THE THERAPEUTIC POTENTIAL OF TRANSCRANIAL MAGNETIC STIMULATION IN ADDICTION

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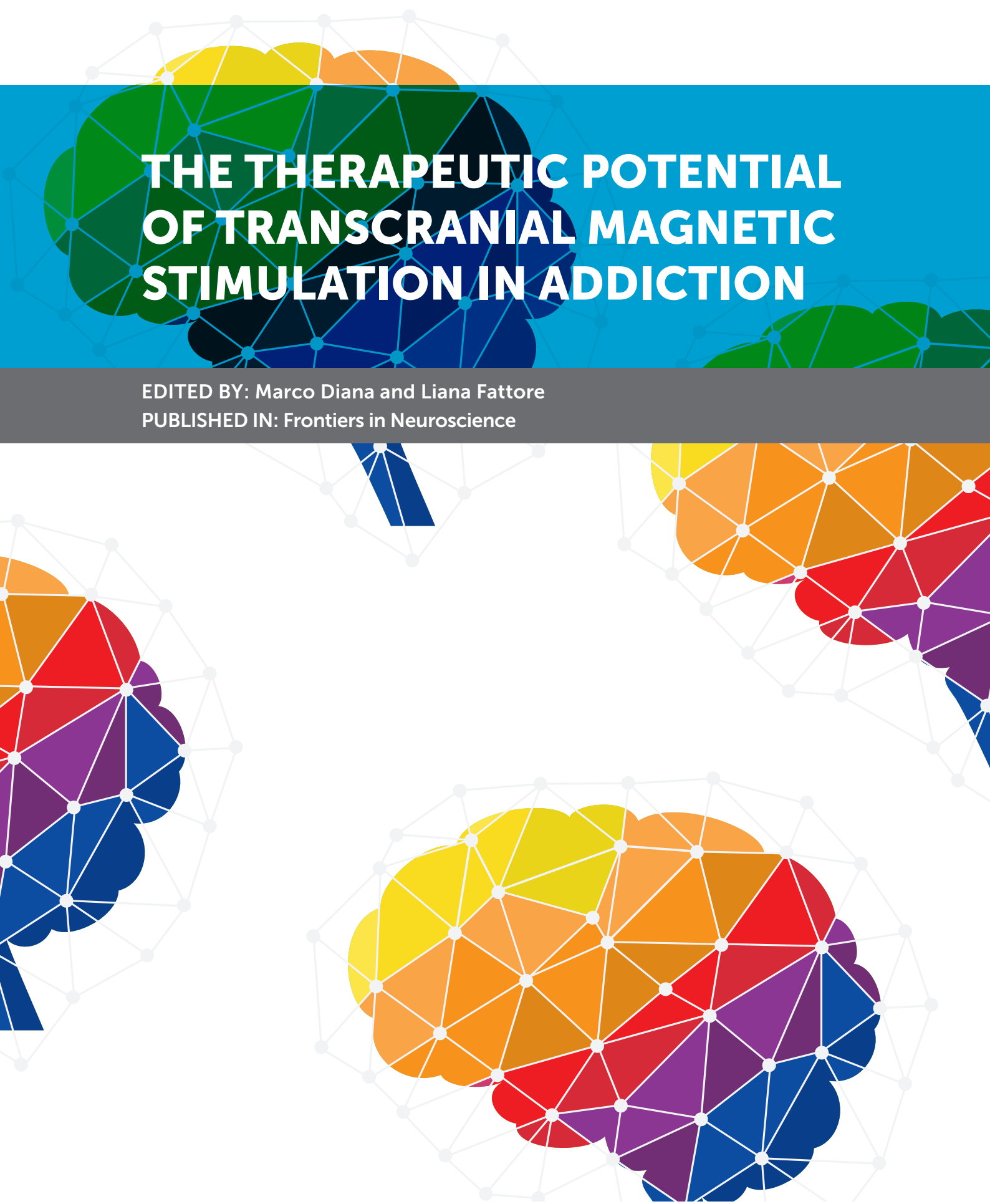

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THE THERAPEUTIC POTENTIAL OF TRANSCRANIAL MAGNETIC STIMULATION IN ADDICTION

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EDITORIAL
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Editorial: The Therapeutic Potential of Transcranial Magnetic Stimulation in Addiction

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Keywords: drug addiction, gambling, neuromodulation, food addiction, TMS (repetitive transcranial magnetic stimulation), virtual reality

Editorial on the Research Topic

The Therapeutic Potential of Transcranial Magnetic Stimulation in Addiction

This Research Topic aims to draw the attention of researchers and medical staff to the promising evidence supporting the use of Transcranial Magnetic Stimulation (TMS) in addiction (Diana et al., 2017). A second aim is to promote a change in the way we consider addiction and, as a consequence, in the therapeutic approach of addicts (Fattore and Diana, 2016). Harm reduction has dominated the field in the last 40 years (Ritter and Cameron, 2006), but it would seem overwhelmed by current data indicating (1) an increment in the diffusion, marketing, and abuse of psychostimulants like cocaine and amphetamines (World Drug Report, 2020), a sector plagued by a lack of specific therapeutic tools, (2) appearance on the drug market of new psychoactive substances (NPS) like phenethylamines, synthetic cannabinoids and synthetic cathinones (Weinstein et al., 2017), and (3) the dramatic resumption of opioid abuse, as revealed by the overdose epidemic recorded in the US in the recent past (Lyden and Binswanger, 2019). All cues that call for a change and the need to involve the patient in the therapeutic path that (s)he him/herself has requested in order to obtain "the drug free" status (too often, in the past, portrtayed as an unattainable goal) (Peele, 2016).

We felt that the time has come to deepen and expand our understanding of the potential therapeutic effects of TMS in the treatment of addicts. We have invited leading groups of scientists working in the field to "make the point" on the effectiveness of TMS in addiction. As a result, the present Research Topic brings together 12 papers, namely one perspective study, two commentaries, two original articles, two clinical trials, two opinion articles, and three reviews of high quality and broad impact, which encompass commonly abused drugs, i.e., cocaine, amphetamine, methamphetamine, and alcohol, also including food addiction and gambling.

In their perspective study, Stramba-Badiale et al. propose and discuss the integration of TMS over the dorsolateral prefrontal cortex (dlPFC) with virtual reality (VR) food exposure as therapeutic interventions for food addiction. Indeed, increasing cortical activity through high-frequency rTMS over the left dlPFC and simultaneously improving the management of the emotional and behavioral component of craving in fully immersive VR environments is expected to reduce craving in patients with food addiction and consequent eating disorders. In the two commentaries to the paper by Quoilin et al. (2018) entitled "*Deficient Inhibition in Alcohol-Dependence: Let's Consider the Role of the Motor System!*", Zhou et al. and Nardone et al. discuss the potential of motor cortex stimulation, which plays a pivotal role in the deficient inhibitory control, as a target site for intervention. In particular, Zhou et al. suggest that, since improved inhibitory control plays a significant role in preventing relapse in alcoholics, using TMS over the related motor cortex to modify inhibitory processes may be a prospective treatment for patients

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with addiction. Then, Nardone et al. note that altered motor cortical excitability may be caused not only by a dysfunction in the neural inhibitory (mainly GABA) circuits, but also by an impairment of the intracortical excitatory circuits and, therefore, also the excitatory (mainly glutamatergic) neurotransmission should be considered in alcohol-dependence.

The two original articles are both focused on the use of Intermittent Theta-Burst Stimulation (iTBS), a more tolerable protocol administered at lower intensities and shorter intervals than conventional repeated TMS (rTMS) protocols, as a treatment for cocaine use disorder (CUD). The paper by Sanna et al. shows the efficacy of iTBS of the PFC in reducing cocaine intake and craving in treatment-seeking CUD patients, with iTBS protocol being as efficacious as high-frequency stimulation in reducing cocaine intake and with dropouts and adverse side effects also being similar in the two protocols. Efficacy of iTBS on cocaine intake is supported by Steele et al. that show that accelerated iTBS to the left dlPFC administered in active, chronic cocaine users is both feasible and tolerable in actively using cocaine participants. Two further clinical studies analyzed the effect of TMS on other drugs of abuse, namely alcohol and methamphetamine. Specifically, Schluter et al. investigated the effects of add-on rTMS treatment on impulsivity measures in abstinent individuals under treatment for alcohol use disorder (AUD). Yet, contrary to the authors' hypotheses of a rTMS-induced increase in impulse control abilities, results suggest no additional effect of rTMS on impulsivity measures, suggesting that some protocol modifications could be necessary to bypass procedural limitations. The clinical efficacy and tolerability of intermittent and continuous theta burst stimulation protocols targeting left or right dlPFC on craving and mood changes in abstinent methamphetamine-dependent subjects are elegantly demonstrated in the study by Zhao et al..

Studies investigating the effects of TMS on cocaine, amphetamine, and methamphetamine craving are systematically illustrated by Ma et al. who in their systematic review and meta-analysis provide persuasive evidence for the feasibility of using high-frequency repetitive TMS to alleviate craving induced by dopaminergic drugs in chronic users. The rationale and potential for rTMS to treat cocaine and methamphetamine dependence are explained by Moretti et al. who reviewed findings from studies performed in healthy humans and animal models to identify and understand the neurobiological mechanisms underlying rTMS effects, with a focus on the dopaminergic and glutamatergic systems. Less robust, although promising, are findings in support of the effectiveness of TMS in treating gambling disorders, as illustrated by the systematic review by Zucchella et al. who points out the clinical and methodological heterogeneity of the studies performed so far and the need of methodologically sound, robust, and well-powered studies to reach reliable conclusions. In their opinion article, Spagnolo et al. propose combining pharmacotherapies, psychotherapies, and cognitive interventions (e.g., cognitive behavioral therapy) with neuromodulation interventions, since the state of the brain during the application of the stimulation may critically modulate the effects of brain stimulation and ultimately change treatment outcomes (state-dependency). Finally, Steele concludes by highlighting the importance of further evaluating the use of rTMS to treat not only cocaine, amphetamine, methamphetamine, and alcohol but also eating and gambling disorders.

It is worth noting how important it is to change the approach, also in the experimental design, and to shift from a "trial and error" observation, too often (ab)used in the past, to a "hypothesis-driven" approach, based on previous observations already acquired and confirmed in the field.

In this context, non-invasive techniques such as TMS and VR will likely help advance knowledge on their possible application as therapeutic options for addiction.

AUTHOR CONTRIBUTIONS

Both authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Intermittent Theta Burst Stimulation of the Prefrontal Cortex in Cocaine Use Disorder: A Pilot Study

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Transcranial Magnetic Stimulation (TMS) is earning a role in the therapeutic arsenal of cocaine use disorder (CUD). A widespread and still growing number of studies have reported beneficial use of repeated TMS (rTMS) in reduction of craving, intake and cue-induced craving in cocaine addicts. In spite of these encouraging findings, many issues are still unresolved such as brain area to be stimulated, laterality of the effects, coil geometry and stimulation protocols/parameters. Intermittent theta burst stimulation (iTBS) is a more tolerable protocol administered at lower intensities and shorter intervals than conventional rTMS protocols. Yet, its effects on cocaine craving and length of abstinence in comparison with standard high frequency (10–15 Hz) protocols have never been evaluated so far. In the present paper, we describe the effect of the bilateral iTBS of the prefrontal cortex (PFC) in a population (n = 25) of treatment-seeking cocaine addicts, in an outpatient setting, and compare them with 15 Hz stimulation of the same brain area (n = 22). The results indicate that iTBS produces effects on cocaine consumption and cocaine craving virtually superimposable to the 15 Hz rTMS group. Both treatments had low numbers of dropouts and similar side-effects, safety and tolerability profiles. While larger studies are warranted to confirm these observations, iTBS appears to be a valid approach to be considered in treatment-seeking cocaine addicts, especially in light of its brief duration (3 min) vs. 15 Hz stimulation (15 min). The use of iTBS would allow increasing the number of patients treated per day with current rTMS devices, thus reducing patient discomfort and hopefully reducing drop-out rates without compromising clinical effectiveness.

Keywords: cocaine, transcranial magnetic stimulation, intermittent theta burst stimulation, craving, neuromodulation

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INTRODUCTION

According to the World Drug Report 2017, 17 million people were past-year cocaine users in 2015 and cocaine seizures were reported in 153 countries during the period 2010–2015 (United Nations Office on Drugs and Crime [UNODC], 2017), suggesting that trafficking in cocaine is a global phenomenon. Noteworthy, after cannabis, cocaine accounts for the largest quantities seized. After a long-term decline, coca bush cultivation increased over the period 2013–2015 and

current data on drug production, trafficking and consumption confirm an extension of the market for cocaine (United Nations Office on Drugs and Crime [UNODC], 2017). In recent years, a wealth of clinical and animal studies has advanced our understanding of the brain mechanisms sustaining cocaine use and promoting dependence (Hanlon and Canterberry, 2012; Castilla-Ortega et al., 2017; Dobbs et al., 2017). Numerous efforts are being made to target novel molecular and cellular targets and effective strategies against cocaine addiction (Blum et al., 2009; Penberthy et al., 2010; Davidson, 2016). To date, though, pharmacological and psychological therapies for treating cocaine dependence have shown only limited success. Hence, research is very active and different experimental approaches are currently under investigation.

Cocaine use alters several brain processes of the addiction cycle, from reinforcement learning to inhibitory control (Koob and Volkow, 2010; Everitt, 2014). The prefrontal cortex (PFC) is strongly involved in cognitive impairment induced by chronic cocaine use and represents a crucial brain area where cognitive mechanisms are thought to be generated. Clinical evidence links PFC hypo-functionality to the loss of inhibitory control over drug seeking (Goldstein and Volkow, 2011). Among others, neuroimaging studies have greatly contributed to disentangle the neural circuits that become dysfunctional after repeated use of cocaine and contribute to the development of dependence. Chronic cocaine users typically present significant alterations and dysfunctions in the PFC, including cortical hypoactivity (Kaufman et al., 2003), brain volume reduction (Moreno-López et al., 2012), impaired executive functions and dysregulated neurotransmitters systems (Volkow et al., 2003; Licata and Renshaw, 2010). Cocaine users were also consistently found to have lower baseline cortical excitability, i.e., higher motor thresholds, than non-cocaine users (Boutros et al., 2001; Sundaresan et al., 2007; Gjini et al., 2012). A tonically stable hypofunctioning dopaminergic state (Melis et al., 2005) and a general malfunctioning of the PFC (Nogueira et al., 2006), accompanied by increased salience attribution to the drug (Volkow et al., 2005), have been postulated to promote compulsive cocaine intake. As for other drugs of abuse, persistent compulsive use of cocaine is hypothesized to be maintained by enduring changes induced by the drug in specific forebrain circuits that are involved in affective (e.g., ventral striatum) and cognitive (e.g., PFC) mechanisms (Fattore and Diana, 2016). Specifically, a progressive decrease in PFC control over drug-seeking and drug-taking behavior along with a shift from cortical to dorsal striatal control of behavior has been postulated to be at the basis of the transition from intentional to habitual and progressively compulsive drug use (Everitt and Robbins, 2013). Further, *in vivo* optogenetic and electrical stimulation of the infralimbic cortex (a portion of the cingulate cortex) significantly prevents compulsive cocaine seeking in animals (Chen et al., 2013), supporting the hypothesis that stimulation of PFC could mitigate cocaine seeking and consumption. Intriguingly, the modulation of prefrontal cortical areas through rTMS has been shown to be beneficial in reducing cocaine intake and alleviating some drug-related aspects in cocaine addicts (Bolloni et al., 2016). Indeed, generation of an electromagnetic field able to cross painlessly the skull and to influence the brain matter appears a promising approach to cocaine use disorder (CUD) and other substances use disorders, especially in light of its minimal side-effects.

Transcranial magnetic stimulation (TMS) has been reported to be useful in the treatment of several neuropsychiatric diseases (Daskalakis et al., 2002; Kobayashi and Pascual-Leone, 2003; Lefaucheur et al., 2014). A single TMS pulse lasts a few milliseconds, but when pulses are applied repetitively, as in the repetitive TMS protocol (rTMS), they can modulate long-term cortical excitability and affect the function of neuronal circuits in a frequency-dependent manner (Eldaief et al., 2011). Specifically, through electromagnetic induction rTMS at a low frequency (1 Hz) is typically considered to have inhibitory effects and induce long-term depression (LTD)-like changes (Chen et al., 1997) while rTMS at a high-frequency (from 5 Hz upward) is excitatory and can induce long-term potentiation (LTP)-like effects (Pascual-Leone et al., 1994). In rats, acute high-frequency (20 Hz) rTMS of the frontal cortex was shown to induce dopamine release in several parts of the brain reward system, including the dorsal hippocampus and the nucleus accumbens (Keck et al., 2002). In humans, high frequency rTMS of the human PFC was reported to stimulate dopamine release in the ipsilateral caudate nucleus (Strafella et al., 2001) and to modulate dopamine release in the ipsilateral anterior cingulate and orbitofrontal cortices (Cho and Strafella, 2009). Moreover, in alcohol dependent patients, rTMS significantly reduced blood cortisol levels and decreased prolactinemia, which suggests an increase in dopamine levels (Ceccanti et al., 2015). In light of its modulatory effect on both the mesolimbic and the mesostriatal dopaminergic systems, high frequency rTMS of frontal brain regions has been proposed to be useful in neuropsychiatry disorders associated with subcortical dopamine dysfunction such as alcohol and drug addiction in general (Diana, 2011).

Drug craving has been acknowledged as a relevant construct in the pathophysiology of addiction. As such, it has been included by the DSM-V in the list of crucial clinical symptom of substance use disorders and has been proposed to be routinely included as a clinical outcome in research on treatments for substance-use disorders (Tiffany and Wray, 2012). Patients seeking treatment for cocaine dependence often identify amplified craving as a major trigger of drug relapses. High frequency (15 Hz) rTMS-for several days-to the left dorsolateral prefrontal cortex (dlPFC) using "figure-of-eight" coil was shown to reduce cocaine craving and intake as compared with a standard pharmacological treatment (Terraneo et al., 2016). Further, a single session of high frequency (10 Hz) rTMS transiently reduced cocaine craving when applied to the right dlPFC but not the left dlPFC (Camprodon et al., 2007), although discrepant results were also reported (Politi et al., 2008). In fact, high frequency rTMS targeting the left dlPFC was reported to not affect craving but to gradually reduce cocaine consumption over 10 daily sessions (Politi et al., 2008). Other rTMS protocols and types of coils are currently under evaluation for their ability to reduce craving and cocaine intake in addicted patients. Some authors, for example, tested 20 Hz deep TMS using a Hesed (H)-coil that stimulates bilaterally and simultaneously the area

of interest and observed a reduction of cocaine craving in patients with CUD after a month of treatment (Rapinesi et al., 2016). Using the same type of coil, 10 Hz rTMS was also shown to improve abstinence from cocaine in patients with CUD at 3 and 6 months, but not at 1 month, i.e., immediately after the treatment (Bolloni et al., 2016), thereby suggesting a lasting and prolonged effect. More recently, Martinez and colleagues demonstrated that 10 Hz rTMS delivered with the newly designed H7 coil, which allows to target the medial prefrontal cortex (mPFC) and the dorsal anterior cingulate, reduces cocaine self-administration in volunteers with CUD (Martinez et al., 2018).

The insular cortex, with its important connections with the orbitofrontal and the anterior cingulate cortices, the thalamus, amygdala and globus pallidus, is another interesting brain target for TMS that showed to be promising in treating drug addiction. By using a peculiar H-shaped deep coil that allows rTMS to target deeper brain structures like the insula (Roth et al., 2002) it was observed, for example, that 10 Hz deep rTMS of the insular and prefrontal cortices significantly decrease the number of cigarettes smoked in nicotine dependent heavy smokers (Dinur-Klein et al., 2014). Given the crucial role of the insula in incentive motivational processes (Naqvi and Bechara, 2010; Naqvi et al., 2014) and in the contextual control over cocaine-seeking (Arguello et al., 2017) and cue-induced reinstatement (Cosme et al., 2015), modulating the function of both the prefrontal and insular cortices could result in a novel therapeutic strategy to be extended to cocaine addicts. In partial support to this hypothesis, deep rTMS of the insular cortex was recently reported to significantly modulate dopamine release in healthy subjects (Malik et al., 2018).

Theta burst stimulation (TBS), is a patterned form of TMS that can be applied using continuous or intermittent protocols (Huang et al., 2005; Di Lazzaro et al., 2008) that is widely believed to represent cellular learning in a Hebbian form of long-term synaptic plasticity (Larson et al., 1986). Unlike high frequency rTMS, TBS mimics endogenous theta rhythms thus improving induction of synaptic LTP (Suppa et al., 2016). Like high frequency rTMS, when applied in an intermittent (LTP-like) and continuous (LTD-like) manner TBS induces, respectively, a potentiation and a depression of cortical excitability. Continuous theta burst stimulation (cTBS) to the left ventromedial prefrontal cortex (vmPFC) significantly attenuated cue-related functional connectivity between the left vmPFC and a number of other brain regions, including the left and right insula (Kearney-Ramos et al., 2018). In keeping with this, when tested as add-on treatment to cognitive-behavioral therapy, 4 sessions of iTBS were reported to reduce nicotine craving and improve long-term abstinence in smokers (Dieler et al., 2014). Noteworthy, iTBS gives short TBS trains intermittently and is administered at lower intensities and shorter intervals than conventional rTMS protocol, improving tolerability and safety in patients (Oberman et al., 2011). Moreover, application of iTBS requires 2–3 min vs. 15–30 min typically required by application of rTMS, making the iTBS protocol more acceptable to patients.

At present, no study has compared the effects of iTBS treatment sessions vs. standard high-frequency TMS protocol in cocaine-dependent patients. Thus, a key practical question remains unaddressed: does iTBS perform comparably to the existing standard of care in cocaine addicts? This study aims to evaluate the effectiveness of iTBS targeting the PFC and the insular cortex bilaterally on cocaine craving and intake and to compare safety and effectiveness for PFC-rTMS with 15 Hz (15 min) versus iTBS (3 min) protocols in cocaine addicts.

MATERIALS AND METHODS

The study was conducted at the rTMS Center in Milan, Italy. All participants provided written informed consent to participate in the study. The consent form included all information regarding the nature of the TMS treatment and possible side effects. The study endorsed the Principles of Human Rights, as adopted by the World Medical Association (18th WMA General Assembly) in 1964 in Helsinki (Finland) and then amended by the 64th WMA General Assembly in 2013 in Fortaleza (Brazil).

Subjects

Patients were treatment-seeking outpatients in treatment for CUD diagnosed according to DSM-V criteria (American Psychiatric Association [APA], 2013) that were enrolled in the study from September 2017 to September 2018. Inclusion criteria were: age between 18 and 65 years, current CUD (i.e., have a positive urine drug screen for cocaine), motivation to stop intake, ability to understand and sign the informed consent. Exclusion criteria were: medical devices (pace-maker, metal implants, device for inflating), personal or family history of epilepsy, pregnancy (Rossi et al., 2009). Screening included medical history, physical and neurological examinations. Patients were asked about the weekly amount of cocaine consumed at baseline and at the end of the treatment; cocaine consumption was evaluated twice a week by means of a commercial urine drug screen test (Home Health Ltd., Hertfordshire, United Kingdom).

Questionnaires

Craving for cocaine was assessed once a week using the cocaine craving questionnaire (CCQ-brief) (Tiffany et al., 1993), a 5 questions questionnaire with 0–9 score visual analogical scale (Weiss modified CCQ) shown to be a valid and reliable measure of cocaine craving that exhibits high internal reliability (Sussner et al., 2006). The patient's risk for developing problems based on his/her use of cocaine was calculated at baseline and at the end of the treatment by means of the NIDA Modified WHO ASSIST questionnaire (*World Health Organization, WHO). Alcohol, Smoking and Substance Involvement Screening Test, Version 3.0*), a quick screening test for patients with a substance use disorder that the United States National Institute on Drug Abuse (NIDA) recommends as Resource Guide designed to assist clinicians screening adult patients for drug use was used to calculate. In this study 22 and 25 patients were enrolled for HF and TBS protocol, respectively.

High Frequency (HF) and Intermittent Theta Burst Stimulation (iTBS)

Magstim Rapid stimulator (Magstim Company, Whitland, Wales, United Kingdom) was used along with H4-Coil (Brainsway Ltd., Jerusalem, Israel) (Zangen et al., 2005), specifically designed to stimulate bilateral PFC and insula symmetrically (Tendler et al., 2016). As illustrated in **Figure 1**, for both the high-frequency (HF) and the iTBS protocols, subjects received 20 stimulations over 4 weeks: 10 stimulations during the 1st week (2 daily sessions from Monday to Friday, with at least 1 h interval between the two sessions), 4 stimulations during the 2nd week (1 daily session for 4 days, Mon-Tue-Thu-Fri), 3 stimulations during the 3rd and 4th week (1 daily session for 3 alternate days).

For HF treatment the intensity of stimulation was set at 100% of resting motor threshold determined using visual observation of muscle twitch of the left hand. PFC was stimulated bilaterally at 15 Hz frequency, 40 trains of 60 pulses each (4 s) with 15 s inter-stimulus between trains for a total of 2400 pulses. ITBS was performed at 80% of active motor threshold determined using visual observation of muscle twitch of the left hand after a voluntary contraction. ITBS protocol consisted of bursts containing 3 pulses at 50 Hz repeated at 200-ms intervals for 2 s (i.e., at 5 Hz). A 2-second train of iTBS was repeated every 10 s for 190 s and 600 pulses (Huang et al., 2005).

Statistical Analysis

In order to compare demographic features, multiple independent samples Student's *t*-test and Chi Squared test was used for normally distributed variables and for categorical variables, respectively. Two-way Analysis of Variance (ANOVA) was used to evaluate the effect of the two TMS protocols on cocaine intake, craving scale and WHO ASSIST questionnaire between and within groups. Kaplan Meier curves were used to plot the cumulated proportion of event free patients in the groups and Log Rank was used to test the significance between pairs of curves.

RESULTS

Before starting the study, no statistical differences were found in the characteristics of the patients between the two groups at baseline (**Table 1**). Two patients in each group dropped out within the first 2 weeks of treatment.

As shown in **Table 2**, a few participants in both the 15 Hz rTMS and the iTBS group reported mild discomfort at the start of stimulation, especially during the first session, but overall there were no significant differences across groups. Both treatments were safe and there were no serious or unexpected adverse events related to the treatments.

Effects on Cocaine Intake

The effect of rTMS on cocaine consumption was evaluated twice/week by means of a urine test and by asking the patient about the quantitative of cocaine consumed every week. **Figure 2A** shows cocaine intake during the rTMS (HF, black bars) and the intermittent TBS (iTBS, white bars) treatments. With respect to the baseline value, both treatments significantly reduce the intake of cocaine with no statistical differences between the two groups. Indeed, two-way ANOVA revealed a significant effect of time ($F_{1,90}$ = 49.97; $P < 0.0001$) but not of treatment ($F_{1,90}$ = 0.67) or time × treatment interaction ($F_{1,90}$ = 0.66). **Figure 2B** shows the Kaplan Meyer curves displaying the proportion of positive urine tests during the high-frequency rTMS (HF, dashed line) and the iTBS (solid line) treatments. The analysis revealed a significant decrease of positive tests at the end of the treatment with no difference between protocols (log rank $P > 0.05$). At the end of the treatment, 80 and 82% of the patients who underwent the HF and iTBS protocol, respectively, were found negative at the urine test.

Effects on Craving and Risk

Figure 3A shows the craving score in the HF (black bars) and the iTBS (white bars) groups. With respect to the baseline value, both treatments significantly reduce craving for cocaine with no statistical difference. Two-way ANOVA revealed a significant effect of time ($F_{1,90}$ = 127.3; $P < 0.0001$) but not of treatment ($F_{1,90}$ = 1.48) or time × treatment interaction ($F_{1,90}$ = 0.03). In line with it, the reduction of the WHO ASSIST questionnaire score was similar for both protocols (**Figure 3B**), as two-way ANOVA revealed a significant effect of time ($F_{1,90}$ = 232.9; $P < 0.0001$) but not of treatment ($F_{1,90}$ = 0.27) or time × treatment interaction ($F_{1,90}$ = 0.03).

DISCUSSION

The main finding of the present study is the efficacy of PFC-iTBS in reducing cocaine intake and craving in treatment-seeking CUD patients. In addition, our iTBS protocol is as safe and effective as a high frequency (15 Hz) protocol. In both HF and iTBS protocols, about 80% of urine screen test were negative for cocaine within the 4th week of treatment and the majority (72 and 75%, respectively) of the patients reported to have quitted cocaine consumption by the same time. In line with it, craving significantly decreased by the end of treatment. We did not find significant differences between the two protocols for any of the parameter analyzed, showing that iTBS is as efficacious as HF stimulation in reducing cocaine intake. Dropouts and adverse side effects were also similar in the two protocols. Importantly, in our patients we did not observe focal seizures or any other transient neurological event that have been occasionally reported for both rTMS (Hu et al., 2011) and, more recently, for iTBS (Steele et al., 2018).

At present, only a limited number of studies have been conducted to explore the potential therapeutic effect of TMS in treating cocaine addiction (for recent comprehensive reviews see Bolloni et al., 2018; Rachid, 2018). Previous studies aimed at treating cocaine-dependent patients used high frequency protocols ranging from 10 to 20 Hz, from 90 to 100% resting motor threshold (rMT), and from 600 to 2400 pulses during 1 up to 10 sessions lasting about half an hour (Camprodon et al., 2007; Politi et al., 2008; Terraneo et al., 2016). We previously described that bilateral rTMS of PFC at 10 Hz reduces cocaine

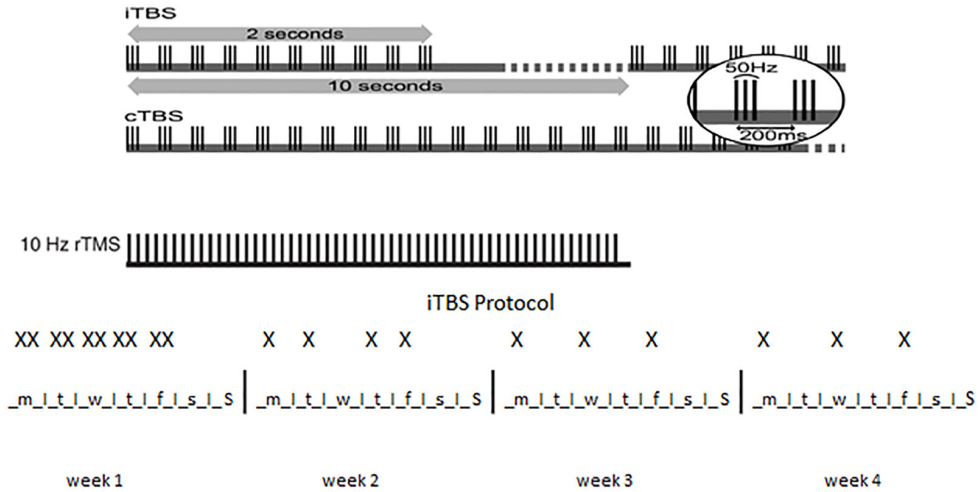

FIGURE 1 | Patterns of TBS. *Top*: the basic element of TBS is a 3-pulse burst at 50 Hz delivered every 200 ms (i.e., 5 Hz). A train of 10 bursts lasting for 2 s is given every 10 s for 20 cycles in iTBS, for a total of 190 s (iTBS) while 100 or 200 continuous bursts are given continuously for 20 or 40 s, respectively, in cTBS. 10 Hz rTMS is illustrated for comparison. *Bottom*: X indicates a single iTBS session in the 4 weeks of treatment. Note that two sessions are administered in the same day during the 1st week of treatment.

TABLE 1 | Baseline socio- demographic characteristics of the sample and clinical variables (M ± SD and range).

		HF group (*n* = 22)	TBS group (*n* = 25)	Difference
Gender (F/M)		1/22	1/25	
Age (years)		35,9 (8,5)	38,9 (8,0)	NS
Duration of cocaine use (years)		12,6 (8,0)	16,1 (9,2)	NS
Weekly cocaine amount (g)		9,6 (8,2)	8,1 (6,9)	NS
Route of administration	Inhalation	13	19	NS
	Smoke	7	6	NS
	Injective	2	0	NS
Psychiatric comorbidities		7/22	7/25	NS
	Mood disorder	4/22	4/25	NS
	Personality disorder	3/22	1/25	NS
	Anxiety	3/22	3/25	NS
Psychoactive prescription drugs		8/22	10/25	NS
	Mood stabilizers	2/22	1/25	NS
	Benzodiazepines	4/22	4/25	NS
	Antidepressants	3/22	3/25	NS
	Antipsychotics	2/22	3/25	NS
Other actual addiction		12/22	12/25	NS
	Nicotine	12/22	12/25	NS
	Alcohol	3/22	5/25	NS
	GAP	1/22	3/25	NS
	Heroin	2/22	2/25	NS
Past quit attempts		15/22	19/25	NS
Drop out		2/22	2/25	NS

intake in CUD patients (Bolloni et al., 2016), an effect still present after 6 months. Intermittent TBS is a safe and effective procedure in the treatment of neurological disorders, such as Parkinson's disease (Suppa et al., 2016), and psychiatric disorders, such as Tourette's syndrome, schizophrenia and obsessive-compulsive disorder (Rachid, 2017). Pilot studies showed beneficial effects of iTBS in both addicted (Dieler et al., 2014) and depressed (Blumberger et al., 2018) patients but no study so far has tested its effectiveness in cocaine-dependent patients. To this regard, our study is the first to show that iTBS is safe and effective also in reducing cocaine intake and craving in addicted patients and that its effects are not inferior to those obtained by using conventional HF rTMS protocols. However, a clarification between effects on craving and intake deserves attention. Craving

is a core symptom of addictive disorders and refers to the strong sense of compulsion to take the drug again, either to diminish negative effects or re-experience its positive effects. Although frequently studied, craving cannot, however, be interpreted as a 'proxy' of cocaine intake, which remains the main desirable clinical outcome. A number of compounds, such as topiramate, disulfiram, or N-acetylcysteine, are known to diminish the desire to use cocaine and, hence, to induce anti-craving effects (for a review see Lin, 2014). Yet, their anti-craving effects not always parallel their effects on drug intake, which represent an important clinical problem since reduction in drug consumption is clinically much more desirable than reduction in craving, i.e., the most critical achievement. Therefore, the efficacy of iTBS and high frequency (15 Hz) stimulation not only on craving but also on the intake of cocaine possesses clinical relevance.

In this study, iTBS targeted the PFC, a brain region regulating executive functions, levels of stress, motivation and reward, which are all strongly affected by exposure to drugs, including cocaine (Diana, 2013; Fattore and Diana, 2016; Diana et al., 2017). Chronic cocaine users typically exhibit decreased basal levels of dopamine receptors (Volkow et al., 1993) in the ventral and dorsal striatum and lower drug-induced dopamine release than non-addicted users, which implies a reduced experience of reward (Diana, 2011). During abstinence, characterized by dysphoria, anxiety and increased sensitivity to stress, craving is high and drug cues may easily trigger relapse. Motivation to seek the drug and inability to stop use are typically associated with changes in prefrontal circuits (involved in salience and attribution) and in hippocampus and amygdala (which mediate conditioned responses). After repeated exposure to cocaine the PFC, that in a drug-naïve conditions allows inhibitory control and promotes awareness of long-term consequences of emotional choices, becomes hypofunctional

TABLE 2 | Side effects of HF and TBS protocols.

Symptom	HF group (n = 22)	TBS group (n = 25)	Difference
Headache	2/22	3/25	NS
Dizziness	1/22	1/25	NS
Sleepiness	4/22	4/25	NS
Insomnia	0/22	1/25	NS

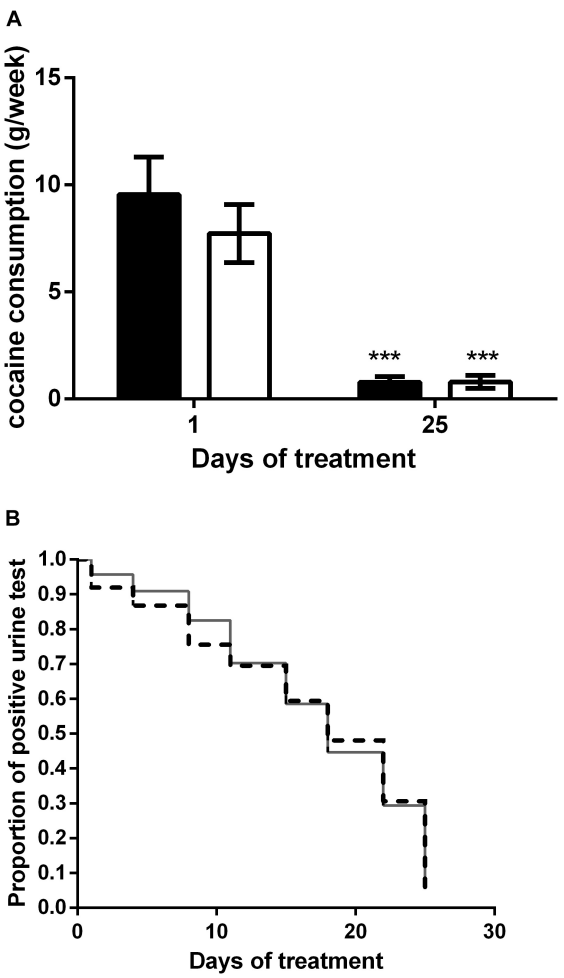

FIGURE 2 | (A) Effect of HF (*black columns*) and iTBS (*white columns*) treatment on cocaine consumption (g/week). Data are presented as mean ± SEM. ***$P < 0.001$ vs. day 1. **(B)** Kaplan Meier curve comparison between HF (*dashed line*) and iTBS (*solid line*). Data are presented as proportion of positive tests for each time point.

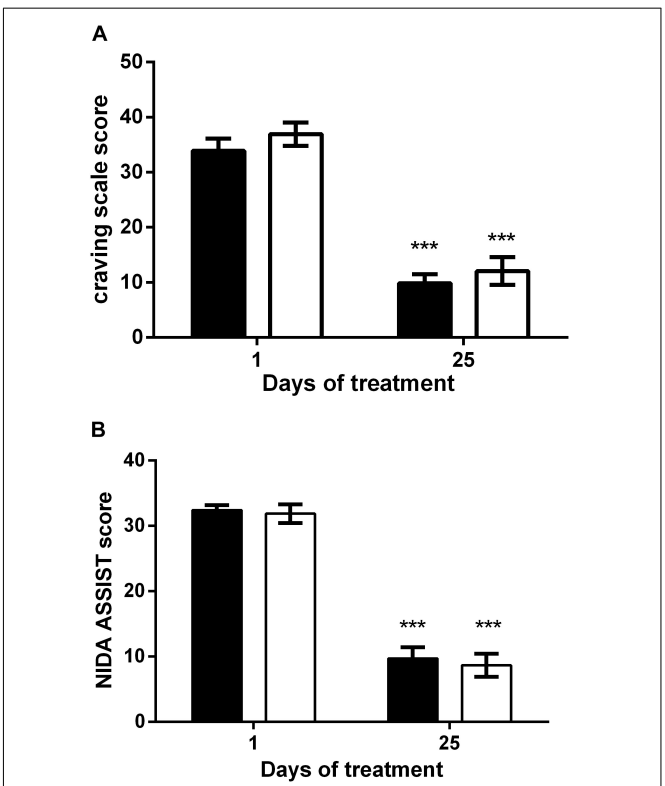

FIGURE 3 | Reduction of the craving scale **(A)** and WHO ASSIST scale **(B)** after HF (black columns) and iTBS (white columns) treatment. Data are presented as mean ± SEM. ***$P < 0.001$ vs. Day 1.

while limbic circuits are hyperactive, a combination than renders particularly difficult to stop the impulse of taking the drug. Since rescuing cocaine-induced hypoactivity in the PFC prevents compulsive drug seeking behavior (Chen et al., 2013), it seems reasonable to stimulate this area in an attempt to restore neural homeostasis by boosting dopamine signaling (Diana, 2011). In line with this, imaging studies revealed that high frequency rTMS targeting the PFC is able to increase the release of dopamine not only in the ventral striatum and cortical areas but also in the hippocampus, which is crucially involved in memory and engram retrieval (Strafella et al., 2001; Cho and Strafella, 2009; Diana et al., 2017). Along with the PFC, the insular cortex has also been tested as a promising target of TMS in drug addiction. Due to its projections to the PFC, the amygdala and the ventral striatum, the insula is in fact able to influence both the executive functions and reward-related behavior (Belin-Rauscent et al., 2016), and is activated during craving in cocaine addicts (Bonson et al., 2002). In light of these and other neurobiological and clinical evidence we decided to use in our study an H4 coil that was specifically designed to stimulate the PFC bilaterally and the insula symmetrically (Tendler et al., 2016).

Theta rhythms are present in many brain areas, including those regulating executive functions, which synchronize with related regions. Theta synchronized activity is considered a central neuronal mechanism supporting several cognitive functions as it subserves critical cognitive functions underlying the selection of a choice during goal-directed behavior (Womelsdorf et al., 2010). Rhythmic theta synchronization of neural circuits have been described in the evaluation of stimulus-reward associations and a significant relationship between theta oscillations and the reward system has been reported (Knyazev and Slobodskoy-Plusnin, 2009). Importantly, repeated use of cocaine can cause changes in synchronized network activity along limbic cortico-striatal circuits that may last long into abstinence (McCracken and Grace, 2013). Although with no data at hand at present, we could therefore speculate that iTBS in CUD patients may restore the synchronized network activity altered by chronic cocaine. PFC theta rhythms, for example, synchronizes with strongly connected structures like the anterior cingulate cortex and the posterior parietal cortex (Phillips et al., 2014; Babapoor-Farrokhran et al., 2017), which are both involved in regulating neuropsychological functions that became dysfunctional by cocaine use (Crunelle et al., 2012).

Although the results of this study are promising, we need to consider some caveats, including the small samples of patients involved in the study and the lack of a sham/control group, which does not control for placebo response. Moreover, certain aspects were not systematically assessed, including the psychiatric traits of the patients and the concomitant use of other drugs of abuse like alcohol, nicotine and cannabis. Moreover, further studies with larger samples of patients are needed to better assess the inter- and intra-individual variability in the efficacy of iTBS (Hinder et al., 2014) which is likely dependent upon the pre-intervention network connectivity of the stimulated cortical system (Nettekoven et al., 2015). Furthermore, other baseline stimulation parameters, such as intracortical inhibition and resting motor threshold, may contribute to the individual response pattern (López-Alonso et al., 2014).

CONCLUSION

In conclusion, despite these limitations, this study shows the beneficial effects of iTBS in attenuating craving for cocaine, reducing intake and prolonging abstinence in treatment-seekers. Importantly, we show that iTBS and deep high-frequency rTMS are similarly effective. Considering that a typical iTBS treatment session (including setup) requires not more than 10 min, compared to the 25–30 min for standard 15 Hz rTMS, this relatively new protocol deserves further studies and clinical evaluations as it results more tolerable by patients by being less disruptive and less time-consuming than standard HF protocols.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript and/or the supplementary files.

ETHICS STATEMENT

The experimental protocol was approved by internal review board at the University of Sassari.

AUTHOR CONTRIBUTIONS

PB, GC, and MD conceived the study and designed the experiments. MD supervised the research. AS and VC performed the study. AS and LF analyzed the data. AS, LF, and MD discussed the data and prepared the manuscript. All authors read and approved the final manuscript.

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GENERAL COMMENTARY
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Commentary: Deficient Inhibition in Alcohol-Dependence: Let's Consider the Role of the Motor System!

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Keywords: transcranial magnetic stimulation, alcohol dependence, motor system, inhibitory control, motor evoked potentials, action preparation

A Commentary on

Deficient Inhibition in Alcohol-Dependence: Let's Consider the Role of the Motor System!
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Inhibitory control has a significant capacity to abort undesirable or inappropriate responses (Logan et al., 2014). As a part of executive functioning, it plays an important role in goal-directed behaviors (Luna et al., 2015). Previous literature has demonstrated that heavy drinking is related to higher impulsivity, including a reduced response inhibition (Ahmadi et al., 2013). Abstinent patients with alcohol dependence (AD) have shown impairments in response inhibition, which could increase alcohol-elicited craving (Papachristou et al., 2012), contributing to compulsive drug-seeking behaviors and enhanced relapse risk (Dalley et al., 2011).

Substantial evidence has indicated that inhibitory control depends mainly on prefrontal areas (Berlin et al., 2004; Trantham-Davidson and Chandler, 2015; Klenowski, 2018). However, the motor system may have an impact on inhibitory control. Transcranial magnetic stimulation (TMS) studies have revealed a relationship between the corticospinal excitability changes and motor inhibition in the motor system (Duque et al., 2017); therefore, motor system excitability may be suppressed during response inhibition. Research on teenagers who suffered from heavy prenatal alcohol exposure recruited less primary motor areas in an easy inhibition response task when compared with control individuals (Ware et al., 2015). This highlights the influence of motor cortex on inhibitory function.

Single pulse TMS of the primary motor cortex (M1) can measure the extent of motor inhibition, reflected by motor-evoked potentials (MEPs) (Beck et al., 2008). MEPs decrease before a motor response, which corresponds with the results showing that the motor system is inhibited during the preparation of action (Greenhouse et al., 2015a). Although impairments in inhibitory control are found in individuals with addictive behaviors, it remains unclear whether the response inhibition is modulated by motor system in alcohol use disorders during action preparation.

This hypothesis is addressed in a recent paper published in the *Neuropsychopharmacology* (Quoilin et al., 2018). In this study, the authors explored the role of motor system in inhibitory control, behavioral inhibition, and relapse in patients with AD. Their main approaches involved the collection of demographical data, including the Spielberger State Trait Anxiety Inventory, Beck Depression Inventory, and UPPS Impulsive Behavior scale, behavior tests, and a TMS procedure. Quoilin et al. hypothesized that patients with AD had reduced neural motor inhibition during action preparation. To test this hypothesis, they utilized a 115% resting motor threshold of single-pulse TMS over the non-dominant or dominant hand area of the M1 to elicit MEPs corresponding to finger muscles during an instructed-delay choice reaction time (RT) task.

The results were consistent with previous studies (Henges and Marczinski, 2012; Greenhouse et al., 2015b). Firstly, patients with AD showed a lack of behavioral inhibition and higher scores in trait impulsivity compared with the control group. Second, although suppression of MEPs was observed in the delay period relative to baseline in all participants for the forthcoming movement, the suppression for patients with AD was weaker than the controls (Greenhouse et al., 2015b; Lebon et al., 2016). Besides, both behavioral inhibition and suppression of MEPs were not associated with trait impulsivity. This supports the independence of diverse types of impulsivity, including impulsive choice (also referred to discounting of delayed rewards), impulsive action (response or motor inhibition), and impulsive personality traits (MacKillop et al., 2016). Delay discounting (but not response inhibition) is different between heavy drinking smokers and heavy drinkers only or smokers only (Moallem and Ray, 2012). Hence, the distinction of response inhibition during action preparation in different addictive groups should be addressed in the future. Finally, the authors extended these results by illustrating that the loss of inhibition was only found in relapsing patients after a year, while the persistent abstainers displayed comparable inhibitory control to healthy group in the neural and behavioral measurements. That is, a stronger disinhibition in patients indicated a higher probability of relapse. Hence, we can classify patients with AD, those prone to relapse and those who remain abstinent, and efficiently intervene through cognitive training and TMS technology to enhance their inhibitory control (Kohl et al., 2019), which may promote better rehabilitation. In addition, this is the first study to show that the paucity of inhibitory function is modulated by the motor system in patients with AD, which provides a new target of TMS for the future treatments.

Nonetheless, this study highlights some limitations. Addiction is characterized by alterations in multiple regions and brain circuits, but the effect of these related regions is not considered in the paper. In fact, the right frontotemporal (Gan et al., 2014), medial prefrontal cortex (Klenowski, 2018), and striatum (Cheng et al., 2017) are involved in inhibitory control in relevant alcohol studies; weaker functional connectivity between the frontal cortex and striatum has been found when serious alcohol users perform the response inhibition tasks (Courtney et al., 2013). Thus whether the inhibitory mechanism of M1 during action preparation depends on other brain areas should be investigated in the future. For instance, functional connectivity between M1 and other brain networks, such as the pre-supplementary motor area, or right inferior prefrontal cortex, is vital to successful inhibitory control (Duann et al., 2009). Some investigators have found that these prefrontal areas transmit information to the M1 to inhibit premature behaviors by an oscillatory beta rhythm (Picazio et al., 2014); the mechanism underlying these connections in individuals with addiction remains unknown. Combining TMS with fMRI, researchers can observe the changes of functional connectivity between M1 and other brain areas and help improve inhibitory control in patients with AD in the future. As preliminary studies, smokers can decrease their craving by real-time fMRI neurofeedback (Hartwell et al., 2016). Same technology can be applied to help the patients with AD to regulate their inhibitory control.

Besides, additional difference between persistent abstainers and relapsed patients remains unknown. For example, it is not clear whether alcohol consumption and dependence time between these two kinds of patients have significant difference. Previous research has shown that higher alcohol consumption is associated with less total brain volume (Paul et al., 2008) and neurocognitive impairment in multiple regions (Woods et al., 2016). Therefore, alcohol use history should be defined as covariate in the future. Although multiple cognitive functions are impaired in various brain regions for patients with AD, longer alcohol withdrawal period promotes functional recovery (Kopera et al., 2012). Thus, the alterations of relevant brain networks in different abstinent duration should be further investigated.

Finally, M1 mechanism of inhibitory control is also revealed by paired-pulse TMS, including short- (SICI) and long-interval intracortical inhibition (LICI), involving gamma-aminobutyric acid A (GABAA) and gamma-aminobutyric acid B (GABAB), respectively. Previous research has found that reduced LICI of dorsolateral prefrontal cortex, no difference for SICI of motor cortex in AD patients post-detoxification compared with controls (Naim-Feil et al., 2016). However, the changes on LICI and SICI of M1 in patients with AD during action preparation need to be further explored. For healthy individuals, LICI is reduced during the whole response inhibition task, while reduced SICI is only found in informative cues (Cirillo et al., 2018); Individuals with better improvement in motor training show a reduction in GABAergic release in movement preparation (Dupont-Hadwen et al., 2019). Hence, Combining TMS and motor training, researchers should further investigate how to improve inhibitory control in patients with AD.

In conclusion, the current work explored the different capacities for inhibition between patients with AD and healthy controls, including neural motor, behavior, and trait impulsivity. These researchers discovered that patients with AD had reduced motor cortex excitability and higher trait impulsivity compared with the controls. In addition, they reported a dysfunction in the neural inhibitory ability of patients with AD during movement preparation, especially in patients who had relapsed one year later. These findings have revealed the importance of inhibitory processes in forthcoming actions to healthy individuals. These data suggest that improved inhibitory control plays a significant role in preventing a relapse in serious alcoholism. Using TMS over the related motor cortex to modify inhibitory processes may be a prospective treatment for patients with addiction (Dupont-Hadwen et al., 2019).

AUTHOR CONTRIBUTIONS

LZ, WL, and WH conceived the idea, revised all the literature, and wrote the manuscript. BZ read and revised the manuscript. WH and WL contributed to the revision of the manuscript. All authors read and approved the submitted version.

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SYSTEMATIC REVIEW
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Effects of Non-invasive Brain Stimulation on Stimulant Craving in Users of Cocaine, Amphetamine, or Methamphetamine: A Systematic Review and Meta-Analysis

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Dopamine system plays a pivotal role in specific kinds of substance use disorders (SUD, i. e., cocaine and methamphetamine use disorders). Many studies addressed whether dopamine-involved craving could be alleviated by non-invasive brain stimulation (NIBS) techniques. Nevertheless, the outcomes were highly inconsistent and the stimulating parameters were highly variable. In the current study, we ran a meta-analysis to identify an overall effect size of NIBS and try to find stimulating parameters of special note. We primarily find 2,530 unduplicated studies in PubMed, Psychology and Behavioral Sciences Collection, PsycARTICLES, PsycINFO, and Google Scholar database involving "Cocaine"/"Amphetamine"/"Methamphetamine" binded with "TMS"/"tDCS"/"non-invasive stimulation" in either field. After visual screening, 26 studies remained. While 16 studies were further excluded due to the lack of data, invalid craving scoring or the absence of sham condition. At last, 16 units of analysis in 12 eligible studies were coded and forwarded to a random-effect analysis. The results showed a large positive main effect of stimulation (Hedge's $g = 1.116$, CI = [0.597, 1.634]). Further subgroup analysis found that only high-frequency repetitive transcranial magnetic stimulation (rTMS) could elicit a significant decrease in craving, while the outcome of low-frequency stimulation was relatively controversial. Moreover, univariate meta regression revealed that the number of pulses per session could impose negative moderation toward the intervention. No significant moderation effect was found in types of abuse, overall days of stimulation and other variables of stimulating protocol. In conclusion, this meta-analysis offered a persuasive evidence for the feasibility of using NIBS to remit substance addictive behavior directly based on dopamine system. We also give clear methodological guidance that researchers are expected to use high-frequency, sufficiently segmented rTMS to improve the efficacy in future treatments.

Keywords: non-invasive brain stimulation, addiction, substance use disorders, dopamine system, craving

INTRODUCTION

Drug addiction, also known as substance use disorder (SUD), is a severe threat to physical and psychological health, which is suffered by at least 275 millions of people all over the world. This medical situation is defined as the compulsive active use of substances regardless of the potential harms and recruits a series of diagnosis criteria including withdrawal symptoms, craving, physical and mental illness, etc. (American Psychiatric Association, 2013). Addiction to certain kinds of substances has also been found to negatively impact working memory (Yan et al., 2014), response inhibition (Goldstein et al., 2001), emotional empathy (Ferrari et al., 2014), and decision making (Bechara et al., 2001). Hence, unraveling the mechanism of SUD and inventing effective treatments have always been the pivotal goals in neuroscience studies.

Most kinds of SUDs are generally considered to originate from abnormality in dopamine (DA) system (except for opioid and cannabis addiction, see Nutt et al., 2015 for review). Stimuli such as drugs or predictive cues of drugs modulate the firing pattern of dopaminergic neurons in ventral tegmental area (VTA) and elicit a large DA release which represents the reward prediction error (Schultz, 2002). The signal will be projected to GABAergic medium spiny neurons (MSNs) expressing DA receptors in the nucleus accumbens (NAc) of ventral striatum (Paladini and Roeper, 2014; Volkow and Morales, 2015). Weights of connections between MSNs and cortical areas could then be altered. A bunch of imaging studies have revealed that the repeated use of cocaine and amphetamine-like substances will downregulate DA release and DA receptor availability (Ashok et al., 2017) which results in the attenuation of projections to the cortical areas such as the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), and orbitofrontal cortex (OFC) (Black et al., 2010; Volkow et al., 2011). These targeted regions are responsible for executive control functions or salience attribution to the external stimuli (Fuster, 2015). This might explain why the abusers are hardly able to control the craving and consumption of drugs. In general, the dysfunction of dopamine pathway plays a central role in drug addiction and this notion has inspired the development of neurobiological treatments including acupuncture (Lee et al., 2009), pharmacotherapies (Lu et al., 2009), neurosurgical operations (Stelten et al., 2008), and brain stimulations (Müller et al., 2013; Hanlon et al., 2016).

NON-INVASIVE BRAIN STIMULATION AS A POTENTIAL TREATMENT FOR SUD

Although previous studies have constructed relatively thorough understandings toward the brain mechanism of SUD, we still haven't found credible and efficient ways of treatment yet. However, NIBS seemingly gave us a new direction in the recent years. Transcranial magnetic stimulation (TMS) is one typical NIBS technique. It applies magnetic pulses to a certain location on the scalp to induce spike firing in the corresponding brain tissue. Single-pulse TMS has been proved to produce changes in many aspects including visual perception (Van Ettinger-Veenstra et al., 2009), working memory (Ku et al., 2015a,b; Zhao and Ku, 2018; Zhao et al., 2018), motor learning (Bütefisch et al., 2004), interpersonal cooperation (Balconi and Canavesio, 2014), etc. While repetitive TMS (rTMS), which employs multiple trains of pulses within a single block, is more suitable for therapeutic purposes. A common belief is that high-frequency (5–20 Hz) rTMS elicits cortical excitation while low-frequency (∼1 Hz) pulses conversely lead to inhibition. However, there are still exceptions that make the relationship between the stimulating parameter and the subsequent cortical effect controversial (Paus et al., 1998). Besides, the counterpart of TMS, transcranial direct current stimulation (tDCS), which also has broad applications in cognitive enhancement and treatments (Sauvaget et al., 2015; Wang and Ku, 2018; Wang et al., 2019), modulates neural activity by directly imposing current flow into the brain between two electrode patches. Nitsche and Paulus (2000) find that the anode tDCS could increase excitability in motor areas, while cathodal tDCS induces inhibition. However, more studies are needed to test whether this conclusion is robust across different sets of stimulating parameters and whether the activation could transfer to other non-stimulating brain areas as well.

Several clinical trials have reported alleviation of stimulant craving of NIBS compared to control group (Bolloni et al., 2016; Hanlon et al., 2017; Liu et al., 2019). Most of them choose the DLPFC as a stimulating site in the light of the notion that this region is important for executive control. Martinez et al. (2018) recruit Hedes-coil (H-coil) to stimulate deep brain regions (ACC and medial PFC) of analogous functions in the dopamine pathway and find significant alleviation in cocaine craving when stimulating frequency is set to 10 Hz. In line with the conventional view, low-frequency rTMS or continuous theta-burst stimulation (cTBS) does not change the level of craving or even boosts craving in most occasions (Li et al., 2013; Hanlon et al., 2017; Martinez et al., 2018). Nonetheless, Liu et al. (2017) find inconsistent results regarding this issue in a group of methamphetamine abusers. The existing studies also have prominent discrepancies in parameters such as overall days of stimulation, number of sessions, number of pulses other than rTMS frequency. Given these controversial issues, a comprehensive analysis will be fruitful in the development of a more effective and reliable treatment protocol.

Jansen et al. (2013) run a meta-analysis for the potential effect of NIBS toward DLPFC on craving for food or stimulants, and find a medium treatment effect (Hedge's $g = 0.476$, CI = [0.316, 0.636]). Gorelick et al. (2014) separate several groups of independent meta-analysis for each kinds of stimulants and all the results suggest significant decrease in craving. However, these two studies do not discuss the optimal stimulating protocol quantitatively. Furthermore, although Song et al. (2019) test the relationship between stimulating parameters and the outcome of NIBS, they combine the results from SUD, eating disorder, and obesity. It might not be tenable to apply these results to SUD treatment precisely. Thus, in the current study, we take a re-consideration toward the role of NIBS in the treatment of SUD by implementing a meta-analysis which focuses on the prospective modulators that might be of special importance to the stimulating protocol.

Additionally, we only include studies of cocaine, amphetamine and methamphetamine addiction as they are substances that act directly on DA receptors. TMS on rats' frontal cortices could induce DA release (Zangen and Hyodo, 2002). Deep rTMS of human studies reveals similar effects (Ceccanti et al., 2015). Likewise, DA transporter availability in caudate nucleus goes up after a high-frequency rTMS on DLPFC in a recent case study (Pettorruso et al., 2019). Moreover, tDCS on bilateral DLPFC elicits DA increase in the same region as well (Fonteneau et al., 2018). Put all these findings together, the treatment effect of NIBS is possibly derived from the alteration of DA level through the feedback pathway from frontal cortices to striatum (Diana, 2011, **Figure 1**). By prescribing the three types of addiction in the current study, we aim to call the attention to this DA theory of NIBS treatment.

MATERIALS AND METHODS

Study Inclusion Criteria

For the homogeneity and validity of our meta-analysis, we set a few ex ante principles to filter the studies based on the theoretical background.

NIBS Treatment

Qualified studies should employ NIBS as the only method of treatment and report whether it alleviates craving. Deep brain stimulation and other kinds of treatments are expected to be excluded. A study used 5 Hz cTBS (Hanlon et al., 2017) that is also regarded as rTMS, is included in our analysis, whereas it does not join in the meta-regression of stimulation frequency.

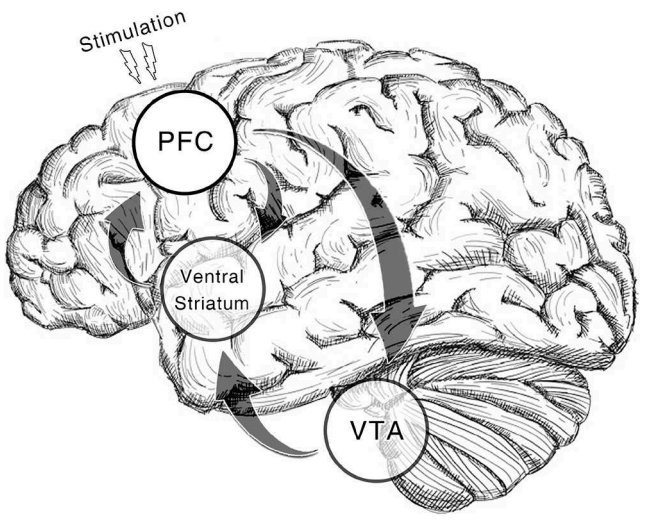

FIGURE 1 | Dopamine reward system involved in the therapeutic effect of NIBS. In the illustrated pathway, dopaminergic neurons in ventral tegmental area (VTA) projects the reward signal to medium spiny neurons (MSNs) in ventral striatum by which the cortico-striatal connection is modulated. While prefrontal regions (pyramidal neurons) including dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), and medial prefrontal cortex (mPFC) give feedback to these regions (Gorelova and Yang, 1996; Frankle et al., 2006). With non-invasive brain stimulation alters activation in prefrontal regions, the VTA reactivity will be enhanced which results in the recovery of DA increase in the downstream areas. The regions with a transparent circle rearward are not on the cortical surface.

Type of Addiction

As previously mentioned, only the trials targeted at cocaine and amphetamine-like drug addiction will be included. Thus, studies with whom take opioid, cannabis, tobacco, alcohol, food abusers, or are non-abusers as participants are invalid. Mixed abuse shall be acceptable as long as the study probed the alteration of craving toward the drug of our interest.

Sham Comparison

Control strategy is necessary in order to rule out the impact of placebo effect. Groups should be randomly assigned. Moreover, sham stimulation is the only valid way of control since the difference between abusers and normal subjects could be possibly attributed to the floor effect of craving in the normal group. Within-group comparison between separated sham and stimulation sessions is also qualified.

Indicators of Craving

Clinical trials have used different methods to acquire craving scores. While in the current analysis, the studies shall not be restricted by the methodology of craving assessment only if the indicator itself could not directly represent the level of craving such as the amplitude of cue-induced event-related potential (Conti and Nakamura-Palacios, 2014; Conti et al., 2014). Bolloni et al. (2016) applied the quantity of cocaine residue in hair samples to indicate craving. Their study is also included in the analysis as cocaine intake is motivated by the underlying desire, so it should be proportional to the level of craving.

Search Strategy and Study Selection

The procedures of study selection are annotated in **Figure 2**. We used 3-by-3 keywords composed by "Cocaine" /"Amphetamine"/"Methamphetamine" and "Transcranial Magnetic Stimulation"/"Transcranial Direct Current Stimulation"/"Non-Invasive Brain Stimulation" (NIBS) in the search across PubMed, Psychology & Behavioral Sciences Collection, PsycARTICLES, PsycINFO, and Google Scholar. All the studies detected in the original search were first unduplicated. Afterwards, the remaining 2,530 studies were visually screened based on titles and abstracts. Then we read the full texts of the 26 studies passed the initial screening. Eleven studies that did not fit the inclusion criteria, 3 studies that were in lack of data were further excluded. At last, 12 eligible studies were viewed again for data extraction.

Data Extraction

Different sessions of the same group of participants that employed different stimulating parameters were treated as independent units of design. Consequently, we detected 16 units of analysis in those 12 studies, covering 321 patients altogether. Given that pretest craving scores of the control group and the stimulating group did not have significant difference in all of the included studies, the therapeutic effect of each unit was coded as the difference of craving in the posttest that was

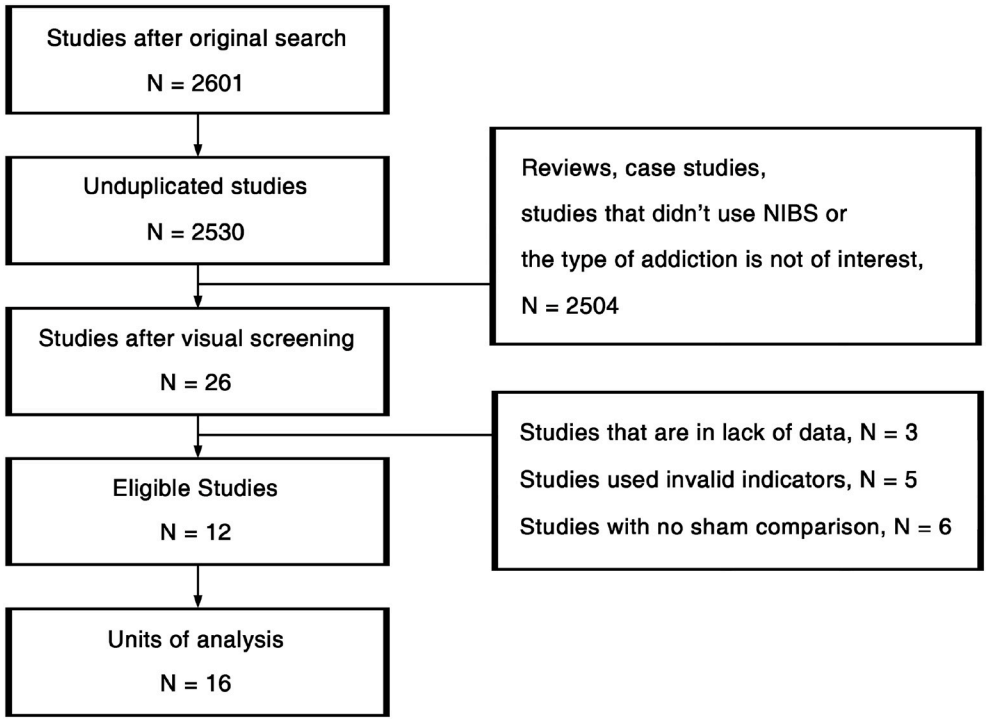

FIGURE 2 | Flow diagram of the study selection procedure.

closest to the end of treatment in terms of time. Subjects' demographics including gender, age, years of education, duration of addiction, and duration of abstinence in each group were extracted. Only gender, age, duration of addiction were coded as potential modulators and forwarded to meta-regression while other variables were lack of detailed information. We coded the stimulation method as "tDCS" or "rTMS." Given that there were only two units of analysis using tDCS, we only discussed the protocol of rTMS in the current study. Overall, categorical variables including sites of stimulation, types of addiction, rTMS frequency (1 Hz or larger than 5 Hz) and continuous variables including sessions, days, pulses, pulses per session of rTMS treatment were further extracted as possible modulators. Results of coding and other information regarding each study are summarized in the Supplementary Material (**Data Sheets 1**, **2**). Note that among the 12 eligible trials, none of them were about amphetamine addiction, so the following analysis was merely about the existing methamphetamine and cocaine studies.

Data Analysis

All of our analysis was done in Comprehensive Meta Analysis V2 (Borenstein et al., 2009). Given that the sample sizes of the included studies are basically small, we used Hedge's g to calculate the effect size which can rectify the bias induced by small samples (Hedges, 1981).

We first estimated the overall effect size of the NIBS's therapeutic effect using a random-effect model which assumed that the observed effect size in each study was a combination of the true effect size sampled from an underlying normal distribution and a random error. The reason for choosing this model is that the effect was expected to vary according to the hypothesized modulation by stimulating frequency and other factors. The heterogeneity between studies was assessed by Cochrane's Q and I^2 value. To test the modulators, we employed subgroup analysis using mixed-effect model and fixed-effect univariate meta-regression for categorical and continuous variables, respectively. Significant level was designated as 0.05 in all analyses.

RESULTS

Therapeutic Effect of NIBS

The meta-analysis revealed a significantly strong effect of NIBS on the alleviation of craving levels (Hedge's $g = 1.116$, CI = [0.597, 1.634], $z = 4.218$, $p < 0.001$, **Figure 3**). Moreover, both of the Rosenthal's (1979) and Orwin's (1983) fail-safe N proved the credibility of our result (Rosenthal's $N = 399$, Orwin's $N = 76$). Given that the number of studies in our analysis was relatively small, the resultant effect size could not be fully explained by publication bias (Ridding and Rothwell, 2007).

Heterogeneity Across Studies

As predicted, heterogeneity among the observed effect sizes was significant ($I^2 = 88.548\%$, $Q = 130.978$, $p < 0.001$) which indicated the between-study variation could not merely be attributed to the random error. Thus, we then traced the possible origin of the heterogeneity by testing the possible modulators.

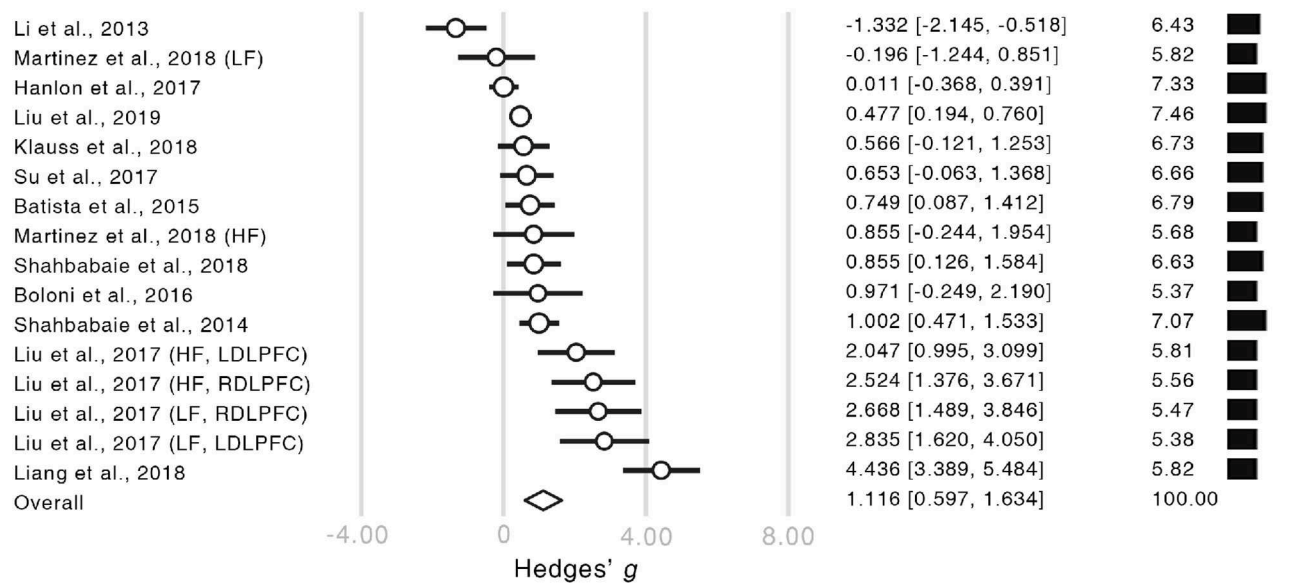

FIGURE 3 | Forest plot of the estimated effect sizes. Authors and years of publication of each unit of analysis are shown in the very left column. The words in the brackets indicate the information of within-study subgroups (HF, high frequency; LF, low frequency; LDLPFC, left dorsolateral prefrontal cortex; RDLPFC, right dorsolateral prefrontal cortex). In the forest plot, the length of each bar illustrates the confidence interval of the corresponding unit. The size of each empty circle illustrates the relative weight of each unit which is also showed by the black bars on the right-hand side.

Modulators

Demographic Variables and Duration of Addiction

We first filtered the studies that did not report enough information for each modulator and the number of remaining studies is then denoted by N. To assess the relationship between the therapeutic effect and the subject variables, we converted the means of age, gender (percentage of males), and duration of addiction in treatment and control group into between-group difference (treatment—control) or across-group average weighted by group sizes. Meta-regression revealed that age difference ($N = 14$) was negatively correlated with the NIBS effect [$Q(1) = 54.04$, $p < 0.001$], while the weighted average ($N = 13$) had null effect [$Q(1) = 1.10$, $p = 0.29$]. As for gender, between-group discrepancy ($N = 10$) could not predict the effect of NIBS treatment [$Q(1) = 0.50$, $p = 0.48$] whereas weighted average revealed a significant positive modulation effect [$N = 10$, $Q(1) = 7.15$, $p = 0.008$]. The regression between group-wise difference in subjects' years of drug use ($N = 9$) revealed a prominent positive relationship [$Q(1) = 14.48$, $p < 0.001$]. However, the weighted average ($N = 8$) showed a significant converse effect [$Q(1) = 7.60$, $p = 0.006$].

Type of Addiction

The mixed-effect subgroup analysis suggested that the treatment for cocaine addiction ($N = 6$, Hedges' $g = 0.397$, CI = [0.022, 0.772], $z = 2.075$, $p = 0.038$) and methamphetamine addiction ($N = 10$, Hedges' $g = 1.541$, CI = [0.735, 2.347], $z = 3.749$, $p < 0.001$) were both effective. There also existed significant difference between the studies of these two kinds of addiction [$Q(1) = 10.974$, $p = 0.001$].

Type of Stimulation

As there were only four tDCS studies included in our analysis, we picked out studies only applying rTMS and found that there still existed an overall significant effect ($N = 12$, Hedges' $g = 1.264$, CI = [0.540, 1.989], $z = 3.419$, $p = 0.001$).

Stimulating Protocol

We then looked at the relationship between NIBS effect and the stimulating parameters. In the studies using high-frequency rTMS ($N = 7$), the craving level did decrease (Hedges' $g = 1.671$, CI = [0.669, 2.673], $z = 3.269$, $p = 0.001$), while there was no such effect in low-frequency rTMS studies ($N = 4$, Hedges' $g = 0.962$, CI = [−1.137, 3.061], $z = 0.898$, $p = 0.369$), though the low-frequency effect did not significantly differ from the high-frequency effect [$Q(1) = 2.50$, $p = 0.113$]. Although the studies employed different sites of stimulation, we only analyzed the overall effect size of stimulating the left DLPFC ($N = 6$, Hedges' $g = 1.465$, CI = [0.170, 2.760], $z = 2.217$, $p = 0.027$) due to lack of studies in other sites (see **Appendix**).

The meta-regression between the total number of sessions ($N = 16$) and the alleviation in craving was not significant [$Q(1) = 0.0006$, $p = 0.98$], so was the number of pulses in rTMS studies [$N = 12$, $Q(1) = 0.37$, $p = 0.54$]. However, we observed a negative relationship between the number of pulses per session and the rTMS outcome [$N = 12$, $Q(1) = 8.04$, $p = 0.005$] (**Figure 4**), while

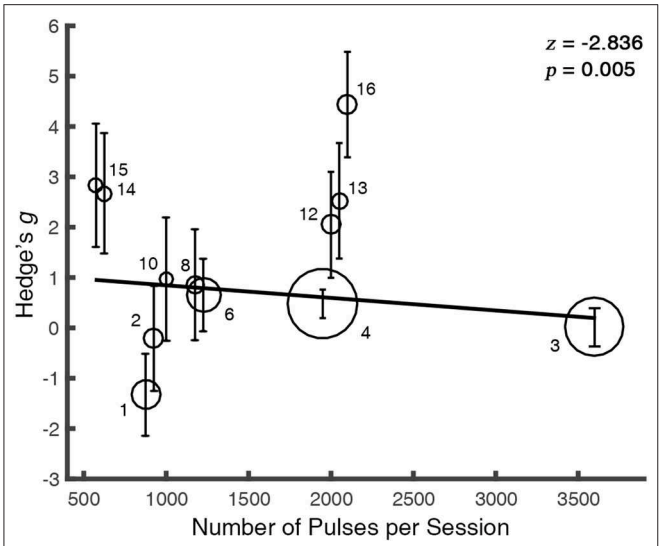

FIGURE 4 | The therapeutic outcome is modulated by the number of pulses per session. For clarity, the overlapped values of regressor were randomly jittered. The solid line is the fixed-effect regressive function for the regressor. The size of each bubble represents the study's relative weight which was calculated as the inverse of the variance. Error bars indicate the 95% CIs. The markers abut to the bubbles correspond to the index of studies in the **Appendix**.

the overall days of stimulation [$N = 16$, $Q(1) = 0.02$, $p = 0.88$] and the number of sessions per day [$N = 16$, $Q(1) = 0.60$, $p = 0.44$] did not reveal significant effect.

DISCUSSION

The current study has confirmed the feasibility of using NIBS to allay cocaine or methamphetamine craving given a large main effect of stimulation (Hedge's $g = 1.116$). While, this effect showed heterogeneity that partly originated from subject variables which is consistent with the ubiquitous individual difference of NIBS effect (Ridding and Ziemann, 2010; López-Alonso et al., 2014). In addition, only high-frequency rTMS could elicit a significant treatment effect while the outcome of low-frequency rTMS was relatively controversial. We also found that the less pulses per session, the larger the NIBS effect would be. These results extended the notion toward NIBS intervention in multiple aspects.

In contrast to the current conclusion, previous clinical guidelines suggested that NIBS might not be applicable in the treatment of SUD (Lefaucheur et al., 2014, 2017). Such difference might stem from two aspects: first, the guidelines are based on qualitative integrations toward previous findings, while we quantitatively assessed the effect by calculating the overall effect size, by adding many recent findings (most of them are published after the year 2017). Meanwhile, other quantitative meta-analyses like Jansen et al. (2013) and Song et al. (2019) found significant main effect of NIBS treatment for SUD as well. On the other hand, we specifically probed the effect of NIBS over DA-dependent SUD, while the guidelines combined different kinds of SUD together. Thus, the inconsistency in the final outcomes might originate from the difference in the mechanisms of addiction among different SUDs.

A great many studies have effectively proved that NIBS could induce changes in cortical excitability (Ridding and Rothwell, 2007; Barr et al., 2008). A pulsatile electromagnetic field around the coil or direct current from the patch can induce an immediate excitatory effect to the neurons beneath the coil or patch (Spagnolo and Goldman, 2017). rTMS targeting at prefrontal areas could impact executive control functions (Stürmer et al., 2007). On the other hand, fronto-parietal circuit dysfunction has been found in stimulant abusers along with resultant deficits in executive functions (Goldstein and Volkow, 2002). Given that the current meta-analysis has revealed a frequency-specific pattern of rTMS treatment, high-frequency stimulation to the scalp may potentially produce long-term-potentiation-like (LTP-like) effects in the target cortical areas in a frequency-related manner (Ridding and Rothwell, 2007). Furthermore, 10-Hz rTMS to the prefrontal regions has been proved to induce changes in DA binding in monosynaptic striatal targets and the downstream frontal cortices (Strafella et al., 2001; Pogarell et al., 2006; Cho and Strafella, 2009). The increase in DA level elicited by rTMS was close to the aftereffect of amphetamine injection (Pogarell et al., 2007). Besides, cocaine and methamphetamine are substances that directly act on DA receptors. Our meta-analysis has ascertained the effectiveness of NIBS in alleviating craving to these two DA-dependent addictions which implied that NIBS treatment might alter DA-related functions. Take all these evidences into consideration, the DA theory of NIBS (Diana, 2011), which assumed that NIBS could antagonize the DA shortage in abusers through the upward spiral of PFC-VTA-NAc circuit (**Figure 1**), should be a tenable explanation to the observed treatment effect. Nonetheless, this hypothesis is still in lack of direct evidence so far. The causal link between the ramping up of DA level caused by NIBS and the alleviation in craving requires further test.

The current study also revealed that scaling up the number of pulses per session rather than the aggregate of pulses could induce harmness to the treatment. This implied that rTMS treatment should be provided in multiple sessions with each session ideally compressed. Stimulants like cocaine and methamphetamine manipulate DA level by physically altering DA receptor functions and gradually lead to desensitization to the external stimuli (Kahlig and Galli, 2003; Volkow et al., 2008; Wang et al., 2012). According to the DA theory of NIBS, rTMS could activate Dopaminergic neurons in VTA through the feedback projections from PFC and elicit DA release in striatal targets (Cho and Strafella, 2009; Diana, 2011). Hence, the negative moderation of the number of pulses per session might possibly stem from the desensitization of neurons in DA system or the brain regions beneath the coil induced by the intensive stimulation. As a result, there's expected to be a saturation point in the rTMS dose-response relationship after a certain number of pulses. Such saturation effects with pulses of over-dosage in SUD need to be further carefully considered, and generated to other applications of treatment with NIBS, such as depression or Parkinson's disease (Chou et al., 2015; Sehatzadeh et al., 2019), which also recruit the PFC-VTA DA pathway.

It should also be noted that Song et al. (2019) find a monotonic positive moderation effect of the number of pulses which is inconsistent with the current result. We argue that this might originate from the different ways of data extraction. The current analysis only used the result of the first probe after the stimulation in each study as the main effect size while Song et al. (2019) averaged all the craving scores in the post-stimulation probes, which could introduce the confounding factor of the relapse effect. Besides, Song et al. (2019) included the treatments of eating disorder and obesity in their analysis and they could have different dose-response properties compared with DA-drugs. Previous clinical guidelines regarding NIBS all focused on the stimulation parameters such as montages, frequency and intensity (Lefaucheur et al., 2014, 2017). However, to our knowledge, none of them attended to the methodology of segmentation. We believe that more future studies are needed to explore the prospective turning point in each session of treatment in order to optimize the stimulating protocol.

Despite the promising findings, the current meta-analysis had several limitations. First, there were only 12 studies survived by the screening, which led to a deficiency in statistical power. Specifically, only four units of tDCS trials were included in the analysis, so it would be premature to make conclusions regarding whether tDCS is useful in helping rehabilitation of SUD although three of the included units all showed positive effect (Shahbabaie et al., 2014, 2018; Batista et al., 2015). Further work is required to confirm the effect of tDCS in the light of its conspicuous convenience and cost-effectiveness. Second, our analysis could not reliably estimate the effect of stimulating regions other than the left DLPFC. Frontal-limbic loop has two separate sub-circuits. Executive control loop consists of DLPFC and dorsal striatum while limbic control loop comprises medial PFC (mPFC), ACC, and ventral striatum (Alexander et al., 1986). Martinez et al. (2018) employ H-coil to stimulate mPFC and ACC in cocaine-dependents. They find significant reduction in craving for the stimulating group after the 13-day high-frequency rTMS while their craving level does not differ from the sham group. However, Hanlon et al. (2015) detect that the decrease in craving for the stimulating condition is larger than the sham condition after a single-session cTBS targeting at the frontal pole in order to stimulate the ventral mPFC. Nonetheless, they do not replicate this effect in a recent study (Hanlon et al., 2017). Thus, the effect of stimulating cortices involved in the limbic control loop is still in controversy. Third, the current study is insufficient to test the follow-up effect. Although some studies have probed craving levels several days after the treatment, not all of them have reported the between-group difference in the relapse rate of craving level. Moreover, the interval between the end of treatment and the follow-up test was chosen inconsistently across those studies. Systematic investigations toward the temporal properties of NIBS effect in reducing craving would be informative in the future. Fourth, the current study should only be treated as a preliminary discussion about the mechanism of NIBS treatment. As a matter of fact, we still could not tell the origin of the rehabilitation: does it come from the direct alteration of excitability in the target cortices induced by stimulation, or through the mediation of Dopaminergic deep brain nuclei, or a mixture of the two candidate mechanisms? We believe that neuroimaging or lesion studies would be especially helpful in this issue.

Altogether, the current study indicated that NIBS is a safe and effective treatment for DA-dependent SUD. The heterogeneity in the previous trials comes from individual differences and the discrepancies in stimulation protocol. Future extensions should focus on the optimization of this promising technique by qualifying the current findings and meanwhile exploring the underlying mechanism in order to find a reliable and powerful treatment against SUD.

DATA AVAILABILITY STATEMENT

The original data of all the results could be found in the **Supplementary Material**.

AUTHOR CONTRIBUTIONS

YK: conceptualization, supervision, writing—review, editing, and funding acquisition. TM and YS: data curation and writing—original draft. TM: data analysis.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2019.01095/full#supplementary-material

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ORIGINAL RESEARCH
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Accelerated Intermittent Theta-Burst Stimulation as a Treatment for Cocaine Use Disorder: A Proof-of-Concept Study

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There are no effective treatments for cocaine use disorder (CUD), a chronic, relapsing brain disease characterized by dysregulated circuits related to cue reactivity, reward processing, response inhibition, and executive control. Transcranial magnetic stimulation (TMS) has the potential to modulate circuits and networks implicated in neuropsychiatric disorders, including addiction. Although acute applications of TMS have reduced craving in urine-negative cocaine users, the tolerability and safety of administering accelerated TMS to cocaine-positive individuals is unknown. As such, we performed a proof-of-concept study employing an intermittent theta-burst stimulation (iTBS) protocol in an actively cocaine-using sample. Although our main goal was to assess the tolerability and safety of administering three iTBS sessions daily, we also hypothesized that iTBS would reduce cocaine use in this non-treatment seeking cohort. We recruited 19 individuals with CUD to receive three open-label iTBS sessions per day, with approximately a 60-min interval between sessions, for 10 days over a 2-week period (30 total iTBS sessions). iTBS was delivered to left dorsolateral prefrontal cortex (dlPFC) with neuronavigation guidance. Compliance and safety were assessed throughout the trial. Cocaine use behavior was assessed before, during, and after the intervention and at 1- and 4-week follow-up visits. Of the 335 iTBS sessions applied, 73% were performed on participants with cocaine-positive urine tests. Nine of the 14 participants who initiated treatment received at least 26 of 30 iTBS sessions and returned for the 4-week follow-up visit. These individuals reduced their weekly cocaine consumption by 78% in amount of dollars spent and 70% in days of use relative to pre-iTBS cocaine use patterns. Similarly, individuals reduced their weekly consumption of nicotine, alcohol, and THC, suggesting iTBS modulated a common circuit across drugs of abuse. iTBS was well-tolerated, despite the expected occasional headaches. A single participant developed a transient neurological event of uncertain etiology on iTBS day 9 and cocaine-induced psychosis 2 weeks after discontinuation. It thus appears that accelerated iTBS to left dlPFC administered in active, chronic cocaine users is both feasible and tolerable in

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actively using cocaine participants with preliminary indications of efficacy in reducing both the amount and frequency of cocaine (and other off target drug) use. The neural underpinnings of these behavioral changes could help in the future development of effective treatment of CUD.

Keywords: cocaine use disorder, intermittent theta-burst stimulation, open-label, accelerated iTBS, dorsolateral prefrontal cortex (DLFPC)

INTRODUCTION

Addiction is a complex neurobiological disease manifested as compulsive substance use in the face of known negative consequences (Volkow et al., 2016). Approximately 25 million Americans use illicit drugs, costing $193 billion annually, in areas such as health care and lost productivity (Ndic, 2010). Nearly 25% of Americans reporting a lifetime drug dependence also report cocaine dependence (Grant et al., 2016). This chronic, relapsing brain disease is characterized by dysregulated circuits related to cue reactivity, reward processing, executive control, and intrinsic network connectivity (Garavan et al., 1999, 2000; Gu et al., 2010; Steele et al., 2014, 2017, 2018a, 2019; Hu et al., 2015; Fedota et al., 2016; Fink et al., 2016; McHugh et al., 2016). Low retention (∼42%) and high relapse (∼70%) rates plague current treatments for cocaine use disorder (CUD; Dutra et al., 2008). As there are no FDA-approved pharmacotherapies for cocaine dependence, it is imperative to identify promising new treatment interventions.

Non-invasive brain stimulation (NIBS), a tool thought to modulate brain circuits, may be a potential treatment approach, as it appears to be efficacious in several neuropsychiatric disorders (Wassermann and Zimmermann, 2012) including addictions (Diana et al., 2017). However, there are only two publications using transcranial magnetic stimulation (TMS) in an open-label fashion for CUD (Terraneo et al., 2016; Sanna et al., 2019). NIBS is designed to transiently stimulate localized cortex (Barker et al., 1985; George et al., 2003; Hallett, 2007; Parkin et al., 2015) and their downstream cortical and subcortical targets. Regions implicated in CUD include dorsolateral prefrontal cortex (dlPFC), anterior cingulate cortex (ACC), inferior frontal gyrus (IFG), orbitofrontal cortex (OFC), striatum, hippocampus, and insula (Jovanovski et al., 2005; Koob and Volkow, 2010; Goldstein and Volkow, 2011; Volkow et al., 2012; Spronk et al., 2013; Steele et al., 2017, 2019). NIBS applied acutely to various circuits has reduced drug craving in nicotine (Li et al., 2013), alcohol (Mishra et al., 2010), heroin (Shen et al., 2016), methamphetamine (Liang et al., 2018), and cocaine (Camprodon et al., 2007; Politi et al., 2008; Hanlon et al., 2015; Terraneo et al., 2016) users.

A potentially viable NIBS application for CUD is intermittent theta-burst stimulation (iTBS; Huang et al., 2005; Bakker et al., 2015). The post-iTBS shift in electrical baseline exceeds the duration measured for repetitive transcranial magnetic stimulation (rTMS; Chistyakov et al., 2010; Holzer and Padberg, 2010; Di Lazzaro et al., 2011) while requiring far fewer pulses and less time to implement, thus allowing for a briefer treatment session, which could improve patient retention. Moreover, a recent non-inferiority assessment showed iTBS to be as effective for treatment-resistant depression as rTMS (Blumberger et al., 2018). Preliminary data from open-label (Camprodon et al., 2007; Politi et al., 2008; Terraneo et al., 2016; Sanna et al., 2019) and single-blind (Hanlon et al., 2015) studies have shown that NIBS can reduce cocaine craving and reduce cocaine usage. However, iTBS in actively using CUD patients, a necessary condition in a treatment environment, needs further exploration. As such, we performed a proof-of-concept study to establish tolerability and feasibility of such an intervention to treat active CUD.

The Current Study

We recruited non-treatment seeking CUD individuals actively using cocaine at the time they entered the study to receive open-label iTBS targeting left dlPFC. As depression interventions with NIBS elicit positive effects after at least 26–28 sessions (Carpenter et al., 2012; Dunlop et al., 2017), we chose to implement 30 iTBS sessions over a 2-week period. We hypothesized that this intervention would be feasible in cocaine positive participants (i.e., a good safety profile in this population), participants would tolerate iTBS, and participants would reduce their cocaine use (both amount and frequency of use) post-iTBS. A thorough battery of clinical assessments was collected to measure potential off-target effects related to the iTBS intervention, including mood and use of other drugs of abuse.

MATERIALS AND METHODS

Participants

Right-handed individuals ($N = 19$) with moderate to severe CUD, who were non-treatment seeking, provided written, informed consent [6 females, mean (± SEM) age = 47.4 ± 2.0 years, IQ = 95.1 (± 2.7), years of education = 12.5 ± 0.4, years of cocaine use = 23.1 ± 2.6; **Table 1**]. All procedures were approved by the National Institute on Drug Abuse Institutional Review Board and the Food and Drug Administration (FDA). Exclusion criteria included lifetime history of schizophrenia or bipolar disorder, current moderate to severe SUD on any substance except cocaine, nicotine, or THC, meeting withdrawal or tolerance criteria to alcohol or a sedative/hypnotic/anxiolytic, contraindications to TMS administration such as a history of seizures, medications that lower seizure threshold, first degree relative with a heritable neurological disorder, pregnancy/lactation, tinnitus, hearing loss, history of myocardial infarction, angina, congestive heart failure, cardiomyopathy, stroke or transient ischemic attack, mitral valve prolapse, or any hearing condition currently under medical care, participation in any NIBS session less than 2 weeks prior to consent and NIBS exposure as a treatment

TABLE 1 | Demographics.

	All participants *N* = 19 Mean (SEM)	Completers *N* = 9 Mean (SEM)	Non-completers *N* = 10 Mean (SEM)
Sex (F/M)	6/13	5/4	1/9
Race (AA/C/+/NR)	14/3/1/1	7/2	7/1/1/1
Ethnicity (H/Not)	1/18	0/9	1/9
Age	47.4 (2.0)	50.8 (1.9)	44.3 (1.9)
IQ	95.1 (2.7)	97.9 (3.9)	93.7 (3.8)
Years of education	12.5 (0.4)	12.9 (0.4)	12.2 (0.8)
Years of cocaine use	23.1 (2.6)	29.4 (2.8)	17.4 (3.4)

F, female; M, male; AA, African American; C, Caucasian; +, multiracial; NR, not reported; H, Hispanic; Not, not Hispanic; SEM, standard error of the mean. Completers include the nine participants who completed at least 26/30 iTBS sessions and returned for at least one follow-up. Non-completers include the remaining 10 participants who were admitted to the study but either did not complete at least 26/30 iTBS sessions (N = 9) or completed 30/30 iTBS sessions but did not return for follow-up (N = 1).

within 6 months, or history of head trauma resulting in loss of consciousness lasting over 30 min or sequelae lasting longer than 1 month.

Study Timeline

Following consent, participants completed questionnaires and were assessed for tolerability of the iTBS intervention. Then, 10 days of iTBS were administered over a 2-week period with two sets of five consecutive days scheduled with a 2-day break between weeks. Participants who completed at least 21/30 iTBS sessions were eligible for two follow-up appointments (1- and 4-weeks post-treatment; **Figure 1**). The first 10 participants were enrolled as inpatients and the last 9 were enrolled as outpatients. Inpatients arrived the night before their first and sixth iTBS day and remained inpatient other than the 2-day break. Upon arrival, participants underwent a search of their person and belongings to ensure abstinence during their inpatient stay. All of the participants who initiated iTBS reported the sessions became more tolerable with number of sessions accumulated. Overall, 335 iTBS sessions were administered with 73% performed on participants with cocaine-positive urine tests.

Study Attrition

Of the 19 participants recruited, 14 initiated iTBS (**Figure 2**). Of the remaining five participants, two did not tolerate the iTBS and three were lost to contact following consent and iTBS orientation session. Ten of the 14 participants who initiated iTBS received at least 26 of 30 iTBS sessions, two of these did not return for a 1-week follow-up while nine (six as inpatient) returned for a 4-week follow-up session and are defined as "Completers." No participant returned for the first, but not the second, follow-up session. "Non-Completers" include the remaining 10 participants who were admitted to the study but either did not complete at least 21/30 iTBS sessions (N = 9) or completed 30/30 iTBS sessions but did not return for follow-up (N = 1). Reasons for not completing include not tolerating iTBS (N = 2), lost to contact after consent and prior to initiating iTBS (N = 3), lost to contact after completing 2 days of iTBS (N = 1), missed a scheduled appointment due to lack of transportation after completing four iTBS days (N = 1), discharged after arriving for iTBS day 7 intoxicated (N = 1; i.e., non-compliance), and withdrawal due to unwillingness to comply with visitation limits on the inpatient unit (N = 1; i.e., non-compliance).

Clinical Assessments

Self-report and interview-based measures probing mood, motivation, and drug use behavior were collected throughout the protocol and are summarized in **Tables 2**, **3**.

Several additional measures generated internally were also implemented. The Cocaine-Induced Psychosis: Screener (CIP: Screener) was designed by one of us (BJS) for efficient assessment of cocaine-induced psychosis and was used to assess changes, relative to baseline, in symptoms of psychosis throughout the protocol. This assessment was administered on all study days after the baseline visit if the participant reported cocaine use since the last visit. Any change from baseline triggered administration of the full Scale of Positive Symptoms for Cocaine-Induced Psychosis (SAP-CIP; Cubells et al., 2005). The iTBS Monitoring Questionnaire is a 13-item interview-based yes/no questionnaire assessing side effects of TMS (e.g., headaches, nausea, seizure). The Positive and Negative Affect Scale (PANAS; Watson et al., 1988) was modified by adding an item "Right now I feel detached" because previous reports of detachment have been reported as a potential side effect of TMS (Levkovitz et al., 2007). The Cocaine Use, Pattern, and Withdrawal Questionnaire was designed (BJS) to assess the general pattern of use and withdrawal of cocaine using participants.

At the beginning of each study day, participants received a nursing assessment, comprised of vital signs (e.g., blood pressure, heart rate, pulse oximetry, respiration, temperature), hours of sleep, observed urine sample for toxicology, urine pregnancy tests, and TMS safety screen. Time and date of last food intake, drug and alcohol use, and prescription medication use were also collected at each nursing assessment. Participants were not required to be cocaine-negative prior to iTBS treatment but did need to pass a neuromotor assessment (Heishman et al., 1996) indicating no signs of acute intoxication. Two hours post-TMS, vitals (blood pressure and heart rate) were assessed.

Monitoring Cognitive and Affective Changes

At the suggestion of the FDA, several measures were collected to specifically assess cognitive and affective changes potentially linked to chronic iTBS administration in an actively cocaine using sample. The timing of these measures was designed to assess potential detrimental off-target effects of iTBS. Several assessments were collected daily, before and after iTBS administration: iTBS monitoring questionnaire, the modified PANAS (Watson et al., 1988), Cocaine Craving Questionnaire (CCQ; Tiffany et al., 1993), and the Cocaine Craving Scale (CCS; Weiss et al., 1997). Assessments of mood disturbance

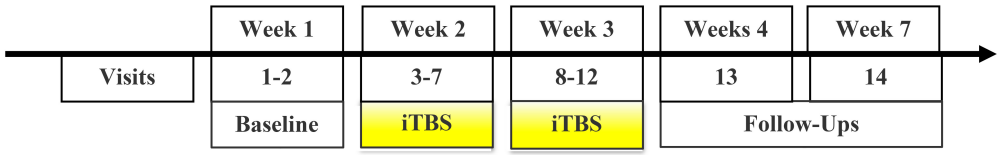

FIGURE 1 | Study timeline: Consent, baseline characterization, and iTBS orientation were implemented over 1–2 visits prior to the initiation of iTBS. Thirty sessions of iTBS were administered over 10 visit days during a 2-week period. Two follow-up appointments were scheduled at 1- and 4-weeks after iTBS.

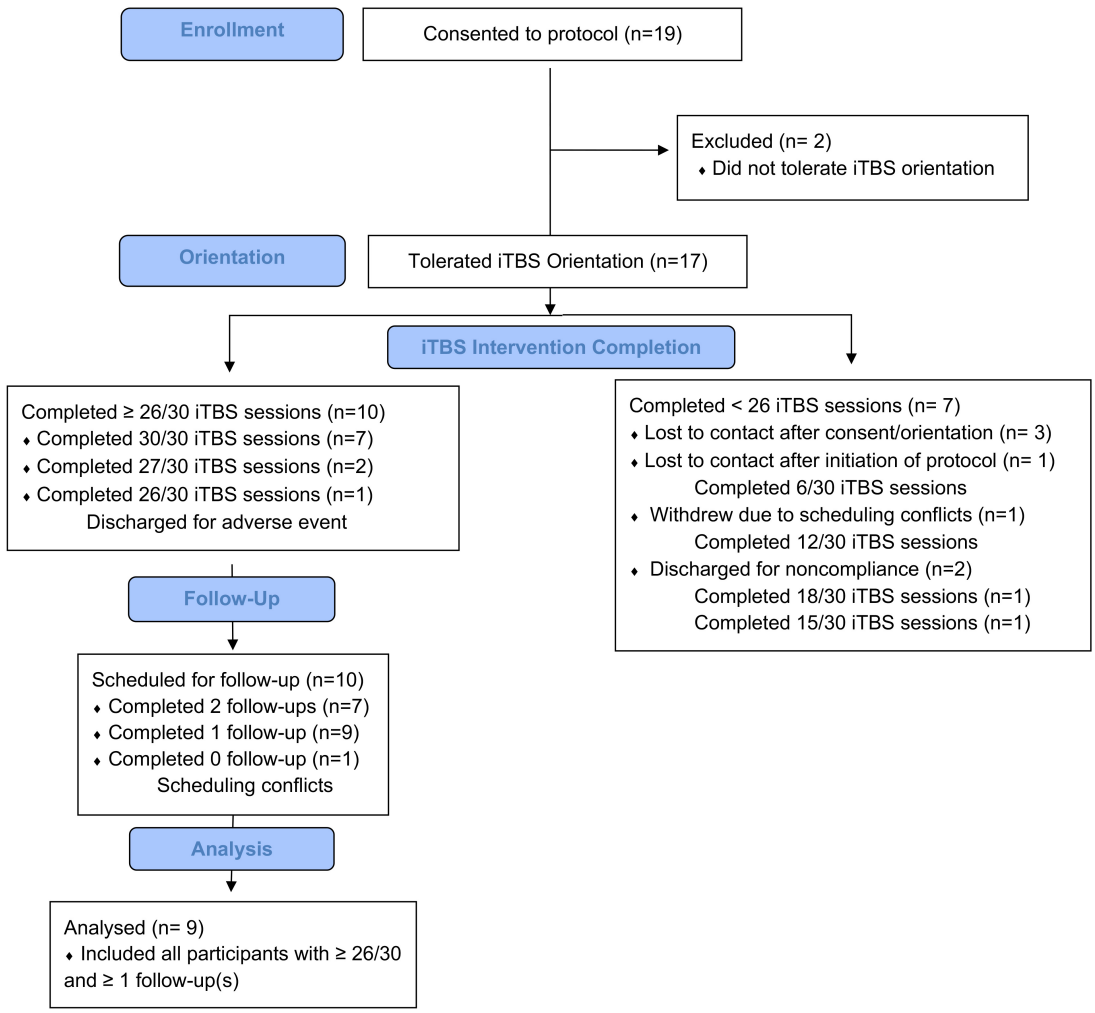

FIGURE 2 | Study attrition: Of the 19 participants consented to the study, 17 of these participants tolerated iTBS orientation, 14 initiated treatment, 10 completed at least 26/30 iTBS sessions. Nine of these 10 returned for at least one follow-up appointment.

and cognition were collected at the beginning and end of the 2-week iTBS administration: Columbia Suicide Severity Scale – (C-SSS; Posner et al., 2011), Montgomery-Asberg Depression Rating Scale (MADRS; Fantino and Moore, 2009), Profile of Mood States (POMS; McNair et al., 1989), Trail Making Task (TMT; Lezak et al., 2004), and Young Mania Rating Scale (YMRS; Young et al., 1978). The Timeline Follow Back (TLFB) was collected at the beginning of each study day whenever the participant was not an inpatient to assess ongoing drug use (in addition to daily urine toxicology).

Transcranial Magnetic Stimulation

Equipment

A MagVenture MagPro X100 with MagOption Stimulator was used throughout the study. Two MagVenture figure-of-8 coils were used: CB 60 was used for single pulses and the

TABLE 2 | Characterization measurements across treatment timeline.

	Screening	Orientation	iTBS day 1	iTBS day 10	One-week follow-up	Four-week follow-up
Adult ADHD Self Report Scale	*N* = 17	—	—	—	—	—
Attitudes Towards Risk Questionnaire	—	*N* = 18	—	—	*N* = 7	*N* = 9
Addiction Severity Index	*N* = 18	—	—	—	—	—
Beck Anxiety Inventory	—	*N* = 19	—	—	*N* = 9	
Brief Externalizing Inventory	—	*N* = 18	—	—	*N* = 7	*N* = 9
Brief Cocaine Cessation Motivation Assessment	*N* = 19	—	—	—	—	—
Chapman Scales for Physical and Social Anhedonia	—	*N* = 18	—	—	*N* = 7	*N* = 9
Cocaine Craving Questionnaire	—	*N* = 18	*N* = 14	*N* = 9	*N* = 7	*N* = 9
Cocaine Craving Scale	—	*N* = 18	*N* = 14	*N* = 9	*N* = 7	*N* = 9
Cocaine Use, Pattern, and Withdrawal Questionnaire		*N* = 14	—	—	*N* = 7	*N* = 9
Columbia Suicide Severity Scale	—	—	*N* = 14	*N* = 9	—	—
Montgomery-Asberg Depression Rating Scale	—	*N* = 17	*N* = 14	*N* = 9	*N* = 9	—
Nursing Assessment: Hours of Continuous Sleep	—	*N* = 18	*N* = 14	*N* = 9	—	—
Multidimensional Social Contact Circle	—	*N* = 17	—	—	*N* = 7	*N* = 9
Positive and Negative Affect Scale	—	*N* = 19	*N* = 14	*N* = 9	*N* = 7	*N* = 9
Profile of Mood States	—	*N* = 19	*N* = 14	*N* = 9	*N* = 9	
Resting Motor Threshold	—	*N* = 19	*N* = 14	*N* = 9	*N* = 2	*N* = 3
Scale for the Assessment of Positive Symptoms for Cocaine-Induced Psychosis	—	*N* = 7	—	—	*N* = 2	*N* = 3
Snaith – Hamilton Pleasure Scale	—	*N* = 17	—	—	*N* = 7	*N* = 9
Sensation Seeking Scale - V	—	*N* = 17	—	—	*N* = 7	*N* = 9
Temperament and Character Inventory	—	*N* = 17	—	—	—	*N* = 9
Trail Making Task	—	—	*N* = 14	*N* = 9	—	—
Young Mania Rating Scale	—	—	*N* = 14	*N* = 9	—	—

Characterization measures were collected at different timepoints throughout the screening, iTBS, and follow-up appointments. Of note, due to adjustments in the protocol during data collection, several measures were collected from a limited number of participants. Namely, collection of the "Scale for the Assessment of Positive Symptoms for Cocaine-induced Psychosis" (SAPS-CIP) began following the previously-described unexpected adverse event during which one participant presented with symptoms of psychosis 2 weeks following the termination of treatment. Additionally, collection of the resting motor threshold (RMT) was initiated during the outpatient phase following protocol changes, so only three participants were eligible to receive TMS at their follow-up appointments. The SAPS-CIP was collected from only two participants at the 1-week follow-up because one participant reported no cocaine use since the last day of iTBS, precluding the necessity to administer the questionnaire according to the protocol (see SAPS-CIP in methods). RMT was collected from only two participants at the 1-week follow-up because one participant had received too little sleep the night prior and was ineligible for TMS that day. These versions of assessments were used: Adult ADHD Self-Report Rating Scale (Kessler et al., 2005); Attitudes Towards Risk Questionnaire (Franken et al., 1992); Addiction Severity Index (McLellan et al., 1992); Beck Anxiety Inventory (Beck et al., 1988); Brief Externalizing Inventory (Hall et al., 2007); Brief Cocaine Cessation Motivation Assessment (Boudreaux et al., 2012); Chapman Scales for Physical and Social Anhedonia (Chapman et al., 1976); Cocaine Craving Questionnaire (Tiffany et al., 1993); Cocaine Craving Scale (Weiss et al., 1997); Cocaine Use, Pattern, and Withdrawal Questionnaire (internally generated); Columbia Suicide Severity Scale (Posner et al., 2011); Montgomery-Asberg Depression Rating Scale (Fantino and Moore, 2009); The Multidimensional Social Contact Scale adapted from Linden et al. (2007); Positive and Negative Affect Scale (Watson et al., 1988) was modified by adding an item "Right now I feel detached" because of previous reports of detachment as a potential side effect of TMS (Levkovitz et al., 2007); Profile of Mood States (McNair et al., 1989); Scale for the Assessment of Positive Symptoms for Cocaine-Induced Psychosis (Cubells et al., 2005); Snaith-Hamilton Pleasure Scale (Snaith et al., 1995); Temperament and Character Inventory (Cloninger(ed.), 1994); Time-Line Follow Back; Trail Making Task (Lezak et al., 2004); Young Mania Rating Scale (Young et al., 1978). Dashes indicate "NA," meaning the questionnaire was not administered at the selected timepoint.

and A/P Coil was used for iTBS administration. Participant-specific motor hotspot and left dlPFC treatment locations were saved via the neuronavigation system Brainsight (Rouge Research, Quebec, Canada). Left dlPFC was located using the software Beam_F3 Locator, which allows localization of the F3 electrode location from the 10–20 EEG system for prefrontal TMS applications (Beam et al., 2009). Adaptive PEST, a non-parametric algorithm for estimating TMS motor threshold (Borckardt et al., 2006), was used to determine resting motor threshold (RMT; described below). All TMS sessions occurred with the participant seated in a comfortable chair, with the ability to recline if needed. A chinrest and head support 60 cm from a computer screen were used during iTBS administration for participant comfort and to ensure similar stimuli viewing experience among participants.

Orientation

During the orientation day, we identified motor hotspot, determined RMT, collected a recruitment curve, and assessed the tolerability of iTBS. Motor hotspot was defined as the region

TABLE 3 | Self-report and interview-guided measurements across participants.

	Completers: baseline Mean (SEM)	Non-completers: baseline Mean (SEM)	Completers: iTBS day 10 Mean (SEM)	Completers: 1-week follow-up Mean (SEM)	Completers: 4-week follow-up Mean (SEM)
Attitudes Towards Risk Questionnaire	110.2 (10.2)	111.2 (7.4)	—	112.3 (12.8)	113.2 (7.5)
Adult ADHD Self Report Scale	20.9 (5.1)	17.2 (2.8)	—	—	—
Addiction Severity Index: Drug Composite	0.18 (0.1)	0.1 (0.02)	—	—	—
Beck Anxiety Inventory	3.0 (1.2)	5.5 (2.5)	—	4.0 (1.7)	—
Brief Cocaine Cessation Motivation Assessment: Drive to Quit	20.1 (2.4)	16.8 (2.0)	—	—	—
Brief Externalizing Inventory	375.8 (27.0)	373.3 (26.3)	—	345.9 (30.1)	368.7 (24.4)
Chapman Scales for Physical and Social Anhedonia	32.0 (3.0)	31.7 (3.1)	—	28.7 (4.1)	32.8 (4.2)
Cocaine Craving Questionnaire	178.7 (12.5)	150.1 (11.6)	110.3 (11.2)	107.3 (15.6)	112.8 (12.6)
Cocaine Craving Scale	28.4 (4.7)	26.4 (5.0)	6.6 (3.4)	9.0 (5.6)	20.9 (5.6)
CUP: Mental Withdrawal	6.4 (3.4)	4.2 (1.4)	—	4.7 (0.6)	4.7 (0.8)
CUP: Physical Withdrawal	6.1 (0.5)	6.4 (1.2)	—	6.3 (1.3)	5.7 (0.8)
CUP: Desire to Quit	10.9 (0.7)	11.6 (0.9)	—	11.0 (0.8)	11.57 (1.7)
CUP: Urgency to Use	7.9 (1.3)	1.9 (0.8)	—	3.9 (1.1)	3.6 (1.0)
CUP: Negative Drive to Use	13.9 (1.1)	12.6 (2.8)	—	12.1 (1.3)	11.9 (1.4)
CUP: Positive Drive to Use	8.8 (1.4)	10.0 (2.2)	—	7.0 (1.5)	8.1 (0.7)
CUP: Social Factors to Use	7.8 (1.0)	6.2 (0.9)	—	7.4 (1.04)	8.7 (0.7)
CUP: Avoidance of people/places associations with use	3.9 (0.6)	4.4 (0.6)	—	5.7 (0.56)	5.9 (0.53)
Columbia Suicide Severity Scale	0.7 (0.6)	0.00 (0)	0.00 (0)	—	—
Montgomery-Asberg Depression Rating Scale	3.9 (41.6)	1.0 (0.8)	1.0 (1.0)	0.7 (0.4)	—
Multidimensional Social Contact Circle	20.2 (5.7)	19.2 (3.8)	—	22.0 (5.6)	15.4 (4.5)
Nursing Assessment: Hours of Continuous Sleep	7.9 (0.3)	7.2 (0.4)	6.7 (0.5)	6.4 (0.9)	6.8 (0.5)
PANAS: Detachment	1.11 (0.1)	1.4 (0.2)	1.25 (0.25)	1.4 (0.4)	1.63 (0.3)
POMS: Fatigue	2.6 (1.2)	2.2 (0.8)	4.0 (1.4)	2.3 (1.0)	—
POMS: Confusion	1.7 (0.7)	1.9 (1.2)	2.4 (1.1)	2.0 (0.7)	—
POMS: Anger-Hostility	1.1 (0.8)	2.3 (1.0)	3.5 (2.0)	2.1 (1.3)	—
POMS: Tension	5.6 (1.0)	7.2 (1.7)	5.4 (1.3)	3.9 (1.1)	—
POMS: Depression	5.7 (2.2)	6.0 (6.3)	7.4 (2.8)	5.2 (1.5)	—
POMS: Vigor	16.2 (7.3)	14.8 (2.2)	16.5 (1.03)	16.6 (2.2)	—
Resting Motor Threshold	62.9 (3.1)	54.1 (4.3)	62.1 (1.8)	55.0 (8.0)	61.0 (6.0)
Scale for the Assessment of Positive Symptoms for Cocaine-Induced Psychosis	5.7 (3.8)	2.25 (0.2)	—	7.5 (5.5)	0.67 (0.67)
Sensation Seeking Scale - V	19.7 (2.7)	17.9 (1.1)	—	21.7 (3.4)	19.1 (2.7)
Snaith – Hamilton Pleasure Scale	0.44 (0.2)	1.1 (0.4)	—	0.9 (0.3)	0.44 (0.2)
TCI: Novelty	23.1 (21.6)	21.8 (1.0)	—	—	21.1 (2.0)
TCI: Harm Avoidance	13.1 (1.5)	13.8 (2.9)	—	—	14.2 (2.)
TCI: Reward	13.3 (1.5)	13.8 (1.1)	—	—	13.4 (1.7)
TCI: Persistence	6.3 (0.4)	4.8 (0.7)	—	—	6.9 (0.5)
TCI: Self-Directedness	26.7 (2.1)	29.8 (2.2)	—	—	26.0 (2.1)
TCI: Cooperativeness	31.8 (1.7)	31.0 (2.3)	—	—	32.7 (1.3)
TCI: Self Transcendence	17.8 (1.9)	11.9 (2.4)	—	—	19.7 (2.1)
TMT: Trial A (Errors/Duration in seconds)	0.44 (0.2) 30.8 (3.3)	0.0 (0.0) 24.8 (1.7)	0.38 (0.3) 25 (2.0)	—	—
TMT: Trial B (Errors/Duration in seconds)	0.44 (0.2) 54.0 (3.9)	0.80 (0.4) 51.2 (1.7)	0.75 (0.3) 53.5 (3.6)	—	—
Young Mania Rating Scale	0.11 (0.1)	0.00 (10.6)	0.38 (0.2)	—	—

CUP, Cocaine Use, Pattern, and Withdrawal Questionnaire; POMS, profile of mood states; SD, standard deviation; TCI, Temperament and Character Inventory; TMT, Trail Making Task. Dashes indicate "NA," meaning the questionnaire was not administered at the select timepoint. Completers include the nine participants who completed at least 26/30 iTBS sessions and returned for at least one follow-up. Non-completers include the remaining 10 participants who were admitted to the study but either did not complete at least 26/30 iTBS sessions (N = 9) or completed 30/30 iTBS sessions but did not return for follow-up (N = 1).

of the left motor cortex that reliably elicited movement of the contralateral abductor pollicis brevis (APB) muscle and/or an associated motor-evoked potential (MEP). TMS stimulation that elicited any movement in the contralateral hand and/or a MEP of at least 50 microvolts was counted as a positive response. The recruitment curve (i.e., dose/response curve) consisted of 42 total pulses applied to the motor hotspot while MEPs were recorded. Six pulses were administered at each of seven intensities ranging from 90 to 120% of RMT over about 5 min with jittered interstimulus interval (5–10 s). The MagVenture A/P coil was positioned for iTBS on the scalp using the Brainsight neuronavigation location identified previously with Beam_F3. Ramping of the stimulator output starting about 20 percentage points below RMT allowed a gradual increase of intensity as tolerated by the participant. When participants affirmed ramping between trains until they received two trains at their RMT, the toleration was deemed successful. If the iTBS administration was too painful (i.e., intolerable), participants could cease administration at any point. Generally, the stimulator was ramped by five points between each iTBS train until reaching RMT.

Intermittent Theta-Burst Stimulation

We implemented an accelerated iTBS treatment protocol, which entailed three iTBS sessions per day, with at least a 60-min interval between sessions, for 10 days yielding 30 overall iTBS sessions. Each iTBS session consisted of 600 pulses in 50 Hz bursts of three pulses, separated by 200 ms (i.e., a 5 Hz frequency) for 2 s, followed by 8 s of no pulses over about 190 s (Huang et al., 2005). The stimulator was 'ramped' (described above) to 100% of RMT for each session. Prior to each iTBS study day, the CB60 coil was used to confirm motor hotspot and determine the RMT. We collected recruitment curves before and after every iTBS session of the 1st, 5th, 6th, and 10th treatment day. TMS recruitment curves were acquired for two participants at the first follow-up and three participants at the second follow-up. Recruitment curves were not acquired at all follow-up visits because collection of this measure was added to the protocol at the onset of the outpatient phase. One participant was not able to receive TMS [i.e., resting motor threshold (RMT) determination and recruitment curve] at the first follow-up because he reported too little sleep ($<$5 h) the night prior. During each iTBS session, participants viewed cocaine-related pictures and were instructed to actively inhibit their cocaine craving using individualized strategies previously discussed with the study physician based on a cognitive-behavioral therapy intervention for CUD. Pictures (gathered internally and from collaborators) were each presented for 30 s with a 1-s fixation cross between images. TMS-safe goggles were provided for individuals requiring prescription lenses.

Data Analysis

Linear Mixed Models were performed in *R* to test our hypotheses that participants would reduce both the amount and frequency of cocaine use after iTBS, relative to baseline. Only Completers were included in the analyses. Statistical significance was judged against a threshold of $p < 0.05$. Because this was a proof-of-concept study with a small sample size, statistical tests were applied only to primary outcomes of amount and frequency of drug use. Qualitative assessment of trends is discussed for other measures. Although MEPs were recorded during recruitment curves, technical issues (clipped and noisy signals) during data collection preclude analysis of these data.

RESULTS

Drug Use Behavior

There were no qualitative differences in cocaine use at baseline between Completers and Non-Completers based on the TLFB. At the 4-week post-iTBS follow-up, the nine Completers reduced the amount of money (in US Dollars) spent on weekly cocaine consumption from \$197 (SD = \$115) at baseline to \$30 (SD = \$40) at the second follow-up, a 78% reduction (first follow-up reduction = 54%, M = \$61, SD = \$45), $F(2,14) = 17.54$, $p < 0.001$ (**Figure 3A**) and reduced the number of days of use from 4 (SD = 2) days per week at baseline to 1 (SD = 1) days per week at the second follow-up, a 70% reduction (first follow-up reduction = 44%, M = 2 days, SD = 1 days), $F(2,14) = 12.91$, $p < 0.001$, relative to pre-iTBS (**Figure 3B**). Similarly, other drug use generally decreased (**Figures 3C–H**). Specifically, participants reduced their cigarettes per week (baseline: M = 79, SD = 105; first follow-up: M = 25, SD = 22; second follow-up: M = 40, SD = 53. Note a heavy smoker did not return for the first follow-up) by 4%, number of alcohol drinks consumed (baseline: M = 10, SD = 9; first follow-up: M = 12, SD = 15; second follow-up: $M < 1$, $SD < 1$) per week by 8%, and both amount (baseline: M = 9, SD = 12; first follow-up: M = 4, SD = 5; second follow-up: M = 7, SD = 10) and frequency of marijuana joints (baseline: M = 4, SD = 3; first follow-up: M = 5, SD = 4; second follow-up: M = 3, SD = 4) per week by 44 and 90%, respectively. Two individuals increased their nicotine, alcohol, and/or THC use. One participant increased nicotine and THC use relative to baseline because of personal struggles that occurred during the study (i.e., separation from his wife and child). The second participant substantially increased his alcohol consumption relative to baseline because of reported binge drinking while on a date after iTBS. Neither increase in use appeared to be compensation for a reduction in cocaine use nor directly related to participating in this study.

Interestingly, in addition to the reported changes in use, participants also reported a change in their relationship with cocaine post-iTBS. Specifically, they spontaneously reported a reduced drive to use cocaine, an ability to stop using after initiating use (i.e., reduction in compulsive drug use) and, notably, reported they were unable to get as 'high' relative to pre-iTBS. One participant reported using threefold her normal amount of cocaine in an attempt to replicate her previous cocaine 'high' but was unsuccessful and was then able to stop using. Another participant returned for an unrelated study 1-year post-iTBS and reported her reduced cocaine use had persisted. She reported only using a limited amount on Friday and Saturday nights, would skip using for family events, her drive to use was

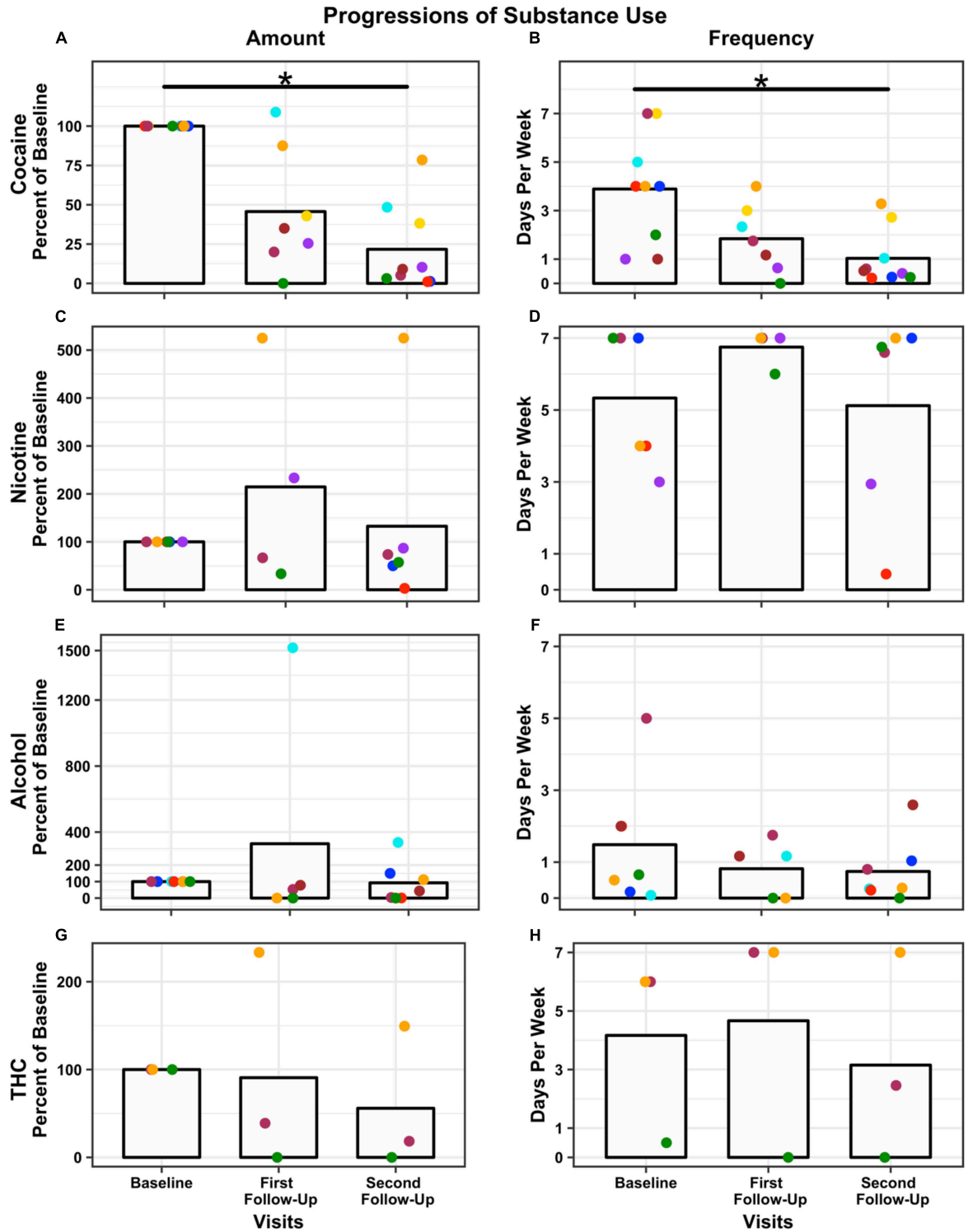

FIGURE 3 | Change in drug use over time: Amount (percent used relative to baseline) and frequency (days used per week) are presented for each time point, baseline, first follow-up at 1-week, and second follow-up at 4-week post-iTBS. Amount of use is plotted for each substance: cocaine **(A)**; nicotine **(C)**; alcohol **(E)**, and THC **(G)**. Frequency of use is plotted for each substance: cocaine **(B)**; nicotine **(D)**; alcohol **(F)**, and THC **(H)**. $N = 9$ used cocaine, $N = 5$ used nicotine, $N = 7$ used alcohol, and $N = 3$ used THC. Bars represent the average across participants at each time point (note two participants did not return for the first follow-up). Each dot represents a participant; dot color remains consistent within participant across time points and substance. Significance was assessed for cocaine only and not other substance use. Both amount and frequency of cocaine use significantly decreased post-iTBS $^{*}p < 0.001$. Results are presented graphically for qualitative assessment only.

reduced, and she was able to maintain the full-time employment she secured post-iTBS, whereas prior to iTBS she used cocaine daily and was not regularly employed.

Other Effects

Self-report craving measured with the CCS and CCQ decreased during the 2-weeks of iTBS administration and then increased at the follow-up visits, although they did not return to pre-iTBS levels. There were also qualitative changes in urgency to use (slight decrease), increase avoidance of people/places associated with use, decrease MADRS, and decrease SAP-CIP from baseline to follow-up visits. Other measures remained unchanged in the Completers following iTBS (**Table 3**). All participants who completed at least 4 days of iTBS exhibited improved mood. Many spontaneously reported a shift toward a positive outlook. Daily RMT remained consistent throughout the study (**Table 4**).

Adverse Events and iTBS Monitoring Questionnaire Results

Across all participants over the entire protocol, there were no unexpected, serious adverse events. Nine of the 14 participants who began iTBS sessions experienced at least one headache, usually beginning during or shortly after iTBS but a few in the evening after sessions were completed. Four experienced three or more headaches throughout the protocol. Most were mild and resolved without intervention. Seven headaches were reported after iTBS that required a single dose of acetaminophen; two participants each had two headaches and one participant had three. One participant experienced sudden pain around her eyes about an hour after completing her final iTBS session on day 7, which was accompanied by muscle twitching around the left eye and a dark spot in her left lateral peripheral vision which resolved in a few minutes. One experienced muscle soreness in the right forearm at the start of the second week of iTBS which resolved in 1 day. No negative side-effects in cognitive and affective assessments were reported or observed after iTBS. No participant experienced any signs of mania or suicidality.

One participant experienced two adverse events of note. After completing 26/30 iTBS sessions during the inpatient phase, the participant reported right-hand supination/pronation at the wrist 10–15 min following the iTBS session. These rhythmic hand movements continued for about 3 min, reduced to one twitch every 3–5 min, and dissipated within 1 h. Her participation in the iTBS portion of the protocol was terminated. This was classified as a neurological event of unknown etiology. Two weeks following the iTBS termination, this same participant reported visual illusions and tactile hallucinations after using cocaine. These symptoms likely reflected cocaine-induced psychosis, a common occurrence in chronic cocaine users (Vergara-Moragues et al., 2014) but one this participant had never previously experienced prior to study participation. Her symptoms developed slowly over several days but cleared promptly with a single dose of olanzapine. This participant prompted the inclusion of the SAPS-CIP and CIP: Screener in the outpatient phase of the study. Further details can be found in a previously published case report (Steele et al., 2018b).

The iTBS Monitoring Questionnaire revealed no seizures, fainting, difficulties speaking or understanding speech, or impairment of thought. One participant noted brief, mild dizziness after the second iTBS session on the fifth day. One participant reported wakening suddenly with a jerk once a night after iTBS days 3, 4, and 5, something she had not experienced previously. One participant noted some intermittent tinnitus after completing all sessions.

DISCUSSION

This accelerated iTBS protocol was well-tolerated with a good safety profile in an actively-using, non-treatment seeking CUD population. The most frequently reported side effect was the occasional mild headache, which remitted either spontaneously or following acetaminophen administration. Individuals who completed the protocol reduced their weekly cocaine consumption by 78% in amount of dollars spent and 70% in days of use relative to pre-iTBS cocaine use patterns.

TABLE 4 | Resting motor threshold throughout the study.

Participant	Baseline	iTBS day 1	iTBS day 2	iTBS day 3	iTBS day 4	iTBS day 5	iTBS day 6	iTBS day 7	iTBS day 8	iTBS day 9	iTBS day 10	One-week follow-up	Four-week follow-up
04	58	55	63	56	57	60	57	59	62	51	60	—	—
05	51	53	59	49	54	58	51	51	53	59	62	—	—
07	74	76	79	78	79	77	73	74	77	76	69	—	—
08	59	60	67	52	52	60	51	56	56	52	59	—	—
09	54	53	46	47	40	42	47	46	49	43	—	—	—
10	77	73	76	77	76	74	80	74	70	79	57	—	—
16	57	52	59	57	57	57	58	59	62	—	57	47	54
17	72	71	68	—	78	65	68	71	71	68	63	—	73
18	64	62	62	61	63	68	57	68	61	62	70	63	56

Resting motor threshold (RMT) was recorded at each study visit throughout the study. Recording RMT at follow-up visits was implemented only in the outpatient phase of the study. RMT was collected from only two of three eligible participants at the first follow-up because one participant reported too little sleep (<5 h) the night prior and was ineligible for TMS that day. Numbers represent percent of maximum stimulator output of the MagVenture MagPro X100 with MagOption used in this study. Dashes indicate "NA," meaning the RMT was not collected at the given timepoint.

Similarly, Completers reported modest reductions in their weekly consumption of nicotine, alcohol, and THC. Much of this polydrug usage was not associated with cocaine use, suggesting that iTBS may have modulated a common neural circuit engaged across drugs of abuse. The safety profile was good, although a single participant developed a transient neurological event of uncertain etiology on iTBS day 9 and cocaine-induced psychosis 2-weeks after iTBS termination (Steele et al., 2018b).

The anecdotal improvements in mood were striking in their similarity across individuals along with reduced compulsive cocaine use post-iTBS. Participants also reported a reduction in short-term craving during the protocol, similar to previous reports of NIBS in cocaine using populations (Camprodon et al., 2007; Politi et al., 2008; Hanlon et al., 2015; Terraneo et al., 2016; Sanna et al., 2019). However, these were short-lived in that craving increased at the 4-week follow-up visit, though without returning to the higher baseline levels.

Although no attempt was made in this open-label study to measure neural circuit alterations, the behavioral changes reported herein are likely attributable to left dlPFC iTBS affecting dysregulated circuits related to CUD. Broad fMRI activity changes (Fox et al., 2012) and increases in DA release in the caudate nucleus (Strafella et al., 2001; Keck et al., 2002) have been reported with left dlPFC stimulation. In fact, network connectivity between the dlPFC and the anterior cingulate cortex [ACC; a dysregulated hub in both depression and addiction and part of a functional network predictive of CUD treatment outcomes (Hong et al., 2009; Steele et al., 2018a)] is normalized with this intervention in major depression (Fox et al., 2012), supporting network malleability with NIBS. The cognitive and affective dysregulations seen in SUD are associated with neural alterations in the ACC, insula, and/or striatum and may be susceptible to left dlPFC NIBS modulation (Fox et al., 2012). Together, these data suggest that stimulation of the left dlPFC is a potential intervention in addiction (Diana et al., 2017).

Transcranial magnetic stimulation treatment targets should be related to clinically significant outcomes (e.g., relapse, treatment completion) and neural circuitry known to be dysregulated in addiction. During our iTBS administration, participants were instructed to actively inhibit their cocaine craving while viewing cocaine-related pictures. Perhaps, the iTBS and behavioral interventions influenced executive control leading to reduction in cocaine use post-iTBS. Executive control, dysregulated in SUD, requires circuits including dlPFC, ACC, IFG, OFC, striatum, hippocampus, and insula (Jovanovski et al., 2005; Koob and Volkow, 2010; Goldstein and Volkow, 2011; Volkow et al., 2012; Spronk et al., 2013; Steele et al., 2017, 2019). Both, event-related potential (ERP) measures of executive control, specifically error-processing (Marhe et al., 2013; Marhe and Franken, 2014; Steele et al., 2014; Fink et al., 2016) thought to originate in the ACC (van Veen and Carter, 2002; Edwards et al., 2012), and fMRI measures (Luo et al., 2013; Steele et al., 2018a) predict drug treatment outcomes. Bolstered post-error processing in ERP measures (Steele et al., 2014) and stronger functional connectivity between ACC and striatum, amygdala, and hippocampus (Steele et al., 2018a) is predictive of treatment completion. Enhancing executive control (i.e., increasing post-error processing) and functional connectivity of dysregulated circuits via iTBS while inhibition of craving could provide a viable treatment target for CUD.

Limitations

Although our findings are promising for use of iTBS as a treatment for CUD, there are study limitations to consider. First, this was an open-label study. All participants knew they would receive active iTBS, posing the risk for a placebo effect, as with any intervention. Additionally, participants actively participated in craving suppression during each of the three daily iTBS sessions, so our results may also relate to the intensive practice of craving reduction, independent of iTBS. As a proof-of-concept study, our goal was to assess feasibility and tolerability of iTBS as a potential intervention in actively using cocaine dependent individuals, not to differentiate the effects of active and sham stimulation during craving suppression. Second, we report a small number or participants ($N = 9$) who completed a substantial number of iTBS sessions and returned for a follow-up visit. Based on this limited number of observations, strong conclusions cannot be drawn. Nonetheless, Completers did reduce their substance use post-iTBS with largely similar anecdotal accounts of changes in their interactions with cocaine, warranting further study with a larger sample to better understand this phenomenon. Recall that subjects were explicitly recruited as non-treatment seekers in a non-treatment intervention-although they were told that their cocaine use might change after TMS. Third, we had a limited duration of follow up as our primary concern was to establish the feasibility of undertaking a large, sham controlled study; our only 1-year follow up was serendipitous. Finally, the neural underpinnings of behavioral changes reported here remain untested; uncovering these should benefit future iTBS applications as a SUD treatment. Based on these pilot data, we have now begun a large-scale, double-blind, sham-controlled trial of iTBS as an experimental treatment for CUD with longitudinal fMRI and follow-up (NCT02927236). Because, substance users are known to have dysregulated cue reactivity, reward processing, executive control, and intrinsic network connectivity (Garavan et al., 1999, 2000; Gu et al., 2010; Hu et al., 2015; Fedota et al., 2016; Steele et al., 2017, 2019), we will assess these cognitive processes and measure their related neural mechanisms before and after acute and chronic application of iTBS. The study is specifically designed to measure the trajectory of neuroplastic change induced by an iTBS intervention and how that relates to drug use behavior.

CONCLUSION

In this open-label, proof-of-concept study of accelerated iTBS in CUD, we measured and reported the safety and tolerability of this intervention as well as multiple clinical assessments relevant to SUD treatment. Even in this cohort of non-treatment seeking cocaine dependent individuals, substance use decreased both for hypothesized targeted cocaine and also for 'off-target' use of other substances, including nicotine, alcohol, and THC along with improved mood. Adverse side-effects were limited, and we did not observe seizures, fainting, difficulties speaking or

understanding speech, or impairment of thought, all of which are occasionally reported following NIBS interventions. We offer three main take-away messages. First, individuals with active CUD can tolerate accelerated iTBS and adhere to an intense 2-week, 30 session schedule. Second, iTBS applied at 100% of RMT to actively using cocaine users did not result in a concerning rate of negative side effects in this small sample. Third, as an open-label, small sized study, no strong conclusions can be made. Generally, however, we believe this report lays the groundwork for larger studies in active cocaine using CUD individuals to assess neuroplastic changes interrogated with neuroimaging techniques to better understand those circuits affected by iTBS, in what manner, the longevity of such effects, and their relationship to drug use behavior (cf. Ekhtiari et al., 2019).

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the National Institute on Drug Abuse Institutional Review Board and the Food and Drug Administration. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

VS, ES, and BS conceived the study approach. VS, AM, and BS collected the data. VS devised and implemented the analytical approach, and performed the data analysis. VS and AM drafted the manuscript. All authors contributed to the interpretation of the data, provided critical revisions, and approved the final version of the manuscript submitted for publication.

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GENERAL COMMENTARY
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Commentary: Deficient inhibition in alcohol-dependence: let's consider the role of the motor system!

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Keywords: alcohol-dependence, inhibition, cortical excitability, gabaergic, glutamatergic, transcranial magnetic stimulation

A Commentary on

Deficient inhibition in alcohol-dependence: let's consider the role of the motor system!
by Quoilin, C., Wilhelm, E., Maurage, P., de Timary, P., and Duque, J. (2018). Neuropsychopharmacology 43, 1851–1858. doi: 10.1038/s41386-018-0074-0

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We have read with great interest the commentary "Deficient inhibition in alcohol-dependence: let's consider the role of the motor system!" (Zhou et al., 2019), recently published in this Journal, on the manuscript "Deficient inhibition in alcohol-dependence: let's consider the role of the motor system!" published in 2018 in "Neuropsychopharmacology" (Quoilin et al., 2018).

In their interesting study, Quoilin et al. tested the hypothesis that appropriate neural inhibition of the motor output pathways is altered in alcohol-dependence (AD). During an instructed-delay choice reaction time task, suppression of the motor evoked potentials (MEP) elicited by transcranial magnetic stimulation (TMS) in the delay period relative to baseline for the forthcoming movement was significantly weaker in subjects with AD than in healthy control subjects, thus suggesting a storage of neural inhibition in AD patients. In their commentary, Zhou and colleagues highlighted the role of the motor system in the deficient inhibitory control.

The importance of neural inhibitory mechanisms at motor cortical level in subjects with AD clearly emerges from both articles. In fact inhibitory, mainly GABAergic, transmission plays a key role in the neurochemical mechanisms on the basis of intoxication, tolerance and withdrawal (Koob, 2004).

However, altered motor cortical excitability may be caused by a dysfunction in the neural inhibitory circuits, but also by an impairment of the intracortical excitatory circuits.

Quite surprisingly, in both papers the role of excitatory, mainly glutamatergic, neurotransmission in AD has not been specifically considered.

Indeed, ethanol abuse also affects the central nervous system by altering the function also of excitatory transmission (Rudolph et al., 1997; Harris et al., 2003), resulting in reduced overall brain excitability. Acute ethanol intake enhances the effects of GABA on $GABA_A$ receptors and inhibits glutamatergic function by decreasing cationic conductance through the ionotropic type of glutamate receptors. Chronic alcohol exposure appears to create inverse changes in the functions of these systems leading to decreased GABAergic and increased glutamatergic functions bringing about the development of tolerance and/or physical dependence on alcohol (Littleton, 2001).

Several cell and animal studies (Di Chiara et al., 1998; Nagy et al., 2005) suggest that the glutamatergic system is an especially important factor in the mediation of the addictive effect of alcohol. In particular, the N-methyl-D-aspartate (NMDA) receptors exhibit the highest affinity targets for ethanol in the CNS (Lovinger et al., 1990; Grant and Lovinger, 1995; Hoffman and Tabakoff, 1996).

Transcranial magnetic stimulation (TMS) can be applied in different paradigms to obtain a measure of various aspects of cortical excitability. The different TMS paradigms provide information about different neurotransmitter systems and neurochemical pathways (Hallett, 2000; Rossini et al., 2015). In particular, TMS given in a paired-pulse paradigm allows the assessment of the intracortical facilitatory and inhibitory circuits that influence the cortical motor output (Paulus et al., 2008; Groppa et al., 2012).

A TMS study demonstrated that chronic ethanol abuse alters glutamate-dependent mechanisms of short-term cortical plasticity (Conte et al., 2008). Interestingly, another TMS study showed a selective increase in intracortical facilitation to paired TMS (Nardone et al., 2010) in AD and alcohol withdrawal. This parameter is thought to depend upon the activity of intracortical glutamatergic circuits (Tokimura et al., 1996; Liepert et al., 1997; Ziemann et al., 1998; Di Lazzaro et al., 1999; Reis et al., 2006).

Prolonged ethanol exposition leads to a compensatory "upregulation" of NMDA receptors mediated functions, which is thought to play a crucial role in the occurrence of ethanol tolerance and dependence.

Therefore, AD is characterized by a motor cortical hyperexcitability, which can be secondary to an increased glutamatergic action rather than to a reduced GABAergic activity. Anti-glutamatergic approaches could thus represent an efficacious and preferable alternative for treating AD and alcohol withdrawal symptoms.

On the other hand, not only GABA and glutamate, but many other neurotransmitters and neuromodulators (De Witte et al., 2003) can be involved in the complex system of AD neurobiology.

As pointed out by Zhou in the above-mentioned commentary, deficient neural motor inhibition can serve as objective TMS-based biomarker, which help to detect people at high-risk of alcohol relapse, and also represent a promising target for pharmacological and training interventions. Therefore, it is of crucial importance to correctly identify and define the mechanisms of the impaired inhibition in AD, and the role of the concomitant enhanced glutamatergic transmission cannot be overlooked.

AUTHOR CONTRIBUTIONS

RN conceived the idea and wrote the manuscript. ET read and revised the manuscript. LSe, VV, and LSa revised the literature and wrote the manuscript.

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Effects of Ten Sessions of High Frequency Repetitive Transcranial Magnetic Stimulation (HF-rTMS) Add-on Treatment on Impulsivity in Alcohol Use Disorder

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Introduction: Alcohol use disorder (AUD) is characterized by increased impulsivity, which is multifactorial and can be assessed by tests like the delay discounting, Go-Nogo, and stop signal task (SST). Impulsivity has been related to poor treatment outcomes in substance use disorders, including AUD. In order to decrease impulsivity or improve inhibitory control, high frequency transcranial magnetic stimulation (HF-rTMS) has gained interest. Studies applying HF-rTMS over the DLPFC of individuals suffering from AUD assessing its effects on impulsivity measures are scarce, and results are inconclusive.

Methods: The current study (registered in Netherlands Trial Register with trial number 5291: https://www.trialregister.nl/trial/5151) applied 10 sessions of HF-rTMS [sixty 10 Hz trains of 5 s at 110% motor threshold (MT)] over the right DLPFC of 80 alcohol dependent patients in clinical treatment on 10 consecutive workdays. At baseline, halfway and after the HF-rTMS treatment, the delay discounting, Go-NoGo, and SST were assessed.

Results: Ten sessions of HF-rTMS over the right DLPFC versus sham HF-rTMS did not affect performance on the delay discounting, Go-NoGo, and SSTs. A significant effect of age was found for the Go-NoGo task, with higher age associated with better performance. Furthermore, no significant correlations were found between difference scores of task performance and baseline impulsivity or severity of AUD.

Discussion: Results of this study, in combination with other studies using HF-rTMS studies in alcohol and substance use disorder, indicate mixed and inconclusive findings of HF-rTMS on impulsivity. Future studies within patient groups hospitalized at the same department are recommended to consider using a sham coil that mimics the sensations on the scalp of active HF-rTMS and to measure motivation across test sessions.

Keywords: alcohol use disorder, alcohol dependence, transcranial magnetic stimulation, impulsivity, delay discounting, go-nogo, stop signal, neuromodulation

INTRODUCTION

Worldwide approximately 2.6% of the population is suffering from alcohol use disorder (AUD) (World Health Organization, 2018). AUD is characterized by loss of control over alcohol intake despite awareness of the negative social, health, and financial consequences (Baler and Volkow, 2006). The loss of control over intake is caused by decreased inhibitory control capacities observed in AUD (Lawrence et al., 2009). From a neurobiological perspective, this has been associated with diminished functioning of the prefrontal cortex (Koob and Volkow, 2010).

Impulsive behavior can be defined as acting without foresight or careful deliberation (Dalley and Robbins, 2017) and therefore can result in unduly risky or inappropriate behavior, often with undesirable consequences (Dawe et al., 2004; Lee et al., 2019). Impulsivity has been related to poor treatment outcomes in substance and AUD (Goudriaan et al., 2011; Stevens et al., 2014; Loree et al., 2015; Moeller et al., 2016). Impulsivity is a multifaceted construct which can be subdivided into *delayed reward (choice) impulsivity* and *rapid response impulsivity* (Hamilton et al., 2015a). The former reflects the preference for immediate reward in favor of a larger later reward. The latter reflects the tendency toward immediate action, which is often incompatible with present demands of the situation. Within the rapid response impulsivity construct, two more types can be dissociated, namely *failure to refrain from action initiation* and *inability to stop an initiated response* (Hamilton et al., 2015a). These different constructs of impulsivity can be assessed using different computerized tasks. Choice impulsivity can be assessed using the delay discounting task (DDT) (Bickel and Marsch, 2001). In this task, the more often a participant chooses the lower immediate reward, the more the subjective value of the larger later reward reduces over time, and the more impulsive an individual is considered to be (Odum, 2011; Hamilton et al., 2015b). The Go-NoGo Task (GNGT) assesses the failure to refrain from action initiation. In this task, the more often a participant responds to a stimulus when no response was required (i.e., a false alarm), the more impulsive the individual is considered to be (Hamilton et al., 2015a). The inability to stop an initiated response can be assessed by using the stop signal task (SST) (Verbruggen and Logan, 2008). The task determines the time a participant needs between the go-signal and the stop-signal in order to be able to stop the initiated response in 50% of the time [i.e., the stop signal reaction time (SSRT)]. The higher the SSRT, the more impulsive an individual is considered to be (Hamilton et al., 2015a). Taken together, previous research has shown that individuals with substance use disorders (including alcohol) show impaired performance on the above described impulsivity tasks (Lipszyc and Schachar, 2010; Smith et al., 2014; Wright et al., 2014; Amlung et al., 2017; Sion et al., 2017).

In order to decrease impulsivity, or improve inhibitory control, Transcranial Magnetic Stimulation (TMS) has gained interest (Bellamoli et al., 2014). With TMS, a strong magnetic pulse, originating from an electromagnetic coil, penetrates the skull and changes neuronal activity in the underlying tissue. When pulses are repetitively applied in trains, it is referred to as repetitive TMS (rTMS). Depending on the stimulation frequency this can either be inhibitory (low frequency; LF) or excitatory (high frequency; HF) (Rossi et al., 2009; Guse et al., 2010). A target area frequently chosen within the inhibitory control network, consisting of the prefrontal cortex (Ridderinkhof et al., 2004), is the dorsolateral prefrontal cortex (DLPFC). Results from studies applying HF-rTMS over the DLPFC in substance (including alcohol) dependence show inconsistent effects on impulsivity measures. While one single session of 10 Hz did not improve accuracy on the GNGT (Herremans et al., 2013), four sessions of 10 Hz stimulation did increase accuracy on the GNGT (Del Felice et al., 2016) in alcohol dependent patients. In nicotine dependence, one single session of 10 or 20 Hz stimulation improved performance of the DDT (i.e., less discounting for monetary as well as cigarette rewards) (Sheffer et al., 2013), suggesting decreased impulsivity. So far, no studies tested the effect of HF-rTMS in alcohol dependence on DDT and SST performance.

In the current study, the effect of 10 HF-rTMS sessions on impulsivity in individuals in treatment for AUD is investigated. We hypothesized that 10 HF-rTMS sessions would improve impulse control abilities. We, therefore, expected to find that after active treatment compared to sham treatment, impulsivity would be decreased. Eighty AUD individuals were included in the study and treated with either 10 active or 10 sham HF-rTMS sessions on 10 consecutive workdays added on to their treatment as usual. Impulsivity tasks were assessed before, in between, and after the HF-rTMS treatment.

METHODS

Study Design

The effect of the HF-rTMS add-on treatment on impulsivity was studied in a parallel, single center, single blind trial in abstinent alcohol dependent subjects, randomized (1:1) to either treatment as usual (TAU) plus 10 sessions of active HF-rTMS or TAU plus 10 sessions of sham HF-rTMS, as described elsewhere in detail (Schluter et al., 2018). This study was approved by the Medical Ethical Committee of the Academic Medical Centre Amsterdam (2015_064) and is registered in The Netherlands Trial Register (NTR) with trial number 5291. Informed consent of all participants was obtained after explanation of all study procedures and before screening for the in- and exclusion criteria.

Study Sample

All participants were recruited at an addiction treatment centre in Amsterdam (Jellinek, Amsterdam, The Netherlands), and were abstinent during participation to the current study. Here they received 6 weeks of a fulltime treatment program of Cognitive Behavioral Therapy (CBT) or Acceptance and Commitment Therapy (ACT) supplemented with emotion regulation training and motivational enhancement therapy. Besides these group sessions, every participant had individual sessions with a psychologist and a mentor every week. In the session with the psychologist, comorbidities, and other

problems of the patients that occurred during treatment were discussed. During the mentor sessions supportive CBT or ACT focusing on remaining abstinent were given. Finally, some of the patients received pharmacotherapy. Inclusion criteria were a recent DSM-IV diagnosis of alcohol dependence (i.e., less than 4 months after detoxification) and an age between 20 and 65. Exclusion criteria were (1) insufficient knowledge of the Dutch language, (2) Montreal Cognitive Assessment (MOCA) score below 10, (3) current DSM-IV diagnosis of depression, schizophrenia or another psychotic disorder, (4) current recreational drug use, and (5) HF-rTMS contraindications [such as a history of epileptic seizures, metal implants near the head or use of the following medication: imipramine, amitriptyline, doxepine, nortriptyline, maprotiline, chlorpromazine, clozapine, foscarnet, ganciclovir, ritonavir, theophylline (Rossi et al., 2009)].

Procedure

When an individual met all inclusion and no exclusion criteria, he or she was enrolled in the study. In order to assure concealed randomization, participants were randomized into the sham or active stimulation group, based on the stratification factors anti-craving medication (yes/no) and age (20–40/41–65) using the randomization module implemented in the data management system Castor EDC (Castor Electronic Data Capture, Ciwit BV, Amsterdam, Netherlands, 2016). After randomization, participants started with the research procedure, which took place on 10 consecutive workdays. During the first session (baseline), sample characteristics were assessed, after which the impulsivity tasks were performed. Subsequently, stimulation intensity and location were determined, and the first HF-rTMS treatment was delivered. During the second to fourth session, HF-rTMS treatment was delivered. During the fifth session, HF-rTMS treatment was performed, followed by assessment of the impulsivity tasks. The sixth to ninth session only contained HF-rTMS treatment. The 10th session was identical to the fifth session. For an overview of the procedure, see **Figure 1**.

Intervention

The active intervention existed of 10 HF-rTMS (sixty 10 Hz trains of 5 s at 110% MT treatment sessions over the right DLPFC (rDLPFC) as previously succesfully applied by our research group (Jansen et al., 2015). For the sham intervention, stimulation parameters were identical, however, the coil was tilted 90° relative to the scalp. The rDLPFC was located at position F4 using the International 10–20 EEG system (Herwig et al., 2003). MT was determined at rest using single pulse TMS over the motor cortex. Stimulus intensity was adjusted until the muscular (left abductor pollicis brevis) response of the thumb muscular abduction was observed in five out of 10 stimuli. HF-rTMS treatment was applied using a 70 mm double air film coil (Magstim Co., United Kingdom) and a Magstim Rapid2 stimulator (Magstim Co., United Kingdom). The HF-rTMS treatment was added to the TAU provided by the Jellinek Addiction Treatment Centre in Amsterdam.

Measures

Sample Characteristics

The following sample characteristics were assessed: age, gender (man/woman), IQ by means of the Dutch version of the adult reading test (NLV) (Schmand et al., 1991), years of education, handedness (left/right), MOCA score, presence of comorbid posttraumatic stress disorder (PTSD), cocaine or cannabis dependence by means of the Mini-International Neuropsychiatric Interview (MINI) (Sheenhan et al., 1998), duration of problematic alcohol use (years), number of DSM-IV criteria fulfilled (11 in total), use of anti-craving medication (naltrexone or acamprosate) (yes/no), use of anti-depressant medication at baseline (yes/no), use of sedative medication at baseline (yes/no), The Barratt Impulsiveness Scale (BIS) (Patton, 1995) total score and Urgency, Premeditation, Perseverance, Sensation Seeking (UPPS-P) impulsive behavior scale (Whiteside et al., 2005).

Impulsivity Assessments

Delay discounting task

The computerized version of the DDT (Wittmann et al., 2007) was used to assess choice impulsivity. During this task, participants were presented with a choice between a hypothetical smaller immediate or larger delayed reward. To choose the immediate reward option participants had to press the "c" key, while for the later reward participants had to press the "m" key on a keyboard. The task consisted of six blocks, each containing eight choices. Delay in days (i.e., 5, 30, 180, 365, 1095, 3650) and delayed reward in euros (ranging from 476 to 524 euros) were equal for all trials of a given block (**Figure 2A**). The immediate reward value varied across trials within each block, depending on the responses made. Within each block the indifference point (i.e., when the immediate reward has the same subjective value as the delayed reward) was determined. Using the normalized indifference points, a discounting curve was created for each participant. Subsequently, the area under the curve (AUC) (Myerson et al., 2001) was calculated with normalized delay (x-axis) and reward value (y-axis). The AUC was the primary outcome measure of this task. Lower values indicated higher choice impulsivity.

Go-nogo task

An adapted version of the GNGT (Durston et al., 2003) was used to assess failure to refrain from action initiation. During this task, white numbers (1–9) were projected in the middle of a black screen for 500 ms. Between the numbers, a fixation cross was projected for an average duration of 1500 ms (1000 $\pm$ 2000 ms). Participants were instructed to respond (press the spacebar of the keyboard) as fast as possible whenever a number (Go trial) was projected, but to refrain from responding when a "3" was projected (NoGo trial) (**Figure 2B**). The task consisted of five runs, each containing 57 trials (approximately 75% Go trials). During the entire task, 215 Go trials and 70 NoGo trials were presented. The primary outcome measure of this task was the percentage responses to NoGo trials (i.e., % false alarms) – with

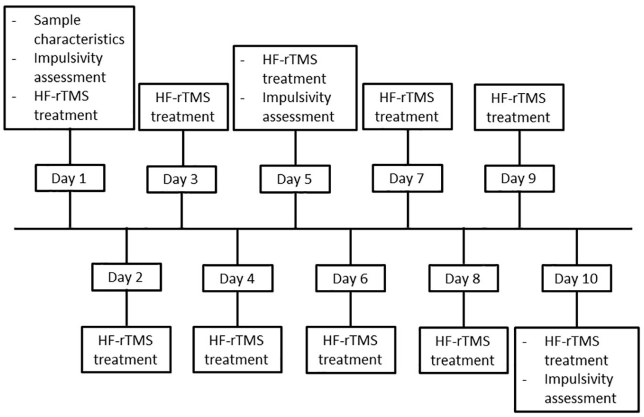

FIGURE 1 | Flowchart of the study procedure.

higher percentages indicating higher impulsivity. Furthermore, responses to Go trials (i.e., hits) and reaction time (RT) to Go trials were recorded.

Stop signal task

The CANTAB ([Cognitive assessment software]. Cambridge Cognition (2019). All rights reserved.[1]) version of the SST was used to assess the, inability to stop an initiated response. The task consisted of five blocks, each containing 64 trials. During each trial, a white circle was projected in the middle of a black screen wherein a white arrow pointing to the left or right appeared (**Figure 2C**). Participants were instructed to make a rapid response in the direction of the arrow [left button (F7) and right button (F8)] (Go trial). In some rare cases, the arrow was followed by an auditory beep (Stop trial), which indicated participants had to stop their initiated response and refrain from pressing the button. After each block, a feedback screen was displayed, which showed a blue bar representing the response time of the last block (each bar representing performance during one block). The higher the bar, the faster the participant responded during the last block. This was explained to the participant by the experimenter, and subsequently, the participant was encouraged to respond faster in the next block, but also to stop the initiated response when the stop signal was heard. In total, the task contained 240 go trials and 80 stop trials. During the stop trials, the time between stimulus presentation and stop signal in which a participant was able to stop in 50% of the trials was determined using a staircase procedure (with a successful inhibition the stop signal delay increased by 50 ms, whereas with failed inhibition it decreased with 50 ms). This time – referred to as the SSRT – was the primary outcome measure of this task, with higher numbers indicating higher impulsivity. Furthermore, the proportion of correct stops during stop trials and reaction time on go trials were recorded. All computerized tasks were performed on a manually operated touch screen tablet (Hewlett-Packard; Windows 8.1) with the keyboard attached.

[1]www.cantab.com

Blinding

After the 10 HF-rTMS treatments, participants indicated whether they believed to have received the active or sham treatment.

Safety and Tolerability

In order to list the discomfort or side effects that participants experienced after treatment, a predetermined list of possible side effects was used. The list contained: headache, pain or beep in the ear, reduced hearing, fainting or epileptic seizure. In case a participant reported other side effects that were not on this list (uncomfortable sensations at stimulation site after the stimulation, and tiredness after stimulation), these side effects were registered as well.

Analyses

Statistical Package For Social Sciences (SPSS) version 25.0 was used for analyses of sample characteristics, baseline differences in taks performance, blinding and safety and tolerability (IBM Corp., Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY, United States: IBM Corp.). The R environment (RStudio Team (2015). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA, United States) was used for statistical analyses of the treatment effect.

Sample Characteristics

Baseline sample characteristics were compared between the active and sham group. In case of a categorical variable, Chi-square tests were used (in case the expected counts is less than 5, Fisher's exact test were used as an alternative). In case of a continuous variable, normality was tested by means of the Kolmogorov Smirnov test. A two-sample T-test was used in case of normality, otherwise the Mann–Whitney-U test was applied. P-values < 0.05 were considered significant.

Impulsivity

Determination of outliers

To determine whether participants performed the task according to instructions, specific criteria were set for each cognitive task.

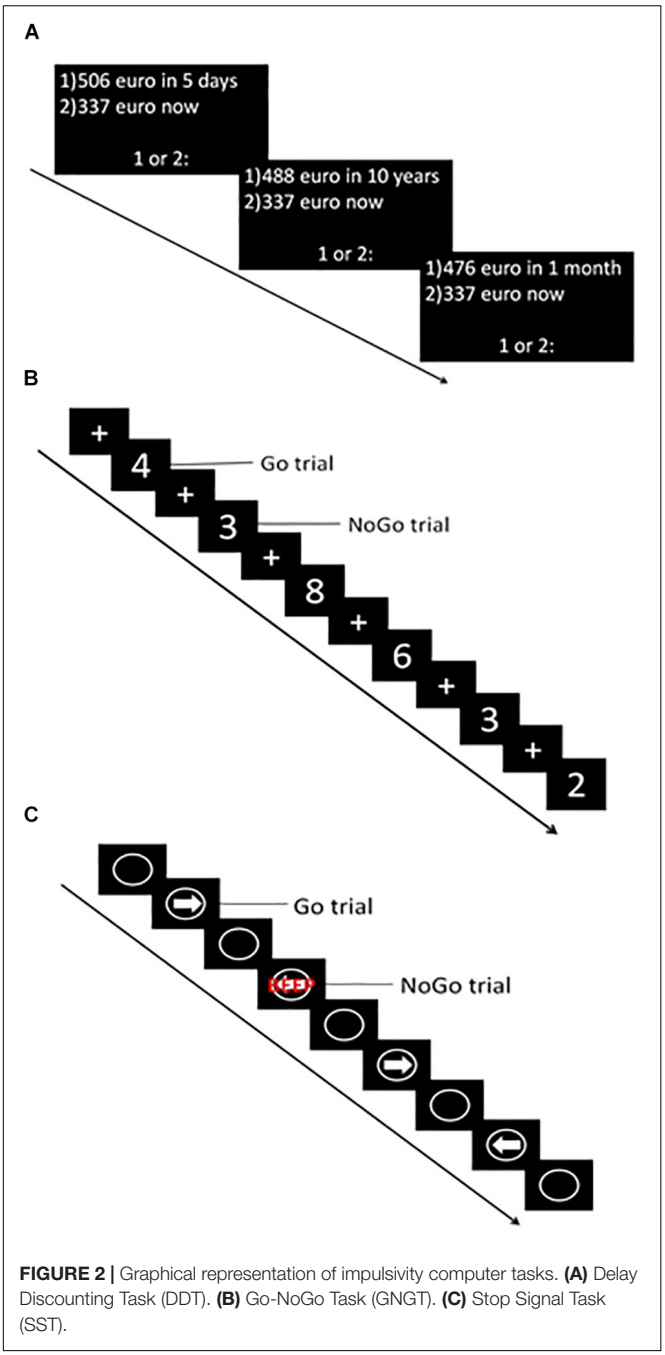

FIGURE 2 | Graphical representation of impulsivity computer tasks. **(A)** Delay Discounting Task (DDT). **(B)** Go-NoGo Task (GNGT). **(C)** Stop Signal Task (SST).

Participants determined as outlier were discarded from further data analysis for that specific task.

DDT: An outlier was defined based on non-systematic choice behavior and participants were excluded when: (1) at least one individual indifference point was greater than the preceding indifference point by a magnitude greater than 20% of the larger later reward; or (2) the last indifference point was not less than the first indifference point by at least a magnitude equal to 10% of the larger later reward (Johnson and Bickel, 2009).

GNGT: Outliers were determined based on the mean and standard deviation of RT on Go trials (three sessions combined). When a participant's mean RT on Go trials exceeded this group mean by two times the standard deviation or more, the subject was considered an outlier.

SST: Outliers were based on the proportion of successful stops on NoGo trials (Bø et al., 2019). When the proportion of successful stops was lower than 0.4 or higher than 0.6 (indicating a failed staircase procedure), a participant was considered an outlier.

Baseline differences

To determine baseline differences between the active group and sham group, the primary outcome measures of the baseline session were tested for normality and accordingly compared using a two-sample *t*-test (normal distribution) or Mann–Whitney-*U* test (non-normal distribution). *P*-values < 0.05 were considered significant.

Treatment effect

The effect of treatment and session was determined using linear mixed-effects models. To check assumptions, the residuals of the primary outcome measures were visually inspected for normality using histograms and quantile-quantile-plots. The final model was selected by statistical (Chi-square) model comparison, assessing model fit using the Akaike Information Criterion (AIC) values, with lower values indicating better fit. The dependent variables were the primary outcome measures of the task, i.e., AUC for the DDT, false alarm percentage for the GNGT and SSRT for the SST. We started with a model including the fixed effects of treatment (active/sham) and session (pre/mid/post), as well as interaction term of treatment and session, and the random intercept of subject. Step-by-step extra fixed or random effects were added to this first model. The second model contained a fixed effect of age, whereas the third model contained a fixed effect of gender. The fourth model contained both age as well as gender as extra fixed effects. The fifth model added a random slope for session to the first model. The sixth model contained age as a fixed effect, the seventh model contained gender as a fixed effect and the eighth model contained age and gender as fixed effects. The AICs of all these models were compared by means of Chi-square tests. *P*-values < 0.05 were considered significant. The result of this test determined which model was chosen as final model for each specific task.

DDT: The final model included the fixed effects of session (pre/mid/post) and treatment (active/sham), as well as the interaction term of session and treatment and the random intercept of subject [AUC $\sim$ Session $*$ Treatment_Group $+$ (1 | Subject)]. Adding fixed effects of age [$X^2(1) = 0.106$, $p = 0.744$], or age and gender [$X^2(1) = 0.102$, $p = 0.750$], to this model did not significantly improve the model fit. Furthermore adding a random slope for session resulted in singular fit of the model (i.e., the variance- covariance matrix was estimated as zero), and was therefore not included in analyses of the AUC.

GNGT: The final model included fixed effects of session (pre/mid/post), treatment (active/sham), and age, as well as the interaction term of session and treatment, and a random intercept of subject and random slope for session [Percentage false alarms $\sim$ Session $*$ Treatment Group $+$ Age $+$ (Session | Subject)].

Adding gender to this model did not significantly [$X^2(1) = 0.7518$, $p = 0.386$] improve the model fit. This shows that gender does not explain variance, and was therefore not included in the final analyses of the false alarm percentage.

SST: The final model included fixed effects of session (pre/mid/post) and treatment (active/sham), as well as the interaction term of session and treatment, and a random intercept of subject and random slope for session [SSRT ∼ Session ∗ Treatment Group + (Session | Subject)]. Adding age [$X^2(1) = 2.712$, $p = 0.0996$], or age and gender [$X^2(2) = 2.809$, $p = 0.246$] to this model did not significantly improve the model fit. This shows they do not explain any variance, and were therefore not included in the final analyses of the SSRT.

Exploratory Analyses

Baseline impulsivity

In order to assess whether baseline impulsivity (measured with the BIS and UPPS-P) had an effect on HF-rTMS treatment response, the baseline BIS, and the baseline UPPS-P score, were independently correlated (Pearson correlation) to the difference score (value session 10 – value session one) of the AUC (for the DDT), percentage false alarms (for the GNGT) and SSRT (for the SST) in the active group. Individuals that dropped out before the 10th session were discarded from these analyses. *P*-values < 0.05 were considered significant.

Severity of alcohol use disorder

To assess whether severity of AUD had an effect on HF-rTMS treatment response, the total number of DSM-IV criteria met was correlated (Pearson correlation) to the difference score (value session 10 – value session one) of the AUC (for the DDT), percentage false alarms (for the GNGT) and SSRT (for the SST) in the active group. Individuals that dropped out before the 10th session were discarded from these analyses. *P*-values < 0.05 were considered significant.

Blinding

In order to assess whether blinding succeeded, the percentage of individuals who guessed their treatment allocation correctly were calculated. Subsequently, a binomial test was used to determine whether this was significantly different from chance level (50%). *P*-value < 0.05 was considered significant.

Safety and Tolerability

Chi-square tests, and Fisher's exact tests were performed to assess whether there were any statistical differences in reported discomfort or side effects between the active group and the sham group. A *p*-value < 0.05 was considered significant.

RESULTS

Sample Characteristics

In total, hundred individuals were screened, which resulted in 82 enrolled individuals. Two participants withdrew informed consent before the procedure started, therefore in total eighty participants started the study (see **Figure 3**). No significant differences in age, gender, IQ, years of education, handedness, MOCA score, presence of comorbid PTSD, cocaine or cannabis dependence, duration of problematic alcohol use, number of DSM-IV criteria fulfilled, anti-craving medication use at baseline, use of sedative medication, BIS total score and UPPS total score between the active and sham group were found. Use of anti-depressive medication did significantly differ between the sham and active group, with more use in the active group [$X^2(1) = 4.013$, $p = 0.045$] (see **Table 1**).

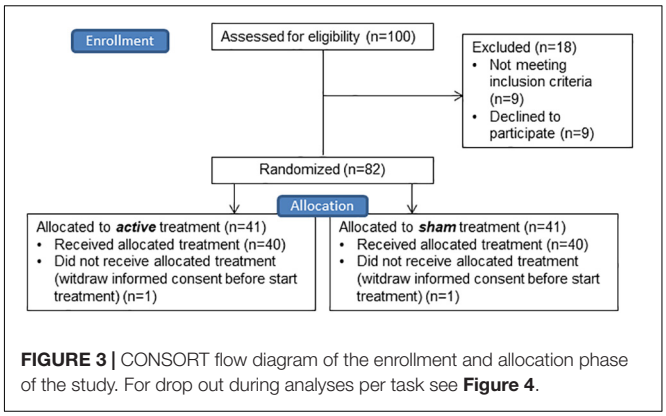

FIGURE 3 | CONSORT flow diagram of the enrollment and allocation phase of the study. For drop out during analyses per task see **Figure 4**.

Impulsivity

Data Loss per Task

For a schematic overview of drop-outs, data loss, and outliers per task see **Figure 3**.

Baseline Differences

DDT: The two sample *t*-test showed no significant difference in mean AUC between the active [0.40 (0.214)] and sham [0.50 (0.279)] group [$t(58) = -1.509$, $p = 0.137$].

GNGT: The Mann–Whitney-*U* test showed no significant difference in false alarm percentage between the sham [28.571% (11.429–84.286%)] and active [27.143% (2.857–75.714%] treatment group ($U = 864.500$, $p = 0.298$).

SST: The two sample *t*-test showed no significant difference between the mean SSRT of the active [190.75 ms (46.383 ms)] and sham [188.61 ms (54.688 ms)] group [$t(67) = 0.174$, $p = 0.862$].

Treatment Effect

DDT: The linear mixed-effects model showed no significant main effects of session [$T(102.30) = 0.910$, $p = 0.365$], or treatment group [$T(120.50) = 1.006$, $p = 0.317$], nor an interaction effect between session and treatment [$T(102.2) = 0.025$, $p = 0.980$] was found (**Figure 5A**).

GNGT: The linear mixed-effects model showed no significant main effects of session [$T(69.260) = -0.364$, $p = 0.717$], treatment group [$T(73.919) = 0.936$, $p = 0.353$] or an interaction effect between session and treatment [$T(68.267) = -0.468$, $p = 0.642$] was found (**Figure 5B**). However, the fixed effect of age was significant [$T(72.446) = -2.004$, $p = 0.049$], such that higher age was related to lower percentage of false alarms.

SST: The linear mixed-effects model showed no significant main effects of session [$T(73.745) = -0.653$, $p = 0.516$], or treatment group [$T(76.160) = -0.228$, $p = 0.820$],

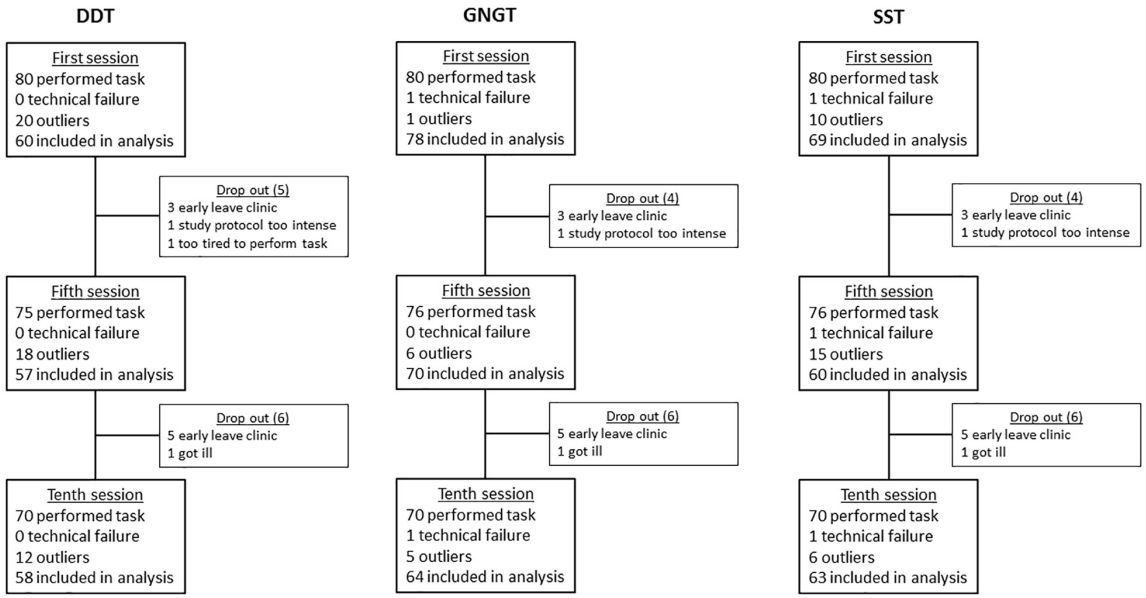

FIGURE 4 | Schematic overview of drop out, data loss, and outliers of the Delay Discounting Task (DDT), Go-NoGo Task (GNGT), and Stop Signal Task (SST).

TABLE 1 | Sample characteristics.

	Active group (*N* = 40)	Sham group (*N* = 40)	Statistic
Age [mean (SD)]	44.95 (10.03)	43.75 (11.41)	$t(78) = 1.498$, $p = 0.619$
Gender (man: woman)	29: 11	31: 9	$X^2(1) = 0.267$, $p = 0.606$
IQ [median (range)]	83 (47–97)	84 (42–100)	$U = 772.500$, $p = 0.791$
Years of education [mean (SD)]	7.5 (3.44)	7.238 (3.61)	$t(78) = 0.333$, $p = 0.740$
Handedness (right: left)	37: 3	38: 2	$p = 1.000$, Fisher's exact test
MoCA score (>27: 18–26)	26: 13	30: 10	$X^2(1) = 0.664$, $p = 0.415$
PTSD (yes: no)	5: 35	6: 34	$X^2(1) = 0.105$, $p = 0.745$
Cocaine dependence (yes: no)	9: 31	5: 35	$X^2(1) = 1.385$, $p = 0.239$
Cannabis dependence (yes: no)	8: 32	8: 32	$X^2(1) = 0.000$, $p = 1.00$
Duration of problematic alcohol use in years [mean (range)]	11 (2–36)	10 (1–36)	$U = 652.500$, $p = 0.211$
Number of DSM-IV criteria fulfilled [median (range)]	9 (3–11)	9 (4–11)	$U = 775.000$, $p = 0.808$
Anti-craving medication (yes: no)	15: 25	12: 28	$X^2(1) = 0.503$, $p = 0.478$
Anti-depressant medication (yes: no)	15: 25	7: 33	$X^2(1) = 4.013$, $p = 0.045$
Sedative medication (yes: no)	3: 37	1: 39	$p = 0.615$, Fisher's exact test
BIS score [mean (SD)]	69.53 (8.72)	69.58 (9.42)	$t(78) = -0.025$, $p = 0.980$
UPPS score [mean (SD)]	108.60 (14.40)	110.65 (16.00)	$t(78) = -0.602$, $p = 0.549$

No significant differences were found between the active and sham group on any of the characteristics, except for the use of anti-depressant medication. Depending on whether the outcome measure was continuous or categorical, and whether it was normally distributed, two sample T-test, Mann–Whitney-U test, Chi–square tests or Fisher's exact test were used. P-values < 0.05 were considered significant. Abbreviations: SD = standard deviation; PTSD = post-traumatic stress disorder; DSM-IV: diagnostic and statistical manual of mental disorders version 4; BIS = barratt impulsiveness scale; UPPS = urgency, premeditation, perseverance, sensation seeking impulsive behavior scale.

nor an interaction effect between session and treatment [$T(71.870) = 0.371$, $p = 0.712$] was found (**Figure 5C**).

Exploratory Analyses

Baseline impulsivity

DDT: The Pearson correlation revealed no significant relationship between UPPS-P score ($r = -0{,}131$, $n = 24$, $p = 0{,}543$) or BIS score ($r = -0.154$, $n = 24$, $p = 0.472$) and AUC difference score.

GNGT: No significant correlation was found between the UPPS-P score ($r = -0.064$, $n = 30$, $p = 0.738$) or BIS score ($r = 0.128$, $n = 30$, $p = 0.502$) and the difference score of false alarm percentage.

SST: A correlation trending significance was found between the UPPS-P score and the SSRT difference score ($r = 0.349$, $n = 25$,

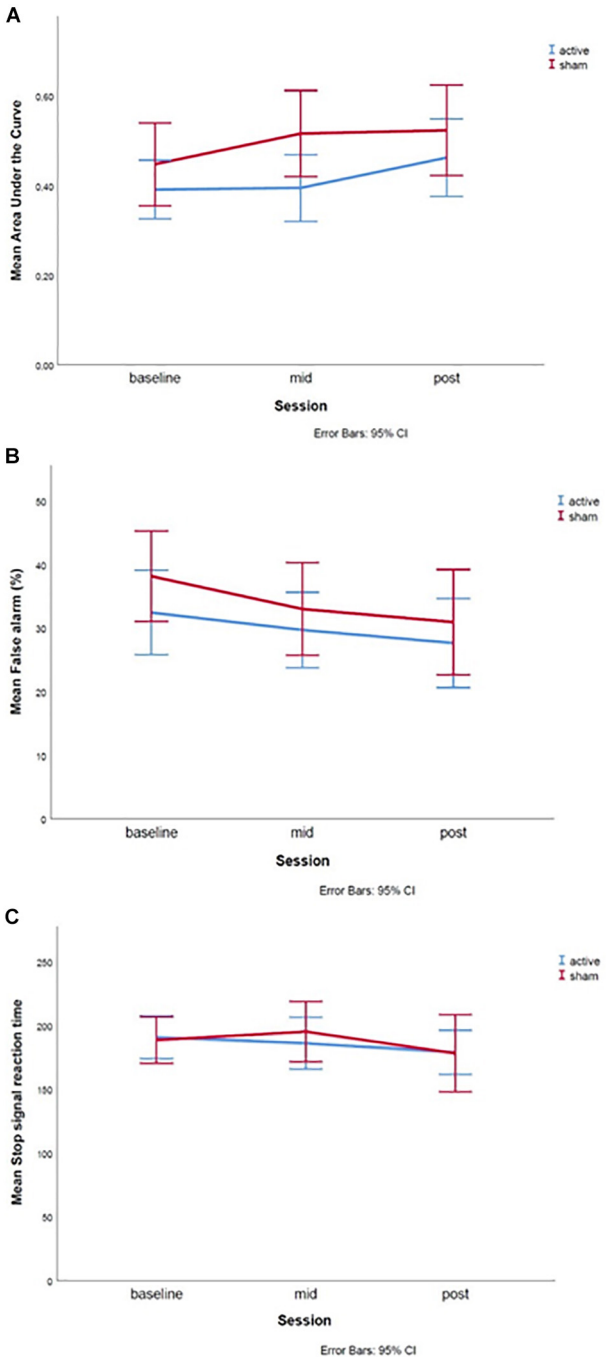

FIGURE 5 | Graphs of the treatment effect for the **(A)** Delay Discounting Task, **(B)** Go-Nogo Task, and **(C)** Stop Signal Task. The baseline measures were assessed during the first test day, mid during the fifth test day and post during the 10th test day. Error bars represent 95% confidence intervals.

p = 0.088). However, this effect was driven by one participant with a high difference score and high UPPS-P score. When this participant was removed from analyses the correlation decreased (r = 0.100, n = 24, p = 0.641). No significant correlation was found between BIS score and SSRT difference score (r = −0.032, n = 25, p = 0,880).

Severity of alcohol use disorder

DDT: Pearson correlation did not reveal a significant relationship (r = −0.174, n = 24, p = 0.417) between severity of AUD and AUC difference score.

GNGT: No significant correlation (r = 0.147, n = 30, p = 0.439) was found between the severity of AUD and the difference score of percentage false alarms.

SST: Severity of AUD and SSRT difference score also did not significantly correlate (r = 0.193, n = 25, p = 0.356).

Blinding

Data on treatment allocation was collected from 68 participants. 39 individuals believed to have received active treatment while 29 believed to have received sham treatment. 63.24% of the participants guessed their treatment allocation accurately. The binomial test indicated that the observed proportion of individuals who guessed their treatment allocation correctly (0.63) is significantly higher than the expected chance level (0.50) (p = 0.038).

Safety and Tolerability

In the active group in total 372 stimulation sessions were applied. Headache after stimulation occurred seven times (1.9%), pain or beep in the ear occurred three times (0.8%), tiredness after stimulation occurred two times (0.54%) and unpleasant sensation at stimulation site after stimulation occurred nine times (2.4%). In the sham group in total 366 stimulation sessions were applied. The same side effects were reported: headache occurred 17 times (4.6%), tiredness after stimulation occurred two times (0.55%) and unpleasant sensations at stimulation site occurred two times (0.55%). No pain or beep in the ear was reported in the sham group. The active group experienced significantly less headache compared to the sham group [$X^2(1)$ = 4.477, p = 0.034]. However, the sham group experienced significantly less unpleasant sensations at the stimulation site after stimulation [$X^2(1)$ = 4.407, p = 0.036], compared to the active group. Groups did not differ on the other reported side effects [pain or beep in the ear (p = 0.249, Fisher's exact test)/tiredness after stimulation (p = 1.000, Fisher's exact test)].

DISCUSSION

The current study aimed to elucidate the effect of 10 HF-rTMS sessions on impulsivity measures in abstinent individuals in treatment for AUD. The add-on HF-rTMS treatment was tolerated well, since no severe side effects were reported. Impulsivity was assessed by the Delay Discounting, Go-NoGo and SSTs that were performed before, midway, and post HF-rTMS treatment. Contrary to the hypotheses, the current results suggest no effect of 10 HF-rTMS sessions on performance on any of the impulsivity tasks.

To the best of our knowledge, this study was the first to assess the effect of 10 sessions of HF-rTMS treatment in AUD

on impulsivity, as measured by three impulsivity tasks. The SST was never before used to study improvements of impulsivity in alcohol (or substance) dependence using HF-rTMS, however, impulsivity, using the GNGT and DDT, was studied in this population. The lack of an effect on accuracy on the GNGT in the current study is in line with the study of Herremans et al. (2013), who also did not find an effect of one session of HF-rTMS treatment on GNGT accuracy in alcohol dependent patients. Contrarily, however, a sham-controlled study of Del Felice et al. (2016), in which four sessions of HF-rTMS treatment were applied, did find increased accuracy on the GNGT in AUD patients. Furthermore, the current results are contrary to the study of Sheffer et al. (2013) who report decreased discounting as measured by the DDT after one single session of HF-rTMS in nicotine dependent patients. The discrepancy is unexpected in light of the number of stimulation sessions, since applying multiple sessions of HF-rTMS could induce summation of the effect of a single session (Valero-Cabré et al., 2008) and therefore could be expected to have a larger effect. This was, however, not confirmed in the current study since we applied 10 sessions and did not find an effect on impulsivity measures. An explanation for this inconsistency might be the difference in the clinical status of the treated individuals. In the current study, severe AUD patients in treatment with an intention to quit were included, whereas Sheffer et al. (2013) treated nicotine dependent patients who did not have the intention to quit smoking. Individuals suffering from alcohol or marijuana dependence are more prone to facing social and economic problems in society (Cerdá et al., 2016). Hence, one may argue that worse clinical status requires more stimulation sessions in order to achieve an effect. However, this is not in line with the studies of Herremans et al. (2013); Del Felice et al. (2016) and the current study, since these studies included clinical groups, but have different results. Altogether, this suggests that results of HF-rTMS studies in alcohol and substance use disorders interfering with impulsivity are still mixed and inconclusive.

The current study did find a significant effect of age on GNGT performance: older individuals made less false alarms, indicative of decreased impulsivity. This is in line with Steinberg et al. (2008), who report a negative association between age and impulsivity. For the GNGT specifically, it has been found that with increasing age performance improves, however, when individuals reach older adulthood, performance decreases again (Votruba and Langenecker, 2013). However, these studies were performed in a sample of non-clinical individuals. Although, several studies address impulsivity in different age categories in substance use disorder (Argyriou et al., 2018), the relationship between age and impulsivity task performance in AUD has not been studied directly. However, it should be noted that we only find the effect of age for the GNGT, which assesses the failure to refrain from action initiation. Choice impulsivity (as measured with the DDT) and failure to inhibit an already initiated response (as measured with the SST) were not affected by age in the current study. Whether age only has a positive effect on action initiation is a topic for future research.

Some variability in inter-individual factors might contribute to the effect of non-invasive neuromodulation (Li et al., 2015) on certain outcome measures. Although deriving from transcranial Direct Current Stimulation studies, these inter-individual factors might also hold for HF-rTMS. Suggested inter-individual factors are: baseline performance, severity of disorder, age and gender. We performed several analyses in order to see whether the null results of the current study changed when these factors were taken into account. To begin with, baseline impulsivity measures as well as severity of AUD, did not affect the effect of HF-rTMS treatment on cognitive measures. Moreover, no significant effects of age and gender on the effect of HF-rTMS on impulsivity measures was found. Therefore current null findings cannot be explained by these factors. Other factors that might contribute to the effectiveness of non-invasive neuromodulation, and which were not directly measured in the current study are: anatomy, functional organization of local circuits, task related neurophysiology, neurochemistry and genetics (Li et al., 2015). Future studies should address whether these factors also influence effect of HF-rTMS in AUD. However, it is debatable whether trials studying the clinical application of HF-rTMS in psychiatry are suitable for these – more fundamental – neurobiological factors. Finally, the effect of HF-rTMS might depend on the choice of stimulation parameters. To begin with, one might argue that longer stimulation (more TMS pulses per session) induces stronger effects (Schulze et al., 2018). Furthermore, the number of repetitions, with the perfect interval, also influences the effect. However, studies systematically comparing different repetition schemes are currently missing (Ekhtiari et al., 2019). Additionally, the stimulation intensity might also influence the effect of stimulation (Lefaucheur et al., 2014). Altogether, future research must determine whether there are optimal settings for treatment of AUD (Ekhtiari et al., 2019).

The current study is the first randomized controlled clinical trial to apply 10 sessions of HF-rTMS over the right DLPFC to eighty AUD patients in treatment. One limitation of the current study was the sham condition. During sham treatment, the coil was tilted away 90 degrees from the scalp, which caused the magnetic field to flow away instead of passing the skull. The downside of this type of sham stimulation is that sensations on the scalp are also eliminated. Moreover, the participants of the current study were able to communicate with each other about the physical sensations they were experiencing during the HF-rTMS treatment since they were all admitted at the same department of the addiction treatment center. In line, participants guessed their treatment allocation correctly slightly above chance level. Therefore, future studies with patients that are hospitalized at the same department are recommended to consider using alternative types of sham stimulation, for example, a specific sham coil that mimics the sensations on the scalp (Rossi et al., 2007). Furthermore, a recent study in AUD patients (Moritz et al., 2018) indicated that other factors, such as motivation and effort may influence neurocognitive task performance in AUD to a larger extent than in healthy controls. In this study, motivation and effort partially mediated the diminished neurocognitive performance in AUD patients, which may also result in larger variability in between test sessions. In our study, large variability

in the impulsivity measures was present, indicating high variability in impulsivity within the AUD patients, which could partially be explained by motivation. The variability between the test sessions may have resulted in diminished sensitivity to find group by test session interactions. It is therefore recommended to include measures of motivation and effort in neurocognitive test batteries in substance use disorder studies (Moritz et al., 2018), to determine whether high variability in the outcome measures is caused by motivation.

The current study was one of the first assessing the effect of HF-rTMS treatment on impulsivity in patients with AUD in clinical treatment. Results indicated no additional effect of this treatment on impulsivity measures. Future studies are required to investigate whether blinding with a sham coil would affect results and whether impulsivity declines with age in AUD patients.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethical Committee of the Academic Medical Centre Amsterdam (2015_064). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RS, RH, and AG contributed to the design of the study. RS performed the study and analysis. RS wrote the first draft of the manuscript. RH and AG revised the manuscript. All authors read and approved the final version of the manuscript.

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OPINION
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Better Together? Coupling Pharmacotherapies and Cognitive Interventions With Non-invasive Brain Stimulation for the Treatment of Addictive Disorders

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INTRODUCTION

Addictive disorders (AD) are one of the leading causes of morbidity and mortality worldwide (World Health Organization, 2018). Although several pharmacological and behavioral treatments for these disorders have shown efficacy in controlled clinical trials, there is a need for more effective treatments. Recently, there has been an emerging emphasis in investigating neurocircuitry-based treatment options for patients with AD (Diana et al., 2017; Spagnolo and Goldman, 2017). Specifically, an increasing number of studies has evaluated the therapeutic potential of non-invasive bran stimulation (NIBS) techniques, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), in various substance-dependent populations, as well as in subjects with behavioral addictions. The interest in NIBS has been hastened by advances in the neuroscience of addictive disorders, indicating that neurocircuitry dysfunctions (e.g., cortico-striatal and cortico-limbic circuits) underlie the behavioral and clinical alterations commonly observed in patients with AD (Volkow et al., 2016). Since none of the therapies for AD currently available can undo these neuroadaptations, the possibility to target and restore them via NIBS appears particularly promising.

The use of NIBS for AD, however, is still in its infancy, and several questions, including the optimal target, stimulation protocol, and treatment duration, still need an answer before these interventions could be used as a tool for clinical practice in addiction medicine. In this regard, recent rTMS and tDCS trials in AD patients have contributed to identify several factors playing an important role for NIBS efficacy, such as coil and electrodes orientation, scalp-brain distance, and gray/white matter structure, density and integrity. In addition to those, a further factor that appears to critically modulate the effects of NIBS is the *state of brain* during the application of the stimulation. It is well-known that pharmacotherapies, psychotherapies (e.g., cognitive behavioral therapy, CBT) and behavioral or cognitive tasks affect brain activity and connectivity. Thus, using them in conjunction with neuromodulation interventions may ultimately change treatment outcomes, and also explain the interindividual variability often observed in response to NIBS (Silvanto and Pascual-Leone, 2008; Luber and Lisanby, 2014; Romei et al., 2016).

STATE-DEPENDENT EFFECTS OF NIBS: THE ROLE OF PHARMACOTHERAPIES

The "state-dependent" effects of NIBS have been initially studied in regard to pharmacotherapies, and particularly active drugs on the central nervous system (CNS), since these medications have been shown to alter excitability measures and NIBS-induced plasticity (Ziemann et al., 2015; Martinotti et al., 2019). Among the pharmacological interventions evaluated to date, medications such as dextromethorphan (Nitsche et al., 2003), diazepam (Ziemann et al., 2015), baclofen (McDonnell et al., 2007), and propranolol (Nitsche et al., 2004a) appear to block the facilitation or inhibition associated with brain stimulation. However, D-cycloserine (Nitsche et al., 2004b), amphetamine (Nitsche et al., 2004a), and nicotine (Thirugnanasambandam et al., 2011) have been shown to increase the long-term potentiation-like effects of NIBS in healthy individuals, thus suggesting that combining NIBS with pharmacotherapies may also lead to supraordinal effects on neuroplasticity (for a review, see Ziemann et al., 2015).

Few studies have considered this phenomenon also in the context of several psychiatric disorders. For example, a recent observational study in patients with Major Depressive Disorder (MDD) reported that combining rTMS with psychostimulants (e.g., modafinil, methylphenidate) was associated with greater clinical outcomes, compared to other medications (Hunter et al., 2019). Furthermore, atomoxetine combined with rTMS has showed significant clinical advantages compared with both rTMS and atomoxetine in monotherapy (Cao et al., 2018), as well as clozapine efficacy is improved when combined with neuromodulation techniques in clozapine-resistant schizophrenic patients (Arumugham et al., 2016). However, combing deep TMS with SSRIs in patients with treatment-resistant depression was not associated with improved clinical outcomes, compared to deep TMS alone (Tendler et al., 2018). There are presently no studies in the behavioral or substance addiction literature that have directly evaluated the combined effects of NIBS and pharmacotherapy, although several trials have enrolled patients with AD receiving pharmacological treatment (Klauss et al., 2014; Mishra et al., 2015; Del Felice et al., 2016; Wang et al., 2016). Thus, future research should investigate whether concurrent administration of pharmacotherapies could help optimize NIBS therapy, and define the mechanisms by which different medications used for AD interact with NIBS.

COMBINING COGNITIVE TRAINING/THERAPY WITH NIBS

In addition to pharmacological treatments, cognitive and/or behavioral interventions also interact with NIBS, by modulating ongoing neural activity in the targeted circuits and associated networks. The effects of this interaction critically depend on the timing of delivery, as cognitive and behavioral interventions can be applied simultaneously or sequentially to NIBS. Several studies have shown that the behavioral effects of brain stimulation (facilitatory vs. inhibitory) change when TMS is preceded by an initial psychophysical manipulation (Silvanto and Pascual-Leone, 2008; Silvanto et al., 2017). This because brain state manipulations may act as a functional priming of a certain neurocircuitry, which, consequently, may respond differently to neurostimulation (Silvanto et al., 2017). Furthermore, functional engagement of a neurocircuitry with a cognitive task has been proposed to facilitate the long-term potentiation like-effects induced by NIBS (Luber et al., 2007; Tsagaris et al., 2016). Otherwise, when NIBS is applied before or simultaneously to a cognitive or behavioral intervention, it may enhance and facilitate inherent learning processes associated with these interventions, considering the ability of NIBS in boosting DA signaling and the evidences suggesting that strengthening the DA signal may improve memory formation, as well as emotionally relevant information encoding (Cannizzaro et al., 2019). Indeed, TMS has been used in conjunction with cognitive strategies such as CBT or emotional recall in patients with MDD and PTSD, with promising results (Isserles et al., 2011; Neacsiu et al., 2018).

However, the temporal relationship between multimodal interventions remains relatively an unexplored territory (Tsagaris et al., 2016), and is one of the most poorly reported variables in NIBS studies, although identifying the optimal timing of combined interventions may enhance their therapeutic effects, while also helping to avoid inducing maladaptive plasticity.

With regard to the combined effects of NIBS and psychotherapy, research has mainly focused on patients with mood and anxiety disorders, with mixed results (for a review, see Chalah and Ayache, 2019). Differences in the type of psychotherapy as well as in the number of sessions may explain the inconsistency among studies, although cognitive-behavioral therapy seems to enhance the top-down modulatory effects of prefrontal stimulation (Tan et al., 2015; Grassi et al., 2018). In the field of addictive disorders, preliminary evidence suggests that NIBS is most likely to be effective when combined with evidence-based self-help intervention or cognitive-behavioral interventions, as indicated by several studies evaluating the effects of TMS for nicotine addiction (for a review, see Hauer et al., 2019).

One of the most interesting areas of recent methods development in NIBS involves choosing a task for the participants to perform before or during the stimulation. Dinur-Klein et al. (2014) were the first to demonstrate that it is possible to amplify the effects of TMS on smoking cessation by having individuals engage in a smoking cue-reactivity task immediately before the TMS session (Dinur-Klein et al., 2014). Specifically, in this large, double-blind, sham-controlled study of 115 cigarette smokers, half of the participants were presented with visual and olfactory smoking cues before the TMS session (deep TMS targeting insula and lateral prefrontal cortex bilaterally). Individuals that had received high-frequency deep TMS in conjunction to smoking cues exposure exhibited significantly lower cigarette consumption and nicotine dependence than sham TMS. Similar results have also been observed in Obsessive Compulsive Disorder (OCD) patients receiving high-frequency deep TMS of the medial prefrontal cortex (mPFC)—anterior cingulate cortex (ACC) region following exposure to individualized, obsessive-compulsive cues (Carmi et al., 2018).

These results suggest that task-induced plasticity may enhance the behavioral effects of rTMS, although the precise mechanism mediating this phenomenon has not been directly investigated in patients with AD or with other psychiatric conditions.

In addition to cue exposure paradigms, which engage brain circuits mediating cue reactivity, for NIBS studies targeting prefrontal control circuitry [i.e., the dorsolateral prefrontal cortex—DLPFC, a major node of the executive control network (ECN)] the choice of a cognitive task may be the best approach to maximize the benefits to be gained from either intervention. Supporting this concept, emerging evidence indicates that simultaneous tDCS and cognitive control therapy (CCT), a neurocognitive intervention for MDD that engages the left DLPFC (Brunoni et al., 2014), has stronger antidepressant effects compared to tDCS alone (Brunoni et al., 2014; Segrave et al., 2014). Interestingly, the antidepressant effect positively correlated with cognitive performances during CCT, thus suggesting that enhanced cognitive control via tDCS + CCT mediated the clinical outcomes (Vanderhasselt et al., 2015). Similarly, addition of tDCS to working memory tasks has been shown to enhance long-term cognition in schizophrenics (Orlov et al., 2017), while combining tDCS with an attentional bias modification task reduced reactivity to negative environmental stimuli in anxious individuals (Heeren et al., 2017).

Preliminary evidence in the field of AD have also been reported. Specifically, in a recent trial in patients with alcohol use disorders (AUD), 4 sessions of attentional bias training (control or real) were combined with either sham or active tDCS over the DLPFC, using a 2-by-2 double-blind factorial design (den Uyl et al., 2018). Combined active tDCS and real training did not produce any significant effect on alcohol craving and relapse, and on attentional biases toward alcohol. However, as also observed by the authors, individuals enrolled in the study had low baseline craving levels. Furthermore, the number of sessions delivered may not have been enough to produce a clinical meaningful effect (Spagnolo and Goldman, 2017). Interestingly, a further study found that tDCS over the left DLPFC significantly decreased the engagement bias toward drug cues in abstinent methamphetamine users (Shahbabaie et al., 2018). Finally, a recent study evaluated the effects of 4 sessions of combined tDCS targeting the right inferior frontal gyrus and cognitive bias modification training in high-risk drinkers (AUDIT score >8) and found no effect on drinking measures or alcohol approach biases (Claus et al., 2019).

DISCUSSION

The behavioral and clinical effects of NIBS depends on what the brain is doing at the time of stimulation. Brain state can be affected by pharmacotherapies, as well as by behavioral and cognitive interventions, which act by modulating and/or engaging disease-related circuits targeted via neurostimulation. Increasing evidence suggest that this combined approach can be useful for treating various psychiatric disorders (for a review, see Sathappan et al., 2019), and could prove to be a promising approach worth further examination also in the field of AD. Indeed, multimodal, integrated interventions are successfully used to treat patients with chronic conditions.

However, several important issues should be investigated to fully delineate the therapeutic potentials of combined therapies for AD. In particular, attention should be devoted to the complex interplay between AD and factors known to modulate response to both NIBS and cognitive interventions. For example, prolonged exposure to addictive agents has been shown to impair cortical plasticity, including motor cortical plasticity (Huang et al., 2017; Shen et al., 2017), an effect which can reduce response to NIBS protocols. Neurostimulation effects on brain plasticity can also be affected by genetic factors, including polymorphisms at the level of the Brain-Derived Neurotrophic Factor (BDNF) gene (Cheeran et al., 2008). Importantly, many addictive agents lead to changes in endogenous BDNF expression in neural circuits implicated in AD (Barker et al., 2015), thus indicating as response to NIBS is modulated by a complex interaction between stimulation-related factors, individual factors, and AD-related factors. A further example is represented by sex-differences and endogenous estrogen levels, which have been associated to variability in response to both TMS and cognitive interventions (Glover et al., 2015; Chung et al., 2019), and with changes in BDNF levels (Barker et al., 2015).

Taken together, these observations strongly support the need to better characterize the biobehavioral responses to both neuromodulation (TMS, tDCS) and other interventions (cognitive bias modification, medications, psychotherapy). For NIBS, this requires addressing questions related to stimulation parameters, brain targets, number of sessions, factors influencing the stimulation dose delivered, and tools to measures the neurophysiological, circuit-level and behavioral effects of neuromodulation interventions.

With regard to pharmacotherapies, while their action on cortical excitability and brain plasticity have been studies, it will be also critical to define how medications currently used for AD modulate brain activity and connectivity. For example, naltrexone, a medication commonly used in patients with alcohol and opioid use disorders, has been shown to modulate brain connectivity (Morris et al., 2018; Elton et al., 2019). Since NIBS also has a modulatory effect on brain connectivity, particularly when applied to network nodes (Eldaief et al., 2011), future research should investigate whether these effects can be combined in a synergistic fashion.

For psychotherapies, quantifying dose is more challenging since both number and duration of treatment sessions should be evaluated, and optimal measures of treatment responses, which take in consideration the specificity of this interventions (e.g., therapeutic relationship between patient and therapist, internal state of the patient during time of therapy), are still missing. Furthermore, as for medications, the documented effects of CBT on brain connectivity should be studied in the context of combined therapy with NIBS. Mason et al. (2015) reported that CBT increased DLPFC connectivity with amygdala in patients with psychosis, an effect which predicted subsequent recovery (Mason et al., 2015). This may suggest that coupling this

intervention with NIBS targeting the prefrontal control circuit may enhance CBT effects on corticolimbic connectivity.

With regard to behavioral and cognitive tasks, several critical factors should be considered when evaluating the effects of these intervention both alone and in combination with NIBS. With regard to cue exposure paradigms, a recent study has indicated that individual's baseline frontal-striatal reactivity to cues modulates the effects of TMS targeting the medial PFC. This underscores the importance of assessing individual variability with the aim to identify subjects who can benefit more from these interventions (Kearney-Ramos et al., 2019). Similarly, cognitive bias modification efficacy varies whether it is tested in problematic drinkers vs. treatment-seeking patients with AD (Wiers et al., 2018). This is not surprising, as expectations -of a drug or of a clinical benefit -modulate brain responses and affect outcomes (Spagnolo et al., 2015).

As the field continues to grow, we are optimistic the future studies will be designed to address these questions, and that significantly more attention will be given to combined therapies, with the hope to provide a novel, tailored and effective treatment approach to patients with AD.

AUTHOR CONTRIBUTIONS

PS and CM designed the paper and reviewed the literature. PS, CM, MP, GM, and MD wrote the opinion paper and reviewed the manuscript. All authors approved the final paper.

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REVIEW
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rTMS-Induced Changes in Glutamatergic and Dopaminergic Systems: Relevance to Cocaine and Methamphetamine Use Disorders

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Cocaine use disorder and methamphetamine use disorder are chronic, relapsing disorders with no US Food and Drug Administration-approved interventions. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation tool that has been increasingly investigated as a possible therapeutic intervention for substance use disorders. rTMS may have the ability to induce beneficial neuroplasticity in abnormal circuits and networks in individuals with addiction. The aim of this review is to highlight the rationale and potential for rTMS to treat cocaine and methamphetamine dependence: we synthesize the outcomes of studies in healthy humans and animal models to identify and understand the neurobiological mechanisms of rTMS that seem most involved in addiction, focusing on the dopaminergic and glutamatergic systems. rTMS-induced changes to neurotransmitter systems include alterations to striatal dopamine release and metabolite levels, as well as to glutamate transporter and receptor expression, which may be relevant for ameliorating the aberrant plasticity observed in individuals with substance use disorders. We also discuss the clinical studies that have used rTMS in humans with cocaine and methamphetamine use disorders. Many such studies suggest changes in network connectivity following acute rTMS, which may underpin reduced craving following chronic rTMS. We suggest several possible future directions for research relating to the therapeutic potential of rTMS in addiction that would help fill current gaps in the literature. Such research would apply rTMS to animal models of addiction, developing a translational pipeline that would guide evidence-based rTMS treatment of cocaine and methamphetamine use disorder.

Keywords: rTMS, addiction, brain stimulation, cocaine use disorder, methamphetamine use disorder, glutamatergic system, dopaminergic system

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INTRODUCTION

Substance dependence is a chronic, relapsing disorder with significant monetary and societal costs. Moreover, there are still substance use disorders with no US Food and Drug Administration (FDA)-approved interventions, such as cocaine use disorder and methamphetamine use disorder. Therefore, there is a need to investigate possible treatments and interventions that could

help combat these addictions. One avenue of investigation is the use of non-invasive brain stimulation techniques, such as repetitive transcranial magnetic stimulation (rTMS). rTMS therapy has been FDA approved for treatment-resistant depression (O'Reardon et al., 2007; Horvath et al., 2010) and obsessive-compulsive disorder (Carmi et al., 2018) and has also shown promise in several other neurological disorders where its ability to induce plasticity proves useful (Fregni and Pascual-Leone, 2007; Pell et al., 2011; Lefaucheur et al., 2014). The aim of this review is to highlight what is currently known about the effects of rTMS within the field of addiction, specifically on cocaine and methamphetamine dependence. In this review, we consider human and animal studies, which together allow us to relate the outcomes of rTMS therapy to the neurobiological mechanisms that seem most involved in addiction – changes in the glutamatergic and dopaminergic systems.

MAJOR PATHWAYS INVOLVED IN ADDICTION

Addiction is a complex condition that involves several neural pathways and mechanisms of dependence that can be specific to the substance of abuse. Broadly speaking, however, the main pathways implicated in addiction are the glutamatergic afferents from the prefrontal cortex (PFC) to the nucleus accumbens (NAc) of the ventral striatum and ventral tegmental area (VTA) of the midbrain, and the dopaminergic efferents from the VTA to the striatum. Abnormal function of these pathways in addiction results in the disruption and dysregulation of dopaminergic activity (Koob and Volkow, 2010). Together these pathways are referred to as the mesocorticolimbic system.

Drug addiction is characterized by changes at all points of the mesocorticolimbic system. Exposure to addictive substances such as cocaine and methamphetamine is accompanied by a fast and steep release of dopamine in the NAc (Volkow et al., 2007; Fowler et al., 2008), affecting mesocorticolimbic pathways and characterizing the first stage of addiction – intoxication (Koob and Volkow, 2010). Although transient, this substance-induced elevation in dopamine may exceed that observed following "normal" physiological processes (Volkow et al., 2007). Several other neurotransmitters, including opioid peptides (Daunais et al., 1993; Spangler et al., 1993), serotonin (see Müller and Homberg, 2015), and acetylcholine (Imperato et al., 1993; Zocchi and Pert, 1994; Berlanga et al., 2003), are also increased during the intoxication stage (Koob and Volkow, 2010).

Repeated exposure to addictive substances can result in maladaptive sensitization within the mesocorticolimbic system, specifically toward dopamine release, whereby conditioned incentive sensitization (increase in "wanting" without necessarily a change in "liking") toward drug-associated stimuli occurs (Berridge and Robinson, 2016). The PFC to NAc glutamatergic pathway, which includes afferents from the dorsolateral PFC (DLPFC), is involved in modulating these value signals (Hayashi et al., 2013). Chronic drug use may also induce long-term neuroadaptations as a result of the repeated hyperactivity of dopaminergic transmission, for example, facilitating the development of learned associations between drug-related cues, such as images or videos of drugs, drug paraphernalia in an experimental setting, the anticipation of drug intoxication, and the accompanying physiological changes such as the induction of dopamine release in the striatum (Wolf et al., 2004; Berridge and Robinson, 2016). Such neuroadaptations may underpin the impact of cues, which are usually specific to the drug of interest and induce an increase in striatal dopamine that is thought to underlie craving (Goldstein and Volkow, 2002; Volkow et al., 2006, 2008; Volkow and Morales, 2015). Neuroplastic changes from chronic drug use are also associated with reduced cognitive control, compulsive drug use, and impulsivity to continue addictive behavior (Koob and Volkow, 2010).

It is also thought that the inability to inhibit drug-seeking behaviors is partly underpinned by a weakened executive control network and PFC dysfunction (Bechara, 2005; Hu et al., 2015; Ekhtiari et al., 2019), which are thought to contribute to the development of behaviors that are characteristic of addiction (Volkow and Fowler, 2000; Goldstein and Volkow, 2002). The PFC is made up of several regions that may each contribute to different aspects of addictive behavior (for a review, see Goldstein and Volkow, 2011). For example, the ventrolateral PFC and lateral orbitofrontal cortex are linked with habitual responding and therefore linked with impulsivity and inflexible behavior patterns. In contrast, the ventromedial PFC, which includes the subgenual anterior cingulate cortex (ACC) and medial orbitofrontal cortex, is linked with emotion regulation and incentive salience of drugs and related cues (Goldstein and Volkow, 2011). Furthermore, the DLPFC has a significant role in top-down control and metacognitive functions such as attention bias, motivation, and self-control, among others (Goldstein and Volkow, 2011). It is therefore important to be mindful when reading the literature that different PFC regions can be associated with particular cognitive processes and can also have different anatomical connections and feedback loops.

Contributing to the addiction cycle are the acute withdrawal effects, which include reduced reward sensitivity and motivation for natural rewards (Barr and Phillips, 1999). Cessation of drug use is associated with altered levels of a number of different substances, including a decrease in basal dopamine levels in the striatum (e.g., Rossetti et al., 1992; Weiss et al., 1992). Evidence of the hypodopaminergic tone observed within the mesolimbic system from both experimental and clinical studies led to the development of the dopamine hypothesis of drug addiction (Melis et al., 2005), and progress within the field has been reviewed more recently (Fattore and Diana, 2016). Hypodopaminergic tone has also been associated with a decrease in striatal dopamine terminal density (Lee et al., 2011) and downregulation of dopamine D_2 receptors expressed on both presynaptic and postsynaptic neurons, the latter being important for inhibitory feedback signals (Nutt et al., 2015; Volkow and Morales, 2015). These have been linked to pathological behaviors such as impulsivity and compulsive drug seeking in subjects addicted to methamphetamine and cocaine (Lee et al., 2009; Moeller et al., 2018). Changes within the dopaminergic system contribute to the acute withdrawal effects, which include reduced reward sensitivity and motivation for natural rewards (Barr and

Phillips, 1999), as well as negative affect, such as irritability, states of stress, and malaise (Baker et al., 2006; Fox et al., 2008; Koob, 2009; Koob and Volkow, 2010). This negative state of withdrawal tends to further narrow behavior toward drugs and drug-related stimuli, perpetuating drug use.

MANIPULATING CIRCUITS INVOLVED IN ADDICTION

Our current knowledge of the circuits involved in addiction comes from animal studies as the pathways and brain regions involved are similar in rodents and humans (Kalivas et al., 2006; Madeo and Bonci, 2019). Animal models of addiction are one of the most well-developed and validated models in neuropsychiatric research and are used by researchers and clinicians to gain insight into some of the mechanisms involved in addiction (Kalivas et al., 2006; Venniro et al., 2016). These findings have since been supported by follow-up studies that alter activity in a targeted brain region (Conrad et al., 2008; Chen et al., 2013; Venniro et al., 2016). This has been done mostly in one of two ways: direct electrical stimulation and, more recently, optogenetics.

Direct evidence of brain stimulation altering compulsive drug-seeking behaviors has been shown following application of localized electrical stimulation to the PFC of cocaine-addicted rats and mice *via* implanted electrodes (Levy et al., 2007). Following 20-Hz stimulation (30 min, 10 pulses/train, one train every 2 s) in the PFC, cue-induced cocaine-seeking behavior and motivation for its consumption were reduced (Levy et al., 2007), which is likely related to the release of dopamine and glutamate in the NAc following stimulation in the PFC (Taber et al., 1995; You et al., 1998). Comparison of various stimulation frequencies in the medial PFC (mPFC) showed that 10- to 20-Hz electrical stimulation that lasted >5 s resulted in peak extracellular dopamine levels, compared to 30-, 40-, and 60-Hz stimulation frequencies, possibly due to its similarities to endogenous bursting rhythms of the VTA (Hill et al., 2018).

Since the development of genetic techniques such as optogenetics (Boyden et al., 2005; Han, 2012), researchers have been able to manipulate neural circuits with greater specificity (e.g., purely glutamatergic neurons) to gain a better understanding of the circuits involved in pathological drug-seeking behavior. It is important to note, however, that caution must be taken when interpreting results of studies that utilize optogenetics methods, and inclusion of rigorous control groups is necessary (see Tye and Deisseroth, 2012). For example, certain illumination protocols can induce temperature fluctuations within the surrounding tissue, affecting behavioral outcomes (Owen et al., 2019). Therefore, control experiments should include a viral construct that does not encode for light-sensitive ion channels (Yizhar et al., 2011; Owen et al., 2019). Despite these limitations, a study has shown that optogenetics stimulation of hypoactive glutamatergic neurons of the PFC can modulate compulsive drug seeking in cocaine-addicted rats (Chen et al., 2013). Using adeno-associated viruses, light-sensitive ion channels [channelrhodopsin for depolarization and halorhodopsin for hyperpolarization (Tye and Deisseroth, 2012)] were transfected into glutamatergic neurons of the prelimbic cortical area. Activation of the transfected neurons (1 Hz, 10-ms wide pulses, 10–15 mW, 473 nm) *via* channelrhodopsin led to reduced compulsive drug-seeking behavior, whereas inhibition with halorhodopsin led to increased drug-seeking behavior (Chen et al., 2013). Therefore, it appears that excitatory stimulation of PFC glutamatergic efferents can rescue its hypoactivity and may result in downstream effects that can increase dopamine transmission, ultimately reducing compulsive drug seeking in addicted subjects.

The dynamic plasticity of the mesocorticolimbic pathways is thus central in addiction, particularly the maladaptive changes that occur within glutamatergic and dopaminergic systems, and offers a compelling target for therapeutic interventions to modulate circuit activity. In order to translate these findings into humans and manipulate the activity of relevant circuits for therapeutic purposes, many studies have used rTMS, which allows non-invasive modulation of brain activity. Studies with rTMS can vary in which stage of the addiction cycle they lie; however, most clinical studies on cocaine and methamphetamine addiction tend to focus on patients who are in the preoccupation/anticipation stage after chronic withdrawal from the drug. Therefore, this review will focus on the anticraving effects of rTMS on substance dependence, with a particular focus on cocaine and methamphetamine dependence. The aim of this review is to highlight potential neurobiological mechanisms that can guide future rTMS research within the field.

FUNDAMENTALS OF *R*TMS

Repetitive TMS has shown promising results for the treatment of a range of neurological disorders and has been shown to induce plasticity in humans, as measured *via* changes in corticospinal excitability (Pell et al., 2011) and alterations in mood, behavior, and cognition (e.g., O'Reardon et al., 2007; Luber and Lisanby, 2014). Currently FDA approved for major depressive disorder and obsessive-compulsive disorder, this non-invasive brain stimulation technique may also facilitate recovery from substance use disorders. Reasons for how rTMS induces therapeutic effects in various neurological disorders remain unclear; however, a number of preclinical studies have identified mechanisms that could underlie the long-term effects. These mechanisms include alterations to neuron excitability (Sun et al., 2011; Hoppenrath et al., 2016; Tang et al., 2016) and Hebbian-type strengthening of synapses (Vlachos et al., 2012; Lenz et al., 2015), as well as alterations to gene expression (Ikeda et al., 2005; Grehl et al., 2015), trophic factors necessary for neuroplasticity (Gersner et al., 2011; Rodger et al., 2012; Makowiecki et al., 2014), activity within brain regions beyond the induced electrical field (Aydin-Abidin et al., 2008; Seewoo et al., 2018, 2019), and even changes to non-neuronal cells, which may contribute to plastic events (Clarke et al., 2017a,b; Cullen et al., 2019).

Utilizing the principles of Faraday's law of electromagnetic induction, rTMS is delivered via a coil positioned above the scalp to induce electrical currents in the underlying brain tissue. These

electrical currents have the capacity to induce neuroplasticity, either by triggering action potentials in the underlying cortical neurons (Pashut et al., 2014; Li et al., 2017), or by modulating neuronal excitability (Sun et al., 2011; Hoppenrath et al., 2016; Tang et al., 2016). Effects of rTMS depend on multiple stimulation parameters, such as the frequency and rhythm of the pulses delivered, number of pulses, coil and pulse shape, stimulation intensity, and number of sessions (Pell et al., 2011; Rodger and Sherrard, 2015). In addition, morphological differences such as the brain tissue shape (e.g., gyral anatomy) relative to the device can influence rTMS effects (Wagner et al., 2009; Thielscher et al., 2011).

Frequency and Pulse Number

In humans, alteration to corticospinal excitability is the main measure of rTMS-induced plasticity. Changes in excitability can be measured by comparing motor-evoked potentials (MEPs) before and after stimulation. MEPs are recorded by applying a single TMS pulse at a specified intensity to the motor cortex and recording the electromyogram of a peripheral muscle. Changes to human cortical excitability have been shown to be frequency dependent, with a simple high-frequency (HF) ($\geq$5 Hz) or low-frequency (LF) ($<$1 Hz) rTMS protocol able to increase or decrease excitability, respectively (Hallett, 2007; Pell et al., 2011), albeit with high intraindividual and interindividual variability (Ridding and Ziemann, 2010; Hinder et al., 2014; Hamada and Rothwell, 2016). There are also complex patterned protocols, such as theta burst stimulation (TBS), which utilize a train consisting of three pulses at 50 Hz, repeated at 5 Hz, for a total of 600 pulses (although other variants also exist). TBS protocols can be differentiated into two subtypes: continuous (cTBS), wherein 20 trains of uninterrupted pulses are delivered, and intermittent (iTBS), with a 2-s TBS train repeated every 10 s. Intermittent TBS has been shown to have excitatory effects on cortical excitability, whereas cTBS has inhibitory effects (Huang et al., 2005). Compared to simple protocols, these complex patterned protocols may be more effective for inducing long-term changes, with an increase in MEPs induced by iTBS lasting for approximately 60 min (Wischnewski and Schutter, 2015). Recently, an analysis of various rTMS protocols has suggested that frequency is the strongest predictor of the direction of change in cortical excitability, as measured via MEPs (Wilson and St George, 2016).

An additional contributor to frequency effects is the pulse rhythm, or the pattern in which trains of frequency are delivered. There is a wide variety of pulse numbers and pulse rhythms used in the literature, and it is not clear what effect these factors have on rTMS efficacy, and if there is a dose dependency. Train length and intertrain intervals are determined in part by the characteristics of the rTMS device: every pulse generates heat in the coil, and more heat is generated at higher frequencies (Weyh et al., 2005). It is therefore necessary to introduce intertrain intervals to allow the coil to cool down. Human studies suggest that pulse number and train number are not related to the outcome of rTMS in a straightforward way (Huang et al., 2005; Hamada et al., 2013), but results are difficult to interpret because of variability in human subjects. One study specifically explored the effect of pulse number on expression of protein markers in the cortex of healthy rats (Volz et al., 2013). For TBS protocols, increasing the number of pulses did not lead to a simple dose-dependent change, but rather elicited a "waxing-and-waning" effect for the markers of inhibitory interneuron and γ-aminobutyric acid (GABA) activity (Volz et al., 2013). Furthermore, increasing number of pulses led to a progressive reduction in protein expression of the immediate early gene c-Fos, which normally reflects neuronal activation (see Aydin-Abidin et al., 2008). Surprisingly, the reduction occurred following both inhibitory (cTBS) and excitatory (iTBS) protocols (Volz et al., 2013), suggesting a complex relationship between the number and rhythm of pulses and the effect on cortical neurons.

Intensity

The strength of stimulation is a variable parameter. In order to account for interindividual changes in excitatory thresholds, the intensity of rTMS is often applied as a percentage of the resting motor threshold (rMT). Techniques to find a participant's rMT vary, but it is defined as the lowest stimulation intensity that produces at least five MEPs ($\geq$50 μV) out of 10 consecutive stimuli (Rossini et al., 1994). Intensity will usually be set at a % between 80 and 120% rMT, depending on the study. For TBS, lower intensities of 80–90% are usually used, which contribute to its improved tolerability (Oberman et al., 2011). Higher intensities are often associated with more adverse effects (Rossi et al., 2009) but are more likely to elicit action potentials ($\geq$100% rMT), which could have stronger cortical effects. Nonetheless, stimulation below motor threshold (80–95% rMT) is still capable of eliciting cortical and subcortical changes in distinct networks across the brain (Bestmann et al., 2004).

Experimental animal models have shown that high-intensity rTMS [$\geq$1 Tesla (T)] can evoke action potential firing (Pashut et al., 2014; Li et al., 2017) and alter neurotransmitter concentrations (e.g., Ben-Shachar et al., 1997), whereas low-intensity rTMS ($\leq$120 mT) can lower action potential thresholds and increase spike firing frequency for up to 20 min after magnetic stimulation (Tang et al., 2016). In addition, behavioral changes in a mouse model of depression have been shown to be dependent on stimulation intensities (Heath et al., 2018). Low-intensity effects may also contribute to the impact of high-intensity protocols in humans due to the wide distribution of low-intensity magnetic fields within brain tissue outside the site of focal stimulation (Bestmann et al., 2004). Within the field of magnetic stimulation, a limitation is the inconsistency of reporting the induced field intensities (see, for example, **Table 1**, which reports the intensity listed in the original research articles). Some articles mention the induced magnetic field, the induced electric field or a % output of the machine required to evoke an observable muscle twitch (MEP). Adding to this confusion, different units of measurement have also been reported (e.g., mT, V/m, and dB/dT).

Coil Parameters

There are several different coil designs available for rTMS, with changes to coil shape affecting the induced electric field in the brain. The coil properties of various designs have been

TABLE 1 | rTMS effects on dopaminergic systems sorted by sampling method used.

Study	Subject	Session number	rTMS parameters	rTMS coil[a] and target	Sampling method	Sampling time	Significant effect
Zangen and Hyodo, 2002	Rat	Single	2 Hz, 100 s, 500 V/s	5.4-cm circular coil. Over the head, rostral, or caudal side	Microdialysis: DA, DOPAC, HVA	During, 0–45 min pms, 15-min intervals	*NAc*: ↑ DA after rostral or caudal stimulation, returned to baseline within 15 min pms
Keck et al., 2000	Rat	Single	20 Hz, 2.5 s, 2 min ITI, 20 trains, Σ1,000 pulses, 130% MT	5.7-cm circular coil, left FC	Microdialysis: DA, DOPAC, HVA	Baseline, 0–60 (rTMS), 90–120 min pms, 30-min intervals	*Urethane anesthetized – right hippocampus*: ↑ DA 60 and 90 min pms
Keck et al., 2002	Rat	Single	20 Hz, 2.5 s, 2 min ITI, 20 (i) or 6 (ii) trains, Σ1000 or Σ600 pulses, 130% MT	5.7-cm circular coil, left FC	Microdialysis: DA, DOPAC, HVA	(i) Baseline, 0–60 (rTMS), 90–180 min pms, 30-min intervals. (ii) Baseline, 0–30 (rTMS), 60–180 min pms, 30-min intervals	*(i) Urethane anesthetized – right hippocampus*: same as Keck et al. (2000); *right NAc shell*: ↑ DA 120–180 min pms; *right dorsal striatum*: ↑ DA 90–180 min pms. *(ii) Awake – right hippocampus*: ↑ DA 90–180 min pms; *right NAc shell*: ↑ DA 30–180 min pms
Erhardt et al., 2004	Rat	Single	20 Hz, 2.5 s, 2.5 min ITI, six trains, Σ300 pulses, 130% MT	5.7-cm circular coil, left FC	Microdialysis: DA	Baseline, 0–30 (rTMS), 60–120 min, 30-min intervals	*Right NAc shell*: ↑ DA at 0–30 min for morphine sensitized rats + rTMS vs. basal, saline + rTMS, morphine + sham; ↑ DA at 60, 90 morphine + rTMS vs. basal, morphine + sham; ↑ DA at 120 min vs. sham + morphine
Kanno et al., 2004	Rat	Single	25 Hz, 1 s, 1 min ITI, 20 trains, Σ500 pulses, 0.2 T, 0.6 T, and 0.8 T	7-cm F-o8 coil, FC	Microdialysis: DA	Baseline, 0–20 (rTMS), 40–180 min, 20-min intervals	*0.6 T:*↑ DA in dorsolateral striatum for 0–130 min, ↑ DA 0–50 min in PFC; 0.2 and 0.8T: no change
Poh et al., 2019	Mouse	Single	10 Hz, one train, Σ3,600 pulses, 1.2 T	7.5-cm F-o8 coil, over the head	Homogenates: DA, DOPAC, HVA	Immediately after last session	*Striatum*: ↑ DOPAC

(Continued)

TABLE 1 | Continued

Study	Subject	Session number	rTMS parameters	rTMS coil[a] and target	Sampling method	Sampling time	Significant effect
Ben-Shachar et al., 1997	Rat	Single	25 Hz, 2 s, one train, Σ50 pulses, 2.3 T	5-cm coil, over the head	Homogenates: DA, DOPAC, HVA	5 s after last session	*FC*: ↓ DA, ↑ HVA, ↑ turnover; *hippocampus*: ↑ DA, ↓ turnover; *striatum*: ↑ DA, ↑ DOPAC; ↓ turnover; *midbrain*: ↓ HVA
Strafella et al., 2001	Human	Single	Three blocks separated by 10 min: 10 Hz, 1 s, 10 s ITI, 15 trains, Σ450 pulses, 100% rMT*	9-cm circular coil, left DLPFC	PET study: [^{11}C] raclopride BP	Within 65 min pms	*Ipsilateral caudate*: ↓ DA binding potential, suggesting ↑ DA release
Ko et al., 2008	Human	Single	cTBS, 20 s, three trains, Σ900 pulses, 80% AMT	F-o8 coil, left and right DLPFC.	PET study: [^{11}C] raclopride BP	Within 60 min pms	*Left DLPFC – ipsilateral caudate-putamen and contralateral caudate nucleus*: ↓ DA binding potential, suggesting increase DA release. *Right DLPFC:* no change in regions examined
Cho and Strafella, 2009	Human	Single	Three blocks separated by 10 min: 10 Hz, 1 s, 10 s ITI, 15 trains, Σ450 pulses, 100% rMT*	7-cm F-o8 coil, left and right DLPFC	PET study: [^{11}C] raclopride BP	Within 95 min pms	*Left DLPFC – ipsilateral subgenual ACC, pregenual ACC, OFC:*↓ DA binding potential, suggesting increased DA release Right DLPFC: no change in regions examined
Strafella et al., 2003	Human	Single	Three blocks separated by 10 min: 10 Hz, 1 s, 10 s ITI, 15 trains, Σ450 pulses, 90% rMT*	9-cm circular coil, left M1 or occipital cortex	PET study: [^{11}C] raclopride BP	Within 65 min pms	*M1 – ipsilateral putamen:*↓ DA binding potential, suggesting increase DA release, when compared to ipsilateral OCC stimulation
Ohnishi et al., 2004	Macaque	Single	5 Hz, 20 s, 40 s ITI, 20 trains, Σ2,000 pulses, 35% max stimulator output	6.2-cm double-cone coil, right M1 cortex	PET study; [^{11}C] raclopride BP	Within 60 min pms	*Anesthetized – bilateral ventral striatum (incl. NAc)*: ↓ DA binding potential, suggesting ↑ DA release; *ipsilateral putamen*: ↑ DA binding, suggesting decrease DA release. *Dorsal striatum*: no change

(Continued)

TABLE 1 | Continued

Study	Subject	Session number	rTMS parameters	rTMS coil[a] and target	Sampling method	Sampling time	Significant effect
Pogarell et al., 2006	Human-depressed subjects	15 sessions	First session: 10 Hz, 10 s, 30 s ITI, 30 trains, Σ3,000 pulses, 100% rMT; followed by Σ 1,500 pulses	7-cm F-o8 coil, left DLPFC	SPECT study: [^{123}I] IBZM BP	Before and 30 min after first session, before and after 15th session	*Bilateral striatum*: ↓ DA binding potential compared to pre-rTMS within each session, suggesting immediate ↑ DA release.
Pogarell et al., 2007	Human-depressed subjects	15 sessions	10 Hz, 10 s, 30 s ITI, 30 trains, Σ3,000 pulses, 100% rMT	7-cm F-o8 coil, left DLPFC	SPECT study: [^{123}I] IBZM BP	Before and 30 min after first session, before and after 15th session	*Bilateral striatum*: ↓ DA binding potential compared to pre-rTMS within each session, suggesting immediate ↑ DA release. Similar results observed following exposure to D-amphetamine
Hausmann et al., 2002	Rat	Single or 14 sessions	20 Hz, 10 s, two trains, 400 pulses, 1 T	2.3-cm F-o8 coil, over the head	*In situ* hybridization, immunohistochemistry	12 h pms	*Ventral midbrain*: no difference in TH-mRNA or TH protein in all groups
Ikeda et al., 2005	Mouse	Single or 20 sessions	20 Hz, 2 s, 1 min ITI, 20 trains, 800 pulses, 0.75 T	7.5-cm round coil, over the head	RT-PCR: DAT mRNA, monoamine uptake, and ligand binding assay	1, 4, 12, 24 h pms (single and chronic) or 10 d pms (chronic)	*Single-cerebrum:*↑ DAT mRNA 4 and 24 h pms, ↓ DAT mRNA 12 h pms *Chronic-cerebrum*: ↑ DAT mRNA following 24 h and 10 d pms; *synaptosomes*: ↑ DA uptake, transport rate 24 h pms, no changes to affinity
Etiévant et al., 2015	Mouse	Single or five sessions	15 Hz, 10 s, 0.5 s ITI, three trains, 450 pulses, 53% MSO	5-cm Fo8	Western blot	Immediately after single session, 2 h, 5, 10, 20, 60 d pms (chronic)	*Single-PFC:* no change in D_2R expression *Chronic-PFC:*↑ D_2R expression 5 d pms

[a]*Outer diameter of each loop. ACC, anterior cingulate cortex; AMT, active motor threshold; BP, binding potential; cTBS, continuous theta burst stimulation; DA, dopamine; DAT, dopamine transporters; DLPFC, dorsolateral prefrontal cortex; DOPAC, 3,4-dihydroxyphenylacetic acid; FC, frontal cortex; F-o8, figure-of-eight; HVA, homovanillic acid; IBZM, iodobenzamide; ITI, intertrain interval; M1, primary motor cortex; MSO, maximum stimulator output; MT, motor threshold; NAc, nucleus accumbens; OFC, orbitofrontal cortex; PET, positron emission tomography; PFC, prefrontal cortex; pms, post magnetic stimulation; rMT, resting motor threshold; SPECT, single-photon emission computed tomography; TH, tyrosine hydroxylase.*

characterized by Deng et al. (2013). Traditionally, coils can be separated into circular coils or figure-of-eight (F-o8) coils. Circular coils induce the greatest current intensity beneath the coil windings, whereas F-o8 coils have a focalized hotspot in the center of the coil where the windings of the two circular coils are the nearest to each other, with less intense peaks on the opposing outer rings (Deng et al., 2013). Because of this, F-o8 coils are usually used for their high focality.

The depth of stimulation of conventional circular and F-o8 coils, according to the definitions in Deng et al. (2013), ranges from 1.0 to 1.9 cm, and these coils are therefore limited to cortical stimulation. However, because many key structures lie below the cortex, there has been development of different coils to stimulate deeper structures, dubbed deep TMS (dTMS). The most popular coil design for dTMS is the H-coil (Zangen et al., 2005; Roth et al., 2007), of which there are now more than 20 different versions (Roth et al., 2013). H-coils are helmet-like and stimulate the brain bilaterally with a depth of up to 2.4 cm (Deng et al., 2013). However, to achieve this depth, the intensity of the induced stimulation is more diffuse than an F-o8 coil, stimulating a larger surface area with a relatively weaker electric field (Deng et al., 2013).

*R*TMS IN COCAINE AND METHAMPHETAMINE ABUSE – CLINICAL RESEARCH

Stimulation of cortical regions that can alter activity and connectivity between regions is promising for alleviating the withdrawal symptoms in substance use disorders, particularly if it can be done non-invasively. In addition, because compulsive drug use has been associated with abnormal orbitofrontal- and mesolimbic-striatal circuits in subjects who are punishment resistant (i.e. even when faced with consequences, subjects continue to pursue the drug) (Hu et al., 2019), the possibility of using rTMS to stimulate hypoactive prefrontal cortical neurons, which can then modulate interconnected networks, is appealing (Diana et al., 2017; Madeo and Bonci, 2019; Song et al., 2019). An increasing number of studies have shown anticraving effects following rTMS treatment targeting the PFC (see Ma et al., 2019; Madeo and Bonci, 2019; Zhang et al., 2019), presumably through modulation of the efferent glutamatergic and afferent dopaminergic connections (Diana, 2011; Diana et al., 2017; **Figure 1**). Therefore, rTMS modulation of mesocorticolimbic pathways in people with substance use disorders may provide therapeutic effects.

Currently, the clinical studies that have utilized rTMS for treatment of addiction have varied protocols. This lack of consistency is common in rTMS research as there has not yet been a systematic approach to elucidate which parameters best achieve specific goals. Nonetheless, there is a general consensus on the target of stimulation: with the aim of modulating the mesocorticolimbic system, the majority of studies target the DLPFC, with only a few exceptions that stimulate the mPFC (Hanlon et al., 2015, 2017; Kearney-Ramos et al., 2018, 2019). In addition, most studies tend to stimulate only one side of the brain, usually the left, although a sham-controlled study comparing right- and left-side stimulations did not show a significant effect of laterality (Liu et al., 2017).

In 10-Hz stimulation, pulse numbers can range from 720 to 2,400 pulses per session, but 2,000 pulses per session are most common. The rationale is that excitatory stimulation to the PFC will increase the activity of glutamatergic corticostriatal efferents toward NAc and VTA; therefore, HF protocols are the most widespread and have been tested for potential anticraving effects in cocaine and methamphetamine use disorders. Excitatory stimulation generally uses 10- or 15-Hz protocols with an F-o8 coil, although recently there have been a few HF studies using H-coils (dTMS). Generally, 10-Hz stimulation uses a train duration of 5 s with an interstimulus interval (ISI) of either 15 or 10 s. There were only two exceptions for 10-Hz stimulations, one F-o8 study with 10-s train duration, 60-s ISI (Camprodon et al., 2007), and a dTMS study with 3-s train duration, 20-s ISI (Martinez et al., 2018). Similarly, 15-Hz stimulation addiction studies have trains of 60 pulses with 15-s ISIs with the exception of one dTMS study with trains of 36 pulses over 2 s with 20-s ISI (Rapinesi et al., 2016).

Protocols at 1-Hz deliver either 600 or 900 pulses, whereas protocols using cTBS usually deliver 3,600 pulses per session [one instance of 1,800 pulses/session (Hanlon et al., 2015)]. The total number of pulses also depends on the number of stimulation sessions. Within the field of addiction, the number of sessions varies across studies. Stimulation can be acute with a single active session, or chronic, with multiple sessions that range from 5 to 20 sessions applied either five or three times per week in clinical studies of addiction. Overall intensity of stimulation can range from 80 to 110% of rMT, with most studies using 100% rMT. Intensities at 100% rMT or below seem most suitable since several studies reported that intensities >100% rMT had poor tolerability and adverse effects among addiction patients (Su et al., 2017; Martinez et al., 2018).

Here we review the results of clinical studies that use rTMS as a treatment specifically for cocaine and methamphetamine abuse. A recent review of rTMS literature has suggested that the best predictor of rTMS-induced plasticity is pulse frequency (Wilson and St George, 2016); therefore, we have structured the studies by frequency of stimulation below.

5 Hz or Greater

The vast majority of addiction-related clinical rTMS studies use excitatory forms of rTMS in their studies. The goal is to try to increase the activity of the hypoactive frontal circuitry that is characteristic of the withdrawal stage of addiction, which is associated with a weakened executive control network and reduced dopaminergic transmission.

In clinical studies, HF-rTMS over the DLPFC has been shown to have anticraving effects (for an overview, see Ma et al., 2019). Most studies apply chronic stimulation (i.e. >4 stimulation sessions), once per day, but there are some studies that look at single session stimulation, with mixed results. For example, one study reported significantly lower craving scores (self-reported) for methamphetamine-dependent individuals after a single stimulation session for both left and

right DLPFC at 10-Hz stimulation, with no change in the sham condition (Liu et al., 2017). Meanwhile a small sample of cocaine-dependent individuals had reduced craving in response to a single session of right DLPFC, but not left DLPFC, at 10-Hz stimulation (Camprodon et al., 2007), and another sham-controlled study found a single session of 10-Hz rTMS over left DLPFC induced no significant reduction in craving scores (Su et al., 2017).

Excitatory rTMS that is applied across multiple sessions (chronic) seems to have better and more reliable outcomes for substance abuse than single sessions. A recent meta-analysis that looked at single versus multiple sessions of neuromodulation across all addiction domains found that multiple sessions were more effective at reducing craving, with larger effect sizes compared to single sessions (Song et al., 2019). Recent systematic reviews have included several studies that demonstrate anticraving effects with chronic stimulation (Madeo and Bonci, 2019; Zhang et al., 2019). Moreover, in studies where there was no change in craving after the first session, there was a significant anticraving effect by the end of the treatment period (5 days of daily HF-rTMS) for active, but not sham, stimulation (Su et al., 2017). Furthermore, although there is often an underrepresentation of female patients in addiction studies, a recent study with 90 methamphetamine-dependent females showed that female subjects also respond well to chronic HF-rTMS, with significant anticraving effects compared to sham and waiting-list controls (Liu et al., 2019).

Although most clinical studies have applied 10-Hz stimulation protocols, there are also studies that have used 15-Hz stimulation protocols over the left DLPFC and shown significant decreases over time in both cocaine craving (Politi et al., 2008; Terraneo et al., 2016; Pettorruso et al., 2019) and cocaine use (measured by urine drug tests) (Terraneo et al., 2016; Pettorruso et al., 2019). However, so far, all 15-Hz studies have been open-label studies, without sham-controls. Although in one study, the rTMS group was compared with a control group treated with standard psychopharmacological treatments (Terraneo et al., 2016). Compared to the pharmacological controls, the rTMS group did have significantly lower craving scores and significantly more cocaine-free urine tests, supporting the therapeutic potential of rTMS (Terraneo et al., 2016).

In addition to anticraving effects, there have been reports that chronic HF-rTMS can improve withdrawal symptoms (Liang Y. et al., 2018; Pettorruso et al., 2019), anxiety and depression scores (Liang Y. et al., 2018; Pettorruso et al., 2019), sleep quality (Liang Y. et al., 2018; Lin et al., 2019), and several aspects of cognition (Su et al., 2017; Liang Q. et al., 2018). Therefore, chronic rTMS could be beneficial across several aspects of addiction, possibly due to changes in plasticity in the frontal cortex.

Deep TMS

In addition to standard rTMS excitatory protocols, there have now been several HF-dTMS studies that use an H-coil, designed to deliver bilateral stimulation to deeper regions of the brain than is possible with an F-o8 coil and in a more diffuse manner. So far, three dTMS studies have been published looking at cocaine-dependent patients, and in all studies, a reduction in either intake or craving was reported for HF, multisession stimulation.

In an open-label study, craving was reduced compared to baseline midway through the treatment period, and this was maintained to the end of the treatment period (a total of 4 weeks) and 4 weeks after (Rapinesi et al., 2016). However, at the 4-week post-treatment follow-up, there was an increase in craving compared to the end of treatment, suggesting that maintenance sessions may be useful to keep cravings down (Rapinesi et al., 2016).

In a randomized controlled study using bilateral PFC stimulation and measurements of cocaine intake with hair samples, there was a significant reduction in intake over time regardless of stimulation group. However, there was no significant main effect of treatment and no interaction between time and treatment, suggesting that there was no difference between sham and rTMS intervention (Bolloni et al., 2016). However, the authors followed up with some exploratory *post hoc* testing looking at the effect of time on sham and rTMS data separately. Their *post hoc* findings show rTMS but not sham was associated with significant long-term reduction in cocaine intake at 2- and 3-month time points compared to baseline (Bolloni et al., 2016). Taking into account the low sample size and the risk of type 1 error from the exploratory *post hoc* testing, it is not clear whether dTMS is effective in reducing cocaine intake, but the exploratory results suggest that it is worth following up with a larger sample size.

Finally, a recently published randomized, sham-controlled study stimulated both the PFC and ACC (Martinez et al., 2018). They also introduced cocaine self-administration sessions, where participants were given the choice between a dose of smoked cocaine or a monetary reward in a progressive ratio task to measure the choice of cocaine when given an alternative reinforcer. Both HF (10 Hz) and LF (1 Hz) stimulation protocols were tested, but changes compared to sham were observed only for the HF group. There was no change in craving scores, but there was significant reduction in choice of cocaine after 13 sessions of HF-dTMS, 3 weeks in. In addition, the breakpoint of the progressive ratio was also lower for HF-dTMS in the third week (Martinez et al., 2018). This could suggest that after HF-rTMS participants were less willing to work for a reward, implying a drop in the incentive salience of the reward or a reduced motivational drive, both of which are responses underpinned by dopaminergic changes and associated with craving circuitry.

Overall, it is important to note that because of the different design of H-coils compared to other commonly used coils, and the relative paucity of dTMS addiction studies, it is still too early to conclude whether outcomes of the H-coil are markedly different compared to those of the F-o8 coils. Nonetheless, the promising early outcomes with dTMS raise the question of which aspects of the coil design and stimulation protocols are the most influential. Although H-coils are mainly associated with their depth of penetration, there are cone-shaped coils that can penetrate to similar depths (Deng et al., 2013). Double-cone coils (DCCs) have not been as widely used; however, they have been shown to be effective in treating disorders such as tinnitus (Vanneste et al., 2011; Vanneste and De Ridder, 2013; Kreuzer et al., 2015, 2018) and depression (Tastevin et al., 2019). In

relation to addiction, there is limited research with an alcohol addiction case study showing marked reduction in craving with associated functional connectivity changes (De Ridder et al., 2011) and a recent study showing normalization of exteroception in cannabis users after posterior parietal cortex stimulation (Prashad et al., 2019). Although there are a few comparisons of DCC and F-o8 coil treatment (which have not shown any overall superiority of either coil) (Kreuzer et al., 2015; Tastevin et al., 2019), there are no comparisons between DCC and H-coil treatment. It has been mentioned that DCC stimulation may be less tolerable, and even painful, compared to H-coils due to the differences in field decay, but may achieve greater focality (Roth et al., 2002; Deng et al., 2013). These different coils could be directly compared in future trials. It may be that the capacity of the H-coil for bilateral stimulation and targeting of a large surface area with less intense stimulation (Deng et al., 2013) contributes to the effects of dTMS alternatively, or in addition to the depth of H-coil penetration.

Intermittent TBS

So far, there have been no sham-controlled studies that have looked at the effectiveness of iTBS as a possible excitatory protocol to treat stimulant addiction. The shorter stimulation time and high efficacy compared to classic 10-Hz protocols have led to its growing popularity among rTMS therapies, particularly in major depressive disorder (Blumberger et al., 2018). There has, however, been a recent pilot study that compared two groups of treatment-seeking outpatients with cocaine use disorder that received either iTBS (3 min, 600 pulses/session, 80% active MT, n = 25) or 15 Hz (15 min, 2,400 pulses/session, 100% rMT, n = 22) over 4 weeks, with an accelerated protocol of twice-daily stimulations for the first week (Sanna et al., 2019). There was no significant difference in efficacy between the two protocols on measures of cocaine craving and consumption (Sanna et al., 2019), suggesting that iTBS may be as effective as 15 Hz in reducing cocaine consumption and craving. Intermittent TBS could therefore present advantages over 15 Hz because of the shorter stimulation time and lower intensity, which makes it more acceptable and tolerable for patients and more cost-effective for clinicians (Oberman et al., 2011). Although both treatment groups had large and significant reductions in consumption and craving after 25 days of treatment (Sanna et al., 2019), it is important to note that without a sham-control group a general effect of time or placebo response cannot be ruled out.

Interestingly, a small proof-of-concept, open-label study also found that an accelerated protocol of three times daily iTBS for 2 weeks significantly reduced cocaine intake and also nicotine, alcohol, and tetrahydrocannabinol intake in non-treatment-seeking cocaine-dependent individuals who had urine tests positive for cocaine (Steele et al., 2019). Usually, participants are required to test negative for drugs during treatment, so this study presents preliminary evidence that iTBS is effective and feasible as a treatment for active cocaine users.

1 Hz or Less

There are not many studies that have applied inhibitory protocols of rTMS to treat cocaine and methamphetamine addiction as addiction is primarily associated with hypoactivity of prefrontal cortices. However, a few studies have applied inhibitory protocols to methamphetamine and cocaine addicts, with mixed results.

Only two studies have looked at the application of 1-Hz stimulation in methamphetamine-dependent individuals (Li et al., 2013; Liu et al., 2017). The first study recruited non-treatment-seeking methamphetamine users in a sham-controlled crossover study and found that a single session of 1-Hz rTMS (900 pulses) over the left DLPFC increased cue-induced craving compared to the sham group, but not baseline craving (Li et al., 2013). In contrast, in a parallel, sham-controlled study, five sessions of 1-Hz stimulation (600 pulses/session) over either left or right DLPFC significantly reduced cue-induced craving compared to pretreatment baseline immediately after the first session and at the end of the final session (Liu et al., 2017). The very different results of these studies could in part be explained by the fact that the study showing an increase in craving (Li et al., 2013) had recruited current users, although not positive for methamphetamine on the days of experiments. In contrast, the study showing a reduction in craving consisted of participants who were all in rehabilitation, having stopped methamphetamine in the last 2 months (Liu et al., 2017). In support, animal studies show that α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor accumulation is different between stages of addiction (Scheyer et al., 2016), reviewed in the section "Glutamatergic Systems."

Continuous TBS

Similar to iTBS, cTBS is a short protocol, which can have greater effects on cortical inhibition than the classic 1-Hz inhibitory protocols (Huang et al., 2005). Below, we discuss a series of studies that apply acute cTBS over the mPFC in cocaine-dependent individuals, paired with functional magnetic resonance imaging (fMRI) and cue-reactivity tasks to look at changes in craving and brain activity. These are the only cocaine and methamphetamine addiction studies that use fMRI to investigate changes in brain activity and functional connectivity after rTMS. Their rationale is that cTBS, as an inhibitory protocol, may induce long-term depression (LTD)-like effects and dampen the activity of attentional and salience networks activated by drug-related cues (Hanlon et al., 2017).

Preliminary sham-controlled data from 11 chronic cocaine users after a session of cTBS (1,800 pulses/session) over the mPFC showed reduced fMRI activity in the insula, middle temporal gyrus, thalamus, and caudate regions compared to sham stimulation (Hanlon et al., 2015). However, there was no significant attenuation of craving compared to sham (Hanlon et al., 2015). In a larger, sham-controlled follow-up study that included chronic cocaine users, cTBS (3,600 pulses/session) over the left mPFC reduced activity compared to sham in the striatum, ACC, and parietal cortex (Hanlon et al., 2017). These regions can be linked to salience-processing (ACC) (Seeley et al., 2007), attention/executive control (parietal cortex) (Seeley et al., 2007), and craving (striatum) (Kober et al., 2010). The dampening of the salience network and reward processing by cTBS could be promising for reducing salience of drug-related stimuli and drug-cue craving. However, despite the changes in brain activity

reported, there was no significant change in craving after cTBS compared to sham (Hanlon et al., 2017).

In a continuation of this line of investigation, a recent study added a cue-reactivity task before and after receiving real or sham cTBS (left mPFC, 3,600 pulses/session) to assess state-dependent effects of rTMS (Kearney-Ramos et al., 2018). In addition, during stimulation, participants were asked to think about and describe the last time they used cocaine, rather than simply being at rest. For cocaine users at baseline, drug-related cues elicited significantly higher functional connectivity between the mPFC and both striatal and salience-related regions compared to neutral cues (Kearney-Ramos et al., 2018). Following cTBS, the frontal connectivity for drug versus neutral cues was attenuated compared to sham, although there was no significant interaction for any region of interest, indicating a general effect across all regions (Kearney-Ramos et al., 2018).

Because there is considerable evidence for variability of rTMS effects/responsiveness across the population (Ridding and Ziemann, 2010), one study took a different approach and assessed whether baseline activity of striatum could be predictive of response to rTMS (Kearney-Ramos et al., 2019). Participants performed a similar task to the previous year's study with cue recollection during cTBS stimulation over the mPFC (3,600 pulses/session) and a cue-reactivity task during fMRI, before and after cTBS (Kearney-Ramos et al., 2019).They found that baseline striatum activity during the cue-reactivity task predicted treatment response. High striatum activity during baseline cue-reactivity task resulted in reduced striatal activity after treatment, whereas low baseline striatum reactivity was associated with enhanced activity after treatment (Kearney-Ramos et al., 2019). The authors suggest that baseline striatal activity could act as a biomarker to identify positive rTMS responders, implying that state dependency arising from baseline neural activity can account for individual differences with rTMS (Kearney-Ramos et al., 2019).

Overall, there was no significant treatment-related change in general- or cue-induced craving for any of the cTBS studies; however, there were clear changes in functional connectivity, supporting the rationale for using rTMS to alter functional circuitry within the mesocorticolimbic pathways. As discussed previously, multiple stimulation sessions may be required before significant anticraving effects of rTMS can be detected. Accordingly, a clinical trial with multiple sessions using cTBS stimulation over the mPFC has been registered and is expected to be completed in 2020 (Hanlon, 2019, ClinicaTrials.gov identifier: NCT03238859), hopefully shedding light on the potential benefits of chronic cTBS for cocaine addiction.

*R*TMS EFFECTS RELEVANT TO TREATING ADDICTION – LINKING PRECLINICAL AND CLINICAL RESEARCH

Among the many experimental protocols we describe above that aim to alleviate cocaine and methamphetamine use disorders, promising results from novel therapeutic regimes specifically relate to the potential of rTMS to induce anticraving effects (Diana et al., 2017; Madeo and Bonci, 2019). It is generally accepted that craving and relapse in individuals addicted to stimulant drugs such as cocaine and methamphetamine are associated with dysregulation of dopaminergic and glutamatergic systems (Diana, 2011; Diana et al., 2017; Madeo and Bonci, 2019). However, most of the clinical studies discussed above have similar overall designs and are not able to fully explore the mechanisms behind their therapeutic effects; therefore, basic research findings, in both healthy humans and animal models, offer another avenue to help understand the specific mechanisms underlying rTMS therapy.

Here, we review evidence that modification of glutamatergic and dopaminergic function may underlie the therapeutic effects of rTMS in individuals with cocaine and methamphetamine use disorders. We consider these therapeutic effects in the context of changes described in these circuits by experiments in laboratory animals (healthy animals and animal models of addiction) and in healthy humans. Our goal is to provide a mechanistic insight and highlight gaps in the literature that will ultimately facilitate translation and improvement of the current outcomes of rTMS therapy in addiction.

Dopaminergic Systems

Dopamine is a critical neurotransmitter and neuromodulator for the induction and maintenance of neuroplasticity, a process related to learned behaviors (Jay, 2003; Wise, 2004; Kalivas and O'Brien, 2008). Convergence of excitatory and dopaminergic inputs appears necessary for the induction of long-term potentiation (LTP) (i.e. a Hebbian-type increase in synaptic strength) within the striatum. In particular, coactivation of D_1-like receptors (Beninger and Miller, 1998; Smith-Roe and Kelley, 2000; Reynolds and Wickens, 2002) is crucial for reward-related instrumental learning (Wickens et al., 2007; Wickens and Arbuthnott, 2010). The repeated elevation of dopamine levels induced by stimulants such as cocaine and methamphetamine can surpass levels produced by biological stimuli, for which tolerance would normally occur. Such high levels of dopamine may therefore facilitate the abnormal learning or reinforcement of cues associated with the drug and thus initiate drug-seeking behavior (Kalivas and O'Brien, 2008). Repeated amphetamine exposure has been shown to accelerate habit formation (Nelson and Killcross, 2006), suggesting that the transition from voluntary, goal-directed responding to habitual drug use may be due to the recruitment of reward regulatory mechanisms from the ventral to dorsal striatum within the corticostriatal network, which then results in the expression of maladaptive incentive habits (Belin et al., 2009, 2013). In addition, cessation of drug use has been characterized by hypodopaminergic tone, particularly during the withdrawal phase, wherein a reduction of dopamine levels within the NAc is observed (Rossetti et al., 1992). Therefore, dopamine is critical for modulating synaptic plasticity within corticostriatal networks and may be relevant in the context of forming cue-induced drug craving (Wickens et al., 2007) and facilitating drug-seeking behavior by the weakening of executive functions (Arnsten and

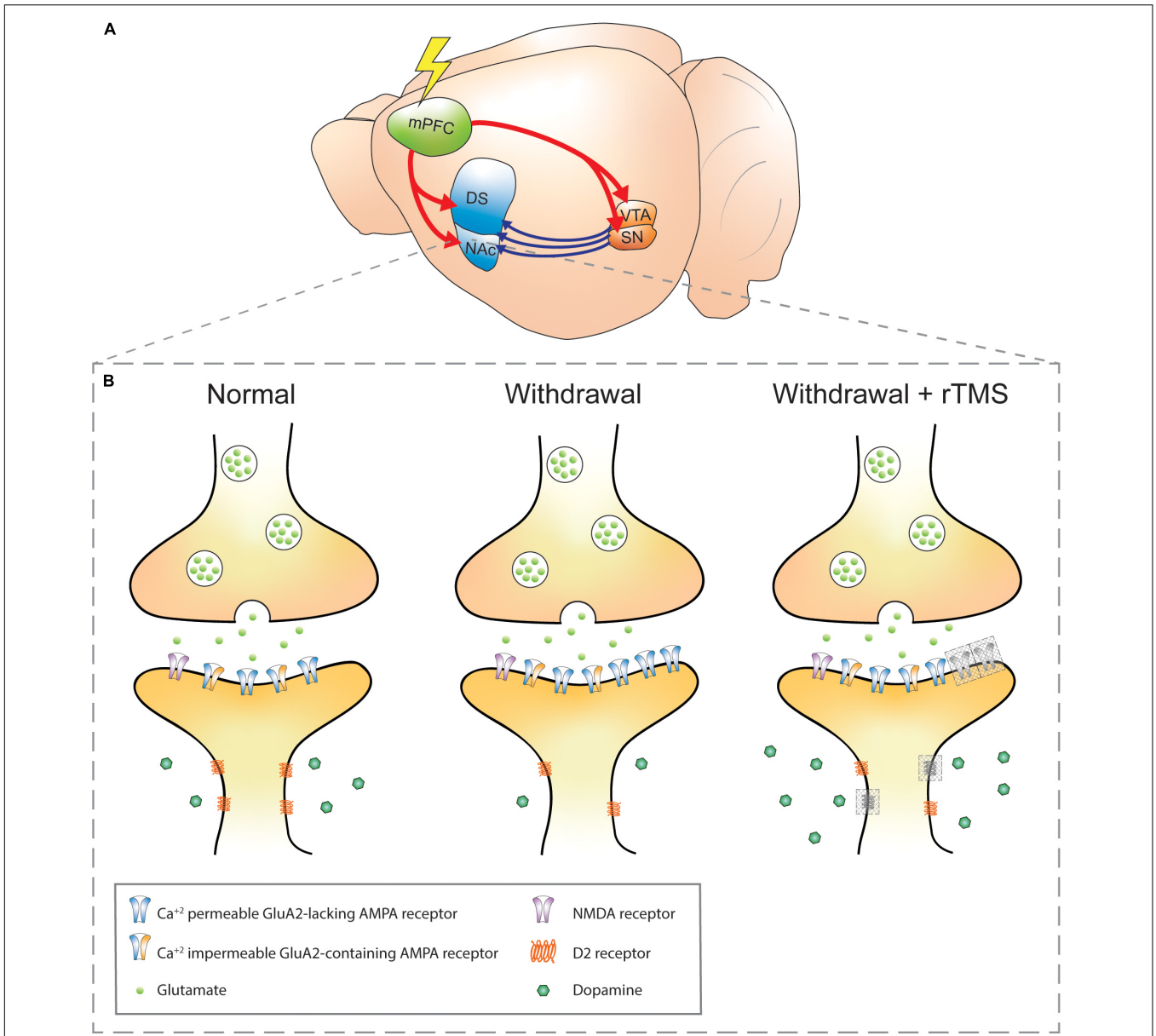

FIGURE 1 | Schematic of addiction circuitry and the synaptic changes between an efferent mPFC glutamatergic neuron axon terminal and accumbal D_2 receptors expressing MSN dendrite. **(A)** Rodent brain with glutamatergic efferents (red) projecting to the striatum and ventral midbrain nuclei. Dopaminergic projections (blue) from the VTA and SN project to the striatum. The rodent mPFC is comparable to the DLPFC in humans, a common site of rTMS stimulation in addiction (Diana et al., 2017). **(B)** Axon terminal of a mPFC glutamatergic neuron synapsing onto a D_2 receptors-expressing MSN in the NAc in normal, withdrawal, and withdrawal + rTMS (proposed) treatment brain state. During cocaine or methamphetamine withdrawal, Ca^{2+}-permeable GluA2-lacking AMPA receptors are upregulated in the NAc, which increases the sensitivity of NAc neurons to excitatory inputs and is a requirement for cue-induced drug craving (Cornish and Kalivas, 2000; Conrad et al., 2008; McCutcheon et al., 2011b). Also during withdrawal, dopaminergic signaling via volume transmission is reduced (i.e. hypodopaminergic tone), and downregulation of dopamine D_2 receptors is observed, both of which contribute to reduced inhibitory feedback signals (Nutt et al., 2015; Volkow and Morales, 2015). These changes are linked to impulsivity and compulsive drug seeking (Lee et al., 2009; Moeller et al., 2018). The combination of reduced dopaminergic and glutamatergic signaling also contributes to aberrant plasticity during drug withdrawal (Huang et al., 2017). Gray-shaded boxes in the "withdrawal + rTMS" MSN dendrite represent proposed and speculative changes based on existing literature: 1. Upregulation of D_2 receptors: rTMS over the PFC has been shown to alter extracellular glutamate and dopamine concentrations in the NAc, likely due to indirect activation of dopaminergic midbrain structures that project to the NAc. D_2 receptor expression has been shown to be upregulated in the PFC following five daily sessions of rTMS in healthy mice (Etiévant et al., 2015). Chronic rTMS may therefore normalize the downregulation of D_2 receptors in the NAc during withdrawal (D_2 receptors, gray shading). 2. Insertion of GluA1-containing AMPA receptors: this has been observed within excitatory postsynapses of organotypic hippocampal slice cultures (Vlachos et al., 2012) and PFC of awake animals (Etiévant et al., 2015); however, it is not known whether this effect also occurs within NAc postsynapses and whether they also contain the GluA2 subunit (AMPA receptor, gray shading). Furthermore, it is not known whether the GluA2-lacking AMPA receptors that accumulate during withdrawal are affected by rTMS. mPFC, medial prefrontal cortex; DS, dorsal striatum; NAc, nucleus accumbens; VTA, ventral tegmental area; SN, substantia nigra; NMDA, *N*-methyl-D-aspartate; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; MSN, medium spiny neuron; rTMS, repetitive transcranial magnetic stimulation.

Li, 2005). Although it seems as though repeated elevation of dopamine levels drives network changes following exposure to drugs of addiction, such as the expression of aberrant synaptic plasticity and the hypodopaminergic tone within the mesolimbic system, dopamine may also be required during recovery (Nutt et al., 2015; Fattore and Diana, 2016).

The dopaminergic system appears susceptible to the effects of HF-rTMS as shown by changes in extracellular dopamine concentrations (microdialysis), or changes in protein concentration in the neuropil (brain homogenates). Although rTMS protocols vary widely between studies (**Table 1**), a consistent trend is an increase in dopamine within subcortical brain regions such as the striatum following rTMS. rTMS targeted to the frontal cortex has been shown to induce dopamine release in the rodent striatum (e.g., Keck et al., 2002; Kanno et al., 2004), and similarly, single-photon emission computed tomography imaging has shown a decrease in dopamine receptor binding after rTMS over the left DLPFC, suggesting an increase in extracellular dopamine in the caudate nucleus (Strafella et al., 2001) or general striatum (Pogarell et al., 2006, 2007). It was suggested that rTMS may have direct effects on striatal dopamine nerve terminals *via* corticostriatal projections, which is one pathway that can mediate subcortical dopamine release (Strafella et al., 2001). Other studies have also shown an increase in dopamine release in the NAc following stimulation of the motor cortex in humans (Strafella et al., 2003) and primates (Ohnishi et al., 2004). Although there has been no direct evidence of dopamine changes within the midbrain, only a limited number of studies have investigated this brain region (Ben-Shachar et al., 1997; Hausmann et al., 2002). Future studies that can more specifically probe changes within the mesocorticolimbic pathway would be valuable for understanding the effects of rTMS in addicted individuals.

Importantly, dopamine function is determined not only by the levels of dopamine, but also by synthesis and metabolism of the neurotransmitters and expression of its receptors and transporters. There is emerging evidence that HF-rTMS may affect these processes; for example, dopamine and its metabolite DOPAC have been shown to be increased in rat brain homogenates following 25-Hz stimulation (Ben-Shachar et al., 1997). A more recent study found that concentrations of DOPAC were altered in the striatum following stimulation at 10 Hz, although dopamine concentrations were not affected (Poh et al., 2019). Chronic stimulation has shown an increase in dopamine transporter mRNA that can last up to 10 days following the last stimulation session within the mouse cerebrum, as well as an increase in dopamine uptake, as measured in mouse synaptosomes (Ikeda et al., 2005). To our knowledge, there has been one study showing a change in dopamine receptor expression following rTMS. Five days of 15-Hz rTMS delivered to the frontal cortex in awake mice resulted in an upregulation of D_2 receptor expression in the PFC (Etiévant et al., 2015). Therefore, rTMS may normalize the downregulation of D_2 receptors that is observed in individuals with cocaine and methamphetamine use disorders. Taken together, these studies indicate that HF-rTMS has the capacity to alter dopamine release, uptake, and the activity of enzymes related to dopamine metabolism.

There is limited research looking at the effects of LF-rTMS on dopamine; however, a recent study looked at positron emission tomography scans of healthy volunteers following bilateral 1-Hz stimulation of the insular region using an H-coil (dTMS). They showed a decrease in dopamine neurotransmission in the substantia nigra, sensorimotor striatum, and associative striatum. Interestingly, there was no effect of 10-Hz stimulation on dopaminergic neurotransmission in the same study, yet these results suggest that it is possible to have an inhibitory effect on dopamine if the appropriate rTMS protocols are applied (Malik et al., 2018).

Glutamatergic Systems

Although dopamine is the neurotransmitter most associated with addiction, glutamate is suggested to play a significant role in reinstatement of drug-seeking behavior after withdrawal (Wolf and Ferrario, 2010). Glutamatergic systems are best known for their key role in supporting synaptic plasticity processes such as LTP (strengthening of synapses) and LTD (weakening of synapses), which are integral in rTMS-induced neuroplasticity (Vlachos et al., 2012; Tang et al., 2015; Cirillo et al., 2017). In the case of cocaine-induced reinstatement of drug-seeking behavior, glutamate activity *via* the AMPA receptors in the NAc appears to be essential (Cornish and Kalivas, 2000; Conrad et al., 2008). For example, when AMPA/kainate receptor, but not *N*-methyl-D-aspartate (NMDA) receptor, activation is blocked in rats, there was no reinstatement of cocaine-seeking behavior in response to an injection of either AMPA or dopamine. Yet, when dopamine receptors were blocked, injection of AMPA still initiated drug-seeking behavior (Cornish and Kalivas, 2000).

Insertion and removal of AMPA receptors at the synapse are related to synapse strengthening (LTP) and weakening (LTD), respectively (Feldman, 2009; Kessels and Malinow, 2009). Subunit composition is also important as GluA2-lacking AMPA receptors are Ca^{2+}-permeable and thus important for the induction of synaptic plasticity. In contrast, GluA2-containing AMPA receptors are Ca^{2+}-impermeable, predominantly expressed in mature neurons, and their expression is associated with scaling down synaptic strength (for a review, see Liu and Zukin, 2007). Expression of LTP in the NAc especially during cocaine and methamphetamine withdrawal is associated with the accumulation of Ca^{2+}-permeable AMPA receptors in the NAc, which results in an increased sensitivity of NAc neurons to excitatory inputs (Cornish and Kalivas, 2000; Conrad et al., 2008; Purgianto et al., 2013; Volkow and Morales, 2015; Scheyer et al., 2016), and is a requirement for cue-induced drug craving (Cornish and Kalivas, 2000; Conrad et al., 2008; McCutcheon et al., 2011b).

Interestingly, the group I metabotropic glutamate receptor (mGluR1) in the NAc appears to be involved in the development of the "incubation" period of cocaine or methamphetamine craving, which is defined as the progressive increase in cue-induced craving for the drug following withdrawal (Mameli et al., 2009; McCutcheon et al., 2011a; Scheyer et al., 2016). Activation of mGluR1 is able to reverse the accumulation of GluA2-lacking AMPA receptors in the NAc, which suggests that this receptor

may be a potential target for addiction therapies to reduce cue-induced drug craving (McCutcheon et al., 2011a; Dravolina et al., 2017). Overall, these experiments suggest that glutamate initiates drug-seeking behavior in relapse, in contrast to dopamine, which is involved in the maintenance of drug-seeking motivation, and not an essential component behind AMPA-evoked craving.

Most studies investigating rTMS effects on glutamatergic circuits have investigated cortical and hippocampal structures. At high intensities, rTMS can evoke action potentials in neurons, and a single TMS pulse has been shown to induce a transient activation of voltage-gated Na^+ channels (Banerjee et al., 2017; Li et al., 2017). Consequently, multiple HF pulses have been shown to induce LTP-like synaptic plasticity in the hippocampus and alter glutamate transporter gene and protein expression *via* miniature excitatory postsynaptic currents and alter dendritic spine sizes up to 6 and 3 h after magnetic stimulation, respectively, in CA1 pyramidal neurons located in the stratum radiatum (Vlachos et al., 2012). This strengthening of glutamatergic synapses requires activation of Ca^{2+}-dependent NMDA receptors, L-type voltage-gated Ca^{2+} channels, and voltage-gated Na^+ channels (Vlachos et al., 2012; Lenz et al., 2015). In addition, upregulation of the density and size of GluA1-containing AMPA receptors was observed within the stratum radiatum after stimulation (Vlachos et al., 2012; Lenz et al., 2015). However, it is not known whether these AMPA receptors also contain the GluA2 subunit. In another study, GluA1 receptor expression, but not GluA2 receptor expression, was upregulated in the PFC following 5 days of 15-Hz rTMS (Etiévant et al., 2015). At lower magnetic field intensities, alterations to neuronal excitability following rTMS within layer V cortical neurons have also been observed up to 20 min after stimulation, although the mechanisms are not known (Tang et al., 2016). Interestingly, an LF 1-Hz rTMS protocol, which is generally associated with inhibitory effects, delivered to Sprague–Dawley rats daily for 14 days (400 pulses per day) increased the excitability of hippocampal CA1 pyramidal neurons as shown by depolarized action potential thresholds (Tan et al., 2013). Therefore, it appears that rTMS may be able to alter intrinsic properties and excitatory synaptic connectivity of hippocampal and cortical neurons, as well as the expression of their neurotransmitter receptors. These findings may therefore be relevant to addiction research as animal models of addiction exhibit aberrant plasticity within the mesocorticolimbic pathway, resulting in dysfunctional neuroadaptations. For example, the hypoactive glutamatergic efferent projections from the mPFC contribute compulsive drug-seeking behaviors, but stimulation of these projections may reverse some of the maladaptive behaviors (Chen et al., 2013).

While receptors such as GluA and mGluR directly mediate neuronal response to glutamate, transporters also have an important modulatory impact on neurotransmission by regulating extracellular glutamate levels and thus controlling the availability of glutamate to bind to receptors. Accordingly, expression of glutamate transporters is a potential contributor to the changes in glutamatergic neurotransmission reported in addiction. For example, glial glutamate transporter I (GLT1) is downregulated following chronic cocaine self-administration, potentially increasing the amount of glutamate available to bind to receptors and increasing glutamatergic transmission (Kalivas and Volkow, 2011). Few studies have looked at glutamate transporter expression following rTMS, but recently a global gene expression study of the mouse cerebrum following 20 days of rTMS has shown upregulation of the glutamate transporter genes EAAT4, GLAST, and GLT1 and downregulation of EAAC1 24 h after the last stimulation session (Ikeda et al., 2019). However, 10 days after the last stimulation session, all of these glutamate transporter genes were upregulated (Ikeda et al., 2019). These findings are the first to demonstrate changes in glutamate transporter gene expression, and it will be interesting in future studies to isolate RNA from specific cortical regions to assess regional differences and impact on areas within the mesocorticolimbic system such as the NAc. Overall, these studies taken together with others showing regulation of vesicular glutamate transporter I (vGluT1) and GLT1 in the cerebellum following different TBS protocols (Mancic et al., 2016) suggest that glutamate transporters are likely to play an important role in mediating rTMS effects and are worth further investigation as therapeutic targets in addiction.

An increase in NAc glutamate and dopamine concentration has been observed following a single session of 2-Hz rTMS (Zangen and Hyodo, 2002), an effect that has been observed following electrical and optogenetics stimulation of excitatory neurons of the mPFC region in rodents (Taber et al., 1995; Kim et al., 2015; Quiroz et al., 2016). In addition, another study found that glutamate concentration was immediately reduced in the striatum following 10-Hz rTMS (Poh et al., 2019). Altered neurotransmitter concentrations within the striatal neuropil may reflect changes within intraneuronal sites and may not necessarily reflect changes in extracellular glutamate release following magnetic stimulation. In contrast, other studies have shown that glutamate levels were unaltered, although they were assessed in other brain regions (Keck et al., 2002; Seewoo et al., 2019). Despite the varied findings, it appears that glutamate release and concentration within the striatum (dorsal and NAc) are altered following rTMS; however, more research (e.g., electrophysiological recordings) is required to understand the effects of rTMS within this brain region.

Consistent with evidence that rTMS can alter glutamatergic neurotransmission, rTMS has been used therapeutically to target the dysfunctional glutamatergic system in aged mice (16–17 months old). Hippocampal CA1 pyramidal neurons of aged mice exhibit a reduced number of evoked action potentials from an injected stimulating current and increased hyperpolarization after an action potential compared to mature mice (9–10 months old), indicating reduced excitability (Potier et al., 1992; Randall et al., 2012; Wang et al., 2015). However, after 14 consecutive days of 25-Hz rTMS, the excitability of CA1 neurons in aged mice was restored to levels seen in mature mice, which suggests that rTMS can "rescue" hypoactive neurons in aged mice (Wang et al., 2015). This experiment suggests that anticraving effects reported in addicted populations following HF-rTMS to the PFC (see below) may be related to an rTMS-induced increase in excitability of hypoactive PFC glutamatergic neurons in addicted individuals.

The hypothesis could be tested by applying HF-rTMS to the PFC of rats that exhibit compulsive cocaine self-administration, as their PFC neurons have been shown to exhibit reduced excitability, compared to rats that do not compulsively seek cocaine (Goldstein and Volkow, 2011; Chen et al., 2013; Madeo and Bonci, 2019).

Animal Models of Cocaine and Methamphetamine Addiction and rTMS

Although at the moment there are only a few studies that have applied rTMS to animal models of addiction and have had promising results, only one has investigated the effects of rTMS following stimulation over the frontal cortex. Following abstinence in morphine-sensitized rats, dopamine levels within the NAc can be acutely altered by a single session of HF-rTMS (20 Hz, 300 pulses) over the left frontal cortex (Erhardt et al., 2004). Morphine-sensitized rats had a significant increase in dopamine, which was sustained for 120 min after stimulation compared to baseline. Non-sensitized control animals who also received rTMS also showed increase in dopamine levels at 30 min after stimulation; however, the morphine-sensitized rats had significantly higher dopamine release compared with the control rats (Erhardt et al., 2004). A caveat of this study was that morphine-sensitized animals did not exhibit lower dopamine levels within the NAc at baseline, even though this would be expected in an animal model of addiction (Nutt et al., 2015); however, the authors attribute this to the low dose of morphine used (Erhardt et al., 2004).

The only other studies of rTMS in an animal model of addiction that we are aware of investigated how rTMS affected the development of methamphetamine-induced conditioned place preference (CPP) and the reinstatement of CPP after extinction (Wu et al., 2018a,b). The stimulation site in one study was between bregma and lambda skull sutures (Wu et al., 2018a) and was not reported in the second study (Wu et al., 2018b). However, large size of the stimulating coils (circular coil: 5-cm outer diameter, 2.5-cm inner diameter) relative to the size of a rat still means that the whole brain (i.e. including the PFC) was likely stimulated (Rodger and Sherrard, 2015; Tang et al., 2015).

In the experiment testing the development of methamphetamine-induced CPP, rTMS, or sham stimulation was given prior to a methamphetamine injection and placement in a conditioning chamber (Wu et al., 2018b). After 4 days of conditioning, CPP was tested three times (2, 4, and 6 days after the end of the conditioning/treatment period). LF stimulation, but not HF stimulation, significantly inhibited methamphetamine-induced CPP (Wu et al., 2018b). In addition, the expression of $GABA_B$ receptor subunit 1 (R1), but not subunit 2 (R2), in the dorsolateral striatum was significantly decreased in the methamphetamine + 1-Hz rTMS group compared to sham (Wu et al., 2018b). Interestingly, $GABA_BR1$ in the dorsal striatum has been linked with rewarding memories of drugs (Jiao et al., 2016) and may be associated with the ability of LF-rTMS to inhibit drug-induced CPP. Furthermore, GABA systems are also modulated by rTMS (Lenz and Vlachos, 2016); however, more extensive review of the potential role of GABA in rTMS treatment of addiction is beyond the scope of this review.

The other experiment looked at the effect of HF-rTMS on methamphetamine relapse behavior (Wu et al., 2018a). After the extinction of CPP behavior, rats were given rTMS for either 1 or 3 days. Twenty-four hours after the final rTMS treatment, a reinstatement test was performed, with methamphetamine injected before placement into the testing chamber. The group that received 3 days of rTMS did not show reinstatement of CPP behavior in the reinstatement test, suggesting 3 days of HF-rTMS can inhibit relapse behavior (Wu et al., 2018a).

Altered Plasticity in Addiction: Implications for rTMS Treatment Efficacy

As alluded to in the previous sections, the molecular changes involving glutamate and dopamine function that result from addiction alter cortical plasticity of addicted individuals in a way that impacts rTMS effects (Shen et al., 2016; Huang et al., 2017). In a methamphetamine self-administration rat model of methamphetamine addiction, corticostriatal plasticity could not be induced after an electrical stimulation protocol in the addicted model, but was normal in saline-administering control rats, as measured by electrical recordings from rat brain slices (Huang et al., 2017). The methamphetamine self-administering rats also demonstrated a deficit in motor learning for a rotarod task compared to control rats (Huang et al., 2017). The impaired plasticity was associated with altered cortical–striatal synapse functioning. Protein analysis of AMPA and NMDA receptor subunit composition in comparison to control rats suggested that the reduced plasticity of methamphetamine-administering rats could be linked to insertion of calcium-impermeable glutamate NMDA receptor subunits in the dorsal striatum and motor cortex (Huang et al., 2017).

Although it is not possible in humans to measure corticostriatal plasticity directly, there is evidence for reduced plasticity in the motor cortex in addiction: methamphetamine-addicted individuals showed a lack of MEP potentiation and MEP depression after a single session of HF-rTMS and cTBS, respectively, when compared to a healthy control group (Huang et al., 2017). Methamphetamine-addicted individuals also performed worse on a motor learning task compared to healthy controls (Huang et al., 2017). When task performance data from all participants were matched with their amount of plasticity induction after HF-rTMS, there was a significant positive correlation, further suggesting the link between reduced plasticity and poor learning behavior.

Therefore, it is important to keep in mind that addicted individuals may have a reduced susceptibility to plasticity induced by rTMS, due to alterations in dopaminergic and glutamatergic systems, and this could be a barrier to rTMS therapy. Nonetheless, there are indications that this reduced susceptibility may be overcome; for example, facilitating dopamine signaling with a dose of L-DOPA during early alcohol withdrawal in rats restored the blunted plasticity and improved limbic memory disruption (Cannizzaro et al., 2019). It would be interesting to explore whether a similar boost in dopaminergic

signaling, whether with L-DOPA or a dopaminergic receptor agonist, could be combined with rTMS to improve or hasten therapeutic effects by improving the cortical–striatal plasticity of addicted individuals.

Overall, despite their limited number, the studies in animal addiction models provide evidence supporting an influence of rTMS on different aspects of addiction. HF rTMS over the frontal cortex increases dopamine release in the NAc and offers evidence that the effects of rTMS may differ in drug-sensitized models compared to control or healthy models, highlighting the need for rTMS studies that specifically investigate a drug-dependent model (Erhardt et al., 2004). HF rTMS can inhibit relapse behavior (Wu et al., 2018a). Furthermore, LF-rTMS appears to prevent the formation of drug-induced rewarding memory by downregulating $GABA_BR1$ (Wu et al., 2018b).

FUTURE DIRECTIONS AND OUTSTANDING ISSUES

Here we have reviewed only two systems (dopaminergic and glutamatergic) of a complex network, focusing mainly on corticostriatal connections. Inputs from other regions such as the amygdala and hippocampus are also involved, as well as inhibitory systems (GABA). However, we hope that summarizing and integrating the current evidence from experimental and clinical research in this narrow focus will help lead research in a direction that could improve outcomes of rTMS therapy for cocaine and methamphetamine use disorders.

Clinical Studies

Need for Consistency and Scientific Rigor

Current drawbacks of clinical studies, which have also been pointed out by recent reviews, include the lack of follow-ups after treatment and the lack of sham-controls in some studies (Ma et al., 2019; Madeo and Bonci, 2019; Zhang et al., 2019). Clinical studies should include follow-up measurements, sham-controls, and greater consistency of stimulation parameters between studies. This would help improve understanding of the temporal effects of rTMS on addiction and facilitate comparisons between studies. We also need a systematic approach to investigate the effects of stimulation parameters. This could allow us to identify which parameters reliably induce long-term changes in target pathways. Having an idea of the most effective parameters regarding dosage (i.e. number of pulses), intensity, and number of sessions (e.g., accelerated protocols; Steele et al., 2019) will significantly improve the reproducibility and impact of therapeutic rTMS.

Better Outcome Measures for Insights Into Mechanisms

Many studies rely solely on subjective measures of craving, most of which are simple rating systems such as the visual analog scale. Craving is the primary surrogate indicator of treatment success (Singleton and Gorelick, 1998) and has noteworthy association with later drug use (Weiss et al., 2003). However, the evidence of an association between craving and instances of relapse or drug consumption can sometimes be conflicting (Miller and Gold, 1994; Weiss et al., 1995). Adding at least one extra measure to look at consumption (which can be measured with objective drug testing), anhedonia, or withdrawal symptoms, for example, could help expand the evidence of the treatment potential of rTMS. Because addiction is a disorder that has several systems and pathways involved, there are multiple possible avenues through which rTMS could induce beneficial change. A range of outcome measures would help establish whether rTMS can treat different aspects of addiction and increase the opportunities to link future animal models of rTMS addiction therapy with the most relevant clinical outcomes and facets of addiction. Current evidence from cellular and animal models suggests that changes within the dopaminergic and glutamatergic systems are the primary mechanisms of rTMS-induced anticraving effects in humans. However, there is still a paucity of research that specifically investigates these rTMS-induced molecular and circuitry changes in the mesocorticolimbic system, particularly in an addicted model. As such, it is our opinion that there are multiple avenues of research involving rTMS and addiction that have rich, as-yet untapped potential, especially with regard to animal models of rTMS. Below, we identify some possible research questions that would be both interesting and beneficial to the field.

Animal Models of Addiction

Animal models of addiction occupy a key position in a translational pipeline because they allow exploration and optimization of rTMS parameters in a uniform and readily available addicted population. The few studies investigating rTMS in animal models of addiction show interesting and promising results (Erhardt et al., 2004; Wu et al., 2018a,b) and hint at further potential: for example, animal models could be used to explore the effects of rTMS on drug-sensitized dopaminergic systems based on the differences in accumbal dopamine after rTMS in morphine-sensitized versus non-sensitized rats (Erhardt et al., 2004). In addition, it would be interesting to investigate the effects of chronic rTMS on dopamine levels following cocaine abstinence. Other experiments that may provide insight into therapeutic mechanisms of rTMS, and how these can be optimized, include the characterization of receptor expression (e.g., GluA2-containing and -lacking AMPA receptors, D_1–D_5 receptors) and measures of dopaminergic tone in addicted subjects with or without rTMS intervention.

The relevance of animal studies in understanding rTMS effects in humans has recently been highlighted by neuroimaging studies showing that rTMS can induce similar changes in functional connectivity in rats and in humans (Cocchi et al., 2016; Seewoo et al., 2018, 2019). More specifically, chronic rTMS in healthy rats was associated with changes to addiction-related networks such as the cortical–striatal–thalamic and basal-ganglia networks, with chronic HF-rTMS potentiating interoceptive/default mode network connectivity and attenuating connectivity in the salience network (Seewoo et al., 2019). Surprisingly, there have been no equivalent studies describing the effects of chronic rTMS on functional connectivity in addicted rodents or human populations. However, acute studies following cTBS in humans

have shown some promising changes in network activity and state-dependent effects that could be used as biomarkers for predicting the suitability of rTMS therapy for drug-dependent individuals (Hanlon et al., 2015, 2017; Kearney-Ramos et al., 2018, 2019). Designing experiments that can be run in parallel in both clinical populations and animal models and linked through matching MRI imaging data would be of great benefit to the field.

SUMMARY

A number of recent studies have shown promising effects of rTMS in treating cocaine and methamphetamine addiction by reducing craving, especially after chronic stimulation, and in some cases reducing consumption and withdrawal symptoms. These effects have been further confirmed by several meta-analyses reporting a treatment effect of rTMS over the PFC. Although the PFC to NAc glutamatergic pathway has been shown to be critical for the development of compulsive drug-seeking behaviors, effects of rTMS on the activity and aberrant plasticity present within this pathway have never been investigated. Despite these current limitations, mechanisms from the field of addiction and studies that have looked at the acute effects of rTMS on the dopaminergic and glutamatergic systems have given us an idea of some of the mechanisms that may underlie the therapeutic effects of rTMS in addiction. Moving forward, it is now imperative to take advantage of the well-defined animal models of substance use disorders to test whether rTMS can counteract the mechanisms that underlie addiction, informing both researchers and clinicians to improve outcomes of rTMS therapy in addiction.

AUTHOR CONTRIBUTIONS

EP and JM conceived and wrote the manuscript. JR edited the manuscript. All authors contributed to the manuscript revision, and read and approved the submitted version of the manuscript.

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Twice-Daily Theta Burst Stimulation of the Dorsolateral Prefrontal Cortex Reduces Methamphetamine Craving: A Pilot Study

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Objectives: Transcranial magnetic stimulation (TMS) holds potential promise as a therapeutic modality for disorders of addiction. Our previous findings indicate that high-frequency repetitive transcranial magnetic stimulation (rTMS) over the left dorsal–lateral prefrontal cortex (DLPFC) and low-frequency rTMS over the right DLPFC can reduce drug craving for methamphetamine. One major issue with rTMS is the duration of treatment and hence potential dropout rate. Theta burst stimulation (TBS) has been recently shown to be non-inferior relative to repetitive transcranial magnetic stimulation for major depression. Here, we aim to compare the clinical efficacy and tolerability of intermittent and continuous theta burst stimulation protocols targeting left or right dorsolateral prefrontal cortex on methamphetamine craving in abstinent-dependent subjects.

Methods: In this randomized single-blind pilot study, 83 abstinent methamphetamine-dependent subjects from a long-term residential treatment program were randomly allocated into three groups: intermittent theta burst stimulation (iTBS) over the left DLPFC (active group), continuous theta burst stimulation (cTBS) over the left DLPFC (active control group), or cTBS over the right DLPFC (active group) was administered twice daily over 5 days for a total of 10 sessions. We measured the primary outcome of cue-induced craving and secondarily sleep quality, depression, anxiety, impulsivity scores, and adverse effects.

Results: We show a pre- vs. postintervention effect on craving, which, on paired *t* tests, showed that the effect was driven by iTBS of the left DLPFC and cTBS of the right DLPFC, reducing cue-induced craving but not cTBS of the left DLPFC. We did not show the critical group-by-time interaction. The secondary outcomes of depression, anxiety, and sleep were unrelated to the improvement in craving in the left iTBS and right cTBS group. In the first two sessions, self-reported adverse effects were higher with left iTBS when compared to right cTBS. The distribution of craving change suggested greater clinical response (50% improvement) with right cTBS and a bimodal pattern of effect with left iTBS, suggesting high interindividual variable response in the latter.

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Conclusion: Accelerated twice-daily TBS appears feasible and tolerable at modulating craving and mood changes in abstinent methamphetamine dependence critically while reducing session length. We emphasize the need for a larger randomized controlled trial study with a sham control to confirm these findings and longer duration of clinically relevant follow-up.

Clinical Trial Registration: Chinese Clinical Trial Registry number, 17013610.

Keywords: addiction, transcranial magnetic stimulation, theta burst stimulation, craving, DLPFC (dorsolateral prefrontal cortex)

INTRODUCTION

Disorders of addiction, or compulsive drug-seeking behaviors despite adverse negative consequences, are characterized by abnormal brain network function (Goldstein and Volkow, 2011; Everitt and Robbins, 2016). Preclinical and translational studies highlight a prominent role for hypoactivity of the prefrontal cortex (PFC) with chronic stimulant exposure, leading to the hypothesis that potentiation of PFC function with brain stimulation might improve addiction management (Diana et al., 2017). In the recent decade, non-invasive, repetitive transcranial magnetic stimulation (rTMS) over the dorsolateral prefrontal cortex (DLPFC) has been used to treat cue-induced craving or drug intake across different types of drug dependence, including methamphetamine, cocaine, and heroin (Shen et al., 2016; Terraneo et al., 2016; Su et al., 2017). A range of prefrontal neural regions have been targeted with rTMS including superior frontal gyrus (Rose et al., 2011) or medial prefrontal cortex (Hanlon et al., 2017), whereas we focus here on DLPFC targeting. Convergent evidence has suggested that facilitating the left DLPFC or inhibiting the right DLPFC may reduce craving and substance consumption in patients with substance dependence (Zhang et al., 2019). High-frequency excitatory rTMS of the left DLPFC has been reported to be effective in cocaine use disorder [e.g., 15 Hz/8 sessions/100% motor threshold (Terraneo et al., 2016), 15 Hz/10 sessions/100% motor threshold (Politi et al., 2008), and 10 Hz/single session/90% motor threshold (Camprodon et al., 2007)] and nicotine use disorder [e.g., high frequency/13 session/120% motor threshold, deep TMS over bilateral lateral prefrontal and insula (Dinur-Klein et al., 2014), 10 Hz/10 sessions/100% motor threshold, and 20 Hz/8 sessions/110% over the DLPFC (Amiaz et al., 2009; Sheffer et al., 2018)]. Other stimulants such as methamphetamine craving similarly decreased with high-frequency left DLPFC rTMS (10 Hz/5 sessions/80% motor threshold) (Su et al., 2017), but with enhanced cue craving observed with low frequency (1 Hz/single session/100% motor threshold) (Li et al., 2013b). In heroin-dependent subjects, high-frequency rTMS of the left DLPFC similarly decreased craving (10 Hz/5 sessions/100% motor threshold) (Shen et al., 2016). In contrast, alcohol-dependent subjects showed a different response as a function of laterality with decreased craving with high-frequency rTMS of the right DLPFC (10 Hz/10 sessions/110% motor threshold) (Mishra et al., 2010), with no effects on craving in female alcoholics with high-frequency rTMS of the left DLPFC (20 Hz/10 sessions/110% motor threshold) (Höppner et al., 2011). The rTMS protocol is commonly administered for up to 10–30 min/day with treatment duration lasting between 20 and 30 days. Critically, as treatment compliance is a major issue in drug addiction, decreasing the duration of treatment might enhance the likelihood of completed treatment. Here, we focus on shorter stimulation protocols to reduce session lengths and visits that might lead to improved accessibility for non-invasive neuromodulation for addiction management.

Intermittent or continuous theta burst stimulation (iTBS or cTBS) are TMS protocols that have been shown to, respectively, enhance or inhibit local brain regional activity with long-lasting effect (Huang et al., 2005; Suppa et al., 2016). The protocols involve 600 pulses and requires 3 min for iTBS and 40 s for cTBS (Huang et al., 2005). Previous studies have demonstrated that iTBS has shown comparable neurophysiological excitatory effects to 10 Hz rTMS (Di Lazzaro et al., 2005; Lopez-Alonso et al., 2014). Continuous TBS for 10 sessions to the medial prefrontal cortex has shown potential efficacy for cocaine use disorder (Hanlon et al., 2017). Recently, iTBS was shown in a randomized trial of major depression to be non-inferior to the 10 Hz rTMS protocol in reducing depressive symptoms with similar tolerability and safety profiles (Blumberger et al., 2018). Moreover, iTBS showed similar efficacy to 10 Hz rTMS but, given its shorter duration, might allow a 10-fold increase in the number of patients treated in cocaine use disorder (Sanna et al., 2019). Preliminary studies in major depression have also reported that twice-daily rTMS appears feasible, tolerable, and capable of achieving efficacy similar to once-daily rTMS while reducing treatment course length twofold (McGirr et al., 2015; Modirrousta et al., 2018; Schulze et al., 2018). A recent study has also shown accelerated iTBS as a treatment for cocaine use disorder (Steele et al., 2019). However, no trials have been published to date that explore the feasibility and clinical effects achieved with accelerated (twice-daily) TBS approaches in methamphetamine-dependent patients.

A recent meta-analysis has supported the different left/right hemispheric roles for craving (e.g., cued craving is associated with left DLPFC) and impulsivity (e.g., the suppression of right DLPFC increases the level of impulsive decision making) (Gordon, 2016). Previous studies have suggested that potentiation of the left DLPFC and suppression of the right DLPFC may be effective in reducing cue-induced craving (Li et al., 2013a; Shen et al., 2016; Terraneo et al., 2016; Yavari et al., 2016; Diana et al., 2017). Furthermore, iTBS to the left DLPFC has been shown to produce transsynaptic suppression

of the right DLPFC (i.e., the dominant hemisphere in right-handed individuals) via transcallosal connections (George et al., 1999). In the present study, the rationale for choosing iTBS over the left DLPFC and cTBS over the right DLPFC is supported by the above-mentioned studies. We hypothesized that iTBS-L DLPFC and cTBS-R DLPFC would demonstrate efficacy in improving craving symptoms and that cTBS-L DLPFC might act as an active control with an increase in craving symptoms. We further included other secondary outcome measures to assess the role of potential confounders given the known effects of neuromodulation of the DLPFC on mood and impulsivity measures. Critically, we hypothesized that a twice-daily TBS would be feasible in methamphetamine use disorder. We further compared tolerability and self-reported adverse events across different sessions of treatment and among the three accelerated TBS protocols.

MATERIALS AND METHODS

Human Subjects

All the participants were right-handed male, 18–60 years old, and recruited from a long-term residential treatment center. Inclusion criteria included those whose main diagnosis was methamphetamine use disorder with a duration of at least 1 year and using more than 0.1 g a day for at least 3 months. Subjects had a positive urine drug screening test upon admission to a long-term residential treatment program. Subjects could use other substances before admission but must have had only methamphetamine use disorder as their primary addiction diagnosis (except nicotine use disorder). The diagnosis of moderate–severe methamphetamine use disorder was confirmed by a senior psychiatrist [Diagnostic and Statistical Manual of Mental Disorder, Version V (DSM-V)]. The psychiatrist ruled out other severe psychiatric disorders including schizophrenia, bipolar disorder, or severe major depression. Exclusion criteria included a history of other psychiatric disorders, epilepsy, cardiovascular complications, and other contraindications to TMS (e.g., metal implants in the skull). Subject characteristics and previous methamphetamine use history is reported in **Table 1**. In the rehabilitation center, all participants received standardized rehabilitation including daily physical exercise, supportive therapy on relapse prevention, but no medications. As the rehabilitation program is an enforced residential drug treatment program, participants maintained abstinence in the study. Ethics approval was granted by the Research Ethics Boards of Shanghai Mental Health Center, Nanjing Normal University and the local safety monitoring board (Chinese Clinical Trial Registry number, 17013610). All participants provided written informed consent in accordance with the Declaration of Helsinki.

A total of 83 inpatients were recruited and randomly assigned (with a computer generated number sequence) into iTBS-L DLPFC (n = 27), cTBS-L DLPFC (n = 26), and cTBS-R DLPFC (n = 30) groups. All patients were naive to TMS. Patients recruited in the study did not participate in other intervention studies before. All patients received twice-daily TBS over five consecutive days for a total of 10 sessions. The following were not included in the data set: six subjects were transferred to a different rehabilitation center before study onset (one iTBS-L and five cTBS-L), and three subjects withdrew before study completion (three cTBS-L). There were no significant differences in demographic variables (e.g., age, years of drug abuse history, number of cigarettes smoked per day, monthly dosage, interval between admission into the rehabilitation center and entry into the study, baseline craving, sleep quality, depression, anxiety, and impulsivity) between study completers and non-completers.

DLPFC-TBS Procedures

TBS was applied with a CCY-I TMS instrument (Yiruide Co., Wuhan, China), using a figure eight or round-shaped coil for targeted stimulation over the left or right DLPFC. The TMS intensity for each individual participant was calculated as 70% of the resting motor threshold. The motor hand area was localized by TMS that evoked responses of the contralateral abductor pollicis brevis (APB) muscle. The resting motor threshold was determined as the TMS intensity that elicited the APB muscle responses in 5 out of 10 TMS pulses, which produced five motor-evoked potentials responses of at least 50 mV in 10 trials (Kammer et al., 2001) (iTBS-L DLPFC, 28% ± 6%; cTBS-L DLPFC, 27% ± 6%; cTBS-R DLPFC, 29% ± 7%). The DLPFC target was located using the Yiruide TMS Location Cap based on the 10–20 electroencephalography (EEG) system [i.e., F3 and F4 localization for the left and right DLPFC, respectively (Herwig et al., 2003)]. The TMS coil was held above the head of participants with a customized coil holder, and the handle of the coil was rotated to a position where the plane of the coil made an angle of 45° relative to the midline, producing a posterior–anterior current flow within underlying cortical areas. The procedure used for iTBS is composed of three pulse trains of 50 Hz at 70% resting motor threshold (MT) (based on pilot study and the tolerance level for most subjects), which was repeated at 5 Hz (2 s on, 8-s interval) for 3 min (600 pulses in total). In the case of cTBS, three pulse trains of 50 Hz at 70% resting MT was repeated at 200 ms for 40 s (600 pulses in total). The interval of time between the two sessions of treatment delivered on the same day was ∼4 h. Baseline craving, quality of sleep, depression, anxiety, and impulsivity were assessed before the first TBS session (pre-TBS) and, on day 6, the day after the final TBS session (post-TBS).

Blinding

In this randomized, single-blind study, one experimenter (who administered the intervention) was not blinded to the group assignment, while both the participants and another experimenter (the outcome assessor) were blinded. After all treatments, we asked them to guess whether they had received effective or non-effective stimulation and how much they felt stimulation may have affected them [1 (much worse) to 9 (much better)] to monitor effectiveness of the blinding.

Measurement

The main outcome measure was the craving score evaluation, which was performed as previously described (Shen et al., 2016).

TABLE 1 | Demographic and clinical characteristics of patients.

	iTBS-L-D (*n* = 26)	cTBS-L-D (*n* = 18)	cTBS-R-D (*n* = 30)	*F*	*P* value
Age (years)	31.30 (9.60)	29.50 (5.50)	28.23 (6.24)	1.19	0.31
Education (years)	8.54 (2.45)	9.50 (1.90)	8.18 (1.95)	2.16	0.12
Number of cigarettes smoked/day	8.88 (6.10)	7.33 (2.4)	8.20 (6.08)	0.44	0.65
Duration of meth use (years)	6.50 (3.71)	5.78 (3.39)	6.80 (3.29)	0.49	0.61
Duration of current abstinence (months)	6.80 (5.20)	7.89 (6.70)	5.43 (4.20)	1.29	0.28
Meth use before abstinence (g/month)	18.80 (8.89)	23.88 (7.96)	22.48 (14.03)	1.47	0.24
Interval between admission into the rehabilitation center and entry into the study (days)	82.35 (62.99)	101.28 (59.48)	99.37 (71.80)	0.615	0.54
Baseline Craving	65.19 (22.20)	65.83 (22.44)	74.83 (19.14)	1.77	0.18
Baseline PSQI	6.7 (3.1)	7.1 (3.1)	8 (2.7)	1.41	0.25
Baseline BDI	13.6 (7.5)	12.8 (7.2)	17.5 (9.4)	2.405	0.1
Baseline BAI	25 (4.5)	29.1 (9.98)	29.8 (8.83)	2.79	0.07
Baseline BIS-11	80.36 (14.43)	87.22 (14.82)	83.67 (14.07)	1.226	0.30

Data are given as mean (SD). BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; BIS-11, Barratt Impulsiveness Scale 11.

The patients watched a video showing methamphetamine intake for 5 min followed by a visual analogue scale (VAS) to evaluate cue-induced craving scores [range: 0 (no desire or wanting) to 100 (very high desire or wanting)]. The same video was used before treatment (pre-TBS) and after 5 days of treatment (post-TBS). Patients were assessed for cued craving score pre- and posttreatment, which was used to categorize subjects as responders or non-responders. For major depression, changes from baseline values were examined for the 17-item Hamilton Rating Scale in two subject groups (responders and non-responders) (Bakker et al., 2015). Response to TMS was defined as 50% symptoms reduction from pre- to posttreatment (Schulze et al., 2018). Similarly, in the present study, a TBS responder was defined as having at least a 50% reduction in cued craving scores post-TBS compared with baseline.

As the mechanism underlying neuromodulation effects targeting the DLPFC may be related to effects on other symptoms, most particularly depression and impulsivity, we also assessed other secondary outcome measures. The 21-item Beck Depression Inventory (BDI) and 21-item Beck Anxiety Inventory (BAI) were used to assess depressive and anxiety symptoms (Beck et al., 1961; Beck et al., 1988). The Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality and consists of 19 self-rated items with 7 components: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction (Buysse et al., 1989). The 30-item Barratt Impulsiveness Scale-11 (BIS-11) is a self-report measure of impulsivity that assesses six different subtypes of impulsivity (attention, motor, self-control, cognitive complexity, perseverance, and cognitive instability impulsiveness) (Reise et al., 2013).

Subjects were assessed for nine adverse reactions after each treatment session including headache, neck pain, scalp pain, tingling, itching, burning sensations, sleepiness, trouble concentrating, and acute mood change. Each item was scored on a scale of 1 (mild)–10 (severe), with the total score recorded as the sum of all nine items. For tolerability comparisons, each patient's mean self-reported total score across all sessions was calculated.

Statistical Analysis

The data were assessed for normality of distribution (Kolmogorov–Smirnov test) and outliers. For data that were not normally distributed, non-parametric statistical analyses were used. There were no outliers. Homogeneity of our intervention groups for baseline demographic and clinical characteristics was confirmed. One-way analyses of variance (ANOVAs) or chi-square test were used to compare group differences for continuous or dichotomous variable comparisons, respectively. A two-way repeated measures analysis of variance (RMANOVA) was used to analyze the effects of TBS on our primary outcome of cued craving and also our secondary outcomes of sleep quality, anxiety, depression, and impulsivity between groups, respectively, with time (pre, post) as a within-subject factor and group (iTBS-L DLPFC, cTBS-L DLPFC, and cTBS-R DLPFC) as a between-subjects factor. Two-sided paired *t* tests were performed between conditions when a significant main effect or time × group interaction was observed. Multiple comparisons were corrected using false discovery rate (FDR) correction (Benjamini and Yekutieli, 2001). When we observed a significant TBS effect in craving scores and other clinical indices (sleep quality, depression, anxiety, and impulsivity), Pearson's correlation was conducted in exploratory analyses for each TBS group separately to test the relationship between the two indices. Multiple comparisons were corrected for pairwise correlations using FDR correction.

In a secondary analysis of the cued craving score, the improvement percentage was calculated as the percentage change between baseline pre- and post-TBS treatment craving scores. Kernel density estimate (KDE), a non-parametric method to estimate the probability density function of a continuous random variable, was then used to model the distribution of craving score changes acting as a continuous replacement for the discrete histogram. The Kolmogorov–Smirnov test showed that the probability distribution was not normally distributed. We then

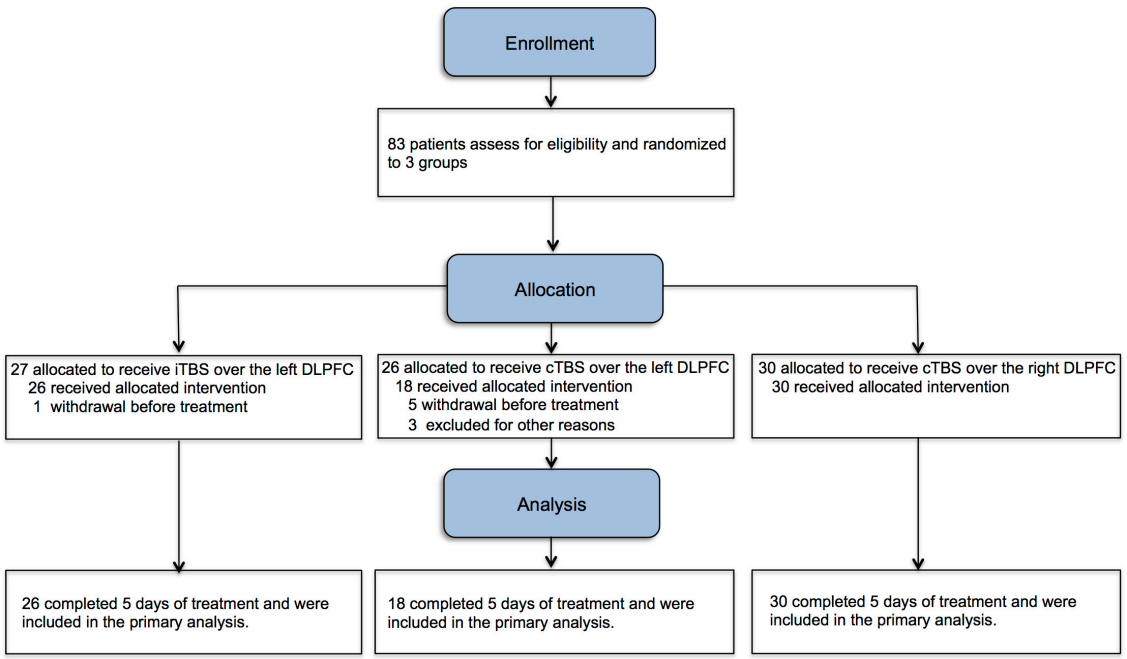

FIGURE 1 | Study flowchart. Eighty-three male methamphetamine-dependent subjects were assigned into three groups for twice-daily theta burst stimulation (TBS) procedures for continuous 5 days (10 sessions). iTBS, intermittent theta burst stimulation; cTBS, continuous theta burst stimulation.

used the non-parametric Wald–Wolfowitz test to compare the distributions between groups.

For adverse effects, the total scores for all nine items (headache, neck pain, scalp pain, tingling, itching, burning sensations, sleepiness, trouble concentrating, and acute mood change) after each treatment were calculated and compared using a two-way RMANOVA with treatment sessions (1–10) as a within-subject factor and group as a between-subjects factor. The total scores for each adverse event were analyzed using one-way ANOVA. Further paired t tests were all FDR corrected.

For blinding effectiveness, the self-report ratings after all treatments were compared using the Kruskal–Wallis Test with group as a factor.

All data were analyzed by IBM SPSS Statistics version 20.1 (IBM Inc., New York, NY, United States) and Matlab R2014b (MathWorks, MA, United States) environments. The statistical significance threshold was set at $P < 0.05$ (two-tailed).

RESULTS

Seventy-four subjects completed 5 days of treatment (iTBS-L DLPFC, $N = 26$; cTBS-L DLPFC, $N = 18$ and cTBS-R DLPFC, $N = 30$) (**Figure 1**). There were no group differences at baseline in age, years of drug abuse history, number of cigarettes smoked per day, monthly dosage, interval between admission into the rehabilitation center and entry into the study, baseline craving, sleep quality, depression, anxiety, and impulsivity (**Table 1**).

Effects of TBS on Craving, Sleep Quality, Mood, and Impulsivity

Table 2 shows the results of ANOVAs conducted for cue-induced craving, sleep quality, mood, anxiety, and impulsivity. The craving score showed a significant main effect of time ($F_{1,73} = 21.01$, $P < 0.001$, $\eta^2 = 0.23$), suggesting that craving

TABLE 2 | Results of the ANOVAs conducted for craving, PSQI, BDI, BAI, and BIS.

Measure	Source	*df*	*F*	Sig.	η^2
Cued-Craving	Time	1	21.01	<0.001	0.23
	Group	2	0.47	0.63	0.01
	Time × group	2	2.00	0.14	0.05
PSQI	Time	1	38.35	<0.001	0.35
	Group	2	3.68	0.03	0.09
	Time × group	2	3.38	0.04	0.09
BDI	Time	1	49.64	<0.001	0.41
	Group	2	0.17	0.84	0.005
	Time × group	2	3.05	0.05	0.08
BAI	Time	1	9.06	0.004	0.11
	Group	2	4.05	0.02	0.10
	Time × group	2	0.27	0.76	0.008
BIS	Time	1	0.18	0.68	0.002
	Group	2	0.75	0.48	0.02
	Time × group	2	0.74	0.48	0.02

Pittsburgh Sleep Quality Index (PSQI); BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; BIS, Barratt Impulsiveness Scale.

improved pre- vs. post-intervention. To assess the role of specific conditions, two-sided paired *t* tests (FDR corrected) were used to compare craving scores before and after treatment. As shown in **Figure 2A**, iTBS-L DLPFC ($P = 0.01$) and cTBS-R DLPFC ($P = 0.001$) significantly reduced craving scores but not cTBS-L DLPFC ($P = 0.52$) (**Figure 2A**). There were no significant main effects of group ($F_{2,146} = 0.47$, $P = 0.63$, $\eta^2 = 0.01$) nor time × group interaction ($F_{2,146} = 2$, $P = 0.14$, $\eta^2 = 0.05$).

KDE of the distribution functions for percentage improvement (cue-induced craving) from pretreatment for each group is shown in **Figure 3**. The Kolmogorov–Smirnov test indicated that the distribution of percent change in craving was not normal for iTBS-L DLPFC ($D = 0.32$, $P = 0.006$), cTBS-L DLPFC ($D = 0.37$, $P = 0.02$), and cTBS-R DLPFC ($D = 0.33$, $P = 0.003$). We showed a significant difference in the probability distribution between iTBS-L DLPFC and cTBS-L DLPFC (Wald–Wolfowitz test, $P = 0.03$) with a marginally significant difference between cTBS-L DLPFC and cTBS-R DLPFC ($P = 0.06$). In the cTBS L-DLPFC group, patients' craving symptoms in three responders (16.67%) improved on average by 45 points (from 65 to 20; 95% CI, −9.1 to 99.1). In contrast, craving scores in 11 responders (36.67%) in the cTBS R-DLPFC group and 6 responders (23.08%) in the iTBS L-DLPFC group demonstrated improvements of 57.3 (from 72.7 to 15.4; 95% CI, 41.9–72.6) and 55 (from 66.7 to 11.7; 95% CI, 40.5–69.5), respectively.

The sleep quality score demonstrated a main effect of time ($F_{1,73} = 38.35$, $P < 0.001$, $\eta^2 = 0.35$) and group ($F_{2,146} = 3.68$, $P = 0.03$, $\eta^2 = 0.09$) and a time × group interaction ($F_{2,146} = 3.38$, $P = 0.04$, $\eta^2 = 0.09$). In the cTBS-L DLPFC ($P = 0.009$, FDR corrected) and iTBS-L DLPFC ($P = 0.0002$, FDR corrected) groups, sleep quality scores showed a significant reduction or improvement with no differences shown with cTBS-R DLPFC ($P = 0.08$, FDR corrected) (**Figure 2B**). Thus, although sleep quality improved pre- vs. posttreatment, this was driven by the cTBS-L and iTBS-L relative to cTBS-R DLPFC groups.

Repeated measures analysis of variance for depressive symptom scores indicated a main effect of time ($F_{1,73} = 49.64$, $P < 0.001$, $\eta^2 = 0.41$), suggesting an overall pre- vs. posttreatment improvement. As shown in **Figure 2C**, compared to baseline, there was a significant decrease in all posttreatment depression scores (iTBS-L DLPFC, $P = 0.0009$; cTBS-L DLPFC, $P = 0.001$; cTBS-R DLPFC, $P = 0.0005$; FDR corrected). Neither a significant main effect of group ($F_{1,73} = 0.17$, $P = 0.84$, $\eta^2 = 0.005$) nor time × group interaction ($F_{2,146} = 3.05$, $P = 0.05$, $\eta^2 = 0.08$) was found.

Repeated measures analysis of variance for anxiety scores suggested a main effect of time ($F_{1,73} = 9.06$, $P = 0.004$, $\eta^2 = 0.11$) and group ($F_{2,146} = 4.05$, $P = 0.02$, $\eta^2 = 0.1$). In the *post hoc* analysis, only iTBS-L DLPFC showed a decrease in anxiety scores ($P = 0.001$, FDR corrected) (**Figure 2D**). The interaction of time × group ($F_{2,146} = 0.27$, $P = 0.76$, $\eta^2 = 0.008$) was not significant.

Repeated measures analysis of variance for impulsivity revealed neither a main effect nor interaction (**Table 2** and **Figure 2E**).

Correlation Analyses Between Changes Across Different Clinical Indexes

We conducted exploratory analyses on the primary outcome measure of craving and secondary outcome measures to assess potential relationships to other clinical outcomes. A positive correlation of changes between craving and sleep quality ($r = 0.56$, $P = 0.045$, FDR corrected) and craving and depression ($r = 0.495$, $P = 0.037$, FDR corrected) was observed in the cTBS-L DLPFC group but critically not in the iTBS-L DLPFC and cTBS-R DLPFC groups, both of which demonstrated significant improvement in craving with intervention. Changes between sleep quality and anxiety in cTBS-L DLPFC was significantly correlated ($r = 0.519$, $P = 0.003$, FDR corrected). In the cTBS-R DLPFC group, changes between depression and anxiety were also significantly correlated ($r = 0.707$, $P = 0.001$, FDR corrected) (**Figure 4**).

Adverse Reactions

All treatments were safe, and no seizures were reported. For the mean self-reported adverse reactions total score after each treatment, RMANOVA showed a main effect of treatment sessions ($F_{9,657} = 13.37$, $P < 0.001$, $\eta^2 = 0.47$) and treatment sessions × group interaction ($F_{18,1,314} = 3.89$, $P = 0.001$, $\eta^2 = 0.27$). Further analysis suggested that total score of adverse reactions in cTBS-R DLPFC was significantly lower than in iTBS-L DLPFC after the first treatment session ($P = 0.01$, FDR corrected) and second treatment session ($P = 0.04$, FDR corrected) (**Figure 5A**). As shown in **Figure 5B** and **Table 3**, the cTBS-L DLPFC group exhibited the lowest percentage (5.5%, 17 out of 18) of adverse effects after the last treatment, and the cTBS-R DLPFC and iTBS-L group demonstrated mild adverse reactions.

Blinding Effectiveness

For the self-report ratings after all treatments, Kruskal–Wallis test displayed no significant main effect of group ($P = 0.906$).

DISCUSSION

Adherence to treatment is a major issue in disorders of addiction. Our findings indicate the possible efficacy and tolerability of accelerated twice-daily iTBS-left or cTBS-right DLPFC treatment over 5 days in reducing craving for methamphetamine but not cTBS-left DLPFC. To our knowledge, this is the first single-blind randomized trial to systematically compare the effects of accelerated TBS procedures for methamphetamine craving targeting the DLPFC. All three interventions similarly improved mood scores, and iTBS-left TBS also improved sleep and anxiety scores, as there was no relationship with craving improvements, our craving findings may be a primary effect. Our findings converge with previous observations of efficacy of high-frequency rTMS of the left DLPFC and low-frequency rTMS of the right DLPFC to modulate craving in disorders of addictions (Li et al., 2013a; Shen et al., 2016; Terraneo et al., 2016; Yavari et al., 2016; Diana et al., 2017). Studies reporting alternate outcomes may be related to difference in TMS protocols or in efficacy as a function of the substance (Mishra et al., 2010; Höppner et al., 2011). These

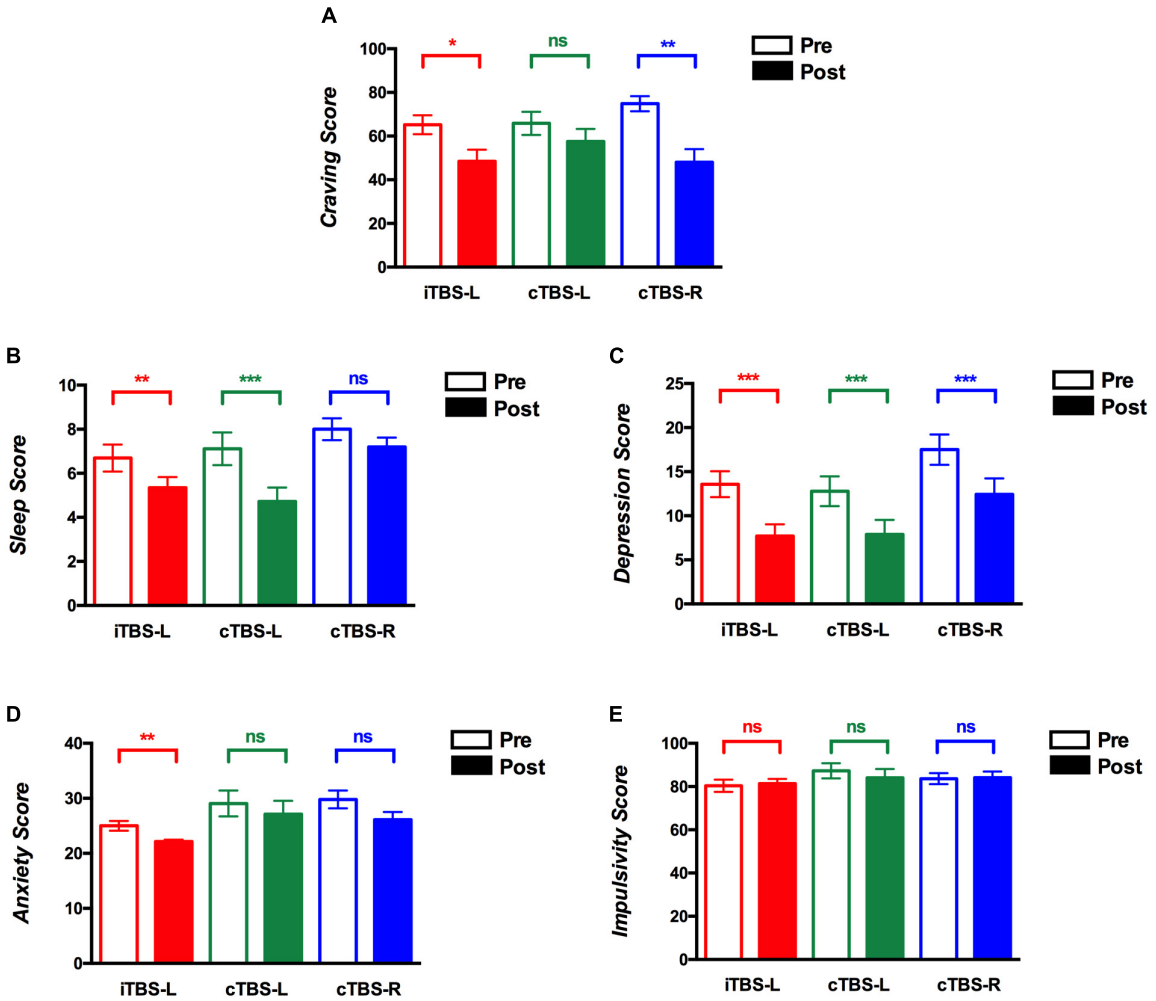

FIGURE 2 | Theta burst stimulation (TBS) intervention on cue-induced craving, quality of sleep, depression, anxiety, and impulsivity scores. The *y*-axis shows mean scores before and after treatment sessions on **(A)** cue-induced craving, **(B)** sleep quality, **(C)** depressive symptoms, **(D)** anxiety symptoms, and **(E)** impulsivity (red, intermittent theta burst stimulation of the left dorsolateral prefrontal cortex (iTBS-L DLPFC); green, continuous TBS of the left DLPFC (cTBS-L DLPFC); blue, continuous TBS of the right DLPFC (cTBS-R DLPFC). Multiple comparisons were corrected using false discovery rate (FDR) correction, $*P < 0.05$, $**P < 0.01$, $***P < 0.001$; error bars denote SEM).

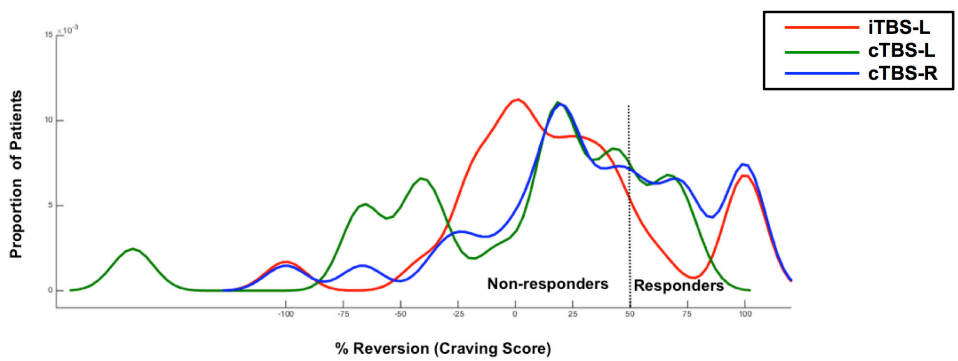

FIGURE 3 | The response distribution curve. Kernel density estimates of cued-craving distributions (shown as percentage improvement from pre- to posttreatment) in methamphetamine-dependent patients ($N = 74$) who were receiving either intermittent TBS of the left dorsolateral prefrontal cortex (iTBS-L DLPFC) (red), or continuous TBS of the left DLPFC (cTBS-L DLPFC) (green) or continuous TBS of the right DLPFC (cTBS-R DLPFC) (blue). A TBS responder was defined as having at least a 50% reduction in cued craving scores post-TBS compared with baseline.

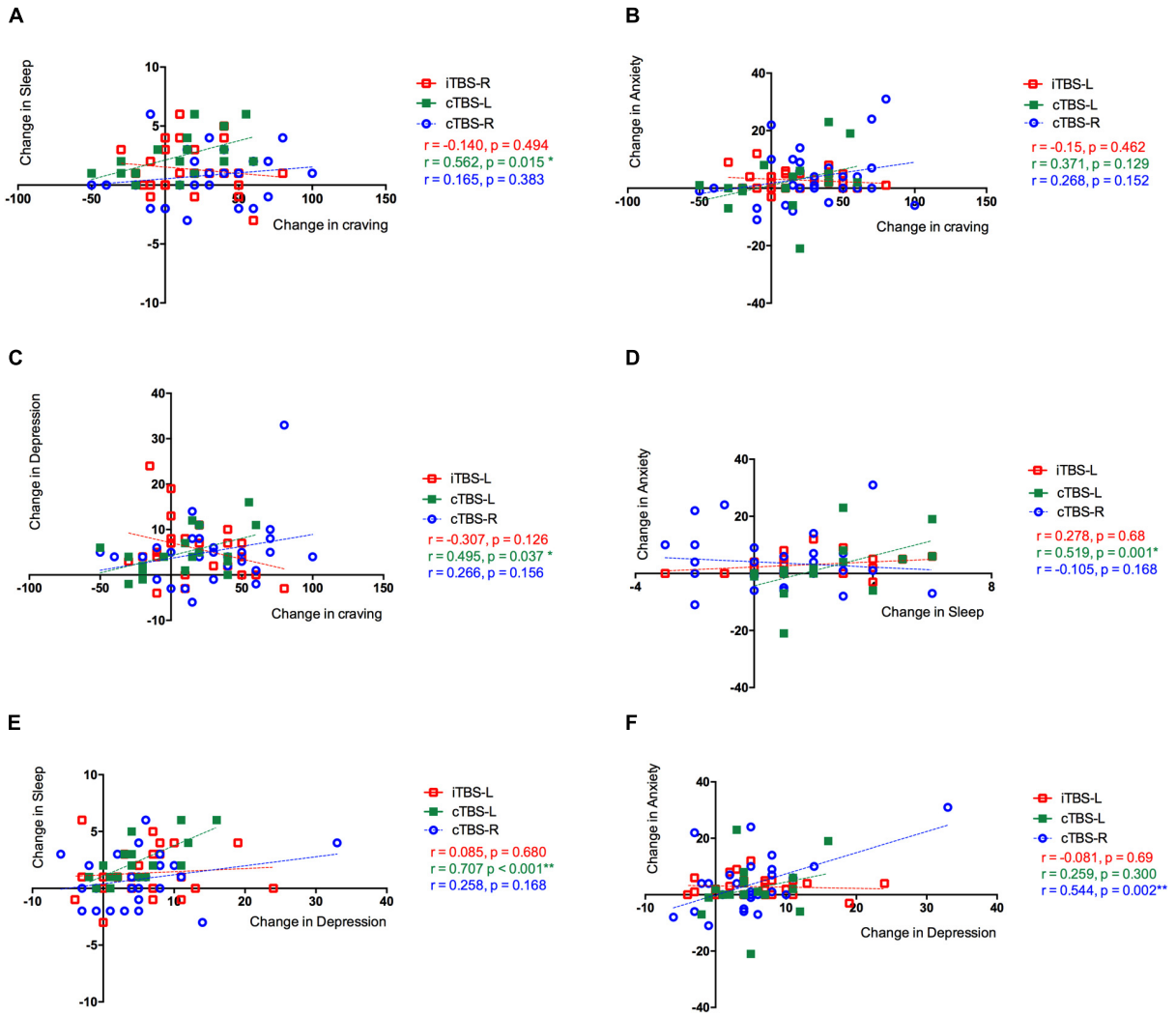

FIGURE 4 | Correlations between changes between clinical outcomes in three groups. The Pearson correlation between changes in **(A)** cue-induced craving and sleep quality, **(B)** cue-induced craving and anxiety level, and **(C)** cue-induced craving and depression level. **(D)** Sleep quality and anxiety level and **(E)** sleep quality and depression level. **(F)** Anxiety level and depression level. The three treatment groups were assessed separately showing the effects of theta burst stimulation (TBS) between clinical symptoms: intermittent TBS of the left dorsolateral prefrontal cortex (iTBS-L DLPFC) (red), continuous TBS of the left DLPFC (cTBS-L DLPFC) (green), or continuous TBS of the right DLPFC (cTBS-R DLPFC) (blue).

findings suggest that the shorter TBS procedure might serve comparably to other standard rTMS procedures in substance use disorder patients and possibly be relevant dimensionally across a range of clinical symptoms. We emphasize the need for a randomized controlled trial study with a sham control to confirm these findings.

The distribution of the percent change in the primary outcome of cue-elicited craving offered a more fine-grained comparison. We observed the highest percentage of responding, defined as a clinically relevant 50% change in craving, in the cTBS-right DLPFC group. The distributions of all three interventions were not normal, suggesting high interindividual variability to differing TBS protocols. For instance, iTBS-left DLPFC treatment may have two subgroups, with one markedly improving and a second with limited change. As this is a small sample size, further larger studies are required to address these interindividual differences in responses to neuromodulation (Li et al., 2015; Suppa et al., 2016).

TBS of the prefrontal cortex might act by enhancing aberrant prefrontal and downstream network function, decreasing aberrant excitability or plasticity or influencing downstream dopaminergic function. Methamphetamine increases synaptic dopamine levels by blocking dopamine reuptake and increasing reverse transport via the dopamine transporter. The chronic use of methamphetamine is associated with impairments in cognition, mood, and sleep (Cruickshank and Dyer, 2009); thus, normalizing mood and sleep symptoms may secondarily improve the secondary consequences of long-term amphetamine use. Chronic psychostimulants are associated with prefrontal hypofunction with impairments related to DLPFC function,

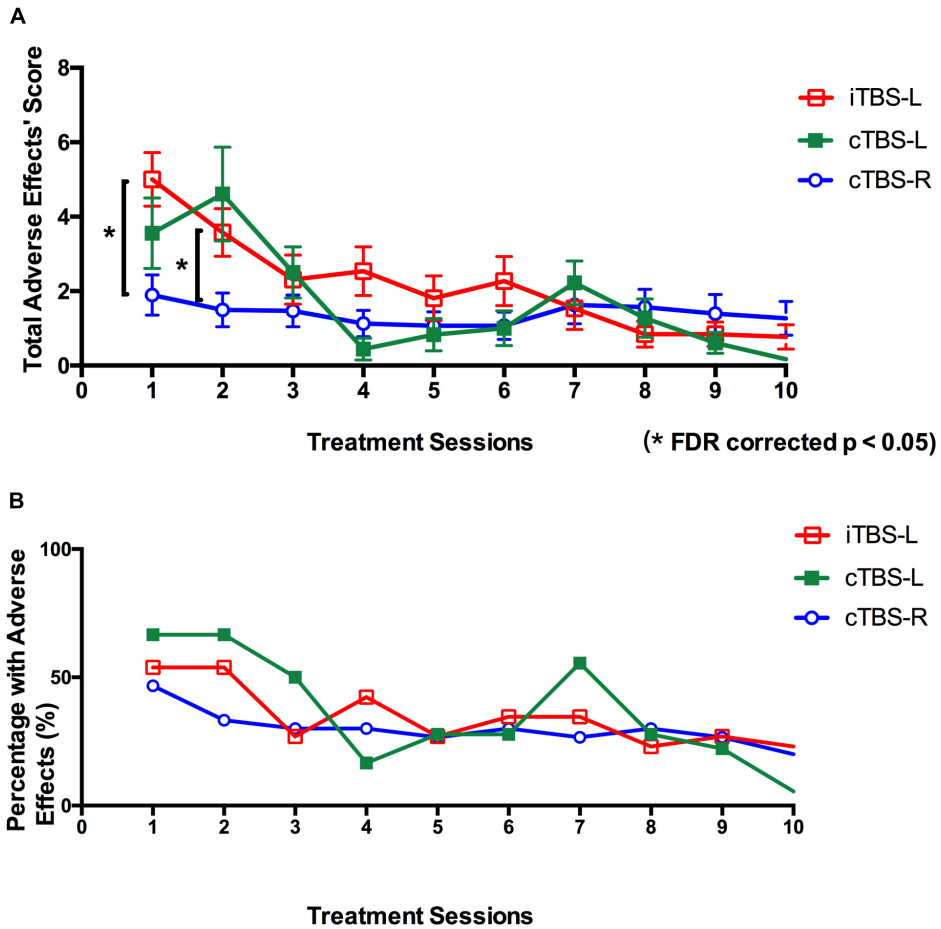

FIGURE 5 | Self-reported adverse effects of twice-daily theta burst stimulation over 10 sessions. **(A)** Mean total scores of adverse effects (headache, neck pain, scalp pain, tingling, itching, burning sensations, sleepiness, trouble concentrating, and acute mood change) after each theta burst stimulation (TBS) treatment session (intermittent TBS of the left dorsolateral prefrontal cortex (iTBS-L DLPFC) (red), continuous TBS of the left DLPFC (cTBS-L DLPFC) (green), or continuous TBS of the right DLPFC (cTBS-R DLPFC) (blue). Multiple comparisons were corrected false discovery rate (FDR) correction (*$P < 0.05$; error bars denote SEM). **(B)** Percentage with adverse effects across all participants after each treatment session (red, iTBS-L DLPFC; green, cTBS-L DLPFC; blue, cTBS-R DLPFC).

TABLE 3 | Scores of adverse reactions.

	iTBS-L-D (*n* = 26)	cTBS-L-D (*n* = 18)	cTBS-R-D (*n* = 30)	ANOVA	*P* value	*Post hoc* (FDR corrected[a])
Headache	1.88 (3.49)	3.67 (5.35)	0.57 (2.0)	$F = 4.23$	0.02	cTBS-L > iTBS-L cTBS-L > cTBS-R
Neck pain	0 (0)	0.11 (0.47)	0 (0)	$F = 1.58$	0.21	NA
Scalp pain	0.92 (3.30)	2.38 (4.50)	0.17 (0.53)	$F = 3.16$	0.05	cTBS-L > iTBS-L cTBS-L > cTBS-R
Tingling	5.35 (7.10)	5.06 (5.98)	3.90 (7.32)	$F = 0.34$	0.72	NA
Itching	0 (0)	0.11 (0.47)	0 (0)	$F = 1.59$	0.21	NA
Burning Sensation	0 (0)	0.27 (0.83)	0 (0)	$F = 3.21$	0.05	NA
Sleepiness	11.61 (18.23)	1.28 (2.49)	6.80 (15.14)	$F = 2.69$	0.08	NA
Trouble Concentrating	0 (0)	1.44 (2.15)	0.233 (1.28)	$F = 6.91$	0.002	cTBS-L > iTBS-L cTBS-L > cTBS-R
Mood Change	0.31 (1.57)	2.44 (4.68)	0.17 (0.91)	$F = 5.19$	0.008	cTBS-L > iTBS-L cTBS-L > cTBS-R

Data are presented as mean (SD). [a]*Multiple comparisons were corrected by the false discovery rate (FDR) correction.*

including executive deficits such as working memory, planning, and goal-directed control (Goldstein and Volkow, 2011; Voon et al., 2015). TBS might thus improve DLPFC function and its associated fronto-striatal network. TMS of the DLPFC paired with functional imaging has shown a decrease in orbitofrontal activity associated nicotine cue-induced craving, particularly when the cue was immediately available, thus implicating a role in intertemporal discounting (Hayashi et al., 2013). Psychostimulants are linked to long-term downregulation of dopaminergic neurotransmission with lower D2/3 receptor levels and blunted dopamine release to psychostimulants (Volkow et al., 2004; Koob and Volkow, 2010). Methamphetamine, in particular, is associated with lower dopamine transporter levels, which can improve with abstinence (Volkow et al., 2001). The downstream influence of TMS to the DLPFC affects caudate synaptic dopamine release in healthy controls (Strafella et al., 2001) and thus may play a role in normalizing methamphetamine-related aberrant dopaminergic function. Further studies are required to assess the underlying mechanisms.

The original TBS neurophysiological study employed 80% active MT targeting the primary motor cortex (Huang et al., 2005), while other clinical trials have also tried 120% resting MT of the DLPFC demonstrating both safety and tolerability (Blumberger et al., 2018). Our previous study has shown that TBS (single session/80% motor threshold) over the motor cortex cannot induce cerebral plasticity, which indicates that neuroplasticity is supposed to be altered in methamphetamine users (Huang et al., 2017). The TBS-related plasticity and behavioral change might highly depend on the intensity, the total number of pulses, the number of sessions, and the stimulating site. In the present study, we adopted 70% resting MT intensity at DLPFC and show in this pilot study that this threshold is both effective and tolerable for most subjects. The percentage of self-reported adverse events across the sessions reduced from >50 to $\sim$20% within the different groups, suggesting enhanced tolerance and adaptation with repeated TBS. We show that a lower intensity (70% resting MT) for TBS might still be effective and perhaps enhance tolerability.

Treatment outcomes appeared to be differentially modulated among the three groups. Notably, the decreases in depression score were moderate (40–50%) across all protocols, suggesting a potential clinically significant response. We did not observe changes in impulsivity as measured using questionnaires. Previous studies have reported that cTBS but not iTBS of the right DLPFC reduced impulsive choice as measured using the delay-discounting task in healthy subjects and pathological gambling subjects (Cho et al., 2010; Zack et al., 2016).

Several limitations should be considered. This study focused on the effects of craving to drug cues without long-term follow-up to assess the duration of effect and impact on clinically valid outcomes such as relapse rate or the relationship to natural rewards. Whether fewer or more sessions (e.g., 8 sessions over 4 days or 20 sessions as compared to 10 sessions), a shorter interval between sessions, or a greater number of sessions per day may have a different effect remains to be investigated. The use of placebo or sham TMS in larger sample sizes would be of utility for comparison purposes, although issues have also been highlighted with the use of other forms of control groups (Davis et al., 2013). We note the larger number of dropouts in the cTBS-L DLPFC condition, thus limiting its utility as an active control; indeed, if fewer subjects had dropped out, we may have demonstrated the critical group main effect and interaction effect. Moreover, the use of neurophysiological or neuroimaging modalities would also be indicated to explore underlying mechanisms and differences underlying interindividual differences or for outcome prediction (Hawco et al., 2018). We applied iTBS over the left DLPFC but neither the right DLPFC nor a wait-list group due to technical reasons, including the limited number of methamphetamine-dependent subjects who could be recruited and the length of the experiment. The clinical effects of iTBS over the right DLPFC and a wait-list group in methamphetamine-dependent subjects should be further investigated. Finally, given that patients were recruited from an ongoing rehabilitation center training program, the findings should be interpreted with caution since daily physical exercise and supportive therapy or individual psychological therapy might alter sleep or mood status. However, crucially, subjects across all groups experienced the same non-TBS-related interventions, and we further show that the improvements in mood and sleep were unrelated to the improvement in craving.

CONCLUSION

Our findings add to the growing evidence that accelerated TBS might be an efficacious method for craving, mood, sleep, and anxiety symptoms and tolerability in abstinent methamphetamine-dependent subjects. Further larger randomized studies with placebo control and comparisons with standard TBS or standard rTMS protocols are indicated. Critically, our results suggest that the use of both TBS and an accelerated design might show efficacy in targeting methamphetamine craving and emphasize efficiency, potentially facilitating the number of patients that can be treated with each TMS machine and shortening the duration of treatment from several weeks to 1 week.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the research ethics boards of Shanghai Mental Health Center, Nanjing Normal University and the local safety monitoring board (Chinese Clinical Trial Registry number, ChiCTR-INR-17013610). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

T-FY and VV conceptualized and designed the study. DZ, YL, and TL performed the study. DZ, VV, and T-FY analyzed the results and wrote the manuscript together. All authors have read and approved the final version of the manuscript.

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PERSPECTIVE
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Transcranial Magnetic Stimulation Meets Virtual Reality: The Potential of Integrating Brain Stimulation With a Simulative Technology for Food Addiction

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The aim of this perspective is to propose and discuss the integration of transcranial magnetic stimulation (TMS) over the dorsolateral prefrontal cortex with virtual reality (VR) food exposure for therapeutic interventions for food addiction. "Food addiction" is a dysfunctional eating pattern which is typically observed in eating disorders (ED) such as bulimia nervosa and binge eating disorder. Food addiction has been compared to substance use disorder due to the necessity of consuming a substance (food) and the presence of a dependence behavior. In recent years, VR has been applied in the treatment of ED because it triggers psychological and physiological responses through food exposure in place of real stimuli. Virtual reality-Cue exposure therapy has been proven as a valid technique for regulating anxiety and food craving in ED. More, TMS has been proven to modulate circuits and networks implicated in neuropsychiatric disorders and is effective in treating addiction such as nicotine craving and consumption and cocaine use disorder. The combination of a simulative technology and a neurostimulation would presumably provide better improvement compared to a single intervention because it implies the presence of both cognitive and neuropsychological techniques. The possible advantage of this approach will be discussed in the perspective.

Keywords: food addiction, TMS, virtual reality, exposure therapy, craving

INTRODUCTION

"Food addiction" is a dysfunctional eating pattern typically observed in eating disorders (ED) such as bulimia nervosa (BN) and binge eating disorder (BED; Meule and Gearhardt, 2014). It has been compared to substance use disorder (SUD) due to the necessity of consuming a substance (food) and the presence of a dependence behavior (Meule and Gearhardt, 2014).

Transcranial magnetic stimulation (TMS) might be effective in modulating circuits and networks implicated in neuropsychiatric disorders and in treating addictions, such as nicotine craving/consumption and cocaine use disorder (Diana et al., 2017; Su et al., 2017; Ma et al., 2019; Steele et al., 2019).

In recent years, virtual reality (VR), a new technology capable of simulating real life scenarios (Riva et al., 2019b), has been applied in the treatment of ED because it can trigger psychological and physiological responses through virtual food exposure in place of real stimuli (Koskina et al., 2013; Pla-sanjuanelo et al., 2015). Virtual reality-based Cue exposure therapy (VR-CET) represents a valid technique for regulating anxiety and food craving in weight and EDs (Ferrer-garcia et al., 2017).

The combination of a simulative technology and a neurostimulation would presumably provide better improvement compared to a single intervention, because it copes with both cognitive-emotional and brain mechanism underpinning EDs. The possible advantages of this approach will be discussed in this perspective.

FOOD ADDICTION

For decades, the idea that specific kind of foods may have an addiction potential and that overeating may be an addicted behavior has been discussed (Meule and Gearhardt, 2014).

Randolph (1956) first introduced the term "food addiction" referring to the reaction of overeating specific kind of foods followed by malaise, addiction, and long-term negative physical consequences as obesity (Randolph, 1956).

In 2009 The Yale Food Addiction Scale (YFAS; Gearhardt et al., 2009) was invented based on the Diagnostics and Statistical Manual of Mental Disorders fourth edition (DSM IV-TR) criteria for substance-related and addictive disorders (American Psychiatric Association, 2000). Food addiction was thus defined by the presence of three or more of the following symptoms: (1) a larger amount of food taken for a longer period than intended, (2) persistent desire or repeated unsuccessful attempts to reduce or stop intake of certain foods, (3) much time/activity to obtain, use, recover from eating certain foods, (4) important social, occupational, or recreational activities given up or reduced as a result of symptoms, (5) continued intake of the food(s) despite knowledge of adverse consequences, (6) tolerance, (7) withdrawal. In 2016, according to the DSM 5 (American Psychiatric Association, 2013) YFAS was changed into YFAS 2.0 (Gearhardt et al., 2016) including four additional symptoms: (8) continued use despite social or interpersonal problem, (9) failure to fulfill major role obligations, (10) intake of certain foods in physically hazardous situations, and (11) craving or strong desire/urge to eat certain foods.

Neurobiological studies revealed altered neural activity both in presence and absence of palatable food cues. For instance, when anticipating palatable foods, activity in left medial orbitofrontal cortex (OFC), left anterior cingulate cortex (ACC) and amygdala positively correlates with food addiction severity (Gearhardt et al., 2011). In addition, higher YFAS scores correlated with greater anticipatory activity of the left dorsolateral prefrontal cortex (DLPFC), which is involved in inhibition and reward control, due to its connections with ventral limbic circuitry (Wallis and Miller, 2003; Jauregui-Lobera and Martinez-Quinones, 2018). Instead, in absence of food exposure, YFAS scores correlate with ACC activity (Gearhardt et al., 2011). As in SUD, (Franken et al., 2004; Coullaut-Valera et al., 2014) food addiction is associated with abnormalities in the dopaminergic system (Davis et al., 2013, 2014) responsible of the reward system (Wang et al., 2011). Substance use disorder and food addiction share also some behavioral features including impulsivity, anxiety, depression symptoms, and attentional biases towards food-drug stimuli (Naish et al., 2018).

Food addiction prevalence appears increased in patients who suffer from BN and BED (Pursey et al., 2014) both characterized by compulsive episodes of disproportionate consumption of highly palatable foods together with a strong sense of loss of control. Three main elements define BED: preoccupation/anticipation, binge/intoxication, and withdrawal/negative effect (American Psychiatric Association, 2013). These three stages interact with each other, gradually becoming more intense and eventually leading to the pathological state known as addiction. Preoccupation and anticipation are known as craving, a physiological condition which, despite a state of satiety, determines food intake of desired food (Jauregui-Lobera and Martinez-Quinones, 2018).

Taken these results together, food addiction is reconcilable to a SUD due the joint dependence on a behavior (eating) and a substance (food) (Meule and Gearhardt, 2014).

TRANSCRANIAL MAGNETIC STIMULATION

Transcranial magnetic stimulation is a non-invasive brain stimulation (NIBS) technique capable of modulating the neural activity of a targeted brain region. It relies on the induction of an electric field in the brain, delivered by a coil, which influences cortical excitability, by activating or deactivating neural networks (Rossi et al., 2009). Transcranial magnetic stimulation effects depend on frequency, intensity, number of pulses delivered, type of coil employed, and location of the stimulation (Diana et al., 2017). It can be distinguished between single-pulse TMS, in which one stimulus at a time is applied; paired-pulse TMS in which pairs of stimuli separated by an interval are applied and repetitive TMS (rTMS), in which pulses are delivered in trains (Pascual-Leone et al., 2000). Specifically, rTMS can be applied either as trains of high-frequency (more than 1 Hz), increasing cortical excitability, or trains of low-frequency (1 Hz or less), inhibiting the targeted region (Fitzgerald et al., 2006; Rossi et al., 2009). Usually, TMS treatments are compared to sham condition in which, by tilting the coil away from the scalp, the magnetic field does not reach cortical neurons, even though sound and scalp contact are similar to those experienced during active stimulation (Sandrini et al., 2011).

Over the past decades, NIBS is being increasingly employed in clinical practice (Brunoni et al., 2019). Both rTMS and transcranial direct stimulation (tDCS) have been primarily applied to patients suffering from depression reporting successful enhancement of mood (Wassermann and Zimmermann, 2012; Shin et al., 2015). Transcranial magnetic stimulation has also been employed as a promising alternative to pharmacological therapies, for several other psychiatric disorders which appear to be drug-resistant/non-responsive to medications including bipolar disorder (Xia et al., 2008), schizophrenia (Shi et al., 2014), obsessive-compulsive disorder (Berlim et al., 2013), anxiety disorder (Dilkov et al., 2017), panic disorder (Mantovani et al., 2013), post-traumatic stress disorder (Watts et al., 2012), and addiction disorder (Diana et al., 2017; Hauer et al., 2019; Steele et al., 2019).

According to the DSM-5, "addiction" is a chronic brain disorder characterized by the need of a substance or an engaging activity, determining a compulsive and uncontrollable behavior difficult to control, despite negative consequences (American Psychiatric Association, 2013). Neuroimaging studies proved that craving implies alterations in brain regions (Koob and Volkow, 2016; Diana et al., 2017) particularly in DLPFC and orbito-frontal cortices (Hayashi et al., 2013). Dorsolateral prefrontal cortex is involved in regulating craving effects, controlling response inhibition and self-regulatory (Brody et al., 2002; Mcbride et al., 2006). Indeed, high frequency rTMS delivered over this area reduced drugs, nicotine, or alcohol consumption (Diana et al., 2017; Su et al., 2017; Ma et al., 2019; Steele et al., 2019). Since neuromodulation have been found to manipulate DLPFC in favor of substance craving reductions (Brody et al., 2002; Mcbride et al., 2006; Liu et al., 2017; Su et al., 2017); some authors studied its efficacy also on food craving symptoms.

TMS and ED

Recent studies have highlighted TMS effectiveness in treating eating and weight disorders including BN, obesity, and BED. For instance, Van Den Eynde et al. (2010) administered one rTMS or sham stimulation over the left DLPFC and reported a decrease in binge-eating episodes and in the urge to eat only in the active condition. More recently, Sutoh et al. (2016) assessed cerebral oxygenation, food craving and bulimic symptoms changes induced by a single rTMS session over the left DLPFC. A significant reduction in food craving was reported by subjective ratings and a significant decrease of cerebral oxygenation in the left DLPFC was observed following rTMS session. Kim et al. (2017) evaluated weight loss in obese patients following four rTMS sessions over the left DLPFC reporting significant weight loss, reduced body mass index and visceral adipose tissue. More recently, Kim et al. (2019) confirmed the same results also at 4-weeks follow-up proving long-term effects on eating consumptions. Rachid (2018) reviewed rTMS single and multiple sessions studies showing relative effectiveness in reducing both craving and ED symptoms. Promising results were reported also in a single case study of a woman with BED and major depression diagnosis (Baczynski et al., 2014): after 20 rTMS sessions over the left DLPFC the Binge Eating Scale (BES) and the Beck Depression Inventory (BDI) scores significantly decreased and the patient reported no binge eating episodes for that week.

These findings together emphasize the role of frontostriatal pathways and of the dopamine in ED, shedding light on the potential contribution of rTMS over DLPFC to correct these abnormalities.

VIRTUAL REALITY

Virtual reality is a computer application by which humans interact with 3D computer-generated environments creating life-like contexts, involving various senses (Bohil et al., 2011). There are different degrees of immersion and interaction that modulate how the user experiments the feeling of being immersed in the VR (Slater, 2009; Cipresso et al., 2018); along with a sense of presence within the environments (Riva and Mantovani, 2014; Riva et al., 2018). Further, virtual stimuli can elicit reflexive responses similar to those produced by equivalent situations in real life (Meehan et al., 2002). These features contribute to the possibility to physically and emotionally interact within the environment: in particular Chirico et al. (2017) found that VR can effectively induce awe (e.g., the feeling of the view from the top of a mountain), usually difficult to reproduce in laboratory settings.

The combination of emotional, physical and mental interaction supports high motivation and engagement (Teo et al., 2016). More, another potential lies on the ability of VR to provide augmented feedback (e.g., auditory, visual, and kinesthetic), complimentary to the ones received through the sensory system. In this regard, VR therapy has been employed as a treatment for cognitive and motor dysfunction to improve neuroplasticity by engaging patients in multisensory training (Adamovich et al., 2009). In recent years, VR technologies have become widely used for the treatment of several disorders including post-traumatic stress disorder (Rizzo et al., 2011), pain management (Matamala-gomez et al., 2019), anxiety and depression (Mishkind et al., 2017; Zeng et al., 2018), neuropsychological deficits (Montana et al., 2019), and traumatic brain injury (Spreij et al., 2014).

VR and ED

Virtual reality has also been employed in the field of EDs since 1990s (Ferrer-garcía and Gutiérrez-maldonado, 2012; Koskina et al., 2013; Ferrer-garcia et al., 2017).

In this regard, Riva et al. (2019a) argued that all EDs share a common "normative discontent" (Rodin and Larson, 1992) about the own body experience. Personal factors (e.g., body mass index, sex, age, and personality), interpersonal factors (e.g., parents and peers' relations) and socio-cultural/economic environment (e.g., body model, ideal size, physical fitness, and athletic body) could determine a negative body representation.

Over the past thirty years, VR technologies have been used to explore the concept of body image (Riva et al., 1997; Perpiñá et al., 1999), its situation-dependent changes (Gutiérrez-Maldonado et al., 2010; Ferrer-garcía and Gutiérrez-maldonado, 2012), and to study emotional and behavioral responses to food cues exposition (Fett et al., 2009; Schienle et al., 2009). Riva

et al. (2019a) identified three different randomized controlled trials that have shown, at one-year follow-up, that VR-CET had a higher efficacy than cognitive behavioral therapy (CBT) in preventing weight regain but not in better managing binge eating episodes in obese BED patients (Cesa et al., 2013; Marco et al., 2013; Manzoni et al., 2016). Moreover, a randomized study by Ferrer-garcia et al. (2017) showed a decrease in craving and anxiety symptoms after exposure to craved virtual food in virtual environments (i.e., kitchen, dining room, bedroom, and cafeteria) in BN and BED patients who were previously treated with classical CBT without significant outcomes. As assessed by self-report questionnaires, patients showed significant reductions in terms of binge and purge episodes, as well as the decrease of the tendency to engage in overeating episodes. In two additional studies, VR treatments reduced eating-related anxiety during and after exposure to virtual food, helping to disrupt the reconsolidation of adverse, food-related memories (Koskina et al., 2013; Pla-sanjuanelo et al., 2015).

Furthermore, based on the *Allocentric Lock Theory*[1], VR plays a role on body image concept, helping to restore allocentric and egocentric representations (Riva and Mantovani, 2014). Finally, VR allows multisensory bodily illusions as well, such as the "Full Body Illusions" that offers illusory ownership over a virtual fake body able to temporarily correct the individual's experience of distorted body shape and size (Keizer et al., 2016; Serino et al., 2016).

THE CLINICAL APPLICATION OF NIBS AND VR

The integration of NIBS and VR has been assessed in different clinical context. On one hand, NIBS is a promising treatment which targets neurophysiology, on the other hand, VR offers an ecological, controlled, and motivating environments tailoring different diseases and needs. Thus, different studies suggested that the combination of NIBS and VR could be more synergistic (Bagce et al., 2012; Kim et al., 2014) compared to stand-alone treatments for stroke rehabilitation. Massetti et al. (2017) reviewed their integration in both clinical (e.g., stroke survivors, children with cerebral palsy, and healthy population) showing positive results in terms of body sway, gait, recovery after stroke, pain management, vegetative reactions, improved learning, and performances with possible applications in neural rehabilitation. The authors supported neuromodulation potential in priming the brain prior to other therapies, enhancing clinical outcomes in neurological conditions even though information regarding its frequency and duration are needed. Subramanian and Prasanna (2018) conducted a meta-analysis on the suitability of NIBS-VR combination in post-stroke upper limb motor rehabilitation showing that effectiveness of NIBS varied depending on the stage of the stroke. Studies that employed in the sub-acute stage contralesional cathodal tDCS (Lee and Chun, 2014) and inhibited TMS (Zheng et al., 2015) showed greater improvements. Benefits from these studies might be related to a decrease of the transcallosal inhibition from contralesional to the ipsilesional hemisphere, which determined motor improvement (Bertolucci et al., 2018). Nevertheless, the generalizability of the findings is limited by the number and the heterogeneity of the studies included. Bassolino et al. (2018) induced embodiment for an artificial hand in a virtual environment through TMS over corticospinal tract, without tactile cues on the hand's skin, typically used to ease rubber hand illusion. Authors argued that this illusory embodiment was determined by neuro-visual integration between TMS over primary motor cortex (and connections with sensory cortex) and hand twitches with visual VR feedback (Bassolino et al., 2018). This effect did not occur when sham TMS was delivered, suggesting that the temporal synchrony between active TMS and VR feedback determined the illusory embodiment.

Fewer studies investigated the combination of these technologies in mood and anxiety disorders. In 2015 Notzon et al. (2015) investigated the efficacy of intermittent theta burst stimulation (iTBS) on anxiety provoked by VR environment. On one hand, VR was effective in inducing anxiety arousal (provoked by virtual spiders) along with typical physiological activations [e.g., heart rate (HR), heart rate variability (HRV)]. On the other hand, iTBS did not provide significant results in subjective and psychophysiological reactions but could modulate HRV, in contrast to other studies that revealed rTMS anxiolytic potential (Lefaucheur et al., 2014; Zwanzger et al., 2009). Future studies should assess the effectiveness of repeated iTBS sessions for anxiety treatment.

Taken these results together, preliminary evidence suggest that employing multiple session of NIBS during the VR therapy might enhance the effects of VR or neuromodulation interventions alone (Teo et al., 2016). Nevertheless, this integrated approach has been employed only for specific disorders including anxiety, stroke and pain recovery and specific information in terms of the number of sessions, the intensity and the duration needed to obtain positive outcomes are lacking. For this purpose. we aim to address this issue by expanding the existing literature about NIBS and VR integration.

A New Integrated Approach

This perspective draws on previous promising studies and aims to propose and discuss the integration of TMS over the DLPFC with VR-CET, for therapeutic interventions of food addiction. This integrated approach might allow the assessment and the monitoring of all the food craving variables (i.e., neuro-psycho-physiological, emotional, behavioral and cognitive) which are involved in food addiction (Ghi and Gutiérrez-maldonado, 2018).

Methods and Procedure

In this section we will propose a possible protocol aimed at assessing this new integrated approach.

The study will be performed in ED patients with at least 3 symptoms assessed by YFAS 2.0. Participants will be randomly assigned to the experimental condition which consists of eight

[1]The Allocentric Lock Theory suggests that ED may be associated with impairment in the ability to update a stored, negative allocentric (offline) representation of one's body with real-time (online/egocentric) perception.

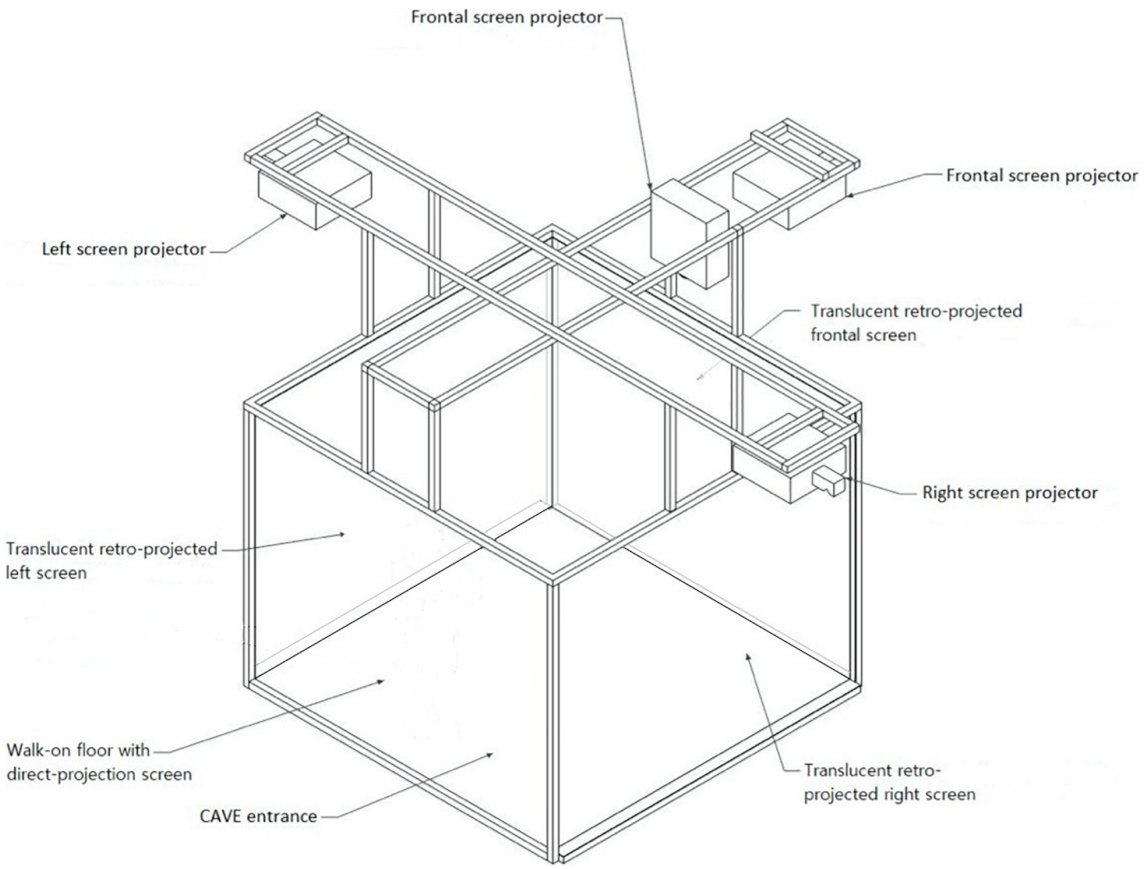

FIGURE 1 | The CAVE is a 3-D immersive four-walled room in which the 3D visualization of the virtual scenario occurs through four stereoscopic projectors. There are three retro-projected screens (frontal, right, and left screens) and a direct-projection screen (floor screen). Four infrared cameras allow to monitor any movements that are made from the 3-D glasses. The depth information is encoded in the virtual scene of the CAVE and is restored and conveyed to the eyes by using the 3-D glasses. The user feels like he is moving around the object 360° thanks to different images and angles. As the user's head moves, the image rotates with it, almost in real-time. This technology guarantees a real life-like experience.

sessions of active rTMS + VR-CET (N = 20) or to the control condition (N = 20) consisting in 8 sessions of sham rTMS + VR-CET. The sample size was estimated based on previous study (Kim et al., 2019) which gave 80% power to detect a significant $p < 0.05$ difference between groups.

Firstly, patients will undertake high-frequency rTMS or TMS sham sessions. TMS frequency will be determined by preliminary investigations. Active rTMS will be delivered over the left DLPCF because neuromodulation over this region has been associated with decreased food craving and ED symptoms and with increased dopaminergic activity.

On top of every TMS session, patients will be immersed in the Cave Automatic Virtual Environment (CAVE) wearing 3-D glasses at IRCCS Istituto Auxologico Italiano (see **Figure 1** for details). In this fully immersive environment they will be exposed to cues associated with binge eating (i.e., highly palatable food) aimed at extinguishing craving, breaking the bond between the food eliciting craving and binge response (Bernabé et al., 2013) in a virtual scenario linked to binging habits (kitchen, cafeteria, restaurant, and dining room). Patients will be asked to explore and handle food with the joypad.

Further, giving that food craving and anxiety are associated with behavioral changes, physiological data (e.g., HR and HRV) will be assessed during the entire intervention. During the VR exposition, patients will be also required to control and monitor their physiological activation exploiting biofeedback technique. Once physiological indexes get back to a normality range, the VR session will be concluded.

Frequency and severity of BE episodes by means of Bulimia Subscale of Eating Disorders Inventory-3 (EDI-3; Garner, 2004); food craving by means of State-Trait Food Craving questionnaire (FCQ; Cepeda-Benito et al., 2000) and anxiety by means of State-Trait Anxiety Inventory (STAI-Y; Spielberger et al., 1970) will be assessed before and after TMS + VR interventions.

DISCUSSION

The combination of a neurostimulation technique with a simulative technology would presumably provide better improvement, compared to a single intervention, because

it implies the joint presence of neuropsychological and cognitive-behavioral techniques. Transcranial magnetic stimulation treatment might produce a beneficial effect in food addiction, in conjunction with a new promising technology that have become widely used in the clinical setting, such as VR.

On one hand, we expect that TMS will attenuate anxiety, urge to eat and food craving to several studies which showed its potential in reducing addictive symptoms and in restoring neural homeostasis in SUD (Koob and Volkow, 2016; Steele et al., 2019) and in ED disorders (Grall-bronnec and Sauvaget, 2014). In fact, in food addiction, similarly to SUD, reduced neural activity of DLPFC and basial ganglia determine decreased control and decision-making skills.

According to previous studies (Riva et al., 2019a), watching high-palatable food in a virtual scenario linked to binging habits is expected to elicit strong emotions, anxiety, food craving, impulse to over-eat, and guilt feelings like those elicited by real food. At the same it should determine the parasympathetic nervous system activation which can be detected by several physiological indices (e.g., HR and skin conductance) (Koskina et al., 2013; Pla-sanjuanelo et al., 2015). Since patients may experience and increase in HR and skin conductance in the VR scenario we aim to investigate first if TMS (active/sham) has an effect on these parameters; secondly, if these parameters decrease with habituation to the scenario and how long it takes.

More, another VR potential consists in reproducing life-like behaviors in an ecological and controlled setting. This exposure therapy aims not only to break the bond between the food eliciting craving and binge response but also to help patients to recognize and monitor symptoms thanks to biofeedback. In fact, biofeedback by providing real-time feedback about their physiological data, teaches patients to change or self-regulate their physiological activity (Arns et al., 2016). In fact, HRV is related to emotional regulation and appears decreased in craving behavior (Rodríguez-Ruiz et al., 2009, 2012). Meule and colleagues (Meule and Gearhardt, 2014) showed that individuals with craving and overeating behaviors reported a significant decrease in preoccupation with food, lacking control and feeling of guilty after HRV biofeedback.

Therefore, anxiety self-reported symptoms, food craving and binge eating episodes are expected to reduce after TMS + VR-CET intervention.

Overall, it is plausible to suggest that this neuromodulation and cognitive-behavioral techniques will give rise to more effective treatments for food addiction. On one hand, TMS involves neuroplasticity in lateral prefrontal regions; on the other hand, VR targets emotional and behavioral monitoring and management.

CONCLUSION

The effects of certain foods on the brain make it hard for some people to avoid them. Food addiction is an addiction to high palatable food, and it has been compared to drug addiction, involving same reward brain areas and neurotransmitters like dopamine. Its prevalence appears increased in patients who suffer from BN and BED. Although several advances in understanding the neural substrates underlying this disease have been made, concomitant improvements in therapies are lacking.

We are proposing an intervention that may reduce craving in patients with food addiction and consequent EDs. This innovative approach would be based on both neurostimulation by rTMS and exposure to fully immersive VR environments. The high-frequency rTMS over the left DLPFC is expected to provide more neural resources by increasing cortical activity and its integration with VR would allow to improve the management of the emotional and behavioral component of craving.

The strength of this approach is represented by the combination of the effects of rTMS and VR. rTMS potential lies in the ability to improve activation and efficiency of prefrontal areas, while VR provides an ecological setting in which patients could learn to self-monitor their reactions to food with the supervision of a clinician. Furthermore, on one hand tracking physiological parameters allows patients to learn changing or self-regulating their physiological activity by providing real-time feedback; on the other hand, it allows to investigate connections between neural-cognitive changes and physiological activity. Considering that TMS effectiveness in treating EDs is not always clear while VR potential in treating EDs has been repeatedly shown (Riva et al., 2019a), we expect that VR could strengthen rTMS effects by increasing cortical excitability.

A study based on this approach may have some limitations. Some users might not be able to complete the intervention due to the occurrence of cybersickness during and after VR sessions (LaViola, 2000) or the occurrence of discomfort and headache induced by the TMS (Rossi et al., 2009). Furthermore, the uncertainty of the neural mechanism underpinning EDs and the unclear beneficial effects of TMS on EDs might influence the effectiveness of this integrated approach.

This novel approach based on the use of two synergistic interventions with high-end technologies might result in a new potential approach for the management and treatment of food addiction in ED.

AUTHOR CONTRIBUTIONS

CS-B and VM conceived, defined, and wrote the first draft of the manuscript. GR supervised the study. All authors revised the final version of the manuscript.

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Non-invasive Brain Stimulation for Gambling Disorder: A Systematic Review

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Background: Gambling disorder (GD) is the most common behavioral addiction and shares pathophysiological and clinical features with substance use disorders (SUDs). Effective therapeutic interventions for GD are lacking. Non-invasive brain stimulation (NIBS) may represent a promising treatment option for GD.

Objective: This systematic review aimed to provide a comprehensive and structured overview of studies applying NIBS techniques to GD and problem gambling.

Methods: A literature search using Pubmed, Web of Science, and Science Direct was conducted from databases inception to December 19, 2019, for studies assessing the effects of repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (t-DCS) on subjects with GD or problem gambling. Studies using NIBS techniques on healthy subjects and those without therapeutic goals but only aiming to assess basic neurophysiology measures were excluded.

Results: A total of 269 articles were title and abstract screened, 13 full texts were assessed, and 11 were included, of which six were controlled and five were uncontrolled. Most studies showed a reduction of gambling behavior, craving for gambling, and gambling-related symptoms. NIBS effects on psychiatric symptoms were less consistent. A decrease of the behavioral activation related to gambling was also reported. Some studies reported modulation of behavioral measures (i.e., impulsivity, cognitive and attentional control, decision making, cognitive flexibility). Studies were not consistent in terms of NIBS protocol, site of stimulation, clinical and surrogate outcome measures, and duration of treatment and follow-up. Sample size was small in most studies.

Conclusions: The clinical and methodological heterogeneity of the included studies prevented us from drawing any firm conclusion on the efficacy of NIBS interventions for GD. Further methodologically sound, robust, and well-powered studies are needed.

Keywords: behavioral addiction, gambling disorder, non-invasive brain stimulation, transcranial direct current stimulation, transcranial electrical stimulation, transcranial magnetic stimulation

INTRODUCTION

Gambling disorder (GD), also known as pathological gambling, affects people of all ages and is a major clinical issue associated with reduced quality of life, psychiatric comorbidity, cognitive deficits, and higher risk of suicide (Ledgerwood and Petry, 2004; Hodgins et al., 2011; Nautiyal et al., 2017). GD and other impulse control disorders (ICDs) are also common in patients with Parkinson's disease (PD) under dopaminergic treatment (Antonini et al., 2017).

Gambling disorder (GD) was previously classified as an ICD but is currently considered the prototypical example of behavioral addiction and is included in the diagnostic category of substance-related and addictive disorders according to the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (*DSM-5*; American Psychiatric Association, 2013; Nautiyal et al., 2017), because a growing evidence suggests that GD and substance use disorder (SUD) share common neurobiological bases and behavioral features (Hudgens-Haney et al., 2013; Limbrick-Oldfield et al., 2013; Tschernegg et al., 2013; Goudriaan et al., 2014). Indeed, human and animal studies indicate that both GD and SUD are characterized by a dysfunction of the reward and cognitive control systems, leading to craving, altered sensitivity to reward, reduced self-control, and abnormal decision-making and executive function (Koob and Volkow, 2016).

The impairment of dopaminergic brain reward circuitries, which are supposed to play a key role in SUD (Vaughan and Foster, 2013), has been reported in GD (Clark et al., 2019). Reduced striatal dopamine transporter availability (Pettorruso et al., 2019b) and increased dopamine synthesis capacity (van Holst et al., 2018) were reported in GD compared with healthy controls. Similarly, PD patients with GD and ICD after dopaminergic treatment showed lower dopaminergic transporter levels in the dorsal striatum and increased dopamine release in the ventral striatum when engaged in reward-related stimuli/gambling tasks (Martini et al., 2018a). An image-based meta-analysis documented striatal hypoactivation in patients with SUD during reward anticipation and in those with GD during reward outcome, in line with the reward-deficiency theory of addiction (Luijten et al., 2017). According to the learning-deficit model (Luijten et al., 2017), these abnormalities are supposed to sustain the transition toward compulsive gambling addiction, characterized both by hypodopaminergic and hyperdopaminergic states in the context of a sensitized dopaminergic system (Pettorruso et al., 2019b).

Executive dysfunction documented in GD patients suggests the involvement of the cognitive control system that can be differentiated into several cognitive sub-processes, i.e., response inhibition, conflict monitoring, decision making, and cognitive flexibility (Moccia et al., 2017). Human functional neuroimaging studies have shown changes in prefrontal regions leading to diminished cognitive control pivotal to the development of GD (Moccia et al., 2017). The cognitive control circuit includes the median prefrontal cortex (mPFC), the dorsolateral prefrontal cortex (DLPFC), the orbital and ventromedial areas, and the anterior cingulate cortex (Van Holst et al., 2010). PD patients with GD and ICD show worse set-shifting and reward-related decision-making and increased depression, anxiety, anhedonia, and impulsivity, pointing to more severe executive dysfunction (Martini et al., 2018b).

GD is considered a full-fledged worldwide public health concern because of its detrimental individual, social, and economic consequences and reduced quality of life (Williams et al., 2012). Moreover, the number of "at risk gamblers" (i.e., people who gamble frequently but not yet pathologically dependent) is increasing (Cavalera et al., 2018). A comprehensive systematic review of empirical researches from 2000 to 2015 across different countries in the world showed that 0.1–5.8% of individuals met diagnostic criteria for problem gambling during the year before the survey and 0.7–6.5% for problem gambling during their lifetime (Calado and Griffiths, 2016). In addition, a recent study estimated the prevalence of GD in Italy to range from 1.3 to 2.2%, and that of "at risk gamblers" to be 1.3–3.8% (ISS, 2018).

Because of the absence of pharmacological treatments with proven efficacy for this condition, the role of non-invasive brain stimulation (NIBS) has been explored for the treatment of GD and other behavioral addictions (Sauvaget et al., 2015). Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (t-DCS) are the most commonly used types of NIBS.

rTMS is delivered to the brain by a rapid phasic electrical current through an insulated wire coil placed over the skull that generates a transient magnetic field, which propagates in space and induces secondary currents that may depolarize neurons in targeted brain regions and lead to neuromodulation and neuroplastic changes (Pascual-Leone et al., 1998; Paulus et al., 2013). High-frequency rTMS is excitatory, while low-frequency rTMS decreases cortical excitability (Paulus et al., 2013), but the effects on synaptic plasticity are often weak, highly variable between individuals, and short-lasting (Huang et al., 2005). Theta-burst stimulation (TBS) is a modified rTMS type that has been found to produce a consistent, long-lasting, and powerful effect on cortex physiology and behavior, with a mixture of facilitatory and inhibitory effects on synaptic transmission according to the TBS protocol used (i.e., prevalent facilitation to intermittent TBS and prevalent inhibition to continuous TBS; Huang et al., 2005). Spatial and temporal resolution of rTMS are high and the former may be modified by the type of coil, with the classical figure-of-eight coil providing superficial and focal stimulation, and more recent H-coils able to target brain regions to a depth of 5–7 cm (Rossi et al., 2009). The main side effects of rTMS are transient scalp discomfort, headache, and hearing disorders, usually following high frequency protocols (Rossi et al., 2009). The risk of inducing epileptic seizures is minimized through the application of the guidelines and an accurate selection of patients (Lefaucheur et al., 2014, 2020).

t-DCS is delivered through a battery-powered device connected to a couple of electrodes that deliver low-amplitude direct intracerebral currents that increase or decrease neuronal excitability in the specific brain area being stimulated through modification of membrane polarization (Nitsche and Paulus, 2000). Generally, anodal t-DCS depolarizes neurons, thus

increasing cortical excitability, whereas cathodal t-DCS hyperpolarizes neurons, reducing cortical excitability (Nitsche and Paulus, 2000). When applied for a sufficient period of time, t-DCS induces sustained changes in cortical excitability (Nitsche and Paulus, 2001; Nitsche et al., 2005). t-DCS is usually safe and may cause only mild side effects, such as burning sensation and skin irritation, especially with daily use or higher current intensity (Antal et al., 2017), but its spatial and temporal resolution is limited.

Recommendations and guidelines for the safe and appropriate application of NIBS for clinical and research application have been published (Rossi et al., 2009; Rossini et al., 2015; Woods et al., 2016). Guidelines on the therapeutic use of NIBS proposed level A recommendation (definite efficacy) for rTMS of the left dorsolateral prefrontal cortex (DLPFC) in the treatment of depression (Lefaucheur et al., 2020) and level B recommendation (probable efficacy) for anodal tDCS of the left DLPFC (with right orbitofrontal cathode) in major depressive episode without drug resistance and anodal tDCS of the right DLPFC (with left DLPFC cathode) in addiction/craving (Lefaucheur et al., 2017). Recent studies highlighted the potential of rTMS for some SUDs (Diana et al., 2017).

Data on the therapeutic options for GD are scarce. Moreover, information on potentially effective treatments for this condition are needed, because of its social and economic impact. Since the application of NIBS to GD is a very recent field of interest, the present manuscript is aimed to offer a systematic review on studies applying rTMS and t-DCS to patients with GD.

METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (Liberati et al., 2009; Moher et al., 2015).

Eligibility Criteria

We included studies assessing the effects of NIBS techniques in subjects with a diagnosis of GD or pathological/problem gambling. Both controlled and exploratory studies were included and considered eligible, and no restrictions were placed on the publication date of the studies.

We excluded reviews, commentaries, letters, abstracts, conference papers, and animal model studies. Studies applying NIBS techniques on healthy subjects were also excluded. Studies considering NIBS techniques without therapeutic goals but only aiming at assessing basic neurophysiology measures were not considered eligible.

Primary outcomes of interest were changes in clinical (i.e., GD severity, craving, relapse, abstinence, psychiatric related symptoms) or para-clinical outcomes (i.e., physiological measures).

Search Strategy

The Pubmed, Science Direct, and Web of Science databases were searched for peer-reviewed studies on NIBS techniques in subjects with/or at risk of GD or pathological/problem gambling and published from databases inception until December 19, 2019. Only studies written in English were considered.

The search string for Pubmed and Web of Science was: (gambling disorder OR pathological gambling OR problem gambling OR compulsive gambling OR gambling addiction OR gambling addictions OR problematic gambling OR pathological gamblers OR problem gamblers OR gamblers anonymous OR gambling addicts OR gambling) AND (transcranial magnetic stimulation OR TMS OR r-TMS OR theta burst stimulation OR theta burst OR TBS OR c-TBS OR i-TBS OR NIBS OR non-invasive brain stimulation OR brain stimulation OR transcranial direct current stimulation OR tDCS OR tES OR transcranial electrical stimulation OR tCS OR transcranial current stimulation).

The search strategy for Science Direct database included: (Gambling OR gamblers) AND (NIBS OR non-invasive brain stimulation OR brain stimulation), then (Gambling OR gamblers) AND (transcranial magnetic stimulation OR TMS OR r-TMS OR theta burst stimulation OR TBS OR c-TBS OR i-TBS), and (Gambling OR gamblers) AND (transcranial direct current stimulation OR tDCS OR tES OR transcranial electrical stimulation OR tCS OR transcranial current stimulation).

Study Selection

Two authors (CZ and EM) independently screened titles and abstracts using Rayyan software (Ouzzani et al., 2016). The reference lists of relevant papers were inspected for additional studies potentially missed in the databases search. Any disagreement was planned to be solved by consensus or consulting a third reviewer (ST).

Data Collection Procedure

Two reviewers (CZ and EM) independently extracted the following data: study design (i.e., randomized, crossover, parallel, open label, single arm trials), sample size, gender, presence of any comorbidity with GD (i.e., psychiatric conditions, SUD), type of rTMS/t-DCS protocol (excitatory/inhibitory effect, session numbers, blinding, sham condition, side effects, follow-up duration), targeted brain area, outcomes of interest (i.e., clinical, surrogate).

Data Analysis

A descriptive analysis of the results was carried out, focusing on the effects of the interventions. A meta-analysis was not possible due to the small number of studies and subjects, and to the clinical, methodological (NIBS protocol, brain target), and outcome heterogeneity of the included studies.

RESULTS

Identification and Selection of the Studies

A total of 400 records were identified. After removal of duplicates, 269 papers were screened through title and abstract and 13 papers were obtained for full-text screening. The reference lists of the relevant papers were inspected for additional studies potentially missed in the databases search, but no significant papers were further added. Two authors (CZ and EM)

independently evaluated the 13 papers selected for the full-text examination. Disagreement was solved by consensus between the two reviewers, therefore the third reviewer's (ST) advice was not required.

Eleven studies met the inclusion criteria and were therefore included in the systematic review (**Figure 1**).

Description of the Included Studies

The included papers evaluated the efficacy of NIBS interventions based on rTMS or t-DCS techniques for subjects with GD or problem gambling. Studies were grouped according to the NIBS technique employed (i.e., rTMS or t-DCS) and the presence or absence of a sham-NIBS control arm.

rTMS Studies

Seven studies employed rTMS in GD (**Table 1**).

Controlled Studies

Zack et al. (2016) assessed the effect of two rTMS protocols on gambling reinforcement and related responses in nine community-recruited, non-treatment-seeking men with GD. They reported that three sessions of high frequency rTMS targeting mPFC yielded a significant reduction of craving,

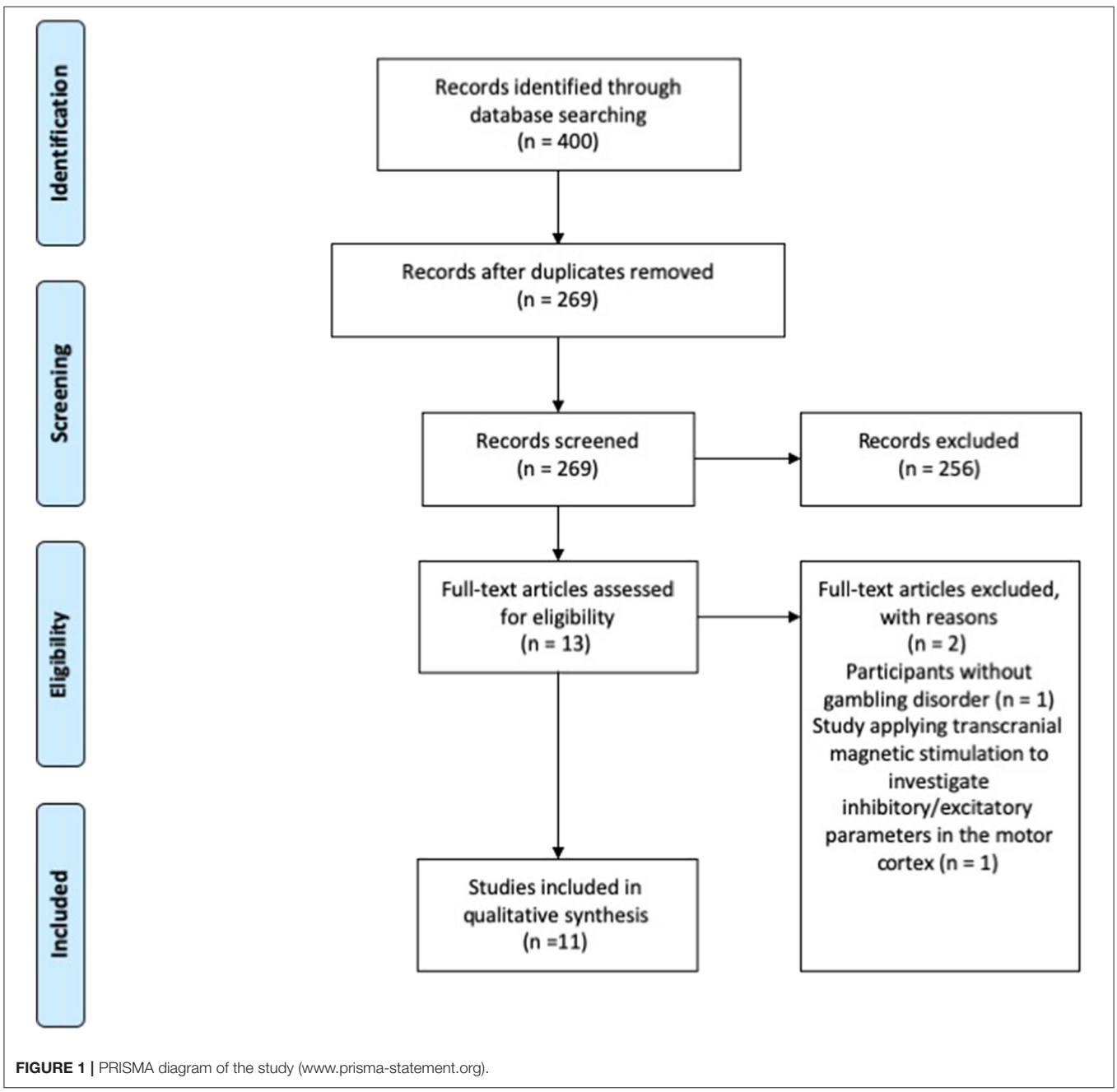

FIGURE 1 | PRISMA diagram of the study (www.prisma-statement.org).

TABLE 1 | Overview of rTMS studies included in the review.

References	Study design	Population	Sample size	Stimulation site	Stimulation protocol	Outcome measures (clinical)	Outcome measures (surrogate)	Follow-up	Side effects	Results
Rosenberg et al. (2013)	Open label	GD patients (men, age 37.8 ± 10.5)	5	Left DLPFC	15 days, one session/day, 10 min duration, 1 Hz, 110% motor threshold	HDRS, HARS, Y-BOCS, SOGS, DAGS, VAS, CGI–I, SAS[1]	None	Interview to families	None	HDRS, HARS, CGI, Y-BOCS, and VAS improved after treatment; all patients returned to gamble
Zack et al. (2016)	Sham-controlled cross-over	Community-recruited, non-treatment seeking men with GD (age 43.2 ± 13.2)	9	mPFC, right DLPFC	rTMS, 10 Hz, 450 pulses (mPFC) cTBS, 50 Hz, 900 pulses (DLPFC) Three sessions (rTMS, cTBS, sham; 1-week washout)	Desire to gamble (VAS)	DDT, Stroop task, arousal (blood pressure, POMS-vigor scale, ARCI)	None	None	rTMS reduced desire to gamble; cTBS reduced amphetamine-like effects and diastolic blood pressure
Gay et al. (2017)	Randomized sham-controlled cross-over	GD patients	22	Left DLPFC	High frequency rTMS (single session)	Gambling craving, PG-YBOCS	None	None	None	Decrease in gambling craving
Sauvaget et al. (2018)	Randomized double-blind sham-controlled cross-over	Men with GD seeking treatment (age range 28–56)	30	Right DLPFC	rTMS, 1 Hz, 360 pulses Two sessions (active, sham; 1-week washout)	Craving (VAS, GCS)	Heart rate, blood pressure	None	None	Both active and sham rTMS were associated with significant decrease in the urge to gamble
Cardullo et al. (2019)	Case series	Men with GD and cocaine use disorder (mean age 42.1 ± 5.7)	7	Left DLPFC	Twice/day for 5 consecutive days, then twice/day once a week for 8 weeks, 15 Hz, 100% motor threshold, 60 pulses per train, 40 trains, 15 s inter-train interval, 13 min duration	G-SAS, CCQ, PSQI, BDI—II, SAS[2], GSI	None	At day 5, 30, at 60 after the beginning of treatment	None	Improvement of gambling severity, cocaine craving, and negative-affect symptoms; results stable at follow-ups
Pettorruso et al. (2019b)	Case report	One man with GD (40 years)	1	Left DLPFC	Twice/day for 5 days/week for 2 weeks (20 sessions), then twice/daily, one/week for 12 weeks (24 sessions), 15 Hz, 100% motor threshold, 60 pulses per train, 40 trains, 15 s inter-train interval, 2,400 pulses/session, 13 min duration	BDI, G-SAS, PG-YBOCS, ISI, YMRS	DAT availability measured by SPECT	One and two weeks, one, two, three, six months	None	No craving for gambling or gambling-related symptoms; decrease in DAT availability in striatal regions
Pettorruso et al. (2020)	Open-label feasibility study	GD patients (age 40.6 ± 11.2)	8 (7 men)	Left DLPFC	Twice/day for 5 days/week for 2 weeks (20 sessions), then twice/daily, one/week for 12 weeks (24 sessions), 15 Hz, 100% motor threshold, 60 pulses per train, 40 trains, 15 s inter-train interval, 2,400 pulses/session, 13 min duration	G-SAS, PG-YBOCS, GTFB, BDI, SAS[2]	None	Two, four, eight, and 12 weeks	None	Reduction of gambling behavior and the number of days spent gambling; results confirmed during all the follow-up period

ARCI, Addiction Research Center Inventory; BDI, Beck depression inventory; BDI-II, Beck depression inventory-II; CCQ, Cocaine craving questionnaire; CGI-I, Clinical global impression improvement scale; cTBS, continuous theta burst stimulation; DAGS, Dannon and ainhold gambling scale; DAT, Dopamine active transporter; DDT, Delay discounting task; DLPFC, Dorsolateral prefrontal cortex; GCS, Gambling craving scale; GD, Gambling disorder; G-SAS, Gambling symptom assessment scale; GSI, Global severity index; GTSB, Gambling timeline follow back; HARS, Hamilton anxiety rating scale; HDRS, Hamilton depression rating scale; ISI, Insomnia severity index; mPFC, medial prefrontal cortex; PG-YBOCS, Pathological gambling adaptation of the Yale-Brown obsessive-compulsive scale; POMS, Profile of mood states; PSQI, 19-item Pittsburgh sleep quality index; rTMS, repetitive transcranial magnetic stimulation; SAS[1], Social adjustment scale; SAS[2], Self-rating anxiety scale; SOGS, South oaks gambling screen; SPECT, Single photon emission computed tomography; VAS, Visual analog scale; Y-BOCS, Yale-Brown obsessive compulsive scale; YMRS, Young mania rating scale.

in particular in the post-game increase in the desire to gamble, and that the same sessions number of continuous TBS targeting the right DLPFC reduced amphetamine-like effects (i.e., psychostimulant-like sensations measured with the Addiction Research Center Inventory amphetamine scale) and behavioral activation measured with diastolic blood pressure, but no changes were reported in impulsive choices or cognitive control on the Stroop task (Zack et al., 2016).

Gay et al. (2017) performed a randomized sham-controlled cross-over study on 22 GD patients using a single session of high frequency rTMS over the left DLPFC and documented a decrease in cue-induced craving and no effect on gambling behavior to real rTMS, but the absence of follow-up impeded to measure the duration of the effect.

In the study conducted by Sauvaget et al. (2018), one session of low frequency rTMS targeting the right DLPFC did not lead to a significant reduction of craving, measured with both self-report scales and physiological measures, compared to sham stimulation.

Uncontrolled Studies

In an open-label study that explored the effect of 15 sessions of low frequency rTMS over the left DLPFC in five participants with GD, despite initial improvement in rating scales, the effect decayed over time and the authors concluded that rTMS treatment failed to demonstrate effectiveness (Rosenberg et al., 2013).

Cardullo et al. (2019) evaluated the effect of 26 sessions of high-frequency rTMS over the left DLPFC in seven men with dual diagnosis of GD and cocaine use disorder and found significant improvement in gambling severity, cocaine craving, and negative-affect symptoms compared to baseline.

Pettorruso et al. (2019a) described a GD patient who was treated with 44 sessions of high frequency rTMS over the left DLPFC and reported a marked reduction in craving for gambling and no episodes of gambling during the 6-month follow-up. Of note, the authors found decreased dopamine transporter availability, a neurobiological marker of dopaminergic pathways modulation, after 2 weeks of treatment.

The same authors investigated eight GD treatment-seeking patients treated with 44 sessions of high frequency rTMS targeting the left DLPFC in an open-label study that showed significant reduction of gambling episodes and the days of gambling throughout the study period in comparison to baseline (Pettorruso et al., 2020).

t-DCS Studies

Four studies employed t-DCS in GD (**Table 2**).

Controlled Studies

Dickler et al. (2018) used a montage to administer anodal t-DCS on the right DLPFC and cathodal t-DCS on the left DLPFC to characterize its effects on neural metabolites levels measured with magnetic resonance spectroscopy. They found that two sessions of active t-DCS induced significantly increased GABA levels in comparison to sham t-DCS, and that metabolite levels were positively correlated with measures of risk taking, impulsivity, and craving (Dickler et al., 2018).

Soyata et al. (2019) reported that three sessions of active anodal t-DCS on the right DLPFC and cathodal t-DCS on the left DLPFC modulated decision making and cognitive flexibility, leading to more advantageous choices during the Iowa Gambling Task and better performances at the Wisconsin Card Sorting Test in participants with GD.

Martinotti et al. (2019) reported that five consecutive sessions of active anodal right DLPFC t-DCS induced a significant reduction of craving levels in comparison to sham t-DCS in a group of treatment-seeking GD patients.

Uncontrolled Studies

Martinotti et al. (2018) reported a young male with 8-year history of GD comorbid with alcohol and cocaine use disorder who was treated with 20 sessions of bilateral DLPFC t-DCS and showed improvement of psychiatric symptoms (depression, anxiety, and impulsivity) and gambling craving, which were maintained at follow-up visits.

DISCUSSION

This systematic review explored the effect of rTMS and t-DCS in people affected by GD. We have found a small number of studies, i.e., seven rTMS and four t-DCS studies, and among them only six were controlled ones, i.e., three on rTMS and three on t-DCS, while the other five reports had an uncontrolled design or were case reports/series.

Despite some differences among outcome measures, most controlled studies (Zack et al., 2016; Gay et al., 2017; Martinotti et al., 2019) and uncontrolled reports (Martinotti et al., 2018; Cardullo et al., 2019; Pettorruso et al., 2019a, 2020) reported a reduction of gambling behavior, craving, or gambling-related symptoms, while the effect on coexistent psychiatric symptoms (e.g., depression, anxiety) was less consistent. Notably, one controlled (Sauvaget et al., 2018) and one uncontrolled study (Rosenberg et al., 2013) reported no changes to rTMS. Two controlled t-DCS studies found improvement in surrogate outcome measures, namely brain gamma-aminobutyric acid levels (Dickler et al., 2018) and neuropsychological testing scores (Soyata et al., 2019), but no improvement in clinical measures.

Taken together, the current evidence lends very limited support to the use of NIBS in patients with GD. It should be noted that the papers we have included in the systematic review were quite heterogeneous in terms of study design, study population, outcome measures, duration of follow-up, comorbidities, all factors that hampered a meta-analytical approach. Moreover, only three studies were comparable in terms of stimulation protocol features and brain target (Dickler et al., 2018; Martinotti et al., 2019; Soyata et al., 2019), but the outcome measures were heterogeneous and impeded a meta-analysis.

All studies targeted the DLPFC, but they were not consistent in terms of brain side, and one study targeted also the mPFC (Zack et al., 2016). The rationale of choosing the DLPFC is because this target is a key structure in the cognitive control circuit (Moccia et al., 2017), which is supposed to

TABLE 2 | Overview of t-DCS studies included in the review.

References	Study design	Population	Sample size	Stimulation site	Stimulation protocol	Outcome measures (clinical)	Outcome measures (surrogate)	Follow-up	Side effects	Results
Martinotti et al. (2018)	Case report	One man with GD and alcohol and cocaine use disorder, 26 years	1	Left and right DLPFC	Twice/day, 20 min stimulation, 1.5 mA, 1-h interval between left and right DLFPFC, 10 consecutive days	SOGS, BPRS, HDRS, HARS, BIS, VAS, PG-YBOCS, G-SAS	None	Ten, 100, and 190 days after t-DCS	None	Significant improvement of gambling, craving severity, and psychiatric symptoms; further improvement at follow-ups
Dickler et al. (2018)	Randomized double-blind sham-controlled crossover	Patients with GD (age range 21–65)	16 (9 men, 7 women)	DLPFC	Anode on right DLPFC, cathode on left DLPFC, two sessions, 1 mA, 30 min (active, sham; 1-week washout)	Craving (GCS)	Metabolite levels (GABA, Glx, NAA), BART, BIS	None	None	Active t-DCS increased GABA levels compared to sham, positive correlations with BART, BIS, GCS
Soyata et al. (2019)	Randomized triple-blind sham-controlled parallel design	Patients with GD (age range 18–55)	20	DLPFC	Anode on right DLPFC, cathode on left DLPFC, three session, 2 mA, 20 min (active, sham)	Not assessed	IGT, WCST, Stroop task	None	None	Active t-DCS yielded better performance at WCST and Stroop task compared to sham
Martinotti et al. (2019)	Randomized, double-blind sham-controlled parallel design	Treatment-seeking GD subjects	34	DLPFC	Anode on right DLPFC, cathode on left DLPFC, five consecutive sessions (active, sham)	Craving (VAS)	None	None	None	Active t-DCS significantly reduced craving levels compared to sham

BIS, Barratt impulsiveness scale; BART, Balloon analog risk taking task; BPRS, Brief psychiatric rating scale; DLPFC, Dorsolateral prefrontal cortex; GABA, Gamma-aminobutyric acid; GCS, Gambling craving scale; GD, Gambling disorder; Glx, Glutamine-glutamate-GABA complex; G-SAS, Gambling symptom assessment scale; HARS, Hamilton anxiety rating scale; HDRS, Hamilton depression rating scale; IGT, Iowa gambling task; NAA, N-acetyl aspartate; PG-YBOCS, Pathological gambling adaptation of the Yale-Brown obsessive-compulsive scale; SOGS, South oaks gambling screen; t-DCS, Transcranial direct current stimulation; VAS, Visual analog scale; WCST, Wisconsin card sorting test; Y-BOCS, Yale-Brown obsessive compulsive scale.

be altered in GD patients, leading to compulsive gambling, craving, impaired reward sensitivity, self-control, and decision-making processes (Van Holst et al., 2010; Koob and Volkow, 2016). Moreover, changes in impulsivity and risky decision-making have been reported after the application of rTMS or t-DCS over prefrontal regions in healthy subjects (Fecteau et al., 2007a,b; Cho et al., 2010; Lantrip et al., 2017). Among the studies we included, however, only two t-DCS reports explored behavioral or neuropsychological measures (Dickler et al., 2018; Soyata et al., 2019).

The studies differed for the site of stimulation, with five rTMS reports targeting the left DLPFC, and two targeting the right one. Conversely, all t-DCS studies targeted both the left and the right DLPFC. The rationale for the left DLPFC preference in rTMS studies may result from studies on SUD, where rTMS over the left DLPFC was reported to be effective in reducing craving, enhancing cognitive control (Politi et al., 2008; Jansen et al., 2013; Rapinesi et al., 2016; Terraneo et al., 2016), and in improving cognitive functioning (Schluter et al., 2018) and the supposed pathophysiological communalities between GD and SUD (Hudgens-Haney et al., 2013; Limbrick-Oldfield et al., 2013; Tschernegg et al., 2013; Goudriaan et al., 2014). Two studies applied rTMS to the right DLPFC and found no improvement in clinical outcomes but some changes in autonomic measures (Zack et al., 2016; Sauvaget et al., 2018). Despite being very preliminary and based on a small number of patients, these data may suggest a preference for the left DLPFC. However, rTMS of the prefrontal regions has been demonstrated to induce bilateral changes in the pattern of brain activation, because of the activation of monosynaptic afferents in the contralateral hemisphere or the influence on functional connectivity patterns of bilateral frontostriatal circuits (Hanlon et al., 2013; Schluter et al., 2017). Because of these concerns, the laterality issue for rTMS of the DLPFC should be further explored in future studies.

In t-DCS studies, DLPFC was targeted bilaterally, either separately in two sessions the same day (Martinotti et al., 2018) or together in the same session through the application of the anode over the right DLPFC and the cathode over the left one (Dickler et al., 2018; Martinotti et al., 2019; Soyata et al., 2019). The choice of this stimulation protocol was based on previous reports that these parameters were associated with a reduction of spontaneous (Batista et al., 2015; Klauss et al., 2018) and cue-induced craving (Fregni et al., 2008a,b; Boggio et al., 2010) and impulsivity (Fecteau et al., 2007a,b; He et al., 2016; Shen et al., 2016; Soff et al., 2017) in patients with SUD and attention deficit hyperactivity disorder.

Stimulation parameters were also not consistent across studies. Two rTMS studies, which used low frequency rTMS (i.e., inhibitory effect), reported no significant changes (Rosenberg et al., 2013; Sauvaget et al., 2018). Conversely, three studies used high frequency rTMS (i.e., excitatory effect) and found significant results (Gay et al., 2017; Cardullo et al., 2019; Pettorruso et al., 2019a, 2020). A single rTMS study compared excitatory high frequency rTMS over the mPFC to inhibitory continuous TBS over the right DLPFC and found differential effects among the two types of NIBS (Zack et al., 2016). Taken together these findings would favor high frequency rTMS for future studies. Studies varied also in terms of the duration of rTMS from a single session to multiple days up to 8 weeks. The very short follow-up periods, which were often limited to the time of rTMS application, impede us from drawing any conclusion whether the changes may outlast the treatment period.

Three out of the four reports on t-DCS used excitatory anodal t-DCS over the right DLPFC and inhibitory cathodal t-DCS over the left one, impeding any conclusion on whether the effects in GD patients were due to excitation or inhibition of the DLPFC.

All studies reported no side effects, confirming the overall safety of NIBS techniques when studies are conducted according to the safety and application guidelines (Rossi et al., 2009; Rossini et al., 2015; Woods et al., 2016; Antal et al., 2017).

Several limitations may have contributed to the inconsistencies across the studies we reviewed. First, all studies had small sample sizes ranging from single case reports to 30–34 patients, with a large majority of men, hampering the generalization of the findings to larger and gender-balanced populations of patients (Ekhtiari et al., 2019; Luigjes et al., 2019). Second, the heterogeneity of the type of stimulation (i.e., excitatory, inhibitory) and duration of stimulation sessions impede any conclusions on the optimal stimulation parameters. Third, targeted brain areas and site varied across studies, with most of them focusing on the DLPFC, despite the inconsistencies on the stimulated side, because of its fundamental role on the cognitive control circuit. This target was probably chosen because of the data from SUD patients (Ekhtiari et al., 2019), and the similarities between SUD, behavioral addiction, and GD. Indeed, these conditions share common behavioral (e.g., impulsivity), neurophysiological, and brain structural and functional changes involving bilateral insula, amygdala, hippocampi, parahippocampal gyri, prefrontal cortex, and anterior cingulate cortex, but they also show some differences, especially in striatal connectivity (Gomis-Vicent et al., 2019). Moreover, studies on the neurobiology of addictive disorders indicate that the reward-related circuitry is much broader, including several other areas, such as the mPFC (Steele and Lawrie, 2004), which was targeted only in one study (Zack et al., 2016) and other subcortical areas that can be reached only with H-shaped coils (Rossi et al., 2009) that was not used in the reports we reviewed. Future studies on GD and behavioral addictions should consider the similarities and the differences between gambling and SUDs, exploring the role of NIBS on other brain areas, including the deeper ones (Spagnolo and Goldman, 2017; Gomis-Vicent et al., 2019). Fourth, another critical issue is the standardization of a panel of GD clinical outcomes together with surrogate measures that represent biomarker of changes related to NIBS. Fifth, most of the studies focused on short-term outcomes (i.e., immediate craving reduction), without adequate follow-up sessions to evaluate the persistence of changes induced by NIBS over time. Sixth, the study design may have influenced the findings. Five of the 11 studies we included were open-label ones, or case reports/series, and their conclusions should be taken with caution because of the risk of placebo effect and overstatement of the findings. Two studies used a parallel design that might have led to an increased probability of the occurrence

of unblinding (Ekhtiari et al., 2019). Only three of them used a cross-over design (Zack et al., 2016; Dickler et al., 2018; Sauvaget et al., 2018) that may not be free from carry-over effects (Fregni et al., 2007; Hallett, 2007). Consensus among experts is needed to define the most appropriate study design for future studies on NIBS in GD.

CONCLUSIONS AND FUTURE DIRECTIONS

Despite the limited amount of information on the role of NIBS that prevented us to draw any conclusion on its efficacy for the treatment of GD and problem gambling, our systematic review highlighted preliminary encouraging results and provided important directions for future studies. The finding that only few studies were available on this topic, to date, in our opinion represents an interesting starting point for future research.

The studies we reviewed suggest the potential of high frequency rTMS over the DLPFC, and excitatory anodal t-DCS over the right DLPFC together with inhibitory cathodal t-DCS over the left one for GD, but these pieces of evidence should be considered still preliminary. Further larger studies should confirm these findings and address the laterality issue (i.e., targeting the left, right DLPFC, or both of them).

Another question that should be explored is whether NIBS is effective as stand-alone or add-on treatment (e.g., associated with pharmacological treatment or cognitive behavior therapy). Finally, methodologically sound and well-powered double- or triple-blind randomized controlled studies, including clinical outcomes and surrogate biomarkers, are needed to document the potential therapeutic role of NIBS in GD.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

This study has been designed by CZ, EM, AF, FL, and ST. Data have been gathered by CZ and EM, under the supervision of ST. Data have been analyzed by CZ and EM. The manuscript has been drafted by CZ, EM, AF, and ST. FL and ST revised the manuscript. All authors approved the final version of the manuscript.

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OPINION
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Transcranial Magnetic Stimulation as an Interventional Tool for Addiction

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Repetitive transcranial magnetic stimulation (rTMS) is implemented to treat many clinical diagnoses. The most common clinical patients receiving rTMS are those suffering from treatment resistant depression (TRD). As a treatment for TRD, rTMS is thought to modulate circuits dysregulated by the disease (Fox et al., 2012). Considering many clinical populations have overlapping dysregulated circuits (Goodkind et al., 2015; McTeague et al., 2017), rTMS holds tremendous potential to treat myriad diseases. One such disease that is manifest by dysregulated circuits is substance use disorder (SUD) (Volkow et al., 2016). The dysregulation spawns from the mesocorticolimbic dopamine (MCL-DA) system and linked to initiation and maintenance of addictive behaviors (Goldstein and Volkow, 2002). Drug use increases DA release in MCL-DA system (Jay, 2003; Kelley, 2004; Nestler, 2005), which is thought to be an important element in learning, goal-directed behavior, and reward processing (Everitt and Robbins, 2005; Kalivas and O'Brien, 2008). The MCL-DA system was modulated with repeated drug exposures to increase dysregulations in SUDs. Cortical rTMS modulates dopamine release in the MCL-DA (Strafella et al., 2001; Strafella, 2003) suggesting rTMS has therapeutic potential for clinical disorders related to DA, such as SUDs.

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OVERVIEW OF THE SPECIAL ISSUE

Recently, a large number of researchers are testing the potential of rTMS to treat SUDs (Diana et al., 2017) and the field is beginning to coalesce toward specific methodological approaches in this regard (Ekhtiari et al., 2019). As with any new field of study, there are many "known unknowns" to uncover to optimize treatment application and increase positive outcomes (i.e., reduce relapse). The topic of this special issue of *Frontiers in Neuroscience* is a timely and important one with a set of papers gathered together that are provocative and wide-ranging. They advance our knowledge by tackling a few known unknowns of how rTMS could be applied to address the negative impact of SUDs on society. The 11 papers range from empirical studies with rTMS applied to treat cocaine, methamphetamine, alcohol, and eating disorders; reviews on rTMS as a treatment for cocaine, methamphetamine, amphetamine, and gambling disorder; and two commentaries discussing the potential of motor cortex stimulation as a target site for intervention. Specifically, motor cortex excitability, and the relationship to glutamate (Nardone et al., 2019), could be used to assess and increase inhibitory control known to be dysregulated in SUDs (Volkow et al., 2016; Zilverstand et al., 2018), as a treatment for alcohol use disorder (AUD) and SUDs in general (Zhou et al., 2019).

The systematic reviews include rTMS studies applied to treat SUD and gambling disorder. Although there are few published studies using rTMS or transcranial direct current stimulation (tDCS), the research topic is ripe for investigation (Zucchella et al., 2020). Gambling disorder has similar behavioral and pathophysiological manifestations as SUDs, suggesting potential overlap in dysregulation and interventional tools for treatment. In treating SUDs with rTMS, these reviews highlight the importance of considering both dopamine and glutamate (Moretti et al., 2020) as well as assessing individual differences in patients (Ma et al., 2019) to better uncover the known unknown of the underlying mechanisms of rTMS interventions. Also, applying high frequency

stimulation (∼5–20 Hz) is more effective than low frequency (∼1 Hz) at reducing craving post-rTMS (Ma et al., 2019). This reflects the shift toward implementing the high frequency, and shorter to implement, continuous and intermittent theta-burst stimulation (c/iTBS) protocols (Huang et al., 2005) than other rTMS protocols.

To implement rTMS in a SUD sample, many target dorsolateral prefrontal cortex (dlPFC) or the medial prefrontal cortex (mPC). Preclinical models of optogenetic stimulation helped motivate these stimulation sites (Chen et al., 2013). In humans, these sites could also be selected to intervene and treat impulsivity, inhibitory control, executive functioning deficits in addiction (c.f., Zilverstand et al., 2018). Additional preclinical models with recent focal coil developments (Meng et al., 2018; Cermak et al., 2020) will continue to influence human rTMS applications. Such models are extremely useful when targeting known aberrant pathways with rTMS. Moretti et al. (2020) outlined the glutamatergic pathway between PFC and nucleus accumbens as one such pathway in need of rigorous study as it is essential for compulsive drug-seeking behaviors.

A fundamental question when implementing rTMS as a treatment is whether cognitive functions are modified. Schluter et al. (2019) implemented an active/sham 10 Hz rTMS treatment protocol in AUD participants and measured cognitive functions before and after the intervention. Although this first randomized clinical trial using AUD and rTMS did not report significant change in the targeted and measured cognitive functions, the authors demonstrated feasibility of applying chronic rTMS to an AUD sample safely. Also, the authors measured a proximal and targeted cognitive function instead of a distal, and common measure of craving as a metric of treatment success.

Known unknowns when applying rTMS to treat SUDs also include which location, which hemisphere, and which stimulation protocol should be selected. Empirically, Sanna et al. (2019) tested whether bilateral 15 Hz rTMS and iTBS applied to the dlPFC differed in effectively reducing cocaine craving. Both treatments reduced craving similarly suggesting the faster iTBS would be easier and more cost effective to apply in a clinical setting. In a methamphetamine treatment seeking sample, Zhao et al. (2020) reported reduced craving in each group that received one of three rTMS dlPFC protocols (left iTBS, left cTBS, or right cTBS) suggesting any TBS intervention could be effective. This adds to recent findings that the general historical understanding that stimulation protocols have opposite effects (Pascual-Leone et al., 1998; Huang et al., 2005) suggesting effects are not universal (Liu et al., 2020; Steele, 2020). Steele et al. (2019) applied accelerated iTBS treatment to the left-dlPFC in cocaine users while they viewed cocaine cues to engage the targeted circuit. Participants reported reduced use (both amount and frequency) 1-month post-treatment. The importance of measuring and reporting off-target effects is demonstrated by the Zhao et al., and Steele et al. articles. Mood, sleep, and anxiety scores improved in the methamphetamine sample by Zhao et al., mood improved and reduced use of other substances were found in the cocaine sample by Steele et al. These measures should be collected and reported as off-target effects related to all rTMS treatments of clinical populations.

The final known unknown addressed in this special issue relates to the state of the participant while receiving the rTMS intervention. Could the state (e.g., physiological, cognitive) of the participant facilitate the effectiveness of the treatment? Stramba-Badiale et al. (2020) outlined how virtual reality (VR) could be implemented in conjunction with rTMS during treatment sessions for eating disorders. This is a very promising development and an exciting area for study with the potential of combining the two interventions to be more effective than each applied serially. Pharmacological interventions could also be considered (Spagnolo et al., 2020). Accounting for the state of the patient will likely prove to be an important variable when developing an effective treatment for SUDs.

CONCLUSION

The articles included in this special issue brought us closer to developing an understanding of how to move forward in using rTMS as a therapeutic intervention for addiction. There are promising results and tantalizing effects to drive thorough research into uncovering more known unknowns. Generally, rTMS used to treat SUDs was tolerated by a wide range of patients. Applying chronic rTMS as a treatment also proved feasible and generally effective at modifying the targeted behavior. Higher frequency stimulation produced greater benefits to the patient. This is all good news and is in line with a recent consensus paper outlining steps toward developing an rTMS treatment for SUDs (Ekhtiari et al., 2019). Some of the most interesting known unknowns are likely soon to be uncovered. Specifically, researchers are diligently working to understand the mechanisms of change induced by rTMS and the effects related to inherent individual differences in patient populations. Also, there is growing evidence that an engaged circuit is beneficial toward positive outcomes (e.g., VR in Stramba-Badiale et al., 2020) and cocaine cues in Steele et al. (2019).

Future directions are apparent from this special issue. Foundational experiments are essential in three areas: (1) develop and integrate preclinical models to clinical applications of rTMS, (2) elucidate effective combinations of rTMS and other treatments, (3) identify individual differences with respect to inducing excitation and inhibition with rTMS. Recent coil technology allows focal stimulation in rodents (Meng et al., 2018) which should speed the parameter space search in optimizing rTMS applications. Also, developing realistic preclinical models could help uncover the true rTMS mechanism of action related to neuroplastic change thus optimizing clinical rTMS applications. Combining rTMS with other interventions (either behavioral or pharmacological) is a promising area of research that should be systematically explored as it could improve treatment outcomes beyond any single intervention (c.f., Spagnolo et al., 2020). Finally, it is essential to understand the universality, or non-universality, of "excitatory" and "inhibitory" rTMS sequences. These individual differences on how rTMS induces

neuroplastic change is the largest factor in applying rTMS within-participant as an effective treatment for SUDs and other clinical population (Steele, 2020), Together, this special issue highlights future directions for the field to explore to evaluate whether rTMS is an effective treatment for SUDs. New findings are rapidly immerging in this exciting area of research. It is only a matter of time before the field uncovers enough known unknowns to implement an optimized therapeutic rTMS intervention for SUDs.

AUTHOR CONTRIBUTIONS

VRS conceived and wrote this commentary.

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