30-day period will demonstrate enhanced rsfMRI connectivity across FPCN, DMN, and Limbic networks. We also hypothesized that participant HIV status will serve to enhance connectivity improvements associated with abstinence, such that those with HIV will see larger relative connectivity changes compared to baseline.

# Methods

## Participants

Participants were part of the 30-Day Challenge study, which is a study to test the effects of alcohol reduction through CM in older adults with heavy alcohol use living with or without HIV who are interested in reducing their alcohol intake. All in-person procedures were conducted at either the University of Miami or Florida International University. To be eligible, participants had to be between 45 and 75 years old, living with or without HIV (confirmed via medical record, medication, or blood test); drink heavily (≥14 drinks/week for women, ≥21 drinks/week for men) in the past 30 days; speak English; be willing to participate in CM to reduce their alcohol use; and be willing to wear the SCRAM for at least 30 days. Participants may have been in treatment for alcohol use in the past, but must not have been actively enrolled in another treatment program or research study at the time of their participation. A total of 39 participants completed MRI at both the baseline and 30-day time points. Of these, one subject was removed due to corrupt rsfMRI data, one was removed for rsfMRI global signal change greater than 3SD from the group mean, and two were removed for rsfMRI motion parameters exceeding 3SD of the group mean, resulting in a final sample of 35 participants. Of the 35 participants in the study, 18 were living with HIV and 17 were people without HIV.

## Objective alcohol use monitoring

As described in our group's previous work (60), after providing consent participants were entered into an enrollment eligibility phase in which they would wear the SCRAM biosensor for a pre-contingency management (pre-CM) "test week" (hereafter referred to as the Pre-CM period) during which they provided self-reported drinking information. The purpose of the pre-CM period was to confirm that the participant did meet heavy drinking criteria, that they could tolerate the SCRAM monitor, and to demonstrate that the monitor accurately detected drinking days prior to participants entering a CM period. The SCRAM monitor was installed on the participant's preferred leg and locked in placed once the participant was ready to leave the lab. The participant was given instructions about the monitor, including not to submerge the device in water, to avoid using alcohol-based items (e.g., perfume, bug spray), and not to wear socks under the monitor. Participants were instructed to drink as they normally would during the pre-CM period for all but 1 day of their choosing, in which a day of abstinence was required to assure that the monitor could accurately distinguish between drinking days and abstaining days. During the Pre-CM period, a research assistant called the participant at the end of the week and collected information about self-reported drinking, including the number of drinks on each drinking day. When the participants returned at the end of the pre-CM period, the data on the ankle monitor were uploaded to the SCRAM system using the DirectConnect device. As detailed in a recent work by our group, "TAC data were collected by the SCRAM-CAM and transmitted to the AMS server using the company's DirectConnect device. Data were downloaded from the server through a password-protected portal. The Transdermal Alcohol Sensor Data Macro (TASMAC Software) read and interpreted data from the SCRAM" (62). The participant took the DirectConnect device home so that the research assistant could check their daily data. The daily compensation was calculated based on their daily data using the social day from 6:00 am to 6:00 am.

## Intervention: contingency management

Contingency management (CM) was implemented in the present study after the pre-CM period through direct payment for alcohol abstinence. Abstinence was determined on a daily basis through remote monitoring (SCRAM) with distribution of funds to the participant upon confirmation of abstinence by a team member. After the pre-CM period, the participant completed a baseline assessment that included neuropsychological testing, additional questionnaires, and blood testing. Subsequently, participants began the 30-day

enrollment "challenge" period during which continuous monitoring of alcohol use was enacted using the SCRAM device. At the conclusion of the 30-day CM period, participants again completed all measures from the baseline assessment listed above.

Payments: On the first day of sobriety, a participant would receive $5. For each consecutive day after their payout, it would increase by $1 (e.g., on day one, participants receive $5, day two participant receives $6, etc.) at day seven, they can receive a total of $45 plus a bonus of $25 for maintaining abstinence for seven consecutive days. The bonus payments increase by $20 every 7 days. Therefore, at 14 days of abstinence, their bonus would be $40. The max amount paid for maintaining abstinence throughout a challenge (30 days) could be a total of $440 (not including payout for assessment visits), and a minimum payout could be $0 if the participant had a drinking episode every day. As for the payouts, the participants often chose to receive payments every 8 days (after earning a bonus) to take advantage of the lump sum of money earned for maintaining abstinence. During enrollment, participants were asked about their preferred method of funds transfer and frequency of payments to collect for adjustments and bonuses.

## Analysis of subjective alcohol use

The timeline follow-back (TLFB) is a self-report measure of alcohol consumption over the past 30 days which is typically used to calculate the average number of drinks per day over the prior month (63). The process involves asking participants to recount their drinking behaviors in terms of number of drinks as a team member moves across a calendar, referencing anchors and reminders (e.g., holidays) about what a participant did each day to assist with memory. For the purposes of this study, 30-day timeline follow-back was completed with each participant at the baseline timepoint and the 30-day follow-up timepoint. The average number of drinks per day was then calculated by dividing their total reported number of drinks by a constant of 30. This provided a TLFB-30 data point at the baseline visit as well as at the 30-day follow-up visit. Lastly, a percent reduction value was calculated from these data such that their post-intervention 30-day TLFB total was subtracted from the pre-intervention 30-day TLFB total and divided by the pre-intervention total.

$$\frac{PreIntervention\ TLFB - PostIntervention\ TLFB}{PreIntervention\ TLFB}$$

## Analysis of objective alcohol use monitoring

The Transdermal Alcohol Sensor Data Macro (TASMAC Software) (64) was utilized to read and interpret data from the SCRAM biosensor. The TASMAC integrates previously published criteria designed to be more sensitive than the default SCRAM criteria (established by the AMS Inc.) to detect drinking episodes (65). The present study used TAC-AUC generated by the TASMAC as the primary estimate of average daily alcohol use over the test week and 30-day test period. Specifically, daily TAC-AUC was calculated as the sum of all TAC-AUC from detected drinking episodes that began on the SCRAM-detected drinking day. If there were multiple drinking episodes within a single drinking day, TAC-AUCs were summed. For the purposes of analysis, three variables were computed, including (1) the TAC-AUC average over the seven drinking days prior to the intervention, (2) TAC-AUC average over the final 7 days of the 30-day intervention period, and (3) the percent reduction from pre- to post-intervention calculated through the formula:

$$\frac{PreIntervention\ TAC\_AUC - PostIntervention\ TAC\_AUC}{PreIntervention\ TAC\_AUC}$$

The rationale for the use of the TAC-AUC during the final 7 days of the 30-day intervention is that doing so creates a time point most proximal to the acquisition of neuroimaging and equivocal both in duration and proximity to the neuroimaging as the pre-CM TAC-AUC data.

*Specific abstinence calculation procedure*: To determine whether the participant remained abstinent based on objective SCRAM data, we used sensitive criteria originally devised by Barnett et al., as follows:

1. The peak of TAC data must reach =>0.02 at least once (basic criteria).
   and
2. Absorption rate must be less than 0.05.
   or
3. For a peak <=0.15, elimination rate must be (>0.003 and < 0.025).
   For a peak >0.15, elimination rate must be (>0.003 and < 0.035).

A drinking episode must meet rule 1 and 2 (based on absorption rate) OR rule 1 and 3 (based on elimination rate). TAC data that do not meet these criteria are not considered to be true drinking episodes and will be ignored. This macro evaluates days based on a 24-h "social day" from 6 AM to 6 AM.

## Magnetic resonance imaging

Participants completed a 1-h MRI acquisition on a Siemens Skyra 3 T MRI scanner (Siemens Medical Solutions, Erlangen, Germany) at the University of Miami. The 3D T1 weighted volumetric magnetization-prepared rapid gradient-echo sequence (MP-RAGE) consisted of 176 slices at slice thickness = 1 mm isotropic, FOV = 256×256, TR = 1.80s, and TE = 2.67 s. The resting-state functional MRI (rsfMRI) scan was administered for 8 min with eyes open consisting of 120 volumes and 48 interleaved slices at a slice thickness = 3.0 mm isotropic, FOV = 212×212, TR = 3.0 s, and TE = 30 ms.

## Functional MRI pre-processing

Functional MRI pre-processing was completed in accordance with past studies by our group (66). Specifically, functional images were preprocessed and analyzed using the MATLAB R2016b based functional connectivity toolbox "Conn toolbox" version 19c and SPM 12 (67, 68). We followed a pre-processing pipeline which included functional realignment and unwarping, functional centering of the image to (0, 0, 0) coordinates, slice-timing correction, structural centering to (0, 0, 0) coordinates, structural segmentation and normalization to MNI space, functional normalization to MNI space,

and spatial smoothing with a kernel of 8 mm FWHM. During pre-processing, the Conn toolbox implements an anatomical, component-based, noise correction strategy (aCompCor) for spatial and temporal processing to remove physiological noise factors from the data (69). The implementation of aCompCor combined with the quantification of participant motion and the identification of outlier scans through the Artifact Rejection Toolbox (ART) allows for better interpretation of functional connectivity results (68–70). The ART was set to the 97th percentile setting with the mean global-signal deviation threshold set at $z = \pm 3$ and the participant-motion threshold set at 0.9 mm. As mentioned above, participants were removed if (1) global signal change was greater than 3SD from the group mean (one participant removed), (2) motion parameters exceeding 0.9 mm (two participants removed), and (3) number of invalid scans exceeding 20% of total scans (no participants removed). Applying linear regression and using a band-pass filter of 0.008–0.09 Hz, data were de-noised to exclude signal frequencies outside of the range of expected BOLD signals (such as low-frequency scanner drift), minimize participant motion, extract white matter and cerebral spinal fluid noise components, and control for within-participant realignment and scrubbing covariates.

## Within- and between-networks analysis of rsfMRI connectivity

For statistical analysis of rsfMRI connectivity, we used a publicly available network parcellation of the brain (71) that has been commonly used in the resting-state literature (72–79). From this atlas, we utilized five main networks to include: (1) the Cingulo-Opercular Network (consisting of the parietal operculum, temporal occipital cortex, frontal operculum, lateral prefrontal cortex); (2) Default Mode Network (prefrontal cortex, posterior cingulate cortex, parahippocampal cortex, and parietal and temporal cortices [corresponding to the angular gyrus and middle temporal gyrus, posterior division, respectively]), (3) the Dorsal Attention Network (posterior cortex [corresponding to the lateral occipital cortex, superior division], frontal eye fields, and precentral ventral cortex), (4) the Fronto-Parietal Control Network (parietal cortex [corresponding to the posterior division of the supramarginal gyrus], temporal cortex [corresponding to the posterior division of the middle temporal gyrus], dorsal prefrontal cortex, lateral prefrontal cortex, orbitofrontal cortex, ventral prefrontal cortex, medial posterior prefrontal cortex, precuneus, and the cingulate cortex), and (5) the Limbic Network (orbitofrontal cortex [corresponding to the frontal pole], temporal pole). The resting-state networks were registered to MNI152 space, and we defined the networks as regions of interests (ROIs) for ROI-ROI functional connectivity analyses. ROI-ROI analyses are Fisher z-transformed bivariate correlations between brain regions' BOLD time-series that quantify associations in the activation at rest and serve as a proxy for functional connectivity. Using the Conn toolbox Results Explorer, within-network connectivity was calculated and compared with one or more variables of interest by computing the mean of the pairwise correlations between the specified ROIs that comprised each of the five higher-order functional networks. Between-networks connectivity comparisons were computed using the Conn Toolbox ROI-to-ROI approach, such that a seed's BOLD time course signal is used as a reference for correlations followed via a search for any correlation with other ROIs' positive and negative BOLD time course signal. Manual error correction settings were utilized such that all analyses were corrected for false discovery rate (FDR) at the connection level (p-FDR < 0.05) and at the cluster level with an MVPA omnibus test (p-FDR < 0.05).

## Statistical approach

PLWH and people without HIV were compared on demographic variables and alcohol use characteristics (both TLFB and TAC-AUC data) with *t*-test or Chi-square analysis, where appropriate. Variables where significant differences exist were inputted as covariates in any rsfMRI analyses comparing groups. Correlational analyses were completed to determine the relationship between all other measures were analyzed for normality and fit, with appropriate normalization applied where necessary.

## HIV status, within-network rsfMRI connectivity, and alcohol use: interactive associations

Statistical analyses were deployed to examine the effect of HIV status on connectivity at the pre- and post-CM periods as well as connectivity change as a function of self-reported and objective alcohol use (TAC-AUC) reduction. Connectivity values for each network at baseline, 30-day follow-up, and change from baseline to follow-up were centered by demeaning each participant's connectivity value. An interaction term was then created between centered connectivity values and HIV status. Given the fact that baseline characteristics may influence later outcomes related to interventions, such as CM, HIV status, the centered connectivity values, and the interaction term were then entered into a linear regression equation predicting either TAC-AUC percent reduction or TLFB percent reduction. All assumptions for normality were met through examination of the P–P plots for potential heteroscedasticity. For interaction analyses, the direction for the overall model equation was computed for each group to confirm association slopes were opposing, as is often the case when an regression interaction is present.

# Results

The majority of participants were male (60%), identified as Black (74.3%) non-Hispanic (85.7%). Participants did not differ on demographic variables when comparing groups by HIV status (Table 1). PLWH did not differ from those living without HIV on any rsfMRI QC metrics related to motion, global signal change, or number of invalid scans.

## Pre- and post-contingency management alcohol consumption

On the pre-CM TLFB-30, participants reported a mean of 253.3 (SD = 119.7) standard drinks consumed, or 8.44 drinks per

TABLE 1 Demographics.

| Variable | Total *N*=35 | PLWH *N*=18 | w/out HIV *N*=17 |
|---|---|---|---|
| Age (mean ± stdev) | 57.2 ± 4.6 | 55.6 ± 3.9 | 57.9 ± 5.3 |
| Current gender identity (%) | | | |
| Male | 60.0% | 55.6% | 64.7% |
| Female | 37.1% | 38.9% | 35.3% |
| Transgender | 2.9% | 5.6% | 0% |
| Race (%) | | | |
| Caucasian | 20.0% | 22.2% | 17.6% |
| Black | 74.3% | 77.8% | 70.6% |
| American Indian/Alaska Native | 0% | 0% | 0% |
| Native Hawaiian/Pacific Islander | 0% | 0% | 0% |
| Asian | 0% | 0% | 0% |
| Multi-racial | 5.7% | 0% | 11.8% |
| Ethnicity (%) | | | |
| Hispanic | 14.3% | 11.1% | 17.6% |
| Non-Hispanic | 85.7% | 88.9% | 82.4% |
| Education level (%) | | | |
| Did not finish high school | 28.6% | 33.3% | 23.5% |
| High school | 34.3% | 22.2% | 47.1% |
| Greater than high school | 37.1% | 44.4% | 29.4% |
| HIV disease duration (years) | – | 18.82 (12.4) | – |
| Viral load (≥40 copies/mL) | – | 0.24 (0.44) | – |
| CD4 Count (cells/μL) | – | 600.28 (345.5) | – |
| Currently taking HIV antiretroviral medication | – | 100% | – |
| Ever diagnosed with AIDS | 0% | 22.2% | 0% |
| Years since first regular alcohol use[a] | 37.74 (7.80) | 36.44 (6.75) | 39.12 (8.78) |
| TLFB-30 pre-CM (mean ± stdev) | 8.44 (3.99) | 8.53 (4.50) | 8.35 (3.50) |
| TLFB-30 post-CM (mean ± stdev) | 0.76 (1.62) | 1.23 (2.14) | 0.27 (0.44) |
| TLFB-30 percent reduction (mean ± stdev) | 89.4% (20.1) | 82.9% (26.2)* | 96.3% (6.1) |
| TAC-AUC pre-CM (mean ± stdev) | 27.50 (27.2) | 24.51 (28.0) | 30.67 (26.9) |
| TAC-AUC post-CM (mean ± stdev) | 6.16 (13.2) | 5.95 (14.1) | 6.39 (12.6) |
| TAC-AUC percent reduction (mean ± stdev) | 60.5% (93.3) | 45.5% (114.3) | 75.5% (66.7) |

*PLWH and people without HIV differ ($p < 0.05$);
[a]Defined as using alcohol at least once per week. TLFB, Timeline Follow-Back 30; TAC-AUC, transdermal alcohol content (TAC) area under the curve; TLFB pre-CM, the reported daily average number of drinks over the 30 days prior to contingency management; TLFB post-CM, the reported daily average number of drinks over the 30 days of contingency management; TAC-AUC pre-CM, average daily AUC over the 7 days prior to contingency management; TAC-AUC post-CM, average daily AUC over the final 7 days of the contingency management period; Percent Reduction = [(Baseline – Follow-up) / Baseline]*100.

day (SD = 3.99), on average. During the 7 days leading up to the intervention, the average daily TAC-AUC was 27.5 h · g/dl (SD = 27.2). Over the 30 days of intervention, participants self-reported an average of 22.8 (SD = 48.6) drinks on the TLFB-30, or 0.76 drinks per day (SD = 1.62). During the final 7 days of the 30-day intervention, the average daily TAC-AUC was 6.16 h · g/dl (SD = 13.2). In terms of percent reduction in alcohol consumption, results indicate an 89.4% reduction in average daily self-reported alcohol use on the TLFB-30 and a 60.5% reduction in average daily objective alcohol use on TAC-AUC (Table 1).

## Baseline functional connectivity

Average TAC-AUC for objective drinking over the 7 days prior to the intervention was not significantly associated with functional connectivity at baseline after correction for false discovery rate (FDR). Baseline functional connectivity within two bilateral nodes of the DAN was positively associated with higher self-reported (TLFB) pre-CM drinking over the seven days immediately before the MRI session ($F[1,33] = 24.96$, p-unc = 0.000019, p-FDR = 0.00012); an association occurring in the opposite direction of our initial hypothesis (Figure 1A).

Baseline functional connectivity between multiple nodes within the CON was negatively associated with TAC-AUC reduction after CM (Cluster 1: $F[2,29] = 5.86$, p-unc = 0.007303, p-FDR = 0.038744; Cluster 2: $F[2,29] = 5.77$, p-unc = 0.0077, p-FDR = 0.0387) (Figure 1D). Baseline functional connectivity within the bilateral orbitofrontal nodes of the limbic network was positively associated with subjective drinking reduction after 30 days of intervention ($F[1,33] = 6.53$, p-unc = 0.0154, p-FDR = 0.0462) (Figure 1B).

## Functional connectivity at the post-CM period: effect of drinking reduction

Neither within- nor between-networks functional connectivity at the 30-day follow-up was associated with drinking reduction as determined by percent reduction of TAC-AUC. Within-network DMN functional connectivity at the 30-day follow-up was significantly negatively associated with self-reported drinking reduction on the TLFB ($F[2,32] = 7.68$, p-unc = 0.0019, p-FDR = 0.0113) (Figure 1C).

## Post-CM change in functional connectivity

After 30-days of attempted abstinence from heavy drinking, between-networks functional connectivity significantly increased as a function of objective reduction in alcohol use as determined by TAC-AUC. Specifically, a connectivity increase was observed between the limbic and frontoparietal control network ($t[30] = 2.54$, $p = 0.008$) driven by the cingulate region of the fronto-parietal control network and the orbitofrontal cortex of the limbic network ($F[2,25] = 8.27$, p-unc = 0.0017, p-FDR = 0.0315) (Figure 1E). There were no within-network associations observed

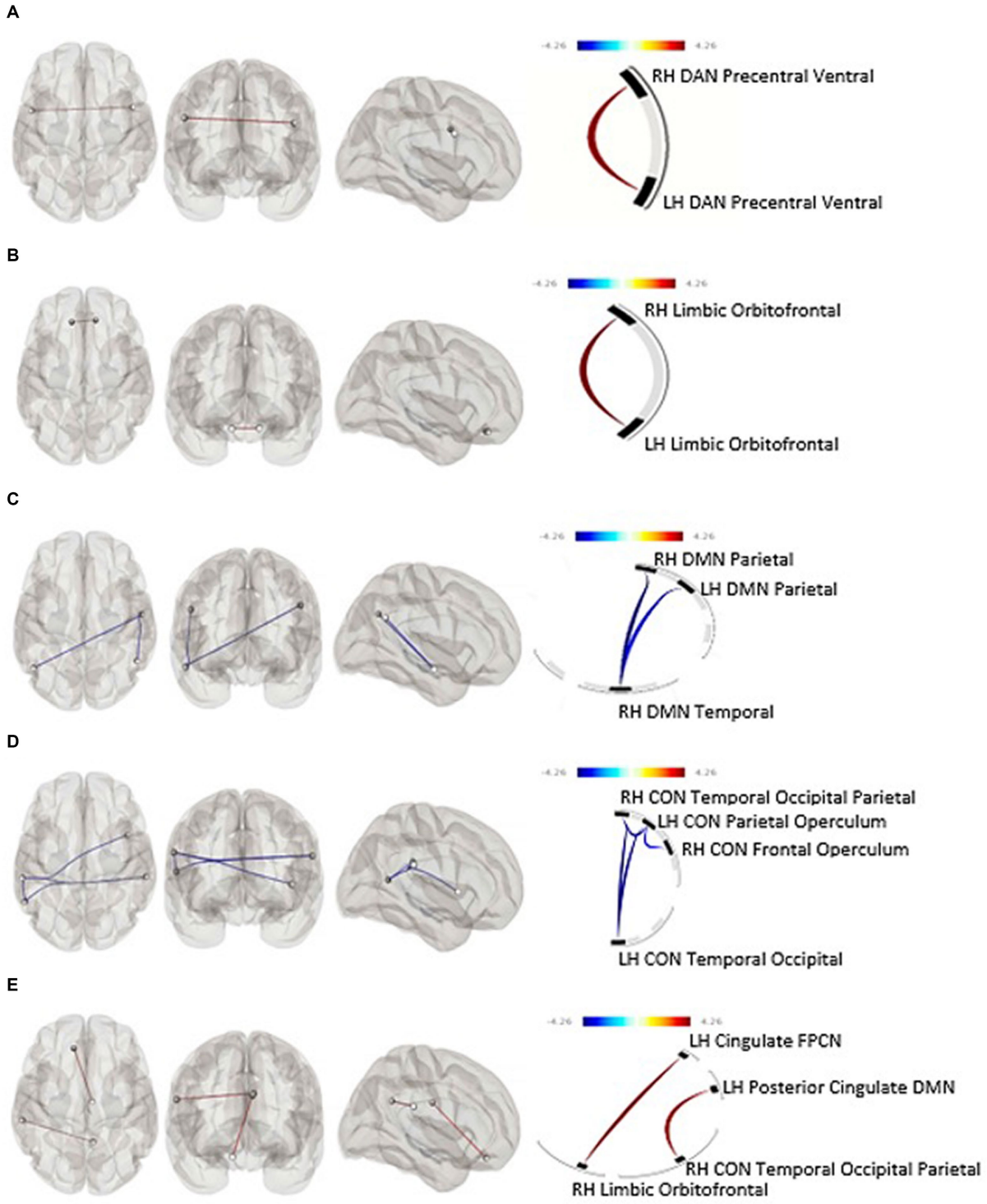


FIGURE 1
**(A)** Within-networks baseline rsfMRI and subjective pre-intervention drinking (p-FDR=0.0001), **(B)** within-networks baseline rsfMRI and predicted 30-day subjective percent drinking reduction (p-FDR=0.046), **(C)** within-networks 30-day rsfMRI and predicted 30-day subjective percent drinking reduction, **(D)** within-networks baseline rsfMRI and objective drinking reduction (p-FDR=0.039), **(E)** between-networks pre-post rsfMRI change and objective drinking reduction. Blue line, positive association between connectivity and drinking reduction; Red line, negative association between connectivity and drinking reduction; CON, Cingulo-Opercular Network; DAN, Dorsal Attention Network; DMN, Default Mode Network; FPCN, Fronto-Parietal Control Network; LH, Left Hemisphere; RH, Right Hemisphere.

between functional connectivity change and objective drinking reduction via TAC-AUC. Similarly, no within- or between-network changes in functional connectivity were observed as a function of self-reported drinking reduction on the TLFB.

## HIV associations with rsfMRI connectivity

As seen in the lower half of Table 1, PLWH demonstrated a statistically lower percent reduction in self-reported drinking

compared to people without HIV (t[33] = −2.12, $p = 0.047$), thus necessitating a comparison of these groups when examining the effect of intervention on resting-state connectivity. Results revealed a significant main effect of HIV diagnosis and DAN connectivity at baseline for self-reported percent alcohol reduction (t[34] = 20.5; $p < 0.001$) as well as a significant interactive effect of HIV status and baseline DAN connectivity (t[34] = 2.11; $p = 0.043$). There was also a significant main effect of HIV status and DAN connectivity at baseline for objective percent drinking reduction on SCRAM (t[31] = 20.0; $p < 0.001$) as well as a significant interactive effect of HIV status and baseline DAN connectivity (t[31] = 2.63; $p = 0.014$) (Figure 2). There were no main effects of HIV status on objective or self-reported percent drinking reduction for any of the five networks at the 30-day follow-up. Similarly, there were no main effects of HIV status on objective or self-reported percent drinking reduction for change in connectivity within the five networks examined.

## Discussion

Although recent advances in neuroimaging techniques have provided insights into functional changes associated with heavy drinking, longitudinal studies assessing functional mechanisms of drinking reduction are rare, especially in PLWH. Following short-term abstinence from alcohol, the current literature indicates that individuals experience greater activity in limbic-striatal regions and lower activity in the medial frontal and cingulated regions, suggestive of difficulties with emotional regulation, self-control, and executive functioning (28, 35). As such, the purpose of the present study was to determine the ability of baseline resting-state functional MRI (rsfMRI) connectivity to predict later reduction in heavy alcohol use as well as how rsfMRI connectivity is altered after 30 days of attempted abstinence from heavy alcohol use. The present study adds to the neuroimaging literature on AUD by identifying changes in resting state functional connectivity associated with drinking reduction, rather than total abstinence, following a contingency management intervention. Furthermore, given that no study to date has examined the association of wearable biosensor detected alcohol use and brain biomarkers, we compared measures of objective (biosensor-based) and subjective (self-report) drinking reduction to neurobiological changes in individuals living with and without HIV.

Results of the present analysis indicated increased between-networks connectivity between the limbic and fronto-parietal control networks in those who demonstrated higher objective abstinence from alcohol. Given the unique nature of the present study, extant literature is limited when investigating between-networks change in rsfMRI connectivity after alcohol reduction. However, this finding suggests a potential improvement in functional network coherence given that previous rsfMRI studies in clinical populations have demonstrated widespread decreases in intranetwork and internetwork correlations, such as in normal aging (80) as well as with increasing severity of Alzheimer's Disease (77, 78). Alternatively, it is possible that increased between-networks connectivity may indicate a "bleeding together" of the typically disparate co-activation patterns due to disruption of physiological and/or neurological homeostasis associated with prolonged alcohol use. However, to confirm that this increase in between-networks connectivity was not the result of decreased network segregation, we additionally completed a segregation analysis following previously described methods (81, 82). These post-hoc findings suggested an overall net increase in between-networks connectivity, indicating increased between-networks segregation from pre-to-post-intervention. These results suggest that these networks maintained unique network connectivity patterns following alcohol reduction in our sample, providing further confidence that the changes in resting-state synchronicity following alcohol reduction indicates improved functional connectivity.

The second major finding of our analysis was lower resting-state functional connectivity of the salience network at baseline was associated with greater post-intervention drinking reduction in individuals who exhibit heavy alcohol consumption. The salience network refers to the co-activation of brain regions, such as the anterior cingulate and ventral anterior insular cortices, as well as the amygdala, hypothalamus, ventral striatum, thalamus, and specific brainstem nuclei with domain-specific functions separating the most relevant internal and extra-personal stimuli to guide goal-directed behavior (17). According to the neuro-circuitry model of addiction, these two brain regions appear to influence the dynamics between large-scale brain networks enhancing salience for alcohol-related cues while inhibiting the response to other stimuli (83, 84). Therefore, our

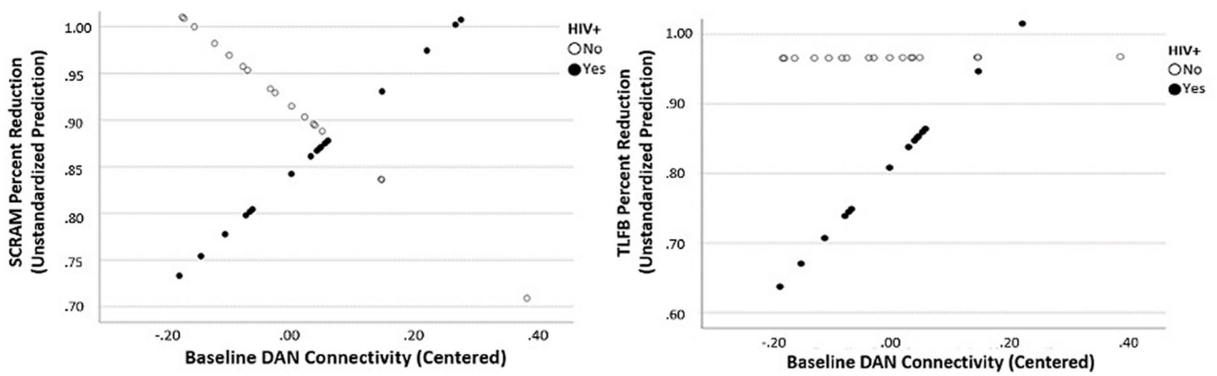


FIGURE 2
Interactive effect of baseline Dorsal Attention Network connectivity predicting percent reduction in objective drinking (SCRAM) and subjective drinking (TLFB) as a function of HIV status.

results suggest that individuals who engage in heavy alcohol use and have lower Salience network resting state functional connectivity at baseline may be less susceptible to the environmental (e.g., alcohol advertisements, billboards, etc.) and social cues (e.g., social gatherings, peer pressure, etc.) that tend to make attempts at alcohol abstinence unsuccessful. In other words, the appetitive synchrony in the salience network associated with long-term alcohol use may render individuals with AUD more vulnerable to alcohol craving and repeated consumption, but individuals with lower resting state functional connectivity in these areas at rest may be better able to engage in drinking reduction approaches.

This study also revealed some important findings in regard to differences between self-reported alcohol use and objective alcohol use in how they relate to baseline rsfMRI connectivity as well as change in connectivity after alcohol reduction. Self-reported alcohol use but not objective alcohol use metrics in the pre-CM period was related to baseline DAN connectivity. As such, it is possible that increased baseline engagement of this network may be related to the cognitive ability for self-apprasial and self-reporting alcohol use, but not for actual alcohol consumption itself. Such an interpretation would reveal why objective alcohol use is not related to baseline DAN connectivity and why DAN connectivity at baseline predicts alcohol reduction after intervention without a post-CM change in DAN functional connectivity. We also found a positive association between limbic connectivity and subjective report of alcohol use reduction after CM (85). Previous studies in other clinical populations, such as those suffering from major depressive disorder (MDD) have found depression symptoms to be related to limbic network connectivity and that increased connectivity in this network is observed after antidepressant treatment. As such, it is possible that mood alterations resulting from decreased alcohol use are driving associations of self-reported drinking reduction and limibic connectivity (86). Further, one question this investigation elicits is in regard to the lack of rsfMRI connectivity associations with drinking reduction at the follow-up period despite associations with *change* in rsfMRI connectivity. It is possible that change in drinking, as a metric, is more readily associated with change in rsfMRI connectivity, but that other health or mood factors at follow-up, such as improved ART medication adherence or depressive symptom reporting, are more strongly linked to an individual's present rsfMRI connectivity patterns after drinking reduction. Such a study would provide increased clinical utility of rsfMRI connectivity in relation to drinking reduction and its effect on clinically-applicable and measurable changes after intervention. As such, future investigations should examine medication adherence, depression symptom reporting, and other health-related factors in relation to enduring rsfMRI connectivity patterns after a short period of drinking reduction.

Finally, results revealed a significant main effect of HIV diagnosis and DAN connectivity at baseline for self-reported percent alcohol reduction. Additionally, there was a significant interactive effect of HIV status and baseline DAN connectivity such that higher DAN connectivity at baseline was predictive of greater drinking reduction in PLWH. The DAN is thought to underlie selective visual attention (87, 88), which is particularly important for goal-directed behavior. Previous rsfMRI research has demonstrated abnormal functional connectivity in the DAN in patients with alcohol-use disorder (89). Therefore, our findings may suggest a disruption of DAN connectivity in PLWH who use alcohol, making it more difficult for individuals living with HIV to maintain abstinence. This finding also ties into the previously described finding of decreased salience network connectivity predicting greater post-intervention alcohol reduction. As the DAN is engaged during externally directed attention, salient environmental cues may be particularly important for reinforcing alcohol consumption in PLWH with heavy alcohol use histories. Important for the present study, our data suggest that PLWH with disrupted DAN connectivity may not benefit as greatly from CM for alcohol reduction as those with higher levels of within-network DAN connectivity at baseline.

We acknowledge some limitations in the current study. First, while this study included a longitudinal design with two data points per participant, the sample size was relatively small and thus limiting power and generalizability. Further, participants in the present study were moderate-to-heavy drinkers but were not dependent on alcohol. Therefore, resting state synchrony should be examined in a larger sample comprising adults with greater severity of alcohol dependence. Additionally, this study examined a set of statistical inferences simultaneously, lending to an issue of multiple comparisons. However, when all networks were evaluated in a single model liberally correcting for multiplicity, increased between-networks connectivity in those with higher abstinence remained significant, suggesting that this is a robust finding despite a small sample size. Relatedly, some HIV-related factors that may have influenced the findings were not considered due to the limited sample size, and future analyses should examine the impact of HIV duration, viral load, AIDS, antiretroviral therapy (ART), duration on ART, CD4 nadir, and CD4 t-cell count. Third, this study was not a randomized clinical trial, meaning participants were not randomized to intervention or control groups. Therefore, conclusions cannot be drawn regarding the efficacy of the contingency management intervention as all participants had the opportunity to receive financial incentives to reduce drinking. Future research should examine the use of non-monetary incentives for drinking reduction (e.g., vouchers, prizes, etc.). Similarly, the alcohol reduction and CM effects on rs-fMRI networks cannot be differentiated in this study. Despite these weaknesses, this is the first study to our knowledge that examined resting state synchrony pre- and post-drinking reduction in a sample of individuals with and without HIV.

## Conclusion

Overall, the present study sought to determine the effects of 30-days drinking cessation/reduction on resting state functional connectivity in people with and without HIV. We found that lower resting-state functional connectivity of the Salience network significantly predicted stronger drinking reduction, and greater drinking reduction following CM was associated with increased between-networks connectivity. Consistent with previous research, our findings also demonstrated a disruption of DAN connectivity in PLWH who use alcohol, making it more difficult for individuals living with HIV and who had lower DAN connectivity to maintain abstinence with CM; this finding was corroborated by results indicating that PLWH with lower DAN connectivity were less successful at drinking reduction following CM compared to those without HIV. These findings not only suggest a potential biomarker for reduced susceptibility to the environmental and social cues that often make alcohol use reduction attempts unsuccessful, but also

indicate that individuals experience benefits in brain connectivity associated with reduced drinking. Therefore, FC alterations associated with chronic alcohol use may be reversible, and may serve as clinical biomarkers of change in drinking behaviors for future studies which do not employ wearable biosensor monitoring devices.

## Data availability statement

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

## Ethics statement

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

## Author contributions

JG contributed to conception and design of the study and performed the statistical analysis. JG and JD wrote the manuscript. ZZ organized the database. RAC and RLC acquired funding for the study. VG and TS supervised the data collection. All authors contributed to the manuscript revision, read, and approved the submitted version.

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## Conflict of interest

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

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# Intermittent theta burst stimulation to the left dorsolateral prefrontal cortex improves cognitive function in polydrug use disorder patients: a randomized controlled trial

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**Background:** Polydrug abuse is common among opioid users. Individuals who use both heroin and methamphetamine (MA) have been shown to experience a wide range of cognitive deficits. Previous research shows that repetitive transcranial magnetic stimulation (rTMS) can change cerebral cortical excitability and regulate neurotransmitter concentration, which could improve cognitive function in drug addiction. However, the stimulation time, location, and possible mechanisms of rTMS are uncertain.

**Methods:** 56 patients with polydrug use disorder were randomized to receive 20 sessions of 10Hz rTMS ($n$=19), iTBS ($n$=19), or sham iTBS ($n$=18) to the left DLPFC. All patients used MA and heroin concurrently. Cognitive function was assessed and several related proteins including EPI, GABA-Aα5, IL-10, etc. were quantified by ELISA before and after the treatment.

**Results:** Baseline RBANS scores were lower than normal for age (77.25; IQR 71.5–85.5). After 20 treatment sessions, in the iTBS group, the RBANS score increased by 11.95 (95% CI 0.02–13.90, $p$=0.05). In particular, there were improvements in memory and attention as well as social cognition. Following treatment, serum EPI and GABA-Aα5 were reduced and IL-10 was elevated. The improvement of immediate memory was negatively correlated with GABA-Aα5 ($r$=−0.646, $p$=0.017), and attention was positively correlated with IL-10 ($r$=0.610, $p$=0.027). In the 10Hz rTMS group, the improvement of the RBANS total score (80.21±14.08 before vs.84.32±13.80 after) and immediate memory (74.53±16.65 before vs.77.53±17.78 after) was statistically significant compared with the baseline ($p$<0.05). However, compared with the iTBS group, the improvement was small and the difference was statistically significant. There was no statistically significant change in the sham group (78.00±12.91 before vs.79.89±10.92 after; $p$>0.05).

**Conclusion:** Intermittent theta burst stimulation to the left DLPFC may improve cognitive function in polydrug use disorder patients. Its efficacy appears to be better than that of 10Hz rTMS. The improvement of cognitive function may be related to GABA-Aα5 and IL-10. Our findings preliminarily demonstrate the clinical value of iTBS to the DLPFC to augment neurocognitive recovery in polydrug use disorders.

KEYWORDS
polydrug use disorders, iTBS, cognitive function, GABA-Aα5, IL-10

# 1. Introduction

Around 275 million people used drugs in 2021 globally; 13% or 36.3 million people had a drug use disorder (1). In China, around 1.458 million people use heroin and other opioids, accounting for 49.3% of the total number of registered drug users. In addition, 1.459 million people used synthetic drugs, including 1.19 million who used methamphetamine, an increase of 40.5% over the previous year (2). As neurotoxic substances, drugs have long been known to cause cognitive deficits. A meta-analysis showed impairment in most cognitive areas of methamphetamine use disorder (MUD), including memory, attention, executive function, verbal/verbal fluency, and social cognition (3). The rate of polydrug use disorders (multiple simultaneous drug use) has been significantly increasing over the past 2 decades (4). Epidemiological studies have reported a high prevalence of polydrug use (30–49.7%), particularly among individuals with opioid use disorder. Chronic polydrug abusers show multiple cognitive impairments (5). Compared to alcohol use disorder, polydrug users show trends for worse performance in general intelligence, auditory-verbal learning, and decision-making tasks (6).

Transcranial magnetic stimulation (TMS) is a noninvasive technique that allows electrical currents to be induced in focal areas of the cerebral cortex, which can stimulate local and related distal cortical and subcortical areas, induce excitatory changes, and the changes can persist for around an hour following the stimulation (7). rTMS has become an evidence-based therapy for treatment-resistant and endorsed by several Clinical Practice Guidelines to be used in the treatment of mental and substance use disorders. Theta burst stimulation (TBS) is a special highly efficient rTMS sequence (8, 9). TBS has two variants: intermittent theta burst stimulation (iTBS) that improves cortical excitability, and continuous theta burst stimulation (cTBS) that reduces excitability. In previous studies, 10 Hz rTMS has been often used to treat substance dependent patients, Su et al. reported that five sessions of 10 Hz rTMS over the DLPFC could improve verbal learning and memory and social–emotional cognition in MA-addicted subjects (10), It has been shown to significantly reduce craving, and improve emotional problems and cognitive function (11). In addition, multiple-day rTMS improved arbitrary face-word pairings memory and hippocampal-cortical functional connectivity (12). In recent years, there have been many studies of iTBS for substance addiction. Previous work suggests that attention bias and beta oscillation during the attentional processing of words in patients with MUD can be modulated by iTBS applied to the left DLPFC, and iTBS significantly reduces craving and improves cognition and sleep quality for methamphetamine addicts (13). The iTBS treatment protocol positively affects behavioral inhibition in patients with heroin addiction (14). 10 Hz rTMS takes around 20 min to complete 900 pulses; iTBS is more efficiently, which takes only 4 min and 52 s to complete the same pulses. Compared with 10 Hz rTMS, TBS maybe more acceptable to patients because of its short treatment time. Even both 10 Hz rTMS and iTBS had similar results of improving cognition in patients with substance addiction, there have no studies to compare the difference between them. So our study was designed to validate previous results and initially compare the efficacy of iTBS with 10 Hz rTMS.

There has been no effective medical treatment for polydrug use disorders. Therefore, novel treatment approaches for polydrug use disorders are desperately needed. Considering the prefrontal dysfunction and cognitive impairments that have been observed in patients with polydrug use disorders and the effectiveness of rTMS for other psychiatric diseases, we hypothesize that iTBS to the DLPFC may also improve the cognitive function of polydrug users. We tested iTBS to the DLPFC as our therapeutic approach. In short, the purpose of this study was to test whether iTBS to the left DLPFC would modulate cognitive function in polydrug use disorders by utilizing a randomized, double-blind, sham-controlled study design. We tested whether cognitive function would be influenced by using a detailed CogState Battery of standardized neuropsychological tasks: The Repeatable Battery for the Assessment of all the Neuropsychological States (RBANS). In addition, we measured several related blood indicators, including epinephrine (EPI), gamma aminobutyric acid receptor Aα5 (GABA-Aα5), interleukin10 (IL-10), and others, to probe the mechanisms involved in cognitive function in these patients.

# 2. Materials and methods

## 2.1. Participant selection

We recruited 56 patients with polydrug use disorder from The First Health Clinic Center for Addiction of Wuhan Mental Health Center, Wuhan, China. Participants were treated with a real or sham iTBS or 10 Hz rTMS protocol from 2019.07 to 2021.10 utilizing a randomized, double-blind, sham-controlled study design. On the day of the clinical intake, patients provided written informed consent. The approval for the protocol was obtained from the Ethical Committee for the Psychological Research of the hospital (Wuhan Mental Health Center). This clinical trial was registered based on the ICMJE guidelines with a clinical trial ID: NCT04264741. Participants were aged between 40 and 62 years and met the diagnostic criteria for heroin and MA use disorder (confirmed by a double positive urine test) according to the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5), as assessed by a clinical psychiatrist specialized in substance use disorders (SUDs). During the study, we did not impose any restrictions on the drugs used; we simply observed and recorded the results.

## 2.2. Clinical measures

The participants were interviewed by trained investigators using a detailed questionnaire including general information, social demographic characteristics, current and prior substance use behaviors, and medical and psychological history.

## 2.3. Blood sampling and serum measurements

We collected serum samples from 37 participants before the first session of iTBS and after the entire treatment course with real or sham iTBS. The serum was separated, aliquoted, and stored at −80°C until analysis. The blood marker levels were measured by a commercial sandwich enzyme-linked immunosorbent assay (ELISA; Beijing rongxinzhihe Biotechnology Co., Ltd., Wuhan, China) according to the manufacturer's instructions. First, the 10 μL serum samples and 40 μL sample diluent were mixed in each well. Then, 50 μL sample diluent was added to the standard well. After that, 100 μL of HRP-conjugate reagent was added to each well, covered with an adhesive strip, and incubated for 60 min at 37°C. The wells were washed and then incubated with HRP Conjugate working solution for 30 min, again washed and incubated with a substrate reagent for 15 min at 37°C and finally the stop solution was added. The Optical Density (O.D.) was read at 450 nm using a microtiter plate reader within 15 min.

The participant ID was coded and the real number IDs were retained by the principal investigator until all biochemical analyses were completed. Inter- and intra-assay variation coefficients were 8 and 5%, respectively.

## 2.4. Cognitive assessment

All participants were administered the RBANS before and after all treatments with rTMS, to measure cognitive function (15). RBANS is designed to assess and characterize cognitive function over time and covers a broad range of difficulties to minimize floor and ceiling effects. RBANS includes five domains, with scores ranging from 40 to 16i for which age-specific normative data are available; these were generated in a Scandinavian population cohort scoring a mean of 100 (standard deviation (SD) ± 15). The five domains are immediate memory, visuospatial function, language, attention, and delayed memory. The RBANS includes 12 sub-tests that are used to calculate five age-adjusted index scores and then a total score and an emotional identification task. The five test indices comprise immediate memory (story memory and list learning sub-test line orientation), visuospatial/constructional (line orientation and figure copy sub-test), language (semantic fluency and picture naming sub-tests), and delayed memory [figure recall, story recall, list recall, and recognition sub-tests, attention (coding and digit span sub-tests), and delayed memory (including figure recall, story recall, list recall, and recognition sub-tests)]. In the eyes-reading test, participants were asked to interpret the emotion associated with 30 images of eyes, which reflects an individual's social cognition. The RBANS was previously translated into Chinese, although Chinese normative data do not exist. Attempts have been made to establish a minimal clinically important difference using an anchor-based approach but without solid results. Therefore, we chose not to use a specific cut-off value for clinical relevance.

## 2.5. rTMS treatment

Fifty-six participants were randomly assigned into a 10 Hz rTMS group ($n = 19$), an iTBS group ($n = 19$), or a sham iTBS group ($n = 18$) by a researcher who was not involved in the assessment used the random number table method. The rTMS stimulation protocol was administered by a trained clinical physiologist. The patient's motor threshold (MT) was confirmed through the left motor cortex, the lowest intensity which can produced a motor response was found in the right abductor pollicis brevis muscles (APB), that could produce motor-evoked responses of at least 50 mV five in 10 trials. During the treatment, the coil was placed over the left prefrontal area at a point 5 cm anterior to the scalp position where the motor threshold was determined. During treatment, patients reclined on a comfortable bed while TMS stimuli were delivered to the left DLPFC. The stimulator device was a CCY-I TMS instrument with a Cool-B80 butterfly coil (Yiruide Co., Wuhan, China). By reviewing relevant literature, about the use of 10 Hz rTMS, there was stimulation for 1.5 s with intervals of 58.5 s (16) and stimulation for 4 s with intervals of 26 s (17). In our study, we aimed to compare the efficacy of the 10 Hz rTMS and the iTBS; hence, the same number of pulses (900 pulses) was used. After discussion and calculation, we determined the parameters of the 10 Hz, which was 10 Hz, 80–100%MT, 2 s on and 18 s off for 15 min, with 900 pulses per day (18). The iTBS applied 3 × 50 Hz pulses in 5 Hz packets over 2 s, followed by 8 s of inactivity, with repeated cycles that continued for 292 s, 900 pulses per day, 80–100% of MT. The total treatment time was around 5 min. In the sham iTBS group, patients received a similar pseudo-stimulation treatment. The treatment site and method were the same as the real stimulation, but the coil was placed at 90° vertical during the stimulation; a treatment-like sound was generated but the stimulation is weak and cannot penetrate the skull. Patients underwent one treatment session per day from Monday to Friday for 4 weeks. Adverse events were self-reported and collected. Each patient was evaluated by the psychiatrist and provided the appropriate dose of methadone (see CONSORT flowchart in Figure 1).

## 2.6. Statistical analyses

SPSS (version 21.0) was used for all statistical analyses. The demographic and clinical variables of all participants were compared using ANOVA for continuous variables and $X^2$ for categorical variables. We compared the difference between groups at baseline, after the intervention, and before and after the intervention. When the data were normally distributed, ANOVA or *t*-test was employed. Changes in cognitive function were calculated by subtracting the post-treatment score from the pre-treatment score. When the data were not normally distributed, nonparametric tests were used. To compare baseline and post-intervention, paired *t*-tests were utilized. Pearson correlation coefficients were calculated to analyze the correlation between cognitive function and biochemical markers in the blood. Data are presented as mean ± SD. All tests were two-tailed with the significance threshold set at 0.05. When making multiple comparisons, we corrected the *p* value (P/n) according to the number of comparisons.

# 3. Results

## 3.1. Demographic and drug use information

Demographic characteristics and drug use summary data are shown in Table 1. There were no differences between the 10 Hz rTMS group or iTBS or sham iTBS group in terms of age, education years,

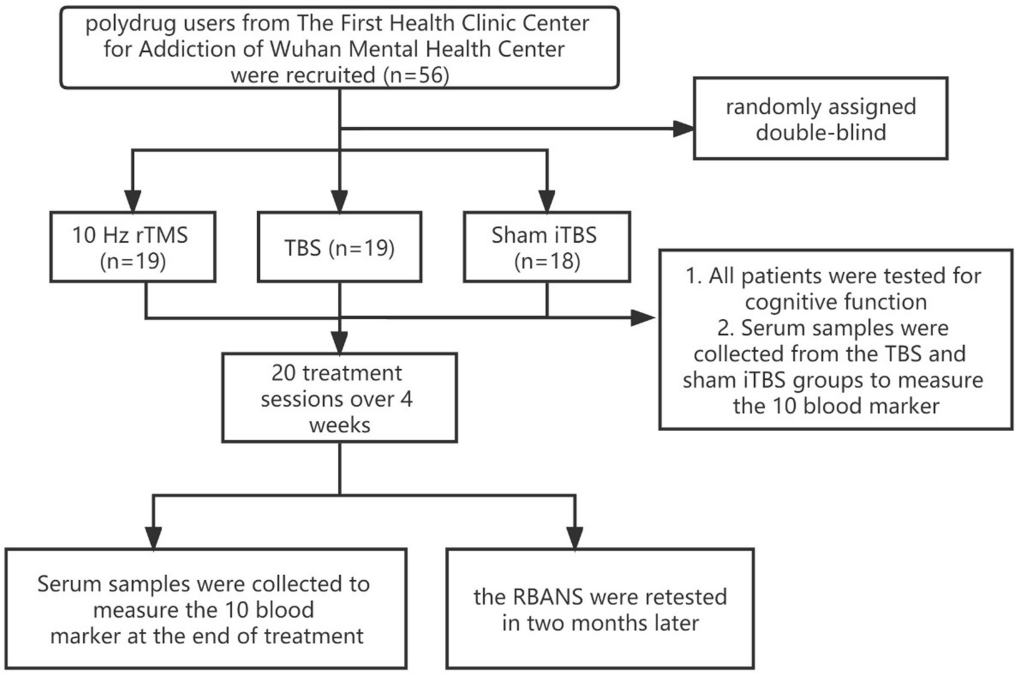


FIGURE 1
CONSORT flowchart of the study.

TABLE 1 Demographic and clinical characteristics of the participants.

| | 10Hz rTMS (*n* =19) | iTBS (*n* =19) | Sham iTBS (*n* =18) | $F/\chi^2$ | *p* |
|---|---|---|---|---|---|
| Age (years) | 49.35 ± 1.86 | 49.89 ± 5.40 | 48.78 ± 6.32 | 1.093 | 0.566 |
| Gender (male/female) | 16/3 | 15/4 | 16/2 | 0.679 | 0.712 |
| Education (years) | 9.62 ± 1.27 | 9.83 ± 1.38 | 9.56 ± 1.54 | 0.060 | 0.573 |
| Marriage | | | | 1.544 | 0.819 |
| Married | 8 (42%) | 8 (42%) | 8 (44.4%) | | |
| Divorced | 7 (36.8%) | 6 (31.6%) | 8 (44.4%) | | |
| Other(including widowed and never have marriage) | 4 (21.1%) | 5 (26.3%) | 2 (11.2%) | | |
| Employment(yes/no) | 5/14 | 6/13 | 6/12 | 0.236 | 0.889 |
| BMI | 21.56 ± 4.13 | 21.69 ± 3.67 | 21.84 ± 4.55 | 0.032 | 0.912 |
| Age at first experience (years) | 41.32 ± 7.61 | 40.47 ± 5.60 | 42.61 ± 8.19 | 3.275 | 0.358 |
| Accumulated use time(years) | 8.36 ± 4.17 | 9.26 ± 3.91 | 7.22 ± 5.42 | 5.264 | 0.196 |
| Baseline | | | | | |
| Dose of heroin use per day (g) | 1.02 ± 2.15 | 1.14 ± 2.26 | 0.85 ± 1.21 | 1.029 | 0.633 |
| Frequency of drug use 30 days before baseline | | | | 7.042 | 0.317 |
| Daily | 8 (42.11%) | 10 (52.63%) | 5 (27.78%) | | |
| 3-5times a week | 7 (36.84%) | 4 (21.05%) | 8 (44.45%) | | |
| Once a week | 2 (10.53%) | 4 (21.05%) | 1 (5.56%) | | |
| 1–3 times a month | 2 (10.53%) | 1 (5.26%) | 4 (22.22%) | | |
| After 20 treatment sessions over 4weeks | | | | | |
| Dose of heroin use per day (g) | 1.01 ± 1.73 | 1.12 ± 1.68 | 1.05 ± 1.36 | 1.542 | 0.807 |
| Frequency of drug use during 4 weeks of intervention | | | | 5.41 | 0.493 |
| Daily | 7 (36.84%) | 9 (47.37%) | 5 (27.78%) | | |
| 3–5times a week | 7 (36.84%) | 3 (15.79%) | 7 (38.89%) | | |
| Once a week | 3 (15.79%) | 5 (26.32%) | 2 (11.11%) | | |
| 1–3 times in all | 2 (10.53%) | 2 (10.53%) | 4 (22.22%) | | |

Data are presented as mean (SD) unless otherwise specified.

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marriage, employment, or body mass index (BMI). No differences were found between the three groups in terms of onset age, abstinence period, duration of MA use, or the MA dose and frequency. All of the patients continued to use drugs throughout the study (Table 1).

## 3.2. The effect of iTBS/rTMS on cognition

At baseline, there were no differences in the total RBANS score between groups (80.21 ± 14.08 in traditional rTMS and 79.42 ± 14.22 in iTBS group and 78.00 ± 12.91 in sham iTBS group; $p > 0.05$), and there were also no differences in all indices between the three groups ($p > 0.05$; Table 2). After 20 treatment sessions over 4 weeks, compared with any other group, the iTBS group showed improvements in the RBANS total score, and immediate memory ($p < 0.05$). Compared with the baseline, iTBS showed a significant improvement in the RBANS score, immediate memory, visual spatial, attention, delayed memory, and read-the-eye test ($p < 0.05$). The 10 Hz rTMS showed a significant improvement in the RBANS score and immediate memory ($p < 0.05$). Compared with the sham group, the D-value of iTBS showed a significant improvement in the RBANS score, immediate memory, attention, and read-the-eye test ($p < 0.017$). Compared with the 10 Hz rTMS group, the D-value of iTBS showed a significant difference in the RBANS score and immediate memory ($p < 0.017$). In the sham iTBS group, no significant difference was found before and after the treatment ($p > 0.05$; Figure 2).

## 3.3. Serum biochemical levels/changes in blood biochemical indices

We tested the concentrations of 10 blood markers. Before treatment, there were no differences in any of the markers, except for IL-10, between the iTBS and sham iTBS groups ($p > 0.05$; Table 3). Compared to baseline, after 20 treatment sessions over 4 weeks, the iTBS group showed lower epinephrine (EPI; 2870.43 ± 441.7 vs. 2578.9 ± 412.13), higher interleukin 10 (IL-10; 931.57 ± 128.68 vs. 1128.94 ± 162.86), and lower γ -aminobutyric acid Aα5 type (GABA-Aα5; 28.65 ± 4.05 vs. 23.05 ± 2.69; Figures 3, 4).

## 3.4. Relationship between cognitive function and rTMS treatment and serum biochemical levels

Pearson correlation analyses showed that immediate memory was negatively correlated with GABA-Aα5 ($r = -0.646$, $p = 0.017$) and attention was positively correlated with IL-10 ($r = 0.610$, $p = 0.027$) in the iTBS group (Table 4). However, no significant correlations were detected between other indices of RBANS and other serum biochemical levels (Table 4).

# 4. Discussion

In our study, we found that iTBS to the left DLPFC significantly improved cognitive function, including memory and attention, and social cognition in heroin and MA-addicted individuals. These results are consistent with previous studies (13, 19). However, another study

TABLE 2 Cognitive function scores before and after intervention.

| Outcomes | Baseline | | | Post-treat | | | Difference value(median) | | | *p* value | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Sham iTBS | iTBS | 10Hz rTMS | Sham iTBS | iTBS | 10Hz rTMS | Sham iTBS | iTBS | 10Hz rTMS | Baseline | Post-treat | Diff |
| Rbans total score | 78.00 ± 12.91 | 79.42 ± 14.22 | 80.21 ± 14.08 | 79.89 ± 10.92 | 92.90 ± 16.46# | 84.32 ± 13.80# | 3.5 | 13& | 4& | 0.885 | 0.021* | 0.039* |
| Immediate memory | 74.17 ± 17.96 | 76.05 ± 18.19 | 74.53 ± 16.65 | 76.06 ± 14.65 | 90.63 ± 16.02# | 77.53 ± 17.78# | −2.5 | 15& | 2& | 0.941 | 0.015* | 0.012* |
| Visual spatial | 73.72 ± 16.07 | 78.63 ± 18.98 | 76.11 ± 15.92 | 81.22 ± 16.24 | 92.37 ± 18.14# | 81.05 ± 15.19 | 1.5 | 8 | 5 | 0.684 | 0.065 | 0.792 |
| Language | 91.72 ± 6.88 | 92.58 ± 11.71 | 92.63 ± 7.87 | 87.61 ± 8.65 | 92.95 ± 7.54 | 90.21 ± 7.50 | −4.5 | 0 | −3 | 0.944 | 0.131 | 0.688 |
| Attention | 91.39 ± 16.45 | 90.74 ± 19.55 | 90.79 ± 19.42 | 91.22 ± 15.67 | 103.11 ± 21.74# | 93.84 ± 21.57 | 0 | 10& | 3 | 0.993 | 0.017* | 0.007* |
| Delayed memory | 83.22 ± 12.90 | 82.53 ± 15.67 | 85.95 ± 14.07 | 87.11 ± 12.65 | 97.37 ± 14.92# | 92.63 ± 18.45 | 2 | 14 | 4 | 0.74 | 0.144 | 0.083* |
| Read the eye test | 19.72 ± 3.36 | 21.42 ± 2.04 | 20.47 ± 3.34 | 19.89 ± 3.41 | 22.84 ± 3.00# | 21.42 ± 3.69 | −0.5 | 2& | 0 | 0.227 | 0.256 | 0.007* |

ANOVA was used,*means $p < 0.05$.
Pair T test was used, #means that compared with the baseline, the group has statistical difference.
Non-parametric tests were used, corrected $p$ was 0.17 = 0.05/3, and & means that compared with the sham group, the group has statistical difference.
Immediate memory (story memory and list learning sub-test line orientation), visual spatial/constructional (line orientation and figure copy sub-test), language (semantic fluency and picture naming sub-tests), attention (including coding and digit span sub-tests), and delayed memory (including figure recall, story recall, list recall, and recognition sub-tests).

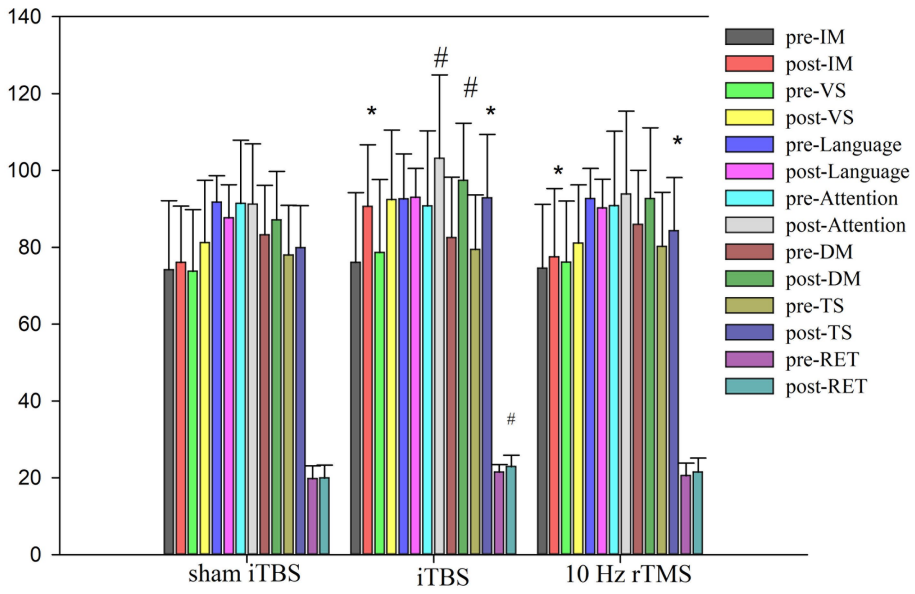


FIGURE 2
Cognitive function scores pre and post intervention. ANOVA was used, • means $p$ <0.05. #Compared with the baseline, group have statistical difference. Immediate memory (IM, story memory and list learning sub-test line orientation), visual spatial/constructional (VS, line orientation and figure copy sub-test), language (semantic fluency and picturenaming sub-tests), attention (including coding and digit span sub-tests), delayed memory (DM, including figure recall, story recall, list recall, and recognition sub-tests), Rbans total score (TS), and Read the eye test (RET).

TABLE 3 Blood indicators before and after real or sham iTBS intervention.

| Blood indicators | Baseline | | Post-treat | | Difference value (median) | | *p* value | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Sham group | iTBS | Sham group | iTBS | Sham group | iTBS | Baseline | Post-treat | iTBS paired T | Diff |
| EPI | 2835.64 ± 515.47 | 2870.43 ± 441.70 | 2930.07 ± 301.31 | 2578.9 ± 412.13# | 60.04 | −416.27& | 0.829 | 0.006* | 0.003* | 0.010* |
| IL-10 | 1059.06 ± 112.02 | 931.57 ± 128.68 | 1045.36 ± 174.25 | 1128.94 ± 162.86# | −77.48 | 154.91& | 0.003* | 0.146 | 0.000* | 0.002* |
| GABA-Aα5 | 28.28 ± 3.26 | 28.65 ± 4.05 | 26.73 ± 3.4 | 23.05 ± 2.69# | −2.15 | −6.93& | 0.764 | 0.001* | 0.000* | 0.004* |
| DA | 82.81 ± 24.22 | 78.2 ± 20.68 | 75.81 ± 18.08 | 84.58 ± 17.37 | −0.13 | 0.08 | 0.613 | 0.239 | 0.312 | 0.214 |
| 5-HT | 2741.03 ± 377.9 | 2586.52 ± 392.3 | 2653.49 ± 366.87 | 2623.94 ± 355.87 | −34.48 | 20.33 | 0.29 | 0.841 | 0.798 | 0.597 |
| BDNF | 32.58 ± 5.82 | 33.4 ± 6.98 | 33.04 ± 4.14 | 32.88 ± 6.35 | 0.05 | 0.12 | 0.733 | 0.943 | 0.953 | 0.368 |
| IL-2 | 7.08 ± 1.3 | 6.97 ± 1.54 | 7.55 ± 1.33 | 6.52 ± 1.53 | −0.04 | −0.23 | 0.841 | 0.089 | 0.416 | 0.291 |
| IL-6 | 21.53 ± 7.84 | 26.89 ± 9.13 | 23.23 ± 7.33 | 24.04 ± 6.31 | −1.09 | −2.05 | 0.103 | 0.768 | 0.099 | 0.093 |
| IL-9 | 31.24 ± 8.22 | 31.7 ± 6.54 | 30.66 ± 7.3 | 33.59 ± 8.25 | −1.44 | −1.35 | 0.868 | 0.363 | 0.669 | 0.351 |
| GABA | 6.83 ± 1.58 | 7.29 ± 1.16 | 6.72 ± 1.45 | 6.18 ± 0.71 | −0.11 | −0.34 | 0.370 | 0.234 | 0.052 | 0.153 |

*$p$ < 0.05. #Compared with the baseline, the group has statistical difference.
&Compared with the sham group, the group has statistical difference.

suggested inconsistent results. For instance, Turriziani's study showed that iTBS to the right DLPFC led to a deterioration in memory performance while iTBS to the left DLPFC had no effect on recognition memory performance in healthy controls (20). Previous research has indicated that the left and right DLPFC serve different functions in memory tasks (21). The inconsistency of previous findings may be attributed to differences in the location of stimulation. Our study found that applying 10 Hz rTMS over the DLPFC can enhance memory in polydrug users, which is consistent with previous research (10). Furthermore, our results suggest that iTBS improves immediate memory to a greater extent than 10 Hz rTMS. Other studies have demonstrated that the frequency of stimulation is the primary factor that determines the direction of excitability modulation (22). Higher frequency iTBS (50 Hz) can increase neuronal activity and cortical excitability, which in turn can improve mood. One clinical study reported that iTBS was more effective than 10 Hz rTMS in alleviating depression (23), and a better mood might contribute to the greater improvement in cognitive function. To date, this is the first trial to investigate the comparative influence of iTBS and 10 Hz rTMS on cognitive function in polydrug users. Compared with 10 Hz rTMS, iTBS takes less time and the effect may be better, so it is more likely to be accepted by patients. We found significantly lower cognitive

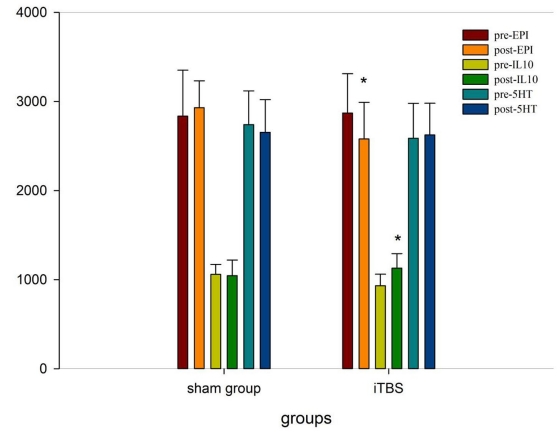


FIGURE 3
Blood indicators pre and post iTBS intervention.

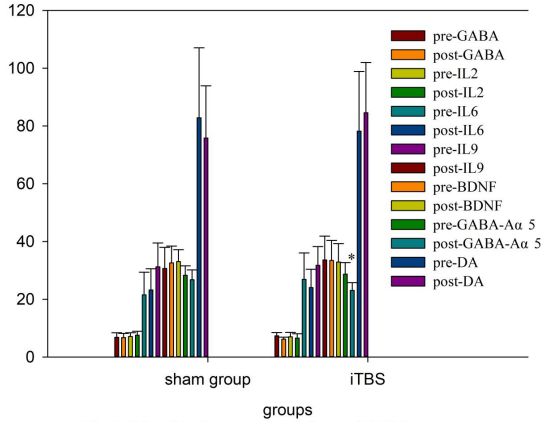


FIGURE 4
Blood indicators pre and post iTBS intervention.

TABLE 4 Pearson correlation analysis of cognitive functioning and blood indicators.

| | GABA-Aα5 | | IL-10 | |
|---|---|---|---|---|
| | *r* | *p* | *r* | *p* |
| Immediate memory | −0.646 | 0.017 | 0.390 | 0.188 |
| attention | 0.377 | 0.204 | 0.610 | 0.027 |

r, Pearson correlation coefficient.

function levels in adults with polydrug use disorders. Using normative data as a reference, polydrug use disorder patients performed significantly worse across all five RBANS indices, with attention and memory and social cognition showing the largest differences. These findings are in agreement with previous studies showing reduced cognitive function in patients who use methamphetamine and heroin (24).

In our study, GABA-Aα5 was significantly reduced and was significantly associated with improved memory function in the iTBS group. Experiments in animals and humans have elucidated some of the potential mechanisms of rTMS in improving cognitive function. Zheng et al. found the increase of GABA-Aα5 might be involved in learning-memory dysfunction in the offspring of chronic ethanol-treated rats and that a GABA-Aα5 inhibitor could be an effective way to treat alcohol-induced cognitive impairment (25). Prévot et al. found that reduced signaling of the GABA-Aα5 receptor can improve cognitive function (26). We found that iTBS could act as a GABA-Aα5 inhibitor, which led to a decrease in GABA-Aα5 levels and an improvement in memory in our study. This is consistent with the results of previous studies. Su et al. found that the effect of rTMS on cognitive function in individuals with methamphetamine dependence may be related to changes in GABA levels in the prefrontal cortex (27).

Inflammation has been shown to play an important role in the cognitive deficits of polydrug use disorders. MA causes an increase in pro-inflammatory cytokines in animal models and humans. Heroin addiction also influences the immune system. Kobeissy et al. showed that three major cytokines (IL-1β, IL-6, and IL-10) were elevated in an MA group compared to a saline group (28). Kohno et al. found that IL-6 levels are higher in MA users than in controls (29). Mice subcutaneously administered heroin showed an increased production of IL-1β, IFN-γ, and IL-12 within 2 h, but the production of the anti-inflammatory cytokines IL-4 and IL-10 was decreased (30). In our study, IL-2, IL-6, and IL-9 levels were not changed by iTBS or sham stimulation, but IL-10 was significantly increased and was significantly associated with improved attention in the iTBS group. This suggests that iTBS may modulate immunity by altering IL-10 expression, and thus improve cognitive function. This is consistent with previous studies, Zhang et al. found that cognitive impairment could be alleviated by IL-10 (31). where IL-10 was reported to be increased after rTMS treatment in middle cerebral artery occlusion model rats, which significantly reduced neuronal apoptosis, promoted neuronal plasticity, and improved cognitive function (32). Multiplex cytokine bioassays showed that iTBS increased IL-10 in injury mice with middle cerebral artery occlusion (33). In addition, our study found a significant decline in EPI after treatment but did not find a correlation between this change and cognitive function. This is inconsistent with relevant research, Jiang et al. found a relationship between sevoflurane-induced cognitive impairment and EPI adrenoceptors in the cerebral cortex of rats (34).

Our study has some limitations. First, participants received only 20 sessions of stimulation without subsequent treatments. Secondly, to avoid time effects on cognitive function, especially for memory, we remeasured cognitive function 2 months after the end of treatment. However, blood was drawn immediately after treatment. This discrepancy in timings may affect the correlation between changes in cognitive function and those blood markers, although it does suggest that early biomarker responses are associated with later cognitive status. Future studies may consider continued rTMS treatment 2–3 times a week after the first 20 sessions, with continued cognitive function tests and longitudinal blood analyses, to better model the relationship between changes in cognitive function and blood indicators, and observe the duration of rTMS effects. In addition, we did not assess depression and anxiety symptoms, which is a related oversight because mood, anxiety, and other psychological symptoms are over represented in drug users. The effective treatment of emotional symptoms by iTBS/10 Hz rTMS may be attributed to improved cognitive

abilities. We will focus on emotional symptoms in a follow-up study.

In conclusion, we preliminary found that iTBS to the left DLPFC could improve cognitive function in polydrug use disorder patients, and its efficacy was superior to that of 10 Hz rTMS. At the same time, serum GABA-Aα5 and EPI levels decreased and IL-10 increased. These findings suggest that iTBS-rTMS may act as a GABA-Aα5 inhibitor and IL-10 agonist. Future studies should focus on related proteins change and functional MRI of the brain to identify the mechanisms of iTBS, and ideally conduct longer treatment and follow-up.

## Data availability statement

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

## Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Wuhan Mental Health Center. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

LD was responsible for the study concept and design and did the rTMS intervention and drafted the manuscript. X-JL, X-BL, and S-JC helped design the study. M-LW, CD, X-rJ, and S-fM acquired the clinical data. W-CC conducted the data analysis. LD, W-CC, HS, M-LW, CD, X-rJ, S-fM, S-JC, X-JL, and X-BL provided critical revision of the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

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

## Publisher's note



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# Right inferior frontal gyrus theta-burst stimulation reduces smoking behaviors and strengthens fronto-striatal-limbic resting-state functional connectivity: a randomized crossover trial

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**Introduction:** Functional and anatomical irregularities in the right inferior frontal gyrus (rIFG), a ventrolateral prefrontal region that mediates top-down inhibitory control over prepotent behavioral responding, are implicated in the ongoing maintenance of nicotine dependence (ND). However, there is little research on the effects of neuromodulation of the rIFG on smoking behavior, inhibitory control, and resting-state functional connectivity (rsFC) among individuals with ND.

**Methods:** In this double-blind, crossover, theta-burst stimulation (TBS) study, adults with ND ($N = 31$; female: $n = 15$) completed a baseline session and were then randomized to two counterbalanced sessions of functionally neuronavigated TBS to the rIFG: continuous TBS (cTBS) on 1 day and intermittent TBS (iTBS) on another. Differences in cigarette cravings, smoking, and fronto-striatal-limbic rsFC were assessed.

**Results:** Relative to baseline, cTBS significantly reduced appetitive and withdrawal cravings immediately after treatment. The effects of cTBS on withdrawal craving persisted for 24 h, as well as produced a reduction in smoking. Furthermore, cTBS significantly strengthened rsFC between the rIFG pars opercularis and subcallosal cingulate (fronto-striatal circuit), and between the rIFG pars opercularis and the right posterior parahippocampal gyrus (fronto-limbic circuit). At post-24 h, cTBS-induced increase in fronto-striatal rsFC was significantly associated with less appetitive craving, while the increase in fronto-limbic rsFC was significantly associated with less withdrawal craving and smoking.

**Discussion:** These findings warrant further investigation into the potential value of rIFG cTBS to attenuate smoking behavior among individuals with ND.

KEYWORDS

**addiction, smoking, tobacco, craving, repetitive transcranial magnetic stimulation, resting state fMRI, right inferior frontal gyrus (rIFG)**

# Introduction

Chronic use of addictive drugs, such as nicotine, results in maladaptive goal-directed behaviors and modifies neural circuitry subserving motivation and executive function (1–3). Relative disturbances in response inhibition and salience attribution to drug cues represent two core factors maintaining smoking behaviors among individuals with nicotine dependence (4–6). The majority of adults that smoke relapse when attempting to quit, even when using first-line FDA-approved cessation products (7). Furthermore, adults that smoke cite disturbances in cognition (8, 9) and craving (8, 10, 11) as primary factors that precipitate relapse. Thus, there is an urgent need to develop innovative strategies for treating deficits in core neurocognitive domains to improve smoking cessation outcomes (12).

Functional magnetic resonance imaging (fMRI) research with individuals with substance use disorders (SUDs) has informed neural circuit-based models for treating addiction pathophysiology (13–18). The extant literature supports a model whereby impaired response inhibition and salience attribution to drug cues are mediated by a common top-down modulatory influence from the ventrolateral prefrontal cortex (vlPFC) [i.e., right inferior frontal gyrus (rIFG)] (19). This model is supported by SUD studies associating rIFG dysfunction with deficits in both inhibitory control (IC) (9, 17, 19–32) and the proactive regulation of craving (19, 25, 33–36). IC refers to the ability to disrupt and withhold a prepotent response (37), while the regulation of craving refers to the ability to modify motivational responses to conditioned drug cues (33). Furthermore, systems neuroscience research assessing resting-state functional connectivity (rsFC) (38) has demonstrated that dysregulated connectivity between the rIFG, striatum, and limbic reward structures (henceforth, fronto-striatal-limbic circuitry) may underlie the capacity to exert top-down cognitive control over motivated behavioral responding (39).

Among individuals with a SUD, dysregulated fronto-striatal-limbic rsFC has been widely reported in the literature and associated with impulsivity (39) and craving (38, 40, 41). Weakened fronto-striatal-limbic rsFC has been reported among individuals with dependence on nicotine (42–45), cocaine (46, 47), and opioids (48), as well as those with addictive behaviors such as internet gaming disorder (49) and problematic smartphone use (50). Though it is not clear whether weaker fronto-striatal-limbic rsFC is a consequence of addiction or a predisposing risk factor for developing a substance or behavioral addiction, the extant literature suggests rsFC in fronto-striatal-limbic circuitry may serve as a treatment target to remediate dysregulated cognitive control over addictive behaviors. However, there remains a dearth of mechanistic research demonstrating the potential clinical value of using neuromodulation to target fronto-striatal-limbic circuitry to improve cessation outcomes.

Theta-burst stimulation (TBS), a patterned form of repetitive transcranial magnetic stimulation (rTMS), shows promise for treating addiction pathophysiology (51). The two common types of TBS are continuous TBS (cTBS) and intermittent TBS (iTBS). Early research that administered TBS to the motor cortex provided evidence to support a model where cTBS produced an inhibitory—long-term depression (LTD)-like effect; whereas iTBS produced an excitatory—long-term potentiation (LTP)-like effect (52, 53). Given the prior literature on the therapeutic value of administering excitatory-like rTMS patterns to the dorsolateral prefrontal cortex (dlPFC), at the start of this study in 2019, we initially hypothesized that excitatory-like rTMS (i.e., iTBS) to the vlPFC would produce a clinically relevant improvement in behavioral inhibition and smoking behavior, as compared to an inhibitory-like pattern (i.e., cTBS). However, during the time we conducted the study, evidence was published suggesting that the effects of TBS on the lateral prefrontal cortices may not correspond to a dissociable inhibitory or excitatory outcome, as once proposed (54). Moreover, cTBS to the right dlPFC has been recently shown to reduce anxiety symptoms (55) and those findings have been subsequently supported by a sham-controlled cTBS clinical trial for generalized anxiety disorder demonstrating that cTBS reduces anxiety (56). Furthermore, recent evidence suggests that the dissociable effects of TBS may also depend on pulse number (57). In sum, recent evidence has cast doubt on our original rationale, suggesting that either iTBS or cTBS to the vlPFC might be effective treatments for smoking cessation and we have analyzed and presented our findings in light of that evidence. Thus, there continues to remain a need for a principled evaluation of the neural and behavioral effects of both iTBS and cTBS on prefrontal-mediated cognitive control, and understanding mechanisms of action of TBS on drug use relevant behaviors.

The most common cortical target for examining the effects of neurostimulation on drug use behaviors is the left dlPFC—an anatomical target adopted from FDA-approved protocols for treating major depressive disorder and shown to improve smoking cessation outcomes (58). However, research examining the effects of neuromodulation over alternative cortical targets in individuals with SUDs remains scarce (59, 60). Given the role of the vlPFC (i.e., rIFG) in mediating IC and craving regulation, its strength of functional connectivity with striatal and limbic reward circuitry mediating drug-seeking behaviors, and its anatomical location being amenable to TBS, the rIFG is an ideal alternative cortical target for examining the potential therapeutic value of neuromodulation for treating addiction pathophysiology. Further support for stimulating the rIFG comes from a recent multisite double-blind sham-controlled randomized clinical trial that administered bilateral deep rTMS over the lateral prefrontal cortices in adults with nicotine dependence and found it reduced both smoking and craving (61). Despite this knowledge, there is a gap in the extant literature on the effects of TBS on the rIFG for modifying addictive behaviors. To address this gap in the literature and extend our previous research (17, 62), relative to a baseline session with no TBS, the current study examined the acute effects of functionally neuronavigated iTBS and cTBS to the rIFG at 80% resting motor threshold (RMT) on smoking behaviors and fronto-striatal-limbic rsFC.

# Materials and methods

## Participants

Participants ($N = 31$) (Table 1; Supplementary Table 1) were recruited from the local community via media outlets in Columbia-Missouri by research staff. Inclusion criteria were

TABLE 1 Demographics and clinical characteristics.

| Measure | Participants ($N = 31$) |
|---|---|
| **Demographics** | |
| Participants (female) | 31 (15) |
| Sex, female, *n* (%) | 15 (48.4%) |
| Age, years, mean (SD) | 47.7 (8.7) |
| **Race, *n* (%)** | |
| Black or African American | 5 (16.1%) |
| Caucasian non-Latinx/Hispanic | 25 (80.6%) |
| Multiple | 1 (3.2%) |
| **Education, *n* (%)** | |
| No high school diploma | 2 (6.5%) |
| High school diploma | 6 (19.4%) |
| Some college | 15 (48.4%) |
| 4-year college degree | 6 (19.4%) |
| Advanced degree | 2 (6.5%) |
| **Household income, annually, *n* (%)** | |
| $16,000 or less | 7 (22.6%) |
| $16,001–31,000 | 7 (22.6%) |
| $31,001–48,000 | 7 (22.6%) |
| $48,001–64,000 | 2 (6.5%) |
| $64,001–80,000 | 1 (3.2%) |
| $80,001–96,000 | 4 (12.9%) |
| $96,001 or more | 2 (6.5%) |
| Not reported | 1 (3.2%) |
| **Clinical characteristics, mean (SD)** | |
| Nicotine dependence, FTND[a] | 5.4 (2.1) |
| Daily cigarettes, past 30-days | 18.4 (4.5) |
| Years smoking | 29.8 (9.0) |
| Pack years | 27.7 (10.7) |
| Impulsivity, BIS[b] total | 61.4 (9.5) |
| NoGo adjusted % correct, IC GGNG task[c] | 44.8 (21.2) |

[a]Fagerstrom Test for Nicotine Dependence (score range: 0–10).
[b]Barratt Impulsiveness Scale (score range: 30–120).
[c]Inhibitory control *GoGo/NoGo* task (score range: 0–100).

being an individual aged between 18 and 65 years; a minimum history of smoking ≥ 10 cigarettes per day (CPD) for ≥2 years; carbon monoxide level of ≥10 (Vitalograph Inc.); stable mental and physical health; and willingness to provide informed consent. Exclusion criteria were contraindication to MRI or TBS; use of substances that lower seizure threshold; history of disorders affecting the brain; unstable cardiac disease, uncontrolled hypertension, severe renal or liver insufficiency, or sleep apnea; current or past psychosis; breath alcohol > 0; or positive pregnancy test. The study was approved by the Institutional Review Board at the University of Missouri, Columbia.

## Design overview

The study's aims and analyses were part of a larger TBS trial in individuals with nicotine dependence (ClinicalTrials.gov Identifier: NCT03960138) (Supplementary Table 1). Based on the extant literature supporting the clinical value of high-frequency rTMS to left dlPFC for depression (58, 63), we initially hypothesized that iTBS would result in clinically relevant improvements as compared to baseline and cTBS. However, during the course of the study, evidence was published (54–57) that casted doubt on this rationale and suggested that either iTBS or cTBS might result in clinically relevant improvements. Thus, the current study examining the effects of i/cTBS on brain and smoking behavior was exploratory.

Following informed consent, participants attended a screening and training session, which included an MRI mock scan and acclimation to the TBS equipment. Eligible participants went on to complete three additional sessions each separated by at least 48 h. Session one was a baseline session, which utilized an IC GoGo/NoGo (GGNG) task (described below) during fMRI to determine each participant's rIFG target for neuronavigation-guided TBS at the following sessions. Successful IC, controlling for novelty detection, elicits activation within the rIFG, particularly the pars opercularis subregion (27, 64). For each participant, their peak rIFG IC BOLD cluster was set as the functional target for the following TBS sessions (Figure 1). Next, participants attended two randomized, counterbalanced, neuronavigated TBS sessions to the rIFG—one administering cTBS, and the other administering iTBS.

Participants were randomized to treatment orders with an allocation ratio of 2:2 in blocks of 4, which was concealed by non-research staff. Participants and research staff collecting data were blinded to treatment orders. All TBS treatments were administered by a dedicated TBS technician who was not involved with data collection. Self-reported electronic questionnaires on cravings and side effect symptoms were collected at the start and end of each session in the laboratory, while electronic questionnaires on cravings, smoking, and side effects were collected remotely 24 h following each session by smartphone. Resting-state fMRI was collected at baseline and 20 min after each TBS treatment. At the end of the last session, participants and researchers that collected data completed a study blind assessment. To control nicotine satiety at the start of each session, participants were encouraged to smoke immediately before coming into the laboratory. No significant differences in session-start carbon monoxide (CO) levels or cravings were detected, which provided confirmation that participants started each session with equivalent levels of nicotine satiety (Supplementary Table 2). By the end of each laboratory session, participants had not smoked for ~2 h.

## Magnetic resonance imaging

### Image acquisition

Whole-brain images were acquired using a 3T Siemens Prisma Fit MRI scanner. A T1-weighted magnetization prepared—rapid gradient echo (MPRAGE) sequence (TR = 2,300 ms, TE = 2.26 ms, FA = 8°, 192 ascending slices, 1 $mm^3$ voxels, FOV = 256 mm, phase

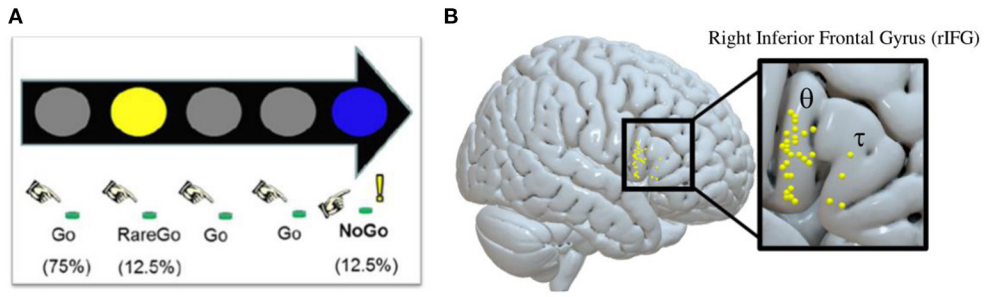


FIGURE 1
Inhibitory control GoGo/NoGo (GGNG) task and corresponding functionally neuronavigated theta-burst stimulation (TBS) targets identified at baseline for each participant. **(A)** Depiction of the inhibitory control GGNG task. **(B)** Depiction of the peak GGNG task-related blood-oxygenation level-dependent (BOLD) response in the right interior frontal gyrus (rIFG) during successful inhibitory control trials, while controlling for lapses in attention and novelty detection for each participant [$\theta$ = rIFG pars opercularis ($n = 27$); $\tau$ = rIFG pars triangularis ($n = 4$)]. The majority of peak BOLD responses lie on the rIFG pars opercularis (rIFGoper).

encoding direction = A >> P) was used to acquire anatomical images. Functional T2*-weighted images were acquired to measure BOLD responses using a simultaneous multi-slice echo-planar imaging (EPI) sequence (acceleration factor = 3, TR = 2,000 ms, TE = 36 ms, FA = 70°, 69 interleaved slices, 2.2 $mm^3$ voxels, FOV = 207 mm, phase encoding direction = A >> P).

## Baseline fMRI GGNG IC task

At baseline, each participant performed an IC GGNG task (17, 65) during an fMRI scan (duration = 7.2 min; volumes = 216) to identify the rIFG treatment target for each participant. During the task, colored circles were presented in rapid succession with instructions to press a button with the right index finger in response to frequent gray circles (Go, 75.4%; $n = 388$) and rare yellow circles (RareGo, 12.5%; $n = 65$) and to withhold a response to rare blue circles (NoGo, 12.5%; $n = 65$). Random, infrequent presentation of NoGo trials facilitated prepotency of response. The inclusion of RareGo trials allowed for the determination of BOLD activation specific to IC after controlling for activation associated with novelty detection. Additionally, to control the effects of attentional lapses during the task, reported NoGo accuracy was adjusted to include only NoGo trials with a correct response to the preceding Go trial. All stimuli were presented for 400 ms and were followed by a 400 ms interval.

To increase the precision of TBS target identification, IC task images were processed in native space. Preprocessing consisted of structural cortical surface reconstruction (FreeSurfer); slice-timing correction and rigid-body head motion correction (FMRIB Software Library); coregistration (FreeSurfer); and the estimation and removal of noise components using an iterative sparse noise-modeling technique (66). Data were entered into a first-level analysis using the general linear model to examine the BOLD response to five event types: NoGo correct, RareGo correct, NoGo incorrect, RareGo incorrect, and Go incorrect. The NoGo correct event was indicative of correctly inhibiting a prepotent response while controlling for lapses in attention. Events were modeled as a delta regressor (0 s) and convolved with the canonical hemodynamic response function. Six intra-run motion parameters ($x$, $y$, $z$, roll, pitch, and yaw) were removed and included as first-level covariates, and a high-pass filter (128 s) was applied. The peak rIFG IC BOLD cluster for each participant was determined by examining the NoGo correct—RareGo correct BOLD contrast, which represents successful IC while controlling for lapses in attention and novelty detection.

## Resting-state functional connectivity

During baseline and 20 min after receiving TBS, participants underwent an eyes-closed resting-state fMRI scan (duration = 10 min, volumes = 300). Images were preprocessed, denoised, and modeled with the CONN toolbox (version 21b, www.nitrc.org/projects/conn, RRID: SCR_009550). Preprocessing consisted of functional realignment and unwarping using b-spline interpolation (first EPI volume as reference image), slice-timing correction, outlier detection (framewise displacement > 0.9 mm or global BOLD signal > 5 standard deviations), and direct segmentation and normalization to MNI 152 space (anatomical resampled to 1 $mm^3$ voxels; functional resampled to 1.5 $mm^3$ voxels) using b-spline interpolation. Unsmoothed images were then put through a denoising anatomical component correction (aCompCor) pipeline to regress out BOLD signal confounds which included five cerebrospinal fluid and five white matter components, six motion parameters, scrubbing, task effects, despiking, and bandpass filtering (0.008, 0.09 Hz). Finally, voxel-wise, Fisher-transformed bivariate correlation coefficient (rZ) maps were calculated, and regions of interest (ROIs) were parcellated according to the Harvard-Oxford atlas (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases, RRID: SCR_001476). rsFC was assessed using the CONN ROI-to-ROI explorer.

# Theta-burst stimulation protocol

## Neuronavigation

The Rogue Research Inc. © Brainsight system was used to perform neuronavigation (67). Within each participant's native space, their anatomical image was co-registered to their peak

rIFG BOLD cluster identified from the baseline IC GGNG task. Skin and full-brain curvilinear reconstructions were generated and anatomical landmarks (nasion, the tip of the nose, and left and right tragi) were created to enable registration between these images and each participant's head. The rIFG BOLD cluster was set as the spatial target, and the target coil trajectory was set. The same setup parameters were used for each TBS session (16). Neuronavigation target errors were recorded (Supplementary Table 3).

### Stimulation equipment and parameters

The MagVenture MagPro X100 TMS Therapy System with a figure-8 Cool-B65 A/P coil at 80% RMT was used to administer TBS. Parameter estimation by sequential testing (PEST) was used to determine RMT at each TBS session by stimulating the motor cortex (68). The duration of the cTBS protocol was 40 s [three pulse bursts at 50 Hz repeated every 200 ms (5 Hz) and 600 total pulses], while iTBS was 190 s [3 pulse bursts at 50 Hz repeated every 200 ms (5 Hz) per train, 2 s per train, 20 trains, 10 s intertrain intervals, and 600 total pulses]. During TBS, participants were reclined in a comfortable chair and wore a mouthpiece and earplugs (16). RMT and treatment dosages were recorded (Supplementary Table 4).

## Blinding

To achieve researcher blinding, and to standardize TBS session duration and administration, this study had a dedicated TBS technician who was not involved with data collection. Excluding the TBS technician, researchers and participants were both blinded to treatment conditions.

## Outcome measures

All questionnaire data (cravings, side effects, and smoking) were collected electronically via REDCap. Questionnaires administered at the start and end of each session (cravings and side effects) were completed on a desktop computer in the laboratory, while questionnaires administered 24 h after each session (cravings, side effects, and smoking) were collected remotely via smartphone. For the remote assessments, participants were sent a text message containing a link that directed them to the questionnaires. Resting-state fMRI data were collected at the baseline session and 20 min after each TBS treatment. At the end of the final session, researchers that collected data and participants completed a study blind assessment.

### Cravings

Differences in cravings were assessed by examining responses to both factors on the Questionnaire of Smoking Urges Brief (QSUB) (69, 70). QSUB factor one measures how strongly a participant desires and intends to smoke (henceforth, appetitive craving), while QSUB factor two measures how strongly a participant anticipates that smoking will provide relief from negative affect and urge to smoke (henceforth, withdrawal craving).

### Smoking

Differences in smoking consumption were assessed by asking participants to report the number of cigarettes per day (CPD) they had consumed during the 24-h period after each session.

### Resting-state functional connectivity

Differences in rsFC were assessed by having participants receive a resting-state fMRI scan at each session. A data-driven approach using the Harvard-Oxford atlas was used to parcellate the ROIs used for the rsFC analyses. ROI-to-ROI analyses were restricted to the right hemisphere, and only connections from the rIFG pars opercularis to the striatum and limbic system were examined. *A priori* striatal ROIs consisted of the subcallosal cingulate and right nucleus accumbens, while limbic ROIs consisted of the right posterior parahippocampal gyrus and right hippocampus. The rIFG pars opercularis was chosen as the primary cortical ROI because this region is associated with IC, regulation of craving, and was directly stimulated across the majority of participants in this study. The subcortical ROIs were selected based on previous literature indicating their involvement in rewarding smoking behaviors (33, 34).

### Side effects

Differences in the total side effect symptoms were assessed by examining responses to the review of symptoms (ROS) questionnaire (71).

### Blinding

The double-blind procedure was assessed by having researchers and participants complete a form indicating which order of treatment they believed was administered as well as provide a confidence rating on a scale from 1 to 10.

## Statistical analyses

To account for missing data and control for session start values, mixed modeling analysis of covariance (ANCOVA) was used to examine fixed effects of session on cravings and side effect symptoms at session end and post-24 h. Since the side effects outcome consisted of count data, a Poisson ANCOVA was used. An analysis of variance (ANOVA) was used to examine the fixed effects of session on smoking and rsFC. Linear regression was used to examine associations among smoking behaviors and if treatment-related change scores from baseline in rsFC (Δ: i/cTBS - baseline) were associated with smoking-related outcomes. Study blinding was assessed using a chi-square test. In all analyses, statistical significance was defined as $p < 0.05$ (two-sided). Graphical techniques such as boxplots, spaghetti plots, and scatterplots were used for the visualization of study outcomes.

# Results

## Cravings

### Appetitive craving

As compared to baseline ($M$ = 27.35, $SD$ = 7.33) when controlling for session start values, appetitive craving at session end was significantly reduced for cTBS ($M$ = 22.97, $SD$ = 8.48; *adj mean diff* = −4.09, $SE$ = 2.00, *95% CI* = −8.02 to −0.17, $p$ = 0.044, *Cohen's d* = −0.373), but not for iTBS ($M$ = 24.45, $SD$ = 7.79; *adj mean diff* = −2.95, $SE$ = 1.98, *95% CI* = −6.82 to 0.93, $p$ = 0.140, *Cohen's d* = −0.268) ($F_2$ = 2.25, $p$ = 0.118). As compared to baseline ($M$ = 19.43, $SD$ = 7.84) when controlling for session start values, appetitive craving at post-24 h was not significantly reduced for cTBS ($M$ = 15.20, $SD$ = 7.34; *adj mean diff* = −3.75, $SE$ = 1.98, *95% CI* = −7.62 to 0.13, $p$ = 0.061, *Cohen's d* = −0.346) or iTBS ($M$ = 16.61, $SD$ = 8.15; *adj mean diff* = −2.80, $SE$ = 1.95, *95% CI* = −6.62 to 1.02, $p$ = 0.154, *Cohen's d* = −0.258) ($F_2$ = 1.95, $p$ = 0.150) (Figure 2A).

### Withdrawal craving

As compared to baseline ($M$ = 16.71, $SD$ = 6.49) when controlling for session start values, withdrawal craving at session end was significantly reduced for cTBS ($M$ = 13.20, $SD$ = 6.24; *adj mean diff* = −3.54, $SE$ = 1.57, *95% CI* = −6.62 to −0.46, $p$ = 0.027, *Cohen's d* = −0.412), but not for iTBS ($M$ = 13.87, $SD$ = 6.72; *adj mean diff* = −2.86, $SE$ = 1.56, *95% CI* = −5.91 to 0.20, $p$ = 0.070, *Cohen's d* = −0.329) ($F_2$ = 2.88, $p$ =0.062). As compared to baseline ($M$ = 13.37, $SD$ = 6.59) when controlling for session start values, withdrawal craving at post-24 h was significantly reduced for cTBS ($M$ = 10.23, $SD$ = 4.91; *adj mean diff* = −2.96, $SE$ = 1.42, *95% CI* = −5.75 to −0.18, $p$ = 0.040, *Cohen's d* = −0.380), but not for iTBS ($M$ = 11.23, $SD$ = 6.64; *adj mean diff* = −2.08, $SE$ = 1.41, *95% CI* = −4.84 to 0.67, $p$ = 0.142, *Cohen's d* = −0.265) ($F_2$ = 2.31, $p$ = 0.106) (Figure 2B).

## Smoking

As compared to baseline ($M$ = 18.84, $SD$ = 5.44), CPD at post-24 h were significantly reduced for cTBS ($M$ = 16.32, $SD$ = 5.53; *mean diff* = −2.52, $SE$ = 0.84, *95% CI* = −4.236 to −0.796, $p$ = 0.006, *Cohen's d* = −0.539), but not for iTBS ($M$ = 17.23, $SD$ = 5.55; *mean diff* = −1.61, $SE$ = 0.82, *95% CI* = −3.277 to 0.051, $p$ = 0.057, *Cohen's d* = −0.353) ($F_{2,29}$ = 4.972, $p$ = 0.014) (Figure 2C).

## Resting-state functional connectivity

### Fronto-striatal circuitry

As compared to baseline ($M$ = −0.112, $SD$ = 0.26), rsFC between the rIFG pars opercularis and subcallosal cingulate was significantly increased for cTBS ($M$ = 0.006, $SD$ = 0.24; *mean diff* = 0.118, $SE$ = 0.04, *95% CI* = 0.029 to 0.208, $p$ = 0.011, *Cohen's d* = 0.530), but not for iTBS ($M$ = −0.058, $SD$ = 0.24; *mean diff* = 0.054, $SE$ = 0.05, *95% CI* = −0.043 to 0.151, $p$ = 0.263, *Cohen's d* = 0.194) ($F_{2,29}$ = 3.530, $p$ = 0.042) (Figure 3A). No significant treatment effects were found on connectivity between the rIFG pars opercularis and right nucleus accumbens (Supplementary Table 5).

### Fronto-limbic circuitry

As compared to baseline ($M$ = 0.038, $SD$ = 0.18), rsFC between the rIFG par opercularis and the right posterior parahippocampal gyrus was significantly increased for cTBS ($M$ = 0.109, $SD$ = 0.19; *mean diff* = 0.071, $SE$ = 0.03, *95% CI* = 0.003 to 0.139, $p$ = 0.042, *Cohen's d* = 0.425), but not for iTBS ($M$ = 0.074, $SD$ = 0.17; *mean diff* = 0.036, $SE$ = 0.04, *95% CI* = −0.037 to 0.109, $p$ = 0.317, *Cohen's d* = 0.162) ($F_{2,29}$ = 2.199, $p$ = 0.129) (Figure 3B). No significant treatment effects were found on connectivity between the rIFG pars opercularis and the right hippocampus (Supplementary Table 5).

## Behavioral associations

Appetitive craving at session end and CPD at post-24 h were significantly positively associated for iTBS ($R^2_{adj}$ = 0.104, $F_{1,29}$ = 4.494, β = 0.261, *95% CI* = 0.009 to 0.513, $t$ = 2.120, $p$ = 0.043), while this association was not significant for cTBS ($R^2_{adj}$ = −0.009, $F_{1,28}$ = 0.729, β = 0.102, *95% CI* = −0.143 to 0.348, $t$ = 0.854, $p$ = 0.400) (Supplementary Figure 1A). Withdrawal craving at post-24 h and CPD at post-24 h were significantly positively associated for cTBS ($R^2_{adj}$ = 0.111, $F_{1,28}$ = 4.604, β = 0.427, *95% CI* = 0.019 to 0.835, $t$ = 2.146, $p$ = 0.041), while this association was not significant for iTBS ($R^2_{adj}$ = −0.010, $F_{1,29}$ = 0.716, β = 0.130, *95% CI* = −0.184 to 0.443, $t$ = 0.846, $p$ = 0.405) (Supplementary Figure 1B).

## Brain-behavior associations

### Fronto-striatal circuitry and appetitive craving

cTBS-induced strengthening of fronto-striatal rsFC was marginally associated with decreased appetitive craving at session end ($R^2_{adj}$ = 0.098, $F_{1,28}$ = 4.160, β = −12.264, *95% CI* = −24.581 to 0.052, $t$ = −2.040, $p$ = 0.051), while this association was not present for iTBS ($R^2_{adj}$ = −0.025, $F_{1,29}$ = 0.277, β = −2.875, *95% CI* = −14.041 to 8.291, $t$ = −0.527, $p$ = 0.602) (Supplementary Figure 2A). cTBS-induced strengthening of fronto-striatal rsFC was significantly associated with decreased appetitive craving at post-24 h ($R^2_{adj}$ = 0.110, $F_{1,28}$ = 4.596, β = −11.087, *95% CI* = −21.681 to −0.493, $t$ = −2.144, $p$ = 0.041), while this association was not significant for iTBS ($R^2_{adj}$ = −0.022, $F_{1,29}$ = 0.343, β = −3.343, *95% CI* = −15.011 to 8.325, $t$ = −0.586, $p$ = 0.562) (Supplementary Figure 2B). No significant associations were found between fronto-striatal rsFC following cTBS or iTBS and withdrawal craving or CPD.

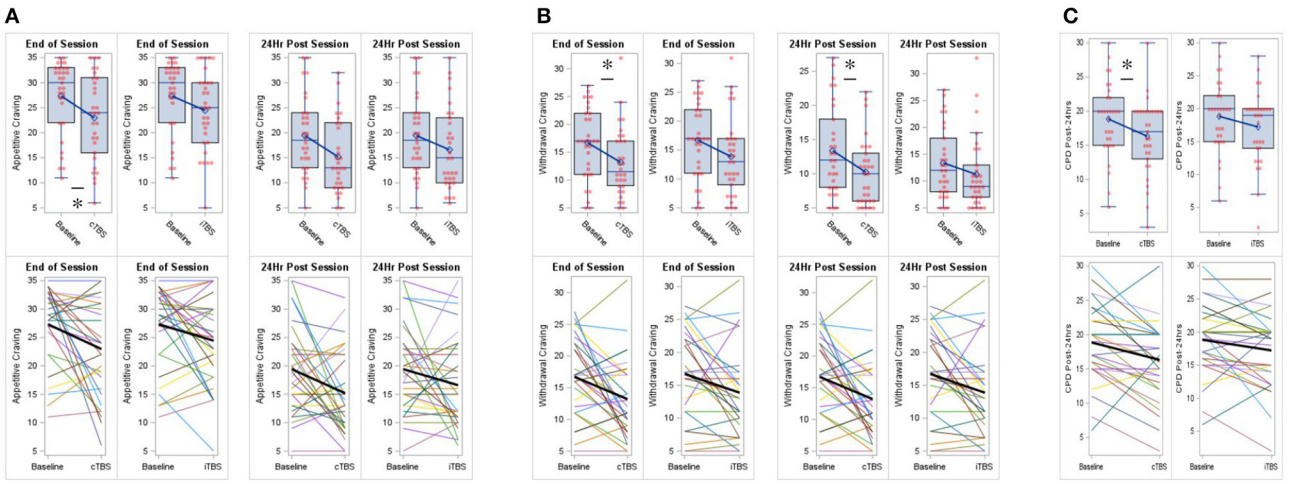


FIGURE 2
Continuous theta-burst stimulation (cTBS) to the right inferior frontal gyrus (rIFG) reduced cigarette cravings and smoking. **(A)** Compared to baseline, cTBS reduced appetitive craving at session end. **(B)** Compared to baseline, cTBS reduced withdrawal craving at session end and at post 24-h. **(C)** Compared to baseline, cTBS reduced smoking at post 24-h. iTBS did not significantly effect cigarette cravings or smoking. Data are presented with boxplots (top row) and spaghetti plots (bottom row). $p < 0.05$ (two-sided). *$p < 0.05$.

## Fronto-limbic circuitry, withdrawal craving, and smoking

cTBS-induced strengthening of fronto-limbic rsFC was significantly associated with decreased withdrawal craving at post-24 h ($R^2_{adj} = 0.193$, $F_{1,28} = 7.954$, $\beta = -12.509$, *95% CI* $= -21.594$ to $-3.424$, $t = -2.820$, $p = 0.009$), while this association was not significant for iTBS ($R^2_{adj} = -0.028$, $F_{1,29} = 0.187$, $\beta = 2.670$, *95% CI* $= -9.966$ to 15.307, $t = 0.432$, $p = 0.669$) (Supplementary Figure 2C). cTBS-induced strengthening of fronto-limbic rsFC was significantly associated with reduced CPD at post-24 h ($R^2_{adj} = 0.105$, $F_{1,29} = 4.520$, $\beta = -10.895$, *95% CI* $= -21.377$ to $-0.414$, $t = -2.126$, $p = 0.042$), while this association was not significant for iTBS ($R^2_{adj} = 0.015$, $F_{1,29} = 1.451$, $\beta = -6.091$, *95% CI* $= -16.433$ to 4.251, $t = -1.205$, $p = 0.238$) (Supplementary Figure 2D). No significant associations were found between fronto-limbic rsFC following cTBS or iTBS and withdrawal craving at session end, or appetitive craving at any time point.

## Side effects

As compared to baseline and controlling for side effect symptoms reported at the start of each session, neither cTBS nor iTBS resulted in elevated reports of total symptoms at visit end. *Post-hoc* tests within each TBS condition comparing symptoms reported at session start to those reported at post-24 h revealed that neither cTBS nor iTBS had elevated symptoms (Supplementary Table 6; Supplementary Figure 3). No serious adverse events were reported.

## Blinding

The double-blind procedure was successful. Across sessions, neither the researchers that collected data [$\chi^2_{(2)} = 1.133$, $p = 0.567$] nor the participants [$\chi^2_{(2)} = 0.619$, $p = 0.734$] could correctly identify the order of TBS conditions administered.

# Discussion

This study assessed the acute effects of cTBS and iTBS to the rIFG on smoking behaviors and fronto-striatal-limbic rsFC within a community sample of nicotine-dependent adult cigarette smokers. The results demonstrated that cTBS reduced cigarette cravings and smoking and strengthened fronto-striatal-limbic rsFC. Furthermore, the magnitude of cTBS-induced change in fronto-striatal-limbic rsFC was associated with the attenuation of smoking behaviors. These findings provide initial support for applying cTBS to the rIFG to strengthen functional connectivity between cognitive control and reward circuitry, thereby attenuating craving and reducing smoking.

## Smoking behaviors

Although the construct of craving reflects a constellation of symptoms (72, 73), it represents a primary predictor of relapse (11). In this study, appetitive and withdrawal cravings were assessed (69), which may represent distinct mechanisms of craving, such as those based on positive and negative reinforcement, respectively (74). cTBS significantly reduced appetitive and withdrawal cravings immediately after treatment and these effects for withdrawal cravings persisted over a 24-h period. Moreover, cTBS produced a significant reduction in smoking over the 24-h period following treatment, and reduction in withdrawal craving was significantly positively associated with smoking fewer cigarettes over the 24-h period.

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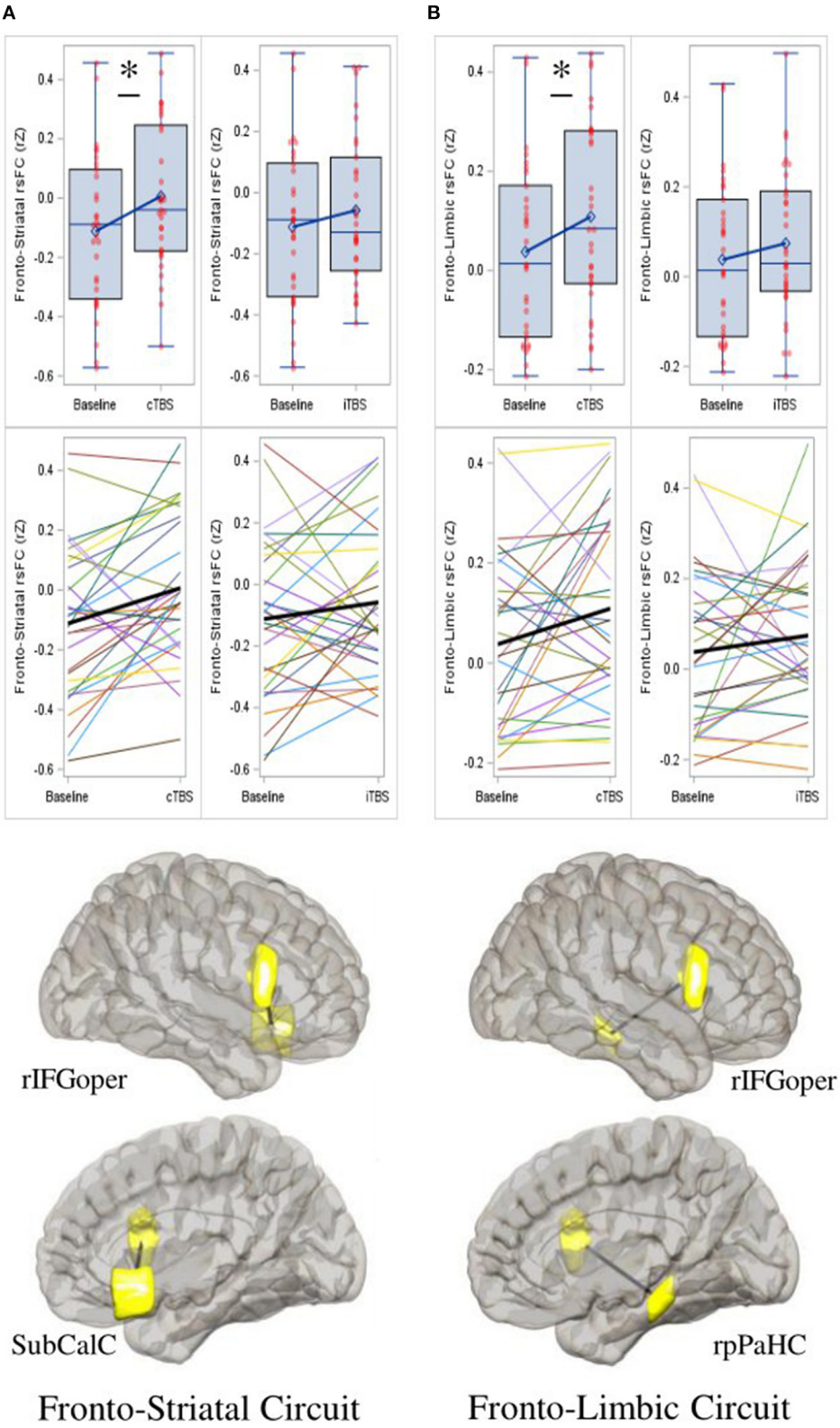


FIGURE 3
Continuous theta-burst stimulation (cTBS) strengthens fronto-striatal and fronto-limbic resting-state functional connectivity (rsFC). **(A)** Compared to baseline, cTBS strengthened rsFC between the right inferior frontal gyrus pars opercularis (rIFGoper) and subcallosal cingulate (SubCalC) (fronto-striatal circuit); and between **(B)** the rIFGoper and right posterior parahippocampal gyrus (rpPaHC) (fronto-limbic circuit). iTBS has no significant effects on either circuit. Data represent Fisher-transformed bivariate correlation coefficient (rZ) values between regions of interest (ROIs) defined by the Harvard-Oxford atlas. Depictions of ROIs are in yellow. Date are presented with boxplots (top row) and spaghetti plots (middle row). $p < 0.05$ (two-sided). *$p < 0.05$.

## Fronto-striatal rsFC and appetitive craving

cTBS strengthened rsFC between the rIFG pars opercularis and subcallosal cingulate (i.e., fronto-striatal circuit), and the magnitude of change in fronto-striatal rsFC was associated with reduced appetitive craving at 24 h post-treatment. These effects may be the result of rIFG cTBS remediating dysregulated top-down IC over appetitive craving elicited by the positively reinforcing effects of daily cigarette cue exposure (75). In studies among individuals that smoke cigarettes, BOLD activation in the subcallosal cingulate is associated with higher appetitive craving (76), whereas proactive downregulation of cigarette craving is associated with lower BOLD response in the subcallosal cingulate and higher BOLD response in the IFG (34), suggesting that these regions work together to regulate craving. Furthermore, an adult smoker's level of nicotine dependence has been shown to negatively correlate with IFG BOLD response during craving downregulation, suggesting that greater nicotine dependence is related to deficits in the capacity to regulate appetitive craving (36). Prior literature demonstrates that individuals with a SUD exhibit weaker fronto-striatal rsFC in comparison to controls (39, 42–46, 48, 77), and that fronto-striatal rsFC is negatively associated with addiction severity (43) and relapse vulnerability (39). Evidence also suggests that excessive glutamate in fronto-striatal circuitry contributes to maladaptive drug-seeking behavior (78). In theory, cTBS to the rIFG may modulate glutamatergic mediated fronto-striatal pathophysiology, improve glutamatergic tone, and help to restore regulatory control over motivationally relevant, yet maladaptive, cigarette cues. However, further research is needed to test this hypothesis.

## Fronto-limbic rsFC, withdrawal craving, and smoking

cTBS strengthened rsFC between the rIFG pars opercularis and posterior parahippocampal gyrus (i.e., fronto-limbic circuit), and the magnitude of change in fronto-limbic rsFC was associated with reductions in both withdrawal craving and smoking at 24 h post-treatment. In a similar line of reasoning as above, these effects may be the results of rIFG cTBS remediating top-down IC over withdrawal craving elicited by the negatively reinforcing emotional significance attributed to memories of past smoking episodes. It is well-known that the posterior parahippocampal gyrus is important for episodic memory (79), which includes memories of past drug use (80). Additionally, among smokers, smoking cues have been found to elicit increased BOLD response in both the parahippocampal gyrus and IFG (81). Prior literature demonstrates that among individuals with a SUD, fronto-limbic circuitry is weaker in comparison to non-SUD controls (39, 43, 45, 47, 49, 50, 77), and that weaker fronto-limbic rsFC is associated with addiction severity (50) and relapse vulnerability (39). Evidence also demonstrates that chronic drug use modifies circuitry underlying learning and memory (82). In theory, cTBS to the rIFG may treat dysregulated fronto-limbic circuitry function and improve regulatory control over the motivational significance attributed to recalling past smoking episodes. Future research that examines the effects of TBS on associative learning processes may shed light on how neuromodulation of fronto-limbic circuitry mediates learning, memory, and smoking.

## Brain-behavior associations

The observed associations between brain and behavioral outcomes following cTBS provide further support for the distinction of separate craving mechanisms in nicotine-dependent adults. To summarize, cTBS-induced strengthening of fronto-striatal rsFC was significantly associated with reduced appetitive craving, while strengthening of fronto-limbic rsFC was significantly associated with reduced withdrawal craving and smoking. These findings are consistent with the extant literature, suggesting that positive reinforcement components of craving are largely mediated by dysregulated fronto-striatal circuitry; whereas negative reinforcement components of craving are largely mediated by fronto-limbic circuitry (74, 75, 83). Moreover, the results from the current study demonstrating that rIFG cTBS modulates both circuits in a corresponding craving process-specific manner are intriguing and provide initial support for conducting a larger-scale sham-controlled study.

## Limitations

Despite numerous strengths of this study including a translational clinical neuroscience model-based approach, well-controlled design, and successful blind and remote assessments, there are notable limitations. First, the current study compared two active TBS treatments to a baseline session without a sham condition. Second, only one treatment session was administered per TBS protocol, thus limiting the ability to evaluate the durability of the observed outcomes. Third, the remote assessments relied strictly on self-report and did not include biochemical verification; however, participants were encouraged to report honestly and were informed they would be compensated for reporting, not for values reported. Fourth, the TBS treatments were delivered at 80% RMT, which is a relatively low dose. Future research following up on this report should consider addressing these limitations in order to further determine the mechanisms and potential value of rIFG cTBS for treating addiction pathophysiology. Additionally, future studies examining dose-response parameters may be warranted.

# Conclusion

Current study findings demonstrating that a single dose of rIFG cTBS at 80% RMT strengthens fronto-striatal-limbic rsFC and is associated with reductions in cravings, and smoking elucidates a neural circuit model that may be further examined for improving smoking cessation outcomes in adults with nicotine dependence. These findings are intriguing because the rIFG is a novel understudied cortical target in addiction therapy, an accessible cortical target for neuromodulation, and may have effects on dissociable neural pathways subserving response inhibition and incentive salience, which are two core neurocognitive deficits underlying addiction. Despite prior theoretical models of the

dissociable effects of cTBS and iTBS, the current study results bolster the rationale for further examination of the effects of repeated rIFG cTBS for treating addiction pathophysiology and promoting smoking cessation.

## 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 Institutional Review Board of the University of Missouri - Columbia. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

SU: conceptualization, data curation, formal analysis, investigation, methodology, visualization, writing—original draft, and writing—reviewing and editing. AB: data curation, visualization, and writing—reviewing and editing. MG: formal analysis and visualization. EG: writing—reviewing and editing. BF: conceptualization, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualization, writing—original draft, and responsible for securing funding. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

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

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1166912/full#supplementary-material

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# The oxytocin receptor rs2254298 polymorphism and alcohol withdrawal symptoms: a gene–environment interaction in mood disorders

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**Objective:** Alcohol use disorder (AUD) is a common mental disorder characterized by repeated withdrawal episodes. Negative emotions during withdrawal are the primary factors affecting successful abstinence. Oxytocin is a critical modulator of emotions. OXTR, the oxytocin receptor, may also be a promising candidate for treating alcohol withdrawal symptoms. Previous studies indicated that people with different genotypes of OXTR rs2254298 were reported to suffer from more significant depressive or heightened anxiety symptoms when experiencing early adversity. The present study aims to explore the modulatory role of the polymorphism OXTR rs2254298 on mood disorders during alcohol withdrawal and to help researchers better understand and develop effective relapse prevention and interventions for alcohol use disorders.

**Methods:** We recruited 265 adult Chinese Han men with AUD. Anxiety and depressive symptoms were measured using the Self-Rating Anxiety Scale and Self-Rating Depression Scale. Alcohol dependence levels were measured using Michigan Alcoholism Screening Test. Genomic DNA extraction and genotyping from participants' peripheral blood samples.

**Result:** First, a multiple linear regression was used to set the alcohol dependence level, OXTR.rs2254298, interaction terms as the primary predictor variable, and depression or anxiety as an outcome; age and educational years were covariates. There was a significant interaction between OXTR rs2254298 and alcohol dependence level on anxiety ($B = 0.23$, 95% confidence interval [CI]: 0.01–0.45) but not on depression ($B = -0.06$, 95% CI: −0.30 – 0.18). The significance region test showed that alcohol-dependent men who are GG homozygous were more likely to experience anxiety symptoms than subjects with the A allele (A allele: $\beta = 0.27$, $p < 0.001$; GG homozygote: $\beta = 0.50$, $p < 0.001$). Finally, re-parameterized regression analysis demonstrated that this gene–environment interaction of OXTR rs2254298 and alcohol dependence on anxiety fits the weak differential susceptibility model ($R^2 = 0.17$, $F$ (5,259) = 13.46, $p < 0.001$).

**Conclusion:** This study reveals a gene–environment interactive effect between OXTR rs2254298 and alcohol withdrawal on anxiety but not depression. From the perspective of gene–environment interactions, this interaction fits the differential susceptibility model; OXTR rs2254298 GG homozygote carriers are susceptible to the environment and are likely to experience anxiety symptoms of alcohol withdrawal.

KEYWORDS

**alcohol use disorder, alcohol withdrawal, mood disorders, single-nucleotide polymorphism, OXTR**

# 1. Introduction

China's alcohol market has grown rapidly over the past 30 years to become one of the world's largest, accompanied by significantly increased consumption (1). According to the World Health Organization, alcohol consumption leads to 3 million deaths each year globally and causes disabilities and poor health in millions of individuals. Excessive alcohol use accounts for 5.1% of the global disease burden (2). Alcohol use disorder (AUD) is the second most common mental disorder, following depression (3, 4). It is a maladaptive pattern of alcohol use characterized by repeated and heavy drinking, cognitive impairment, and a range of symptoms of alcohol withdrawal (5, 6). Alcohol withdrawal has a set of characteristic symptoms that occur when an alcohol-dependent person suddenly stops or reduces the use of alcohol; this behavior can trigger a stress response in the brain and lead to a sudden increase in anxiety and depression (7).

Withdrawal from chronic alcohol exposure is a potent stressor that can affect the functional integrity of the HPA axis and is strongly associated with mood disorders, which may lead to withdrawal failure and relapse into AUD (8–12). However, the literature on alcohol withdrawal suggests that not all individuals experience depression or anxiety in the context of alcohol withdrawal, which suggests a potential physiological mechanism that contributes to alleviate negative emotions during withdrawal and improve the success rate of alcohol abstinence (13). Genetic studies linked individual differences to specific allelic variants arising from single-nucleotide polymorphisms (14). However, single genetic polymorphisms do not act independently, but rather can interact with environmental factors on cognition, emotion, and behavior (14). Gene–environment (G × E) interactions are defined as different gene carriers' differential risk/susceptibility to environmental exposures. Current theoretical gene–environment interaction models include the diathesis-stress and differential susceptibility models. The diathesis-stress model assumes that individuals with risk genes are more likely to develop psychosocial problems in poor situations (15). Based on evolutionary theory, differential susceptibility models emphasize genetic susceptibility, with susceptibility gene carriers being more environmentally sensitive (15).

The oxytocin (OXT) system is a potential target for AUD treatment (16). OXT is a nonapeptide hormone initially known for its role in breastfeeding and childbirth (17). In recent years, the research focus on OXT shifted to regulating human social emotions and related behaviors (18). OXT can regulate several negative emotions and attention mechanisms, which is mediated by the oxytocin receptor (OXTR) expressed on the target neuronal cells (19). The OXTR is a peptide consisting of 389 amino acids located on the short arm of chromosome 3 with three introns and four exons (20). The OXTR gene was associated with social cognition and behavior in specific populations (21–23), particularly concerning its relationship to vulnerability and psychiatric disorder treatment (24). The literature suggests that polymorphic variation of the OXTR impacts human behavior and social cognition (25). During human evolution, comparative genetics suggest that mutations replace guanine (G) with adenine (A) (26). Rs2254298 is situated in the third intron of the OXTR gene, and this single-nucleotide polymorphism (SNP) of OXTR is associated with emotion (27). Girls with the rs2254298 AG genotype reported more significant depressive and heightened social and physical anxiety symptoms when experiencing early adversity (24). Incarcerated Chinese men with the GG genotype of OXTR rs2254298 had a higher vulnerability to the effect of childhood adversity on depressive symptoms. Recent studies showed that the genetic variant of OXTR rs2254298 influences the neurobiology of attention-deficit hyperactivity disorder and anxiety, leading to more significant functional, social, and emotional impairment (28). While these studies support OXTR genotypes conferring greater vulnerability for psychopathology in adverse environments, it is unclear whether genetic variants in OXTR moderate alcohol withdrawal-related anxiety and depression.

OXTR could be a candidate gene for modulating negative emotions during withdrawal. Genetic polymorphisms of OXTR could contribute modestly to individual differences during alcohol withdrawal. However, the interaction between alcohol withdrawal and the OXTR gene polymorphism on anxiety and depression remains unclear. Therefore, this study focused on the interactive effects of OXTR rs2254298 and alcohol withdrawal on depressive or anxiety symptoms, exploring protective genotypes/susceptibility genotypes.

# 2. Materials and methods

## 2.1. Participants

We recruited 265 Chinese Han men from several hospitals in northern China. The inclusion criteria for alcohol-dependent participants were as follows: (1) diagnosis of alcohol dependence by at least two trained psychiatrists based on DSM-IV; (2) sufficient literacy skills; (3) Han ethnicity. The exclusion criteria were as

follows: (1) history of other substance abuse or dependence (excluding nicotine); (2) cardiovascular, liver, or kidney disease; (3) participants or their first-degree relatives with a history of severe psychiatric disorders. The mental health status of all patients undergoing alcohol withdrawal have been evaluated by the experienced psychological counselor prior hospitalization and the subsequent mandatory 3-weeks detoxification. Thus, patients that have pre-existing major depression or anxiety disorders were excluded in the current study based on the evaluation conducted by the experienced psychological counselor. The Institutional Review Board of the Inner Mongolian Medical University approved the study. The participants undergone mandatory detoxification for at least 3 weeks and then were asked to complete a series of questionnaires and provide a blood sample, which was stored at −80°C for DNA extraction. All patients provided written informed consent and were told the blood sample would be subjected to a gene assay.

We considered utilizing continuous variables to quantify the educational levels, which were then applied as covariates in a linear regression analysis to gain a deeper insight into potential influences. We also supplemented the boundaries of high/middle/low education in the Chinese system with an academic years classification: ≤ 9 years as low education; 9 years < middle education ≤12 years; 12 years < high education. The average educational years of the participants in the study was 10.30 ± 2.82 years, with 111 (41.89%) having low educational levels (≤9 years), 105 (39.62%) having middle educational levels (>9 and ≤ 12 years), and 49 (18.49%) having high education levels (> 12 years).

## 2.2. Measures

### 2.2.1. Genotyping

Genomic DNA was extracted from 5 mL of peripheral blood from each participant using standard techniques. The OXTR rs2254298 SNP was genotyped using 5′ nuclease fluorescent TaqManTM primers (Applied Biosystems, Foster City, CA). Reactions were carried out according to the manufacturer's protocol. All laboratory procedures were carried out in a manner blind to case–control status. The conditions of PCR were as follows: 50°C for 2 min, 95°C for 10 min, followed by 50 cycles of 95°C for 15 s and 60°C for 1 min. Ten percent of the DNA samples were duplicated randomly and tested, and no-fault genotyping was found.

### 2.2.2. Alcohol dependence level

Alcohol dependence level was measured using the Michigan Alcoholism Screening Test (MAST) (29), a questionnaire containing a 25-item self-report in which respondents rate the severity of dependence-related alcohol use behaviors (30). The test uses a four-point scale from 1 (not at all) to 4 (very much). The scale has high internal consistency with a Cronbach's α of 0.90 (30).

### 2.2.3. Anxiety

Anxiety was measured by the Zung Anxiety Self-Assessment Scale (SAS), a 20-item scale that covers a wide range of anxiety symptoms, from mental to physical. The questionnaire uses a four-point Likert scale ranging from 1 (none or a small amount of the time) to 4 (most or all the time). Higher total scores indicate more severe anxiety symptoms. The SAS has satisfactory psychometric properties with a Cronbach's α of 0.82 (31).

### 2.2.4. Depression

Depression was measured using Zung Self-Rating Depression Scale (SDS), which contains 20 items. Each item is rated on a four-point Likert scale (from 1 = "rarely or none of the time" to 4 = "most or all of the time"). Higher total scores indicate more severe symptoms of depression. The SDS has internal consistency with a Cronbach's α of 0.79 (32).

## 2.3. Data analysis

All analyzes were performed using R software (R version 4.0.2). The $\chi^2$ test was used to determine whether the genotype distribution of OXTR rs2254298 followed Hardy–Weinberg equilibrium and assessed the association between OXTR rs2254298 polymorphisms and susceptibility to AUD. Pearson and Spearman's correlations were conducted to determine the associations among OXTR rs2254298, age, academic years, alcohol dependence level, anxiety, and depression.

Multiple linear regression was used as a preliminary exploration to test for significant gene–environment interactions (G × E). When significant interactions were found, we used region of significance (RoS) analysis to examine the forms of interaction effects. Based on the simple slope analyzes, this approach generates potential thresholds where the association between gene and alcohol dependence level is significant for estimating the forms of G × E interaction.

Finally, a re-parameterized regression model was used to test the pattern of G × E interaction as follows (15):

$$Y = \begin{Bmatrix} Group: D = 0B_0 + B_1(X - C)B_3X_2 + B_4X_3 + E \\ Group: D = 1B_0 + B_2(X - C)B_3X_2 + B_4X_3 + E \end{Bmatrix}$$

Where Y is the outcome variable of anxiety and depression (standard normalization), group is the OXTR polymorphism group, X is the MAST score (standard normalization), X2 and X3 are covariates (age and academic years), and C is the crossover point where the slopes of different genotypic subgroups cross. C and its 95% confidence interval were the initial criteria for judging the mode of interaction. If the point estimate and 95% confidence interval estimate fall at the maximum MAST score, the interaction fits the diathesis-stress model. Conversely, the forms of interaction fit the differential susceptibility model. To clarify the patterns of the interaction, the models were subdivided into a strong/weak differential susceptibility model and a strong/weak diathesis-stress model. Strong models assume that only individuals carrying the risk/plasticity allele are sensitive to the environment, and those carrying the non-risk/non-plasticity allele are unaffected by the environment. The weak version assumes that carriers of both alleles are sensitive to the environment; however, carriers of the risk/plasticity allele are more sensitive than those carrying the non-risk/non-plasticity allele. The F-test (for nested models), the Akaike information criterion, and the Bayesian information criterion (for non-nested models) were used to determine which model fits best.

# 3. Results

## 3.1. Descriptive statistics

Descriptive statistics of research variables are displayed in Table 1. This study included 265 participants with a mean age of 45.58 ± 9.20 years. Participants' mean education years was 10.30 ± 2.82 years; there were 111 (41.89%) low education (≤ 9 years), 105 (39.62%) middle education (>9 and ≤ 12 years), and 49 (18.49%) high education(>12 years).

The genotype frequencies for OXTR rs2254298 were AA: 8.7%, AG: 43.4%, and GG: 47.9%, indicating that OXTR rs2254298 accorded with Hardy–Weinberg equilibrium ($\chi^2 = 0.18$, $df = 2$, $p > 0.05$; Table 2). The minor allele frequency of this SNP was 30.3%, consistent with the HapMap and 1,000 genomes frequencies (0.30–0.34; Table 3). Participants were grouped as GG homozygote and A allele carriers according to their OXTR rs2254298 genotype (recode: A allele =0, GG homozygote = 1) (33, 34).

Table 4 displays correlations among research variables. OXTR rs2254298 was not significantly correlated with MAST, SAS, or SDS scores. The independent sample t-test showed no significant difference between genotypic groups in MAST, anxiety, or depression scores (MAST: $t = -0.60$, $p = 0.55$; Anxiety: $t = 0.43$, $p = 0.067$; Depression: $t = -1.30$, $p = 0.19$; Table 5). SAS and SDS scores were positively correlated with MAST scores ($r = 0.38$, $p < 0.001$; $r = 0.21$, $p < 0.001$).

TABLE 1 Descriptive statistics ($n = 265$).

| Variables | Mean ± SD |
|---|---|
| Age | 45.58 ± 9.20 |
| Education years | 10.30 ± 2.82 |
| Anxiety symptoms | 35.44 ± 8.86 |
| Depression symptoms | 56.98 ± 10.32 |
| MAST score | 10.71 ± 5.00 |

Alcohol dependence level is measured by Michigan Alcoholism Screening Test (MAST).

TABLE 2 Hardy–Weinberg equilibrium in participants.

| Genotype | Number of people | | Percentage |
|---|---|---|---|
| AA | 23 | | 8.7% |
| AG | 115 | | 43.4% |
| GG | 127 | | 47.9% |
| $\chi^2$ | 0.18 | $p$ | 0.67 |

TABLE 3 Genotype frequency of OXTR rs2254298 in different populations.

| | gnomAD | | | 1000Genomes | | |
|---|---|---|---|---|---|---|
| | AA | AG | GG | AA | AG | GG |
| European | 1.1% | 19.1% | 79.7% | 1.0% | 19.7% | 79.0% |
| American | 4.3% | 32.8% | 62.7% | 4.9% | 37.4% | 60.4% |
| East Asian | 9.4% | 42.5% | 48.2% | 11.6% | 44.9% | 43.4% |

## 3.2. The interactions of alcohol dependence level and OXTR rs2254298 for anxiety

Traditional hierarchical regression analysis was conducted to identify the interaction between OXTR rs2254298 and alcohol dependence level for anxiety symptoms. Alcohol dependence level significantly affected anxiety scores ($\beta = 0.38$, $p < 0.001$), such that a higher alcohol dependence level was associated with higher anxiety scores. There was no significant effect of OXTR rs2254298 on anxiety symptoms ($\beta = 0.04$, $p = 0.54$). In step 3, the interaction of alcohol dependence level and OXTR rs2254298 was included in the regression equation. The interaction of alcohol dependence level and OXTR rs2254298 accounted for a significant portion of the variance in anxiety symptoms ($\beta = 0.16$, $p < 0.05$; Table 6). For the interaction for anxiety, the partial correlation value of 0.13 and the semi-partial correlation value of 0.12 indicated that 1.4–1.7% of the variance in anxiety could be explained by alcohol dependence level × OXTR rs2254298 interaction.

The RoS test was performed to interpret the interaction effect. The simple slopes for alcohol dependence level on anxiety were: A allele carriers: $\beta = 0.27$, $t = 8.60$, $p < 0.001$; GG homozygote carriers, $\beta = 0.50$, $t = 10.72$, $p < 0.001$; Crossover point on predictor = − 0.30. The lower and upper bounds of regions of significance were − 0.60 and − 0.03, respectively, suggesting that GG homozygous subjects would be more likely to experience high anxiety symptoms than subjects with the A allele (Figure 1).

## 3.3. The interactions of alcohol dependence level and OXTR rs2254298 for depression

The same analysis was performed for depression symptoms (Table 7). Alcohol dependence level significantly affected depression scores ($\beta = 0.21$, $p < 0.001$), such that a higher alcohol dependence level indicates a higher level of depression symptoms. Similarly, OXTR rs2254298 was not significantly associated with depression symptoms directly ($\beta = -0.07$, $p = 0.23$). However, unlike the anxiety symptoms, alcohol dependence level and OXTR rs2254298 had non-significant interaction in depression symptoms ($\beta = -0.04$, $p = 0.16$). This exploratory analysis showed no significant interaction between alcohol dependence level and OXTR rs2254298, and thus depression symptoms were not considered in the subsequent analyzes.

## 3.4. Re-parameterized regression analysis

We performed a re-parameterized regression analysis to test a specific pattern of alcohol dependence level × OXTR rs2254298. The weak differential susceptibility (Model B) explained a significant amount of variance in anxiety ($R^2 = 0.17$, $p < 0.001$; Table 8). The crossover point C estimated = −0.30, where the slopes from alcohol dependence level to anxiety in the A allele group ($B_1 = 0.27$, $SE = 0.08$, $p < 0.001$) and GG homozygote group ($B_2 = 0.50$, $SE = 0.08$, $p < 0.001$) were significant. Based on Model B, constraining $B_1 = 0$ led to Model A (strong differential susceptibility); fixed C to the maximum of MAST scores led to Model C (strong diathesis-stress) and Model D (weak diathesis-stress). This study used the F-test with Akaike information criterion and Bayesian information criterion values for model comparison. Compared with Models A and D, Model B added one

TABLE 4 Descriptive statistics and correlations among study variables.

| | rs2254298 | Age | Education years | Alcohol dependence level | Anxiety symptoms | Depression symptoms |
|---|---|---|---|---|---|---|
| rs2254298 | 1 | | | | | |
| Age | 0.04 | 1 | | | | |
| Education Years | 0.01 | −0.30*** | 1 | | | |
| Alcohol dependence level | 0.01 | −0.01 | 0.06 | 1 | | |
| Anxiety symptoms | −0.03 | 0.09 | 0.04 | 0.38*** | 1 | |
| Depression symptoms | 0.08 | 0.05 | −0.01 | 0.21*** | 0.21*** | 1 |

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

TABLE 5 Independent sample test.

| rs2254298 polymorphism | Age | Education years | Alcohol dependence level | Anxiety symptoms | Depression symptoms |
|---|---|---|---|---|---|
| A allele | 45.44 (8.77) | 10.09 (2.88) | 10.54 (5.08) | 35.67 (8.11) | 56.19 (10.84) |
| GG homozygote | 45.73 (9.66) | 10.53 (2.75) | 10.91 (4.93) | 35.20 (9.63) | 57.84 (9.70) |
| *t* | −0.26 | −1.25 | −0.60 | 0.43 | −1.30 |
| *p* | 0.80 | 0.21 | 0.55 | 0.67 | 0.19 |

TABLE 6 Interaction between rs2254298 and alcohol dependence level on anxiety.

| | Variables | Anxiety symptoms | | | | | |
|---|---|---|---|---|---|---|---|
| | | $\Delta R^2$ | *B*(*SE*) | *β* | *t* | *p* | 95%CI |
| Step1 | Age | 0.01 | 0.01 (0.01) | 0.12 | 1.85 | 0.06 | [0.01, 0.03] |
| | Education years | | 0.03 (0.02) | 0.08 | 1.24 | 0.22 | [0.02, 0.07] |
| Step2 | Alcohol dependence level | 0.15 | 0.38 (0.06) | 0.38 | 6.65 | < 0.001 | [0.27, 0.49] |
| | rs2254298 | | 0.07 (0.11) | 0.04 | 0.61 | 0.54 | [0.16, 0.29] |
| Step3 | Alcohol dependence level× rs2254298 | 0.01 | 0.23 (0.11) | 0.16 | 2.03 | 0.04 | [0.01, 0.45] |

more parameter and explained more variance (Model A: $\Delta R^2 = 0.04$, $F = 10.39$, $p < 0.001$, Model D: $\Delta R^2 = 0.01$, $F = 3.67$, $p < 0.05$). Compared with Model C, Model B added two more parameters and explained more variance ($\Delta R^2 = 0.12$, $F = 32.93$, $p < 0.001$). All statistical indexes support Model B (i.e., weak differential susceptibility), in which the A allele was a non-plasticity allele, and the GG homozygote was a plasticity homozygote.

## 4. Discussion

Based on the framework of G × E research on the etiology of alcohol-related mood disorders, we investigated the interaction effect between OXTR rs2254298 and alcohol dependence level on mood disorders in Han Chinese men during alcohol withdrawal. The alcohol dependence level had a primary effect on anxiety and depression. OXTR rs2254298 and alcohol dependence level significantly affected anxiety symptoms that were not present in depression. The interaction pattern between OXTR rs2254298 and alcohol dependence level fits the weak differential susceptibility model. The GG homozygote was a plasticity homozygote, and the A allele was a non-plasticity allele, suggesting that GG homozygote carriers are susceptible to the environment and likely to experience anxiety symptoms in adverse environments.

Consistent with previous studies (35, 36), we found that anxiety and depression symptoms during withdrawal in AUD patients are highly correlated with alcohol dependence levels in withdrawal. There is an established relationship between alcohol and anxiety; high anxiety levels in AUD patients manifest during alcohol withdrawal (37–39). Acute alcohol drinking stimulates gamma-aminobutyric acid (GABA) receptors, dampening brain activity and reducing anxiety (40). However, chronic alcohol consumption can lead to tolerance to GABA-ergic effects, and adaptation puts the brain into a constant state of anxiety and depression (40, 41); regional changes in nicotinic receptor function in the nucleus accumbens and ventral tegmental area have also been reported (42). Such decreases in reward system function may persist in adverse long-term biochemical changes contributing to the clinical syndrome of acute withdrawal and prolonged abstinence (43, 44). In alignment with a previous study, we showed that as alcohol dependence increases, the severity of anxiety and depression symptoms would also increase during alcohol withdrawal.

Hierarchical multiple regression revealed that the OXTR rs2254298 gene polymorphism was not directly associated with

anxiety symptoms during withdrawal; however, the interaction between OXTR rs2254298 and alcohol dependence level had a significant effect on anxiety symptoms. The partial correlation value of 0.13 and half correlation value of 0.12 for the modulating effect of the OXTR SNP on anxiety that we reported can be considered small but meaningful effect sizes, with conversion calculations giving R2 of 0.017 and 0.014. According to Cohen (45), effect sizes R2 values of 0.01, 0.09 and 0.25 are considered small, medium and large, respectively. The R2 values in our study are 0.017 and 0.014, suggesting small but significant effects. Given that natural genetic variation typically exerts very subtle influences, these effect sizes are comparable to some previous single-locus investigations, suggesting similarly small but significant relationships. The RoS test and re-parameterized regression analysis indicated that the interaction of OXTR rs2254298 × current environment (alcohol dependence level) fits the weak differential susceptibility model. OXTR rs2254298 is associated with environmental sensitivity. GG homozygote is a plastic gene whose carriers are sensitive to environmental stress and more to anxiety symptoms in adverse environments.

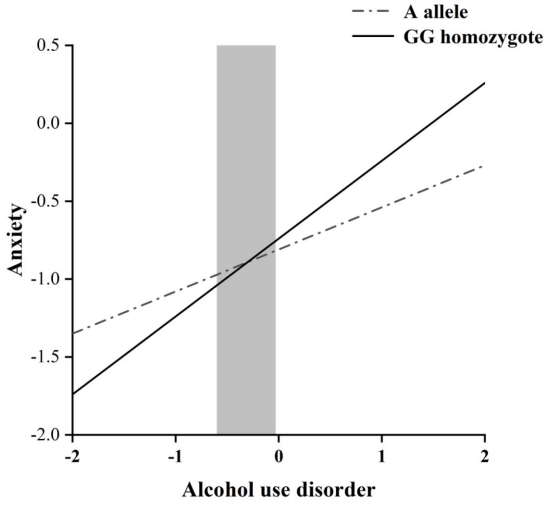


FIGURE 1
RoS test of the simple slopes on anxiety from alcohol dependence level in the OXTR rs2254298 allelic group. The gray shaded area represents the 95% confidence interval of the crossover point C of the interaction on the alcohol use disorder severity axis, 95% confidence interval of the crossover point C ranging from −0.60 to −0.03. Simple slope at A allele = 0.27, $t = 8.60$, $p < 0.001$. Simple slope at GG homozygote = 0.50, $t = 10.72$, $p < 0.001$.

OXT acts as an anxiolytic (44), and the OXTR is the cognate receptor for OXT (46). OXT is a stress hormone, and studies showed that stress induces an increase in oxytocin secretion (47–49). OXT is a neurotransmitter or neuromodulator with central actions in the limbic system, especially the amygdala, an essential structure in mood disorders (50). Slattery et al. reported modifications of neural activity induced by OXT in animal models of depression (51). Milrod et al. reported that altered plasma OXT levels are associated with more significant anxiety and relationship dissatisfaction in persons with separation anxiety disorder (52). Animal studies revealed that oxytocinergic circuits from the hypothalamus regulate GABA signaling, and decreased OXTR expression modulates presynaptic GABA release (53). These findings suggest that the OXTR modulates anxiety-related behaviors by affecting the excitability of branching GABA neurons. The OXTR participates in social processes and underlying traits of anxiety and depression, with little evidence for the effect of the OXTR SNPs in the etiology of clinical expressions of anxiety and depression. OXTR variation (rs53576) interacts with early threat exposure, with the threat-exposed rs53576 A allele demonstrating more significant emotion dysregulation (54). This finding suggests that OXTR SNP mutations are involved in emotion regulation.

We are also curious the reason why only association with anxiety rather than depression were found. Although anxiety and depression frequently co-occurring during withdrawal, these two kinds of mental disorders may be under distinct genetic control in some individuals. The oxytocin system specifically could have a stronger influence on withdrawal-related anxiety compared to depression. Oxytocin is strongly implicated in stress responses and modulation of the anxiety-mediating fight-or-flight sympathetic nervous system activation (55). As alcohol withdrawal represents a profound physiological stressor, OXTR genotypes that worsen oxytocin's regulation of stress reactivity could intensify withdrawal-related anxiety, reflecting the immediate effects of the three-week acute withdrawal period. However, depression is a long-term accumulation of negative emotions that develops over time and may be more associated with other chronic and enduring factors. Therefore, individuals in the acute phase of alcohol withdrawal are more likely to experience heightened anxiety symptoms rather than depressive symptoms.

Because the OXTR rs2254298 is an intronic SNP, the mechanism by which the plastic homozygote works remains poorly understood. Several studies attempted to determine how the rs2554298 genotype regulates psychiatric symptoms. Regarding physiological mechanisms, Smearman et al. reported that rs2254298 GG carriers have more significant methylation at

TABLE 7 Interaction between rs2254298 and alcohol dependence level on depression.

| | Variables | Depression symptoms | | | | | |
|---|---|---|---|---|---|---|---|
| | | $\Delta R^2$ | $B(SE)$ | $\beta$ | $t$ | $p$ | 95%CI |
| Step1 | Age | 0.001 | 0.005 (0.01) | 0.05 | 0.74 | 0.46 | [−0.01, 0.02] |
| | Education Years | | 0.001 (0.02) | 0.002 | 0.03 | 0.98 | [−0.04, 0.05] |
| Step2 | Alcohol dependence level | 0.05 | 0.21 (0.06) | 0.21 | 3.38 | < 0.001 | [0.08, 0.32] |
| | rs2254298 | | −0.14 (0.12) | −0.07 | −1.20 | 0.23 | [−0.38, 0.09] |
| Step3 | Alcohol dependence level× rs2254298 | 0.01 | −0.06 (0.12) | −0.04 | −0.52 | 0.61 | [−0.30, 0.18] |

TABLE 8 Results for re-parameterized regression model for anxiety.

| Parameter | Differential susceptibility | | Diathesis-stress | |
|---|---|---|---|---|
| | Strong model A | Weak model B | Strong model C | Weak model D |
| $B_0$ | −0.88 (0.43) | −0.89 (0.45) | 0.95 (0.44) | 1.60 (0.43) |
| $B_1$ | 0.00 (−-) | 0.27***(0.08) | 0.00 (−-) | 0.35 (0.06)*** |
| $C$ | −0.11 (0.23) | −0.30 (0.51) | 1.94(−-) | 1.94 (−-) |
| 95%CI of C | [−0.56, 0.34] | [−1.30, 0.70] | (−-) | (−-) |
| $B_2$ | 0.50 (0.08)*** | 0.50 (0.08)*** | 0.15 (0.04)** | 0.41 (0.06)*** |
| $B_3$ | 0.02 (0.02) | 0.02 (0.02) | 0.02 (0.02) | 0.02 (0.02) |
| $B_4$ | −0.01 (0.01)* | −0.01 (0.01) | −0.01 (0.01) | −0.01 (0.01) |
| $R^2$ | 0.13 | 0.17 | 0.05 | 0.16 |
| $F$ (df) | 9.90*** (4, 260) | 13.46*** (5, 259) | 4.27** (3, 261) | 12.16*** (4, 260) |
| $F$ vs. A(df) | (−-) | 10.39*** (2, 258) | 22.54*** (1, 259) | (−-) |
| $F$ vs. B(df) | 10.39*** (1, 258) | (−-) | 32.93** (2, 257) | 3.67* (1, 258) |
| AIC | 725.48 | 715.17 | 748.33 | 717.59 |
| BIC | 746.95 | 740.23 | 766.24 | 739.06 |

Anxiety = (OXTR. rs2254298 = AA/AG) [B0 + B1(XMAST-C)] + (OXT. rs2254298 = GG) [B0 + B2 (XMAST-C)] + B3Xage + B4Xeducational years; F versus stands for F tests of the difference in $R^2$ for a given model versus the robust differential susceptibility model; a parameter fixed at reported value; SE is not applicable, and is denoted as –.

the cg11589699 site than AA/AG carriers (56), inhibiting the OXTR expression and reducing OXT levels (57). Lower levels of OXT are associated with more significant anxiety due to dysregulation of the hypothalamic–pituitary axis (58). Moreover, rs2254298 GG carriers exhibit lower attachment security than those with the A allele (59). According to attachment theory, individuals with insecure attachment exhibit more internalizing problems, such as emotional symptoms, and externalizing problems, such as behavioral problems and attention deficits in stressful situations (60). Thus, higher OXTR methylation and less secure attachment styles might be how OXTR rs2254298 regulates alcohol dependence and anxiety during alcohol withdrawal.

There are some limitations in this study. First, because of the size of G × E and the small sample size (single gender composition), these results should be interpreted cautiously, validated in larger samples, and compared with others. Second, our study examined only one OXTR candidate polymorphism in cross-section, which can be investigated by gene set analysis or pathway analysis in longitudinal studies (61). Third, the data including anxiety measures were self-report scales, and self-reporting bias was unavoidable (62). Furthermore, a specific tool designed explicitly for assessing withdrawal symptoms was not employed in the current study. However, the MAST contains several key items that could also aid in assessment of withdrawal symptoms especially among acute alcohol withdrawal patients who have already undergone mandatory detoxification for at least 3 weeks. Finally, though the current study inquired rudimentary information on patients' smoking behavior (do you smoke; on average how many cigarettes do you smoke daily?). Specific assessment tools for smoking behavior should be employed to conduct in-depth to further investigate and distinguish possible effects of nicotine dependence and the role it plays in acute alcohol withdrawal and mood disorders.

Most previous studies focused on the interaction of individual early experiences with SNP (24). Our study investigated the interaction between OXTR rs2254298 and the current alcohol withdrawal environment on anxiety symptoms, providing evidence for the weak differential susceptibility model. Our findings help to elucidate the genetic basis for individual differences in negative emotions during alcohol withdrawal among alcohol-dependent patients. It is recommended that the proposed physiological and psychological mechanisms be validated in future studies.

## 5. Conclusion

The level of alcohol dependence correlates with anxiety risk in AUD patients, which may vary by OXTR genotypes. Specifically, rs2254298 GG carriers with AUD may have higher OXTR methylation, lower OXT levels, less secure attachment, and higher anxiety levels during alcohol withdrawal. These findings suggest that treatment for AUD patients with anxiety would be more effective when combined with pharmacological and psychological therapy (63), especially for the OXTR rs2254298 GG carriers with higher plasticity in the effect of the current environment.

## Data availability statement

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

## Ethics statement

The studies involving human participants were reviewed and approved by Peking University Health Science Center. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the

individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

YL, FaW, and LC designed the study. GS, FaW, SY, and FeW contributed to data acquisition. GS, FaW, SY, and LW drafted the manuscript. GS, FeW, SY, LW, YC, YH, FZ, WW, PL, and LC participated in data analysis and interpretation. All authors read and approved the final manuscript.

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## Conflict of interest

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

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# Preliminary evidence for changes in frontoparietal network connectivity in the early abstinence period in alcohol use disorder: a longitudinal resting-state functional magnetic resonance imaging study

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The early abstinence period is a crucial phase in alcohol use disorder (AUD) in which patients have to find a new equilibrium and may start recovery, or conversely, relapse. However, the changes in brain functions during this key period are still largely unknown. We set out to study longitudinal changes in large-scale brain networks during the early abstinence period using resting-state scans. We scanned AUD patients twice in a well-controlled inpatient setting, with the first scan taking place shortly after admission and the second scan 4 weeks (±9 days) later near the end of the treatment period. We studied 37 AUD patients (22 males) and 27 healthy controls (16 males). We focused on three networks that are affected in AUD and underly core symptom dimensions in this disorder: the frontoparietal networks (left and right FPN) and default mode network (DMN). Both the whole brain and within network connectivity of these networks were studied using dual regression. Finally, we explored correlations between these brain networks and various neuropsychological and behavioral measures. In contrast to the controls ($Z = -1.081$, $p = 0.280$), the AUD patients showed a decrease in within left FPN connectivity ($Z = -2.029$, $p = 0.042$). However, these results did not survive a strict Bonferroni correction. The decrease in left FPN connectivity during the early abstinence period in AUD may reflect an initially upregulated FPN, which recovers to a lower resting-state connectivity level during subsequent weeks of abstinence. The AUD patients showed a trend for a positive association between the change in left FPN connectivity and trait anxiety ($r_s = 0.303$, $p = 0.068$), and a trend for a negative association between the change in left FPN connectivity and delay discounting ($r_s = -0.283$, $p = 0.089$) (uncorrected for multiple comparisons). This suggests that the FPN might be involved in top-down control of impulsivity and anxiety, which are important risk factors for relapse. Although there were no statistically significant results (after multiple comparison correction), our preliminary findings encourage further research into the dynamic neuroadaptations during the clinically crucial early abstinence period and could inform future study designs.

KEYWORDS
fMRI, addiction, alcohol use disorder, resting-state connectivity, recovery

# 1. Introduction

Alcohol use disorder (AUD) is characterized by dysregulation across various neurobiological and neuropsychological domains (1–4). Although empirical studies suggest that both neurobiological and behavioral measures improve substantially after stopping alcohol use, the trajectories over which recovery takes place are still poorly understood (1). While drinking leads to adaptations to alcohol in AUD, a new equilibrium has to be found after stopping drinking (2, 5, 6). The initial weeks of abstinence mark a crucial period in which dynamic adaptations may help to start and subsequently sustain recovery, while failure to adapt may presage relapse (1). The importance of the early abstinence period is highlighted by studies showing that AUD patients are most likely to relapse in the first weeks following attempted abstinence (7, 8). Despite the importance of this early abstinence period, it is still largely unknown how brain function changes during this phase.

Functional brain networks can be identified *via* detection of patterns of synchronized activity between distributed brain regions (9), and have emerged as fundamental, dynamically organized elements of human brain function (10, 11). The frontoparietal networks (left and right FPN) are among the most investigated networks in addiction and are involved in higher-order cognitive processes and top-down cognitive control functions, including inhibition, emotion regulation, working memory, and cognitive flexibility (12–15). In addition, there is mounting evidence for the critical role of the default mode network (DMN) in addiction disorders (4). The DMN facilitates spontaneous and self-referential thought (16). Aberrant patterns in functional connectivity of the DMN have been observed across AUD and other substance use disorders and have been associated with impaired self-awareness, negative emotions, rumination, and craving (4).

Resting-state studies have shown that AUD is characterized by aberrant connectivity patterns of the FPN (17–19) and DMN (4). There is extensive evidence for differences in resting-state connectivity of the FPN between AUD patients and healthy individuals (14, 18, 20, 21). Several studies have shown increased resting-state connectivity of the FPN in abstinent AUD patients compared to healthy individuals, which is often interpreted as compensatory upregulation of the FPN for top-down control (14, 18, 20). In addition, various studies have found differences in DMN connectivity between abstinent AUD patients and healthy individuals (4, 17, 21–23), with among others reduced connectivity between the anterior and posterior DMN in AUD (21). Interestingly, a recent longitudinal resting-state study showed changes in network organization (including core regions of the DMN and FPN) in the period from one month abstinence to three month later, which were related to patterns in abstinence and relapse during this three month follow-up period (24). Although these various studies have significantly contributed to a better understanding of the neural mechanisms of AUD, relatively few studies focus on the first weeks of abstinence. Additionally, the overwhelming majority of the studies are cross-sectional, highlighting the need for more longitudinal studies.

In the studies that have been performed in the early abstinence period, differences have been found between AUD patients and healthy controls for both FPN and DMN connectivity (23, 25). In their cross-sectional study, Zhu and colleagues (23) showed increased connectivity within the FPN in AUD patients in the early abstinence period compared to the controls. When Zhu and colleagues analyzed the anterior DMN and posterior DMN separately they found increased within network connectivity in both these DMN subsystems (23). While there are no studies investigating changes in functional connectivity longitudinally during early abstinence, there are various longitudinal studies investigating changes in brain structure [e.g. (26–29)]. These studies have shown substantial recovery during the early abstinence period (26), with changes in both grey matter (26, 29) and white matter tracts during this phase (27, 28). Longitudinal studies of changes in functional network connectivity in the early abstinence phase can help to better characterize this dynamic and clinically critical period in which patients must cope with the challenges of finding a new equilibrium and staying abstinent (7, 8).

In this study, we set out to investigate the early abstinence period in moderately to severely ill AUD inpatients, from a large-scale functional network perspective, with a focus on the DMN and FPN. A better understanding of the mechanisms underlying the early recovery from AUD may ultimately help to identify biomarkers that may serve as targets for personalized treatments in the future, with the FPN for example being an important target for non-invasive neurostimulation treatments, like repetitive transcranial magnetic stimulation (rTMS) (4, 30, 31). Our main aim was to investigate changes in the connectivity of our networks of interest in AUD patients during this early abstinence period. Within this setup, we primarily focused on the changes within the networks of interest and expanded this to changes in connectivity patterns of these networks across the entire brain. We hypothesized that the AUD group would show an increase in within FPN connectivity during the early abstinence period (to support top-down control) (14, 18, 20), and an increase in within DMN connectivity, reflecting recovery toward more integrative functioning of the DMN (between, among others, the anterior and posterior DMN) (4, 21). Finally, we performed exploratory correlations to investigate how changes in connectivity are associated with various neuropsychological and behavioral measures related to alcohol use, executive functioning, impulsivity, and anxiety.

# 2. Methods and materials

## 2.1. Participants

The present study was conducted at the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Participants in the Alcohol Use Disorder (AUD) group were adult individuals partaking in NIAAA's inpatient treatment program at the National Institute of

Health (NIH) Clinical Center (Bethesda, Maryland) between 2016 and 2018. Patients underwent alcohol detoxification if necessary. All AUD patients and controls were studied within the framework of a Natural History Protocol such that common data elements such as Structured Clinical Interviews for DSM (SCIDs) were collected. Healthy control participants were enrolled through the NIAAA Outpatient Clinic at the NIH Clinical Center in the same time frame. Unlike the AUD inpatients, control participants were not admitted to the inpatient ward during the study period. The human research protocols were approved by the NIH Institutional Review Board and all participants signed informed consent before participation.

Demographic and clinical characteristics [i.e., age, sex, years of education, race, and smoking status (32)] were collected. All participants were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) (33). Since the present study took place during the transition period from DSM-IV to DSM-5 psychiatric diagnoses were made *via* either the Structured Clinical Interview for DSM-IV (SCID-IV-CT) (34) or the Structured Clinical Interview for DSM-5 Disorders (SCID-5-RV) (35). All AUD participants met criteria for either alcohol dependence (DSM-IV) or moderate-to-severe AUD (DSM-5) (36). A control group was included that was matched with the AUD group on age and sex.

All participants were between 30 and 60 years old and physically healthy. Patients were only included if they no longer experienced active withdrawal symptoms as determined by the Clinical Institute Withdrawal Assessment score (CIWA $\leq$8) (37). Exclusion criteria were: a history of neurological disorders of the central nervous system, cranial surgery, diabetes, history of significant head trauma, clinical or laboratory evidence of severe hepatic disease (i.e., ALT or AST > 5 times the upper normal level, INR > 2.0, total bilirubin >2.5 mg/dL, albumin <3.0 g/dL), a positive HIV test, current pregnancy (for women), contraindications related to the MRI scan (e.g., related to nonremovable ferrous metal in the body and claustrophobia), or positive breath alcohol test or urine drug test on the day of the MRI scan (except for benzodiazepines in the patients, as these are used to treat alcohol withdrawal during detoxification and might still show up in the urinary drug screen). Except for two patients, who still had positive urine tests for benzodiazepines at timepoint 1, all other urine tests were negative. The following additional exclusion criteria were used for the control group: a diagnosis of alcohol abuse or dependence (DSM-IV), AUD (DSM-5) or any other current DSM-IV or DSM 5 diagnosis *via* the SCID, use of any psychotropic medication on the day of scanning, more than seven standard drinks/week for females or fourteen standard drinks/week for males, and five or more binge drinking episodes (i.e., for males $\geq$5 standard drinks and for females $\geq$4 standard drinks on one occasion within 2 h) in the past 30 days (NB: while this allowed for binge drinking episodes in the controls, none of the included controls had any binge drinking episodes during this period).

## 2.2. Procedure

All participants were scanned twice to measure functional connectivity. The AUD patients were first scanned at treatment entry, within the first seven days of their admission to the treatment program and subsequent to acute withdrawal (Timepoint 1). The second scan (Timepoint 2) took place at the end of the inpatient treatment program (4 weeks ±9 days later). The control participants were also scanned twice, with a same interval between the two scans as for the patients. Abstinence in the AUD participants was ensured during the stay on the inpatient unit by regular monitoring including breath alcohol tests at least three times a day in the context of their treatment. The NIAAA's treatment program for the AUD patients included group and individual therapy and pharmacological interventions when appropriate.

The complete magnetic resonance imaging (MRI) session consisted of multiple scans, of which we used the T1 structural and resting-state scan for the present study. The T1 structural scan was the first scan in the protocol and the resting-state scan the second scan. During acquisition of the resting-state data participants were instructed to lie still with their eyes open. Participants were instructed not to think about anything in particular. An MRI compatible eye-tracking device using infrared light was used to monitor whether the participants stayed awake during the resting-state scan.

## 2.3. fMRI data acquisition

All images were collected using a 3 Tesla MRI scanner (Siemens Magnetom Prisma) with a 32-channel head coil. T2*-weighted EPI BOLD-fMRI images were acquired for the resting-state scans, using an interleaved slice acquisition sequence (number of volumes: 315, number of slices = 36, TR = 2,000 ms, TE = 30 ms, flip angle = $90^0$, voxel size = 3.8 mm isotropic, slice gap = 0 mm, FOV = 240 mm, GRAPPA acceleration factor 2). High-resolution structural images (1.0 mm isotropic) were acquired using a T1-weighted MP-RAGE sequence (TE/TR = 1.63/2460 ms, flip angle = $5^0$, FOV = 288 × 288 × 208 mm, GRAPPA acceleration factor 2).

## 2.4. fMRI preprocessing

Preprocessing and statistical analyses were performed using FSL 6.0.5.2 (FMRIB, Oxford, UK). The resting-state scans were preprocessed using the FMRI Expert Analysis Tool (FEAT), which is part of the FMRIB Software Library (FSL) (38). To allow for T2* equilibration effects, the first five images of each resting-state scan were discarded. Furthermore, the preprocessing steps included brain extraction, motion correction, bias field correction, high-pass temporal filtering with a cut-off of 100 s, spatial smoothing with a 4 mm full width at half maximum (FWHM) Gaussian kernel, registration of functional images to high-resolution T1 using boundary-based registration and nonlinear registration to standard space (MNI152). We used ICA-based Advanced Removal of Motion Artifacts (ICA-AROMA) for further single-subject denoising (39). Participants were excluded from analyses if motion resulted in more than 3.8 mm (1 voxel) sudden relative mean displacement or translation.

## 2.5. fMRI analyses

We investigated for both the AUD and control group whether there were any changes in connectivity between timepoint 1 and 2. Furthermore, we investigated if there were any differences between the

two groups related to the changes in connectivity between these two time points. Connectivity changes for the networks of interest (i.e., DMN, right FPN and left FPN) were studied at two levels: (1) whole brain connectivity and (2) within network connectivity.

We used the well described network templates that were identified by Smith and colleagues (2009) (10) to study the connectivity of our networks of interest (see Supplementary Figure S1 for the spatial maps of these networks). Smith and colleagues (10) identified these network templates by performing independent component analysis (ICA). ICA is a powerful data-driven approach that can decompose an fMRI dataset into temporally coherent, spatially independent components, which correspond to major functional brain networks (11).

### 2.5.1. Whole brain functional connectivity

The whole brain connectivity of our networks of interest, reflecting the connectivity of these networks with themselves and the rest of the brain, was investigated using dual regression. We applied the unthresholded group ICA maps of all 20 components from Smith and colleagues 2009 as spatial maps into dual regression (10). Dual regression uses these spatial maps as input to generate subject-wise time courses for these networks by correlating the mean time course of each network with all the voxels of the brain. Regression of these time courses against the data resulted in spatial maps of the 20 networks for each individual participant (40). Afterwards, we selected the spatial maps for our three networks of interest (i.e., the DMN, left FPN, and right FPN).

The spatial maps resulting from dual regression were subtracted (timepoint 2 minus timepoint 1) to investigate the effects of time and the differences between the AUD and control group. We used permutation tests via randomize (10,000 permutations) for inference testing (41). The results from these tests were considered significant using a threshold-free cluster enhancement corrected value of $p$ of 0.05 (42) and a minimum cluster size of 5 voxels.

### 2.5.2. Within network functional connectivity

For the within network connectivity analyses we generated a mask for the networks of interest by thresholding ($Z \geq 3$) the statistical maps of each network [selected from the Smith and colleagues' templates (10)]. These masks were used to extract the mean within network connectivity in both resting-state scans (i.e., timepoint 1 and 2), from the individual spatial maps generated in the dual regression procedure. This approach results in one value per participant and network, which represents an aggregate measure of mean within network connectivity. The effect of time (abstinence in the patient group) was investigated with a paired comparison between the connectivity strength between timepoint 1 and timepoint 2, using a Wilcoxon signed-rank test (we used this non-parametric test as the data (for AUD patients and controls) was not normally distributed). The differences between the controls and AUD group were calculated using the Mann–Whitney U test (non-normal distribution) on the difference scores (timepoint 2 minus 1) (alpha = 0.05).

## 2.6. Measures of interest

Various measures were collected for exploratory correlational analyses (see "2.7 Statistical analysis" below). On the days of the MRI scans (i.e., timepoint 1 and 2), we collected measures for 'working memory' [maximum number of reproduced digits on the Letter-number sequencing task (43)], and cognitive flexibility [sum scores for perseverative responses and perseverative errors on the Wisconsin Card Sorting Test (44, 45)]. We included these measures for executive functioning, as there are clear indications for impairments in these functions in AUD, and that these impairments may be related to treatment compliance and everyday functioning (46, 47). Furthermore, during the first week of admission, we collected measures related to trait anxiety, impulsivity, and alcohol use. Trait anxiety was measured with the Spielberger State–Trait Anxiety Inventory-Y2 (STAI-Y2) (48, 49), and (choice) impulsivity with the delay discounting task (50). These measures were included, since studies have shown increased levels of trait anxiety (51, 52) and impulsivity (53, 54) in AUD, which are clinically relevant and may be predictive of relapse (53–55). Alcohol use was quantitated *via* the sum score on the Alcohol Use Disorder Identification Test (AUDIT) (56), and the number of standard drinks in the 30 days preceding admission [measured with the Alcohol Timeline Followback (57)]. Finally, we used the Lifetime Drinking History (LDH) to measure the total number of lifetime drinks, age of first drink, and heavy drinking years [periods of time in which individuals drank >6 standard drinks/day (in accordance with the LDH Manual)] (58). Importantly, the FPN and DMN have been implicated in abovementioned functions and measures related to executive functioning, trait anxiety, impulsivity, and the severity of alcohol use/AUD (3, 4, 12–15, 53, 59–62).

## 2.7. Statistical analysis

Exploratory correlational analyses were performed between any observed significant change in within network connectivity strength and the measures of interest described above. We performed Spearman correlations (non-normal distribution) in both the AUD and control groups separately (alpha = 0.05). Correlation coefficients were compared between AUD patients and controls by comparing the standardized correlation coefficients (Fisher's r to z transform), using an ANOVA for summary data (alpha = 0.05). For the Wisconsin Card Sorting Test and Letter-number sequencing task we correlated the change in performance on these tasks with the change in network connectivity strength. For all these correlations, we performed supplemental partial correlations (controlling for years of education), in order to investigate if this affected the comparison between the AUD and control group [as these groups differed with respect to the years of education (see Results)].

In addition to the correlational analyses described above, we performed for both the Wisconsin Card Sorting Test and Letter-number sequencing task correlations between scores on these tasks at the day of scanning and the network connectivity strength at the same day separately, as a supplemental analysis. These analyses were performed separately, since the change score on these tasks may be more difficult to interpret, as a change in these scores may result from a combination of recovery related to the early abstinence period and the learning effect by performing the same task twice.

We tested for differences between the AUD and control group for the measures of interest described above (a repeated measures ANOVA for the Wisconsin card sorting test and Letter-number sequencing task, and a $t$-test or Mann–Whitney U test for the other measures). Finally,

for the resting state scans Mann–Whitney U tests (non-normal distribution) were performed to test for potential differences in movement between the patient and control group (mean relative and absolute framewise displacement between successive images).

Finally, we would like to note that corrections for multiple comparisons were not primarily performed for either the fMRI analyses or the correlational analyses. We chose this exploratory set up as still little is known about the changes in functional connectivity in the early abstinence period in AUD, and how these potentially relate to neuropsychological and behavioral measures. When interpreting the results, it is important to keep in mind the more exploratory nature of these analyses. Finally, in case of significant fMRI or correlational results, we do also provide the Bonferroni corrected results in order to give more insight into the strength of these findings.

# 3. Results

## 3.1. Participants

In the present study we included 44 AUD patients, of which seven patients were excluded from the final analysis, because of too much movement ($n = 6$) or the resting-state scan not being available for both timepoints ($n = 1$). Of the 37 included AUD patients 22 were males. 27 healthy control participants (16 males) were included, that were matched with the patients with respect to age ($U = 459.0$, $p = 0.581$) and sex ($\chi^2 = 0.00$, $p = 0.987$). Patients and controls differed in years of education ($U = 174.0$, $p < 0.001$) (Table 1). All patients had current alcohol dependence according to the DSM-IV ($n = 16$) or alcohol use disorder according to DSM-5 ($n = 21$). Five (13.5%) of the AUD patients had one or more comorbid substance use disorder(s), with cannabis use disorder being the most prevalent comorbid substance use disorder [$n = 4$ (10.8%)]. Eighteen (48.6%) of the AUD patients had a comorbid psychiatric disorder other than a substance use disorder (with five patients (13.5%) having comorbid major depressive disorder and four (10.8%) an alcohol induced mood/depressive disorder; see Table 2 for an overview of all comorbid diagnoses).

As the AUD participants were participating in a treatment program, pharmacological interventions were started when appropriate. While none of the patients received pharmacotherapy for AUD at timepoint 1, at timepoint 2 eleven participants were treated with naltrexone and one with acamprosate. In addition, while only three patients received antidepressants at timepoint 1, thirteen patients received antidepressants at timepoint 2 (see Supplementary Table A for a more complete medication overview).

## 3.2. Behavioral results

The AUD patients showed higher trait anxiety levels than the controls ($U = 34.0$, $p < 0.001$) (Table 1; Supplementary Figure S2). In addition, the AUD patients showed a trend for a steeper delayed reward discounting compared to controls ($U = 363.5$, $p = 0.098$) (Table 1; Supplementary Figure S3), indicating a trend for a preference for smaller, immediate rewards over larger, delayed rewards.

## 3.3. Functional MRI

### 3.3.1. Movement

There were no significant differences in movement between the AUD and control group with respect to the mean absolute (Timepoint 1: $U = 411.0$, $p = 0.229$, Timepoint 2: $U = 438.0$, $p = 0.403$) or relative framewise displacement (Timepoint 1: $U = 393.0$, $p = 0.148$, Timepoint 2: $U = 392.0$, $p = 0.144$) (Supplementary Table B).

### 3.3.2. Default mode network

Neither the AUD patients ($Z = -0.309$, $p = 0.757$) nor the controls ($Z = -0.336$, $p = 0.737$) showed a significant change in within DMN connectivity between timepoint 1 and 2. There was also no difference between the patients and controls in the change in within DMN connectivity ($U = 466$, $p = 0.649$). Finally, the whole brain analysis did not show any significant results related to the change in DMN connectivity.

### 3.3.3. Frontoparietal networks

While there were no significant results for the right FPN (AUD patients: $Z = -0.249$, $p = 0.803$, controls: $Z = -0.745$, $p = 0.456$, difference between AUD patients and controls: $U = 457$, $p = 0.563$), there were several significant results for the left FPN. The patients showed a decrease in left FPN connectivity strength at timepoint 2 compared to timepoint 1 ($Z = -2.029$, $p = 0.042$). Although the controls did not show a significant change in within left FPN connectivity ($Z = -1.081$, $p = 0.280$), the change in the left FPN connectivity in the patient group did differ significantly from the controls ($U = 352$, $p = 0.045$) (Figure 1; Supplementary Figure S4). *Post-hoc* tests showed that the within left FPN connectivity did not significantly differ between the patients and controls at time point 1 ($U = 455$, $p = 0.545$), or timepoint 2 ($U = 380$, $p = 0.104$) separately (Supplementary Figure S5). When Bonferroni correction was performed for multiple comparisons (i.e., value of *p*s multiplied by three, for the three networks that were investigated), the decrease in within left FPN connectivity in the AUD group (Bonferroni corrected value of $p = 0.126$) and the difference between the AUD and control group (Bonferroni corrected value of $p = 0.135$) were no longer significant.

The whole brain analyses revealed a decrease in left FPN connectivity in AUD patients at timepoint 2 compared to timepoint 1. The result confirmed the decrease in within left FPN connectivity, by revealing that all significant clusters were located within the left FPN template, with significant clusters located in the middle frontal gyrus, posterior parietal cortex and posterior cingulate cortex (Figure 2; Supplementary Table C). None of these clusters survived Bonferroni correction for the three networks that were being studied (Supplementary Table C). The controls did not show any significant changes in whole brain left FPN connectivity over time, nor were there differences between the patients and controls.

## 3.4. Correlational analyses

Table 3 shows the correlations between the change in within left FPN connectivity and measures of interest. Although there were no

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TABLE 1 Demographics and clinical characteristics.

| | Controls ($n = 27$) | AUD patients ($n = 37$) | Comparison between controls and AUD patients ($F/\chi^2/t/U$), Value of $p$ |
|---|---|---|---|
| **Demographics and general information** | | | |
| Age (years), median (range) | 47 (33–59) | 47 (30–58) | $U = 459.0$, $p = 0.581$ |
| Sex, %male (M/F) | 59.3% (16/11) | 59.5% (22/15) | $\chi^2 = 0.00$, $p = 0.987$ |
| Years of education, median (range) | 16 (12–26) | 13 (4–18) | $U = 174.0$, $p < 0.001$** |
| Smokers (%) | 0 | 51.4 | $\chi^2 = 19.72$, $p < 0.001$** |
| **Race** | | | |
| Asian | 0 | 2 | $\chi^2 = 3.40$, $p = 0.493$ |
| Black/African American | 9 | 14 | |
| Multiracial | 2 | 4 | |
| White | 15 | 17 | |
| Unknown | 1 | 0 | |
| Time difference between scan 1 and 2 (days), median (range) | 27 (21–35) | 22 (19–31) | $U = 277.0$, $p = 0.002$** |
| Days between admission date and first scan, median (range) | N/A | 6 (2–7) | - |
| **Alcohol related measures** | | | |
| Age of first drink, mean (SD) | 16.19 (3.77) | 14.63 (3.77) | $t = 1.60$, $p = 0.114$ |
| Heavy drinking years, median (range) | 0 (0–4) | 13 (0–33) | $U = 15.0$, $p < 0.001$** |
| AUDIT sum score, median (range) | 2 (0–6) | 29 (15–38) | $U = 0.0$, $p < 0.001$** |
| Number of drinks in the 30 days preceding admission, median (range) | 3 (0–24) | 335 (45–1,100) | $U = 0.0$, $p < 0.001$** |
| Days since last drink (before first scan), median (range) | - | 6 (2–12) | - |
| **Other measures of interest** | | | |
| Wisconsin card sorting test (mean, SD) | | | |
| Total number perseverative responses T1 | 15.07 (27.07) | 20.54 (15.44) | Time effect: $F(1,61) = 9.62$, $p = 0.003$** Group effect: $F(1,61) = 0.98$, $p = 0.327$ Time by group interaction: $F(1,61) = 0.10$, $p = 0.753$ |
| Total number perseverative responses T2 | 10.77 (17.71) | 14.78 (16.14) | |
| Total number perseverative errors T1 | 12.70 (19.99) | 18.68 (13.13) | Time effect: $F(1,61) = 10.81$, $p = 0.002$** Group effect: $F(1,61) = 1.85$, $p = 0.179$ Time by group interaction: $F(1,61) = 0.35$, $p = 0.559$ |
| Total number perseverative errors T2 | 9.31 (13.25) | 13.38 (13.48) | |
| Letter-number sequencing (mean, SD) | | | |
| Maximum number reproduced digits T1 | 7.93 (1.24) | 7.30 (0.97) | Time effect: $F(1,61) = 1.08$, $p = 0.302$ Group effect: $F(1,61) = 3.93$, $p = 0.052$ Time by group interaction: $F(1,61) = 0.50$, $p = 0.482$ |
| Maximum number reproduced digits T2 | 7.96 (1.26) | 7.53 (1.03) | |
| Trait anxiety (STAI-Y2) (median, range) | 26 (20–38) | 49 (26–69) | $U = 34.0$, $p < 0.001$** |
| Delay discounting (ln k value) (median, range)[¥] | −5.13 (−6.32 – −0.13) | −4.02 (−8.52 – −0.45) | $U = 363.5$, $p = 0.098$ |

[¥]In delay discounting the factor $k$ represents the rate of discounting of the delayed outcome. As $k$ values are not normally distributed, a natural log-transformation is applied, and the $ln(k)$ values are displayed in this table. Higher $ln(k)$ values (i.e., less negative values) mean greater preference for immediate rewards. AUD, alcohol use disorder; AUDIT, Alcohol Use Disorder Identification Test; F, female; M, male; SD, standard deviation; STAI-Y2, Spielberger State–Trait Anxiety Inventory-Y2; $\chi^2$, Pearson's chi square (2-tailed); $t$, independent $t$-test (2-tailed); $U$, Mann–Whitney-U test (2-tailed). *$p < 0.05$, **$p < 0.01$.

significant correlations, the AUD patients showed trends for associations of the change in left FPN connectivity with trait anxiety and delay discounting. The AUD patients showed a trend for a positive association between the decrease in left FPN connectivity and trait anxiety ($r_s = 0.303$, $p = 0.068$), indicating that lower trait anxiety was associated with a larger change (larger decrease from timepoint 1 to timepoint 2) in left FPN connectivity. In addition, the AUD patients showed a trend for a negative association between the decrease in left FPN connectivity and delay discounting ($r_s = -0.283$, $p = 0.089$), meaning that higher (i.e., less negative) discounting scores (indicating a greater preference for immediate rewards) are associated with a larger decrease in left FPN connectivity. These patterns did not differ between the patients and controls (trait anxiety: $F(1,63) = 1.149$, $p = 0.288$; delay discounting: $F(1,62) = 0.507$, $p = 0.479$) (Table 3). Our

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TABLE 2 Current psychiatric disorders according to the SCID-IV/SCID-5 interviews in the AUD patients.

| Current diagnosis | Number of patients with this disorder in the AUD group ($n = 37$) |
|---|---|
| **Current substance use disorders, *N* (%)** | |
| Cannabis use disorder | 4 (10.8%) |
| Cocaine/stimulant use disorder | 2 (5.4%) |
| Opioid use disorder | 0 (0%) |
| Sedative/hypnotic/anxiolytic use disorder | 1 (2.7%) |
| Hallucinogen use disorder | 0 (0%) |
| Other substance use disorder | 0 (0%) |
| **Mood/depressive disorders, *N* (%)** | |
| Major depressive disorder | 5 (13.5%) |
| Dysthymic/persistent depressive disorder | 1 (2.7%) |
| Alcohol induced mood/depressive disorder | 4 (10.8%) |
| Bipolar disorder | 2 (5.4%) |
| **Anxiety disorders, *N* (%)** | |
| Generalized anxiety disorder | 3 (8.1%) |
| Agoraphobia | 0 (0%) |
| Social phobia/social anxiety disorder | 2 (5.4%) |
| Specific phobia | 0 (0%) |
| Anxiety disorder (not) otherwise specified | 2 (5.4%) |
| Panic disorder | 0 (0%) |
| Alcohol-induced anxiety disorder | 0 (0%) |
| **Trauma related disorders, *N* (%)** | |
| Posttraumatic stress disorder | 5 (13.5%) |
| Other specified trauma disorder | 1 (2.7%) |
| **Obsessive compulsive and related disorders, *N* (%)** | |
| Obsessive compulsive disorder | 0 (0%) |
| **Neurodevelopmental disorder, *N* (%)** | |
| Attention deficit hyperactivity disorder | 4 (10.8%) |

Reported as number of participants who met criteria for each disorder based on SCID-IV/SCID-5. Terminology related to substance use disorders reflects DSM-5 classification, in which DSM-IV substance abuse and dependence are combined into substance use disorders according to DSM-5. AUD, alcohol use disorder; SCID, Structured Clinical Interview for DSM.

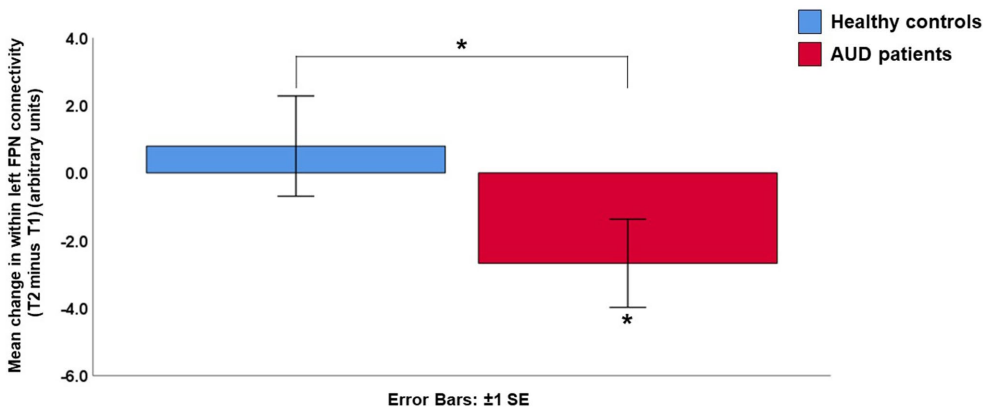


FIGURE 1
Mean change in within left frontoparietal network (FPN) connectivity strength (Timepoint 2 minus Timepoint 1). The alcohol use disorder (AUD) patients showed a significant decrease in within left frontoparietal network connectivity, which differed significantly from the control group. AUD, alcohol use disorder; FPN, frontoparietal network; SE, standard error; T1, timepoint 1; T2, timepoint 2.

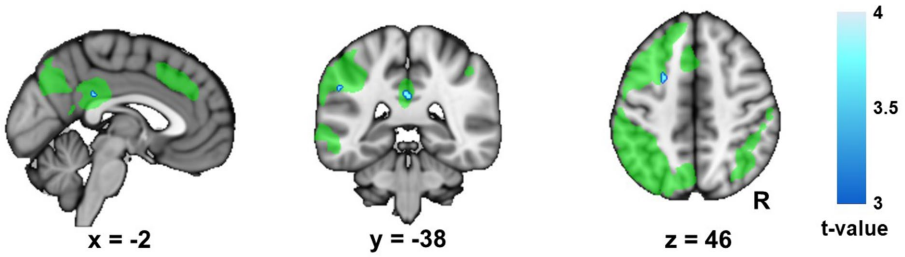


FIGURE 2
Change in left frontoparietal network (FPN) connectivity in the Alcohol Use Disorder (AUD) group. This figure displays the changes (timepoint 2 minus timepoint 1) in whole brain connectivity of the left frontoparietal network (FPN) in the alcohol use disorder (AUD) group. The left FPN template (Smith and colleagues 2009) is shown in green for display purposes, in order to show that the significant clusters are all located within this network. R, right.

supplemental partial correlations showed that this pattern did also not differ between AUD patients and controls when years of education were taken into account (trait anxiety: $F(1,62) = 1.033$, $p = 0.313$; delay discounting: $F(1,61) = 0.003$, $p = 0.956$). The partial correlations were no longer at a trend level in the AUD group for trait anxiety ($r = 0.194$, $p = 0.265$) or delay discounting ($r = -0.175$, $p = 0.314$) (Supplementary Table D). Finally, there were no significant relationships between the left FPN connectivity and the performance on the Wisconsin card sorting test or Letter-number sequencing task, nor related to changes in performance (Table 3), nor with respect to correlations for each scan day separately (Supplementary Table E).

## 3.5. *Post-hoc* analyses

*Post-hoc* analyses were performed to investigate if the change in left FPN connectivity (timepoint 2 minus timepoint 1) differed between the AUD patients that were treated with antidepressants or medication for AUD (i.e., naltrexone or acamprosate) and the patients that were not treated with such medication (using the Mann–Whitney U test). No patients received medication for AUD at timepoint 1 and twelve patients received such medication at timepoint 2. The change in left FPN connectivity did not differ between these twelve AUD patients that did receive medication for AUD and the 25 patients that did not receive such medication ($U = 105.0$, $p = 0.151$). All three patients that were treated with antidepressants at timepoint 1 were still receiving antidepressants at timepoint 2. In total thirteen patients were treated with antidepressants at timepoint 2. There was no difference in the change of within left FPN connectivity between these thirteen patients on antidepressants and the 24 patients that did not receive antidepressant medication ($U = 131.0$, $p = 0.441$).

# 4. Discussion

In this study we investigated longitudinal changes in resting-state connectivity during the early abstinence period in AUD on a large-scale network level. In contrast to the controls, who showed no longitudinal change, the AUD group showed a decrease in within left FPN connectivity during the follow-up period. The results from the whole brain connectivity analysis further confirmed these results, since all clusters that showed a decrease in left FPN connectivity during the early abstinence period in AUD were located within this network itself. However, these results for the left FPN did not survive a strict Bonferroni correction for multiple comparisons. Finally, our exploratory correlational analyses revealed a trend for an association of the change in within left FPN connectivity with trait anxiety and delay discounting in AUD.

The decrease in within left FPN connectivity in the early abstinence period in AUD is a novel finding, as little is known about this critical period. Interestingly, our original hypothesis was that the FPN connectivity would increase during the early abstinence period. As still little is known about changes in resting-state functional connectivity during the early abstinence period, this hypothesis was based on studies after longer durations of abstinence. Camchong and colleagues showed increased resting-state connectivity of the FPN in long-term abstinent AUD patients (average of 7.91 years abstinence) compared to patients who were abstinent for a shorter time period (72.59 days abstinence) (14). It has been suggested that this upregulated FPN after long-term abstinence is a compensatory mechanism to facilitate top-down control (14, 20). We hypothesized that our longitudinal data would show an increase in resting-state FPN connectivity in AUD during the early abstinence period, reflecting an initial step in the process of upregulating the FPN connectivity. However, our findings suggest that the early abstinence period may be characterized by different changes in resting-state connectivity than the changes taking place after long-term abstinence. This highlights the importance of studying different phases of recovery from AUD, as this may further our understanding of the dynamic changes taking place during different phases in the recovery process.

Our results emphasize the importance of performing longitudinal studies, as the change in left FPN connectivity was the most sensitive measure for finding subtle changes in connectivity (both within the AUD group and when comparing the change in connectivity between the AUD patients and controls). As the left FPN connectivity did not differ between AUD patients and controls on timepoint 1 or 2 separately, there is no clear increased or decreased connectivity in AUD compared to health at either of these time points. The decrease in left FPN connectivity in the AUD group over time indicates that the AUD patients have relatively stronger left FPN connectivity at timepoint 1 (shortly after stopping alcohol) compared to timepoint 2. Below we discuss possible explanations for the change in the left FPN connectivity based on what is known from the literature, as this network is implicated in higher-order cognitive processes, emotion regulation and top-down control (12, 15, 61, 62). When we formulate

TABLE 3 Correlational analyses for the relation between the change in within left frontoparietal network connectivity (T2 minus T1) and the measures of interest.

| | Change in within left FPN connectivity in controls (T2 minus T1) | Change in within left FPN connectivity in AUD patients (T2 minus T1) | Comparison between controls and AUD patients for standardized correlation coefficient (*F*, value of *p*)[‡] |
|---|---|---|---|
| Change in Wisconsin card sorting test score (T2 minus T1) | | | |
| Total number of perseverative responses | $r_s = -0.282$, $p = 0.163$<br>$z_r = -0.290$, $SE_{zr} = 0.209$ | $r_s = 0.189$, $p = 0.263$<br>$z_r = 0.191$, $SE_{zr} = 0.172$ | $F(1,62) = 3.198$, $p = 0.079$ |
| Total number of perseverative errors | $r_s = -0.271$, $p = 0.181$<br>$z_r = -0.278$, $SE_{zr} = 0.209$ | $r_s = 0.224$, $p = 0.183$<br>$z_r = 0.228$, $SE_{zr} = 0.172$ | $F(1,62) = 3.534$, $p = 0.065$ |
| Change in Letter-number sequencing score (maximum number of reproduced digits) (T2 minus T1) | $r_s = -0.004$, $p = 0.986$<br>$z_r = -0.004$, $SE_{zr} = 0.204$ | $r_s = 0.059$, $p = 0.733$<br>$z_r = 0.059$, $SE_{zr} = 0.174$ | $F(1,62) = 0.056$, $p = 0.814$ |
| Trait anxiety (STAI-Y2) | $r_s = 0.028$, $p = 0.891$<br>$z_r = 0.028$, $SE_{zr} = 0.204$ | $r_s = 0.303$, $p = 0.068$<br>$z_r = 0.313$, $SE_{zr} = 0.172$ | $F(1,63) = 1.149$, $p = 0.288$ |
| Delay discounting (ln(k) score) | $r_s = -0.099$, $p = 0.629$<br>$z_r = -0.099$, $SE_{zr} = 0.209$ | $r_s = -0.283$, $p = 0.089$<br>$z_r = -0.291$, $SE_{zr} = 0.172$ | $F(1,62) = 0.507$, $p = 0.479$ |
| Age of first drink (years) | $r_s = -0.221$, $p = 0.277$<br>$z_r = -0.225$, $SE_{zr} = 0.209$ | $r_s = -0.060$, $p = 0.732$<br>$z_r = -0.060$, $SE_{zr} = 0.177$ | $F(1,60) = 0.364$, $p = 0.548$ |
| Total number of lifetime drinks | $r_s = 0.279$, $p = 0.187$<br>$z_r = 0.287$, $SE_{zr} = 0.218$ | $r = -0.039$, $p = 0.825$<br>$z_r = -0.039$, $SE_{zr} = 0.177$ | $F(1,58) = 1.355$, $p = 0.249$ |
| Heavy drinking years | N/A | $r_s = -0.104$, $p = 0.554$<br>$z_r = -0.104$, $SE_{zr} = 0.177$ | N/A |
| AUDIT score | $r_s = 0.041$, $p = 0.838$<br>$z_r = 0.041$, $SE_{zr} = 0.204$ | $r_s = 0.076$, $p = 0.653$<br>$z_r = 0.076$, $SE_{zr} = 0.172$ | $F(1,63) = 0.017$, $p = 0.895$ |
| Number of drinks past 30 days before admission | $r_s = 0.070$, $p = 0.730$<br>$z_r = 0.070$, $SE_{zr} = 0.204$ | $r_s = 0.055$, $p = 0.751$<br>$z_r = 0.055$, $SE_{zr} = 0.174$ | $F(1,62) = 0.003$, $p = 0.956$ |

AUDIT, Alcohol Use Disorder Identification Test; FPN, frontoparietal network; N/A, not applicable; $r_s$, Spearman's correlation coefficient; $SE_{zr}$, standard error of the normalized correlation coefficient; STAI-Y2, Spielberger State–Trait Anxiety Inventory-Y2; T1, timepoint 1; T2, timepoint 2; $z_r$, standardized correlation coefficient. [‡]*F*-test comparing the standardized correlation coefficient between the AUD patients and controls.

hypotheses below about the left FPN being upregulated in AUD, then this refers to the hypothesis that the FPN is upregulated in AUD at timepoint 1 relative to timepoint 2 (and not compared to the controls).

The decrease in within left FPN connectivity in AUD may signify that this network is initially upregulated and recovers to a lower resting-state connectivity level over the early abstinence period. This could reflect that the FPN is upregulated over a longer time period for top-down control (63) in order to compensate for the effects of alcohol, with the FPN connectivity decreasing again when patients are abstinent. Alternatively, this result may reflect a more dynamic (short-term) pattern, with the left FPN only being upregulated in AUD shortly after patients stop alcohol consumption. It is clinically well-known that stopping alcohol consumption has anxiogenic effects. The negative affective state that arises when alcohol use is stopped is a negative reinforcer that can trigger relapse (2). From this perspective, the relatively higher left FPN connectivity immediately after stopping alcohol consumption may be an adaptive response to facilitate emotion-regulation and inhibitory control (15) in order to cope with negative affect and tendencies to use alcohol again (2). Finally, the FPN may also be involved more intrinsically in higher-order cognitive processes that arise after stopping alcohol consumption, for example related to problem solving attempts (64), repetitive negative thoughts (65), or thoughts about alcohol, which may diminish in the course of the early abstinence period.

There were no significant correlations between the changes in left FPN connectivity and our neuropsychological and behavioral measures of interest. The AUD patients showed trends for a relationship of the change in left FPN connectivity with trait anxiety and delay discounting. Below we describe these trends and what they might mean in the context of what is known from the literature. However, given the trend level of these results, the interpretations of these results can best be seen as hypotheses regarding what the neural changes might mean on the psychological level. Future studies should investigate if longer treatment/abstinence periods and larger sample sizes may provide sufficient power to drive these trends to a statistically significant level.

The AUD patients showed higher trait anxiety levels than the controls and within the AUD group there was a trend for a positive association between change in left FPN connectivity and trait anxiety. So, patients with lower trait anxiety have a relatively stronger left FPN connectivity directly after stopping alcohol consumption, that decreases during this early abstinence period. Interestingly, numerous studies have shown that the ability to regulate emotions in high-risk situations for relapse in alcohol use are important for relapse

prevention (66). It may be a crucial factor to allocate resources to the FPN for emotion regulation (15) when needed, like in the stressful phase just after stopping alcohol consumption (2). Thus, our results may suggest that resources are allocated to the FPN for top-down control over anxiety directly after stopping with drinking, with FPN connectivity recovering to a lower resting-state connectivity level during the early abstinence period.

Our results showing a trend for steeper delayed reward discounting in AUD are consistent with the observation that smaller, immediate rewards are valued over larger, delayed rewards in AUD patients compared to controls (54). Importantly, steeper discounting serves as a robust measure for (choice) impulsivity (23, 54, 67) and has been associated with relapse risk across various addiction disorders, including AUD (53, 54). In addition, impulsivity, with the inability to inhibit alcohol consumption despite negative consequences, is a core aspect of the addiction cycle (66). We observed a trend for a negative association between change in left FPN connectivity and delay discounting. Previous studies in AUD and various other addiction disorders have shown higher activity in the FPN during choices for larger, delayed rewards relative to choices for smaller, immediate rewards (53). This may suggest that patients with addiction disorders need to recruit greater neural resources to exert restraint and chose for larger, delayed rewards. In line with this, our results may suggest that in patients with a steeper discounting curve the FPN may be upregulated more strongly after stopping alcohol use, which may serve as a compensatory mechanism to resist impulses for more immediate gratification and alcohol use.

Although earlier studies have found differences in the DMN connectivity between AUD patients and healthy controls, still little is known about potential longitudinal changes in this network (4, 17, 21). Importantly, we did not find any changes in DMN connectivity during the early abstinence period. This may mean that the DMN connectivity is more stable over time in AUD. However, we cannot exclude that changes in DMN connectivity take place over longer abstinence periods. Furthermore, we investigated the DMN as a whole and opposite changes at the DMN subsystem level may cancel each other out on the large-scale systems level. Seed based analyses may be more sensitive for finding potential changes in the specific DMN subsystems, since previous studies have shown that resting-state functional connectivity of the anterior DMN (which is involved in emotion regulation) tends to be decreased in addiction, whereas the resting state connectivity of the posterior DMN (which directs attention to the internal world) tends to be increased (4). Future studies should further investigate these hypotheses.

The main strength of our study is that it is the first to longitudinally investigate changes in functional network connectivity during the early abstinence period on a large-scale network level. However, our study has to be interpreted in the light of some limitations. First, our results did not survive a strict Bonferroni correction for multiple corrections. This may be related to the relatively small sample in our exploratory study, making it necessary to replicate our findings in larger samples. Second, although we do formulate hypotheses about what our neuroimaging results may mean on the psychological level, our trends for correlations do not allow us to make causal inferences about this with certainty. Future interventional studies (e.g., neurostimulation studies) should further investigate these hypotheses. Third, in the AUD group there were various comorbid disorders, related to substance use disorders, and other psychiatric diagnoses like major depressive disorder. While the presence of comorbidity may have influenced the observed results, comorbidity is common in AUD in clinical practice (68). Although a sample with AUD, without any comorbidity, may give more specific results, such a sample may raise concerns about the generalizability of results to general clinical populations. Studies in AUD samples both with and without comorbidity are needed, as they can complement each other. In addition, future studies in larger samples could provide opportunities for subgroup analyses, to study the effects of specific patterns of comorbidity. Fourth, while we did not find a difference in the change of within left FPN connectivity between the AUD patients that received medication (i.e., antidepressant medication, or medication for AUD) and the ones who did not, the (sub)groups in these analyses were small (with, e.g., only thirteen patients receiving antidepressants). In addition, the current study was not designed to investigate the effects of specific types of medication on brain function. The patients were studied in a standard treatment setting, in which pharmacological treatments were available according to individual needs. Pharmacological treatments were neither randomized across the AUD patients nor prescribed according to a standardized scientific protocol. Future studies should investigate potential pharmacological effects on functional connectivity in the early abstinence period in AUD in a more controlled study design, for example by comparing the effects of a pharmacological intervention with a placebo. Finally, while our correlational analyses provide tentative hypotheses about the meaning of our results on the psychological level, we did not collect state related measures with respect to anxiety, impulsivity, or (obsessive) thoughts about alcohol on the day of scanning itself. Future studies should include such measures to further test the hypotheses discussed above and investigate if state related measures may be more sensitive for finding associations.

Taken together, our results provide initial insight into the changes in large-scale network connectivity during the early abstinence period in AUD. Our results revealed a decrease in within left FPN connectivity during this phase in AUD patients. This result may reflect that the FPN is initially upregulated after stopping alcohol consumption and recovers to a lower resting-state connectivity level during the subsequent weeks of abstinence. We hypothesize that an initially upregulated FPN is an adaptive response to facilitate top-down control over anxiety and negative emotions, that are common after stopping alcohol use. This initially upregulated FPN may also help to control impulsive tendencies, which are a major risk factor for relapse. However, it is important to note that none of the neuroimaging results survived strict Bonferroni correction for multiple comparisons and the trends for correlations that were found were at uncorrected levels. Still, these initial results related to the clinically crucial early abstinence period could inform future study designs and encourage further studies on the dynamic neuroadaptations during this key period.

## Data availability statement

The raw data supporting the conclusions of this article will be made available in accordance to the Data Management & Sharing Policy set forth by the National Institute on Alcohol Abuse and Alcoholism and The National Institutes of Health.

## Ethics statement

This study involves human participants and was reviewed and approved by the NIH Institutional Review Board. All participants signed informed consent before participation.

## Author contributions

JO and RM contributed to the conception and design of the study and/or analyses approach. MS and RM organized the database. JO performed the statistical analyses and wrote the first draft. ND, DGe, YH, MS, DGo, and RM wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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## Conflict of interest

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

## Publisher's note



## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1185770/full#supplementary-material

SUPPLEMENTARY FIGURE S1
Networks of interest. We studied the connectivity of our networks of interest (i.e. the default mode network (DMN), left frontoparietal network (FPN), and right FPN) using dual regression. For this purpose, we used the well described network templates that were identified by Smith and colleagues (2009) using independent component analysis (ICA). Here, we display the spatial maps of these networks that were identified by Smith and colleagues (2009) (thresholded ($z \geq 3$) for display purposes). Abbreviation: R: right.

SUPPLEMENTARY FIGURE S2
Trait anxiety in the healthy controls and alcohol use disorder patients. This dot plot displays the trait anxiety scores (sum score on the STAI-Y2) for the healthy controls and the alcohol use disorder (AUD) patients. The AUD patients showed higher trait anxiety levels than the controls ($U = 34.0$, $P < 0.001$). Abbreviations: AUD: alcohol use disorder, STAI-Y2: Spielberger State-Trait Anxiety Inventory-Y2.

SUPPLEMENTARY FIGURE S3
Delay discounting in the healthy controls and alcohol use disorder patients. This dot plot displays the delay discounting scores for the healthy controls and the alcohol use disorder (AUD) patients. The AUD patients showed a trend for a steeper delayed reward discounting compared to the controls ($U = 363.5$, $P = 0.098$). In delay discounting the factor $k$ represents the rate of discounting of the delayed outcome. As $k$ values are not normally distributed, a natural log-transformation is applied, and the *ln(k)* values are displayed in this figure. Higher *ln(k)* values (i.e. less negative values) mean greater preference for immediate rewards. Abbreviations: AUD: alcohol use disorder.

SUPPLEMENTARY FIGURE S4
Change in within left frontoparietal network connectivity. This dot plot displays the change in within left frontoparietal network (FPN) connectivity in the healthy controls and alcohol use disorder (AUD) patients (Timepoint 2 minus Timepoint 1). The alcohol use disorder (AUD) patients showed a significant decrease in within left FPN connectivity, which differed significantly from the control group (see also main text and Figure 1). Abbreviations: AUD: alcohol use disorder, FPN: frontoparietal network, T1: timepoint 1, T2: timepoint 2.

SUPPLEMENTARY FIGURE S5
Within left frontoparietal network connectivity at timepoint 1 and timepoint 2. These dot plots display the within left frontoparietal network (FPN) connectivity in the healthy controls and alcohol use disorder (AUD) patients at **(A)** Timepoint 1, and **(B)** Timepoint 2. The within left FPN connectivity did not significantly differ between the patients and controls at time point 1, or timepoint 2. Abbreviations: AUD: alcohol use disorder, FPN: frontoparietal network, T1: timepoint 1, T2: timepoint 2.

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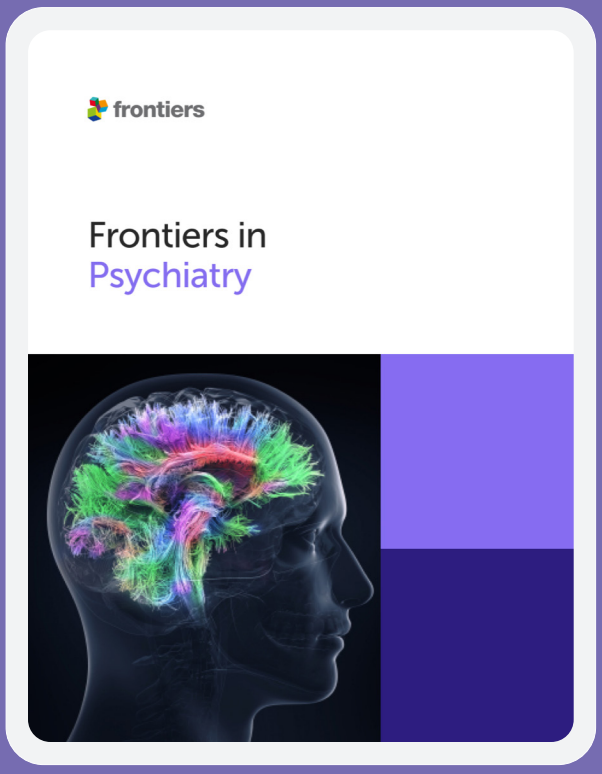


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