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Research paper

The exploration of optimized protocol for repetitive transcranial magnetic stimulation in the treatment of methamphetamine use disorder: A randomized sham-controlled study

Tianzhen Chen[a,#], Hang Su[a,#], Ruihua Li[a], Haifeng Jiang[a], Xiaotong Li[a], Qianying Wu[a], Haoye Tan[a], Jingying Zhang[a], Na Zhong[a], Jiang Du[a], Huijuan Gu[b], Min Zhao[a,c,d,e,*]

[a] aShanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China

[b] bShanghai Drug Rehabilitation Center of Public Security Bureau, Shanghai, China

[c] cShanghai Key Laboratory of Psychotic Disorders, Shanghai, China

[d] dInstitute of Psychological and Behavioral Science, Shanghai Jiao Tong University, Shanghai, China

[e] eCAS Center for Excellence in Brain Science and Intelligence Technology (CEBSIT), Chinese Academy of Sciences, Shanghai, China

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ABSTRACT

Background: The prefrontal-striatal circuit is a core circuit related to substance dependence. Previous studies have found that repetitive transcranial magnetic stimulation (rTMS) targeting the dorsolateral prefrontal cortex (DLPFC) (key region of executive network) had limited responses, while inhibiting hyperactivation of ventromedial prefrontal cortex (vmPFC) (key region of limbic network) may be another strategy. However, there is currently no comparison between these two treatment locations.

Methods: Seventy-four methamphetamine-dependent patients were randomly assigned to one of treatment groups with two-week treatment: (1) Group A: intermittent theta-burst stimulation (iTBS) targeting the left DLPFC; (2) Group B: continuous theta-burst stimulation (cTBS) targeting the left vmPFC; (3) Group C: a combination of treatment protocol of Group A and Group B; (4) Group D: sham theta-burst stimulation. The primary endpoint was the change of cue-induced craving. The trial was registered at ClinicalTrials.gov (NCT03736317).

Findings: The three real TBS groups had more craving decrease effect than the sham group ($p<0.01$). The changes of craving were positively correlated with the improvement of anxiety and withdrawal symptom. With the highest respondence rate, group C also had shorter respondence time than Group A ($p = 0.03$). Group C was effective in improve depression symptoms ($p = 0.04$) and withdrawal symptom ($p = 0.02$) compared with Group D. Besides, Group C was significant in improve sleep quality ($p = 0.04$) compared with Group A. Baseline depression scores and spatial working memory were positively predicting the intervention response.

Interpretation: The rTMS paradigms involving vmPFC with cTBS are optimized protocols and well-tolerated for methamphetamine-dependent individuals, and they may have better efficacies compared with DLPFC iTBS. Emotion and cognitive function are rTMS treatment response predictors for methamphetamine-dependent patients.

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* **Correspondence author:** Min Zhao, MD. & Ph.D., Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, 600 South Wan Ping Road, Shanghai 200030, China.
E-mail address: drminzhao@smhc.org.cn (M. Zhao).

# These authors contributed equally to this work.

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Research in Context section

Evidence before this study

The prefrontal-striatal circuit is a core circuit related to substance dependence, which at least involves dorsal executive control network (including dorsolateral prefrontal cortex and dorsal striatum) and limbic circuit (including ventromedial prefrontal cortex and ventral striatum). Previous studies have found that repetitive transcranial magnetic stimulation targeting dorsolateral prefrontal cortex (key region of executive brain network) had limited response rate (i.e. our lab has found about 27.2% of patients responded after one week-treatment.), while inhibiting hyperactivation of ventromedial prefrontal cortex (key region of limbic network) may be another strategy. However, there is currently no study investigating the efficacy when targeting the ventromedial prefrontal cortex in methamphetamine use disorder, as well as the comparison between dorsolateral prefrontal cortex and ventromedial prefrontal cortex.

Added value of this study

Both these two treatment protocols were tolerable and safe. The repetitive transcranial magnetic stimulation protocols involving ventromedial prefrontal cortex location are potential to be the optimized paradigms compared with the dorsolateral prefrontal cortex protocol. By applying the emotion and cognitive function indicators, we may be able to predict the repetitive transcranial magnetic stimulation treatment response for methamphetamine-dependent patients.

Implications of all the available evidence

Overall, existing studies have indicated the feasibility of multiple interventions protocols targeting the prefrontal-striatum circuit for methamphetamine-dependent patients, including intervention executive control network, limbic network, and joint interventions. This may provide a better alternative treatment parameter for the treatment of substance-dependent patients with various abnormal brain regions. Besides, studies provided a possible way to develop individualized intervention protocols for different subtypes of substance-dependent patients, that is, intervention for different abnormal brain regions.

1. Introduction

The effective treatment for substance use disorder (SUD) has always been one of the most significant concerns in the field of addiction. However, many types of SUD (e.g. methamphetamine dependence) do not even have one FDA approved medication treatment [1]. As a non-invasive brain stimulation technique, repetitive transcranial magnetic stimulation (rTMS) could modulate abnormal brain activation or neural circuits, thereby ameliorating patients' symptoms [2, 3]. In the current rTMS study of SUD, the widely researched brain area is dorsolateral prefrontal cortex (DLPFC) [4]. Studies have shown that rTMS targeting frontal region affects the levels of prefrontal neurotransmitters GABA and Glu, as well as changes in dopamine receptor binding levels [5-8]. Besides, changes in cerebral blood oxygen level and electrophysiological functions can also be observed [9, 10]. These studies have revealed the possible mechanism of rTMS for neuropsychiatric diseases and indicated that rTMS is promising as a tool for regulating neural circuits in brain to treat SUD.

Craving is the core characteristic of SUD [11]. The prefrontal-striatal circuit, neural network involved in the formation of SUD [12], is often considered as a target for rTMS. At least, it involves dorsal executive control network (including DLPFC and dorsal striatum) and limbic circuit (including ventromedial prefrontal cortex and ventral striatum) [12]. Based on previous studies, cue-induced cravings and relapse behaviors may be related to two reasons: (1) decreased activity of executive control network; and (2) enhanced activity of limbic neural circuits under conditions of cue presentation [13]. In other words, enhancing executive control network and/or decreasing limbic circuit may be two possible ways to reduce patient's cues-induced craving and relapse. Existing studies suggested that using high-frequency rTMS or intermittent theta-burst stimulation (iTBS) (i.e. two excitatory intervention paradigm) to target DLFPC (i.e. region within the executive control network) can effectively reduce craving, which is probably associated with enhancement of executive function [4, 14]. That is to say, it is possible to enhance the inhibition ability of substance stimulation by affecting the level of cognitive control [15]. On the other hand, some studies have shown that intervention on DLPFC may indirectly modulate brain areas of limbic neural circuit (e.g. ventromedial prefrontal cortex), thus affect patient's reactivity to stimulus [16, 17]. When substance (e.g. cocaine, marijuana, and opioid) related cues were exposed, the increasing activity of brain regions within front-limbic network were recorded, including ventromedial prefrontal cortex (vmPFC), ventral striatum, and anterior insula [18, 19]. Preclinical studies also found that vmPFC stimulation normalizes the local field potential activity in ventral tegmental area (i.e. the regions within reward circuit and be able to release dopamine), while the abnormal dopamine release is an important factor leading to formation of addiction [20]. However, randomized controlled studies on the efficacy of rTMS targeting the vmPFC area were still limited (i.e. the key region within the limbic circuit).

The response rate of patients with methamphetamine use disorder (MUD) treated with iTBS treatment was 70.9%, while fast response rate was only 27.2% [21]. It means that exploring individualized treatment options for MUD and other SUD would be valuable. However, there are currently limited treatment options with sufficient effective evidence [22]. Existing studies have shown that both DLPFC and vmPFC stimulation may affect patient's substance related reactivity [23, 24]. The interaction between DLPFC and the vmPFC region also participates in the arouse of craving for substance (e.g. nicotine) stimulus [25]. In spite of these preclinical evidences, there are still several questions about the application of these two brain regions for rTMS in MUD patients. By exploring the curative effect of these two regions, it may help us to develop optimized, precise, and individualized rTMS therapy for SUD. In addition to craving, we also sought to determine its impact on cognitive functions and emotion symptoms which were often reported in previous studies [26, 27].

Given the above knowledge, we try to answer three questions in our study: (1) to compare the efficacy in decreasing craving among three rTMS treatment protocols: DLPFC iTBS treatment, vmPFC cTBS treatment, and the combination of DLPFC iTBS and vmPFC cTBS; (2) to explore the baseline clinical predictors for treatment effect of TBS treatment. (3) to evaluate the side effects of these three rTMS treatment protocols.

2. Methods

2.1. Study design and participants

This was a randomized sham-controlled trial conducted at Shanghai Drug Rehabilitation Center in China. All subjects were inpatients that met the DSM-5 criteria for severe MUD. They also met the following inclusion criteria: (1) aged 18−49 years old; (2) normal vision and audition; (3) received no medications during treatment; (4) used methamphetamine in the past 3 months before being recruited in this study. The exclusion criteria for these patients are: (1) serious physical or neurological illness, a diagnosis of any other psychiatric

disorder under DSM-5 criteria (except for nicotine use disorder); (2) any contraindications to rTMS. Sample size were calculated according to superiority test formula ($n = \frac{\psi^2(\sum_{j=1}^{k} S_j^2/k)}{\sum_{k=1}^{k}(\bar{X}_j - \bar{X}^2}$, k is the number of groups, X_j and S_j are the mean value and standard deviation of each group respectively) for multiple groups [28], with α = 0.05, β = 0.1, k = 4. Based on our previous study [27], A conservative estimation for the craving change of DLPFC iTBS, vmPFC cTBS, and sham group at two-week are 25(SD=15), 25(SD=15), and 5(SD=15) respectively. Combining the two treatment methods may have better efficacy, so the estimated value of the combination of DLPFC iTBS and vmPFC cTBS was set as 35(SD=15). After calculating, 15 participants per group were identified. Considering the potential study dropout, the sample size was increased by 20%, that is, each group is determined to be 18, totally 72 patients. All patients provided written informed before they were enrolled in the study and all study procedures were conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the institutional review board and the ethics committee of Shanghai Mental Health Center.

2.2. Randomization and masking

Seventy-four patients who met the eligibility requirements were included (see CONSORT flow diagram in Figure S1). They were allocated to one of the four TBS groups in a 1:1:1:1 ratio (i.e. Group A, B, C, and D), according to the random number table by an independent study researcher. Patients and clinical raters were blinded to treatment status. To improve the blinding arrangement, patients were informed that they received the TBS, but they were blinded to the individual group assignment. Besides, patients were told not to uncover any treatment details with blinded raters. Study blind to patients was assessed after the treatment and patients were inquired if they know the type of stimulation (i.e. active or sham) they have received. Then all patients will be informed of their real treatment protocol. During the inquiry phase, no subjects thought they knew exactly which treatment group they were assigned to.

2.3. Treatment setting

2.3.1. Treatment as usual

The complete treatment duration is two weeks. All patients in the rehabilitation center received routine treatment in accordance with treatment standard of Chinese drug dependence rehabilitation center [21]. The treatment as usual included detoxification, psychological consultation, physical exercise, medical care, and anti-relapse education. No pharmacological treatments were received by patients during the present study.

2.3.2. rTMS treatment

The TBS treatment was delivered using the MagPro X100 device (MagVenture, Denmark). A total of 10 sessions over two weeks (one session/day and five days/ week) were administered to all patients. The TBS parameters in this study were based on the previous safe standard TBS parameters used in our lab [27], with 3-pulse 50-Hz bursts given every 200 ms. The resting motor threshold (RMT) was identified by using the standardized PEST procedure [29] and have also been reported in our previous study [30]. During the continuous TBS, a 60-*sec* train treatment (110% rMT, 900 total pulses per session) was given to the left vmPFC. During the intermittent TBS, a. 5-min train treatment (100% rMT, 2 s on and 8 s off, 900 pulses in total) was applied to the left DLPFC. The EEG international 10−20 system was used to identify the stimulation position (Fp1 for left vmPFC and F3 for left DLPFC). At the beginning of each treatment session, the patient will be asked to wear a cloth EEG cap, and the position of intervention was determined by locating the positions of the two electrodes (F3, Fp1). The figure-of-eight coil B70 was applied in the iTBS protocol. We used Cool D-B80 coil and 110% rMT in the cTBS procedure based on the following the known knowledge: (1) the scalp-to-cortex distance from the vmPFC is greater than other regions (i.e. DLPFC and motor cortex) [31]; (2) 110% is the safe and efficient dose in rTMS treatment for patients with depression; (3) the feasibility of 110% rMT cTBS treatment conducted on cocaine-dependent patients was validated previously [24]. During the TBS procedure in all groups, the output intensity was escalated from 80% rMT to the given intensity in each session to enhance tolerability. All patients could reach the specified intensity. A thin PE foam sheet (thickness = 0.5 mm) was placed between the coil and the target site to increase patient comfort (ShengTaiMing Tech, China). Patients in Group A received iTBS (900 pulses/session, 10 sessions); Group B received cTBS (900 pulses/session, 10 sessions); Group C received a combination of iTBS and cTBS (iTBS-900 + cTBS-900 pulses/session, 10 sessions; randomly assigned the starting order from iTBS or cTBS); while patients in Group D received the sham TBS protocol (900 pulses/session, 10 sessions, randomly assigned to applied the iTBS or cTBS). The placebo research coil (used in the sham condition) had a similar mechanical outline and auditory sensation to the B70, and its electric field was insufficient to induce valid neural activation.

2.3.3. Assessments and outcomes

The following clinical data were evaluated at baseline (T0): demographic data and drug use histories (including age, sex, age of first methamphetamine use, and accumulated years of methamphetamine use) by using the Chinese version of the Addiction Severity Index (ASI-C) [32]; depression symptoms by using Hamilton Depression Scale-17 (HAMD-17); anxiety symptoms by using Hamilton Anxiety Scale-14 (HAMA-14); sleep quality by using Pittsburgh Sleep Quality Index (PSQI); withdrawal symptoms by using Amphetamine Withdrawal Questionnaire (AWQ); and cognitive function using the Chinese version of the CogState Battery. The Cogstate is the computerized test with good reliability and validity [33]. Five tasks were assessed in present study: International shopping list task (ISL, verbal learning and memory), Groton maze learning task (GML, problem-solving/ error monitoring), Two back task (TWOB, working memory), Continuous paired association learning task (CPAL, spatial working memory), and Social emotional cognition task (SEC, social cognition). The following measures were conducted after two weeks of treatment (T2): HAMD-17, HAMA-14, PSQI, AWQ, and the CogState Battery.

Cue-induced craving for methamphetamine use was assessed by Visual Analog Scale ranging from 0 (i.e. no craving) to 100 (i.e. highest craving intensity ever experienced for methamphetamine). It was evaluated at T0, T1/2 (post 1/2 week of intervention), T1 (post 1 week of intervention), T3/2 (post 3/2 weeks of intervention), and T2 (See study procedure flow diagram in Figure S2). Each patient was asked to watch the methamphetamine-related picture for 5 min and then rated their craving. When watching pictures, patients were instructed to recall the last time they used methamphetamine. Patients with a reduction of $\geq$ 60% in craving were defined as treatment responders according to our previous study [21].

The primary outcomes were changes in craving scores. The secondary efficacy outcomes were the treatment response rate ($\geq$ 60% reduction in craving scores). Additional secondary outcome measures were changes in HAMD-17, HAMA-14, PSQI, AWQ, and the cognitive tasks from baseline to post two weeks' treatment. Safety was assessed by the rTMS operator after every session by recording adverse events such as headache, dizziness, and insomnia. All demographic data and outcome evaluations were collected by researchers who were also blinded to treatment settings.

2.4. Statistical analysis

One-way ANOVA (or Student's *t*-test) and chi-square test were used to compare the continuous and categorical data among the four groups. Non-parametric tests were used when assumption of

normality and/or homogeneity of variance was violated. Repeated-measure ANOVA was performed to figure out the potential effect on outcomes, with time as intragroup factors and treatment groups (Groups A vs B vs C vs D) as intergroup factors. To explore the relationship between treatment group and the timepoint of patients becoming the responder, Kaplan–Meier survival analysis (Breslow test) was conducted. The post-hoc pairwise comparison has also been performed. To investigate relationships between changes of the main outcome (i.e. craving) and secondary outcome (i.e. HAMA score, HAMD score, PSQI score, AWQ score, and Cogstate battery), Pearson's correlation analysis was conducted. Bonferroni correction was used for multiple tests.

Multiple linear regression was done with the percent of craving scores changes in 2 weeks as dependent factors, while age, years of education, treatment group (i.e. active TBS or sham TBS), baseline craving scores, drug use history (i.e. age at first drug use and accumulated years of drug use), baseline HAMA-14 scores, baseline HAMD-17 scores, baseline PSQI scores, baseline AWQ scores, and baseline cognitive performance as independent factors. Finally, the logistic regression model was performed to identify risk/protective factors for treatment response ($\geq$ 60% reduction in craving scores). The treatment group (Group D as reference group) was treated as an independent factor. All the other baseline variables were used as alternative independent variables. A backward method was used to screen the independent factors in logistic model. We also analyzed the interaction between treatment group and other potential predictors for which there was no significant interaction, and interactive factors were not included in the final regression model. All analyses were performed using SPSS 20.0. A P-value < 0.05 (2-sided tests) was set statistically significant. For those analyses with multiple tests, the statistically significant p-value should be less than 0.05/N (N equal to the number of comparisons).

2.5. Role of funders

The funders had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

3. Results

3.1. Participant's characteristics

Due to the personnel transfer within the rehabilitation center, one patient in Group B and one patient in Group C dropped out the study after receiving at least one session of treatment and were not available to continue the study. According to the Intention-To-Treat principle, all patients (n = 74) were included in the final analysis. Demographics and other clinical characteristics are presented in Table 1. No differences in age and education between four groups. Drug use characteristics, HAMA-14 scores, HAMD-17 scores, PSQI scores, and AWQ scores were similar in the four groups. Differences in SEC scores (p = 0.05) were recorded in all four groups.

3.2. Treatment outcomes

There was significant time effect (F = 35.77, df=1, $p < 0.01$) and time-by-group effect (F = 6.19, df=3, $p < 0.01$) on the main outcome (craving scores) (Fig. 1 and Table S1). The percent of craving scores changes from T0 to T2 were significantly differed across these four TBS groups ($p < 0.01$) (Table 2 and Figure S3). Post-hoc analysis identified that Group A (p = 0.04), Group B ($p < 0.01$), as well as Group C ($p < 0.01$) had significantly decreased in craving scores compared with Group D. Post-hoc analysis did not found significant difference among Group C, Group A (vs Group: p = 0.08,) and Group B (vs Group C: p = 0.48).

There were significantly more responders in Group A (55.60%), Group B (55.60%), and Group C (73.70%) than in Group D (10.50%) ($p < 0.01$) (Table 2). The Kaplan–Meier survival analysis also showed that average time from baseline to become responder differed among four groups (Group A: 1.69 $\pm$ 0.13 weeks, Group B: 1.42 $\pm$ 0.17 weeks, Group C: 1.21 $\pm$ 0.14 weeks; Group D: 1.90 $\pm$ 0.08 weeks. χ^2=16.01, df=3, $p < 0.01$). Post-hoc pairwise analysis indicated that three treatment groups had a shorter time of becoming responder compared with Group D (Group A, B, $C < D$), and Group C had a

Table 1
Demographic data, clinical variables of patients in four groups (n = 74).

	A DLPFC iTBS	B vmPFC cTBS	C DLPFC iTBS+ vmPFC cTBS	D Sham	F	df_{factor}	df_{error}	P
n	18	18	19	19				
Demographics variables								
Age (SD)	37.72 (4.28)	37.61 (5.33)	34.32 (5.40)	34.95 (4.78)	2.35	3	70	0.08
Years of education (SD)	10.17 (3.17)	10.06 (3.51)	11.11 (3.16)	11.32 (3.27)	0.70	3	69	0.58
Drug use characteristics								
Age at first drug use (SD)	26.61 (4.80)	27.33 (6.61)	27.05 (5.93)	28.95 (5.06)	0.61	3	70	0.61
Accumulated years of drug use (SD)	7.97 (3.65)	6.42 (3.77)	5.53 (3.65)	4.72 (3.43)	2.58	3	68	0.06
Cue-induced craving (SD)	42.67 (24.08)	48.00 (27.78)	50.68 (28.96)	39.37 (24.95)	0.70	3	70	0.56
Cognitive functions								
TWOB (SD)	1.00 (0.23)	1.07 (0.24)	0.90 (0.23)	0.94 (0.22)	1.98	3	68	0.13
GML (SD)	63.56 (19.49)	85.24 (46.05)	74.16 (28.29)	62.94 (22.59)	2.07	3	68	0.11
ISL (SD)	22.00 (4.19)	20.71 (5.93)	22.37 (3.89)	22.78 (3.32)	0.72	3	68	0.54
SEC (SD)	1.09 (0.11)	0.90 (0.27)	0.91 (0.23)	1.01 (0.25)	2.75	3	68	**0.05***
CPAL (SD)	87.78 (56.30)	89.47 (56.25)	79.89 (42.29)	89.17 (61.05)	0.13	3	68	0.94
Emotion								
HAMA-14 (SD)	7.33 (8.62)	6.71 (5.07)	6.63 (5.00)	6.64 (4.95)	0.06	3	69	0.98
HAMD-17 (SD)	5.65 (2.23)	4.29 (4.67)	5.21 (4.37)	7.58 (3.20)	0.30	3	68	0.82
Sleep Quality								
PSQI (SD)	4.17 (2.55)	4.33 (2.20)	5.11 (2.63)	4.11 (1.66)	0.75	3	69	0.53
Withdrawal symptom								
AWQ (SD)	8.17 (3.73)	7.67 (4.52)	8.58 (3.98)	7.68 (4.31)	0.21	3	70	0.89

† F value (ANOVA) was for all variable list in the table (age, year of education, age at first drug use, accumulated years of drug use, cue-induced craving, TWOB, GML, ISL, SEC, CPAL, HAMA-14, HAMD-17, PSQI, and AWQ).
TWOB= Two back task, GML= Groton maze learning task, ISL= International shopping list task, SEC= Social emotional cognition task, CPAL=Continuous paired association learning task, HAMA-14= Hamilton Anxiety Scale-14, HAMD-17= Hamilton Depression Scale-17, PSQI= Pittsburgh Sleep Quality Index, AWQ= Amphetamine Withdrawl Questionnaire, DLPFC=Dorsolateral Prefrontal Cortex, vmPFC= Ventromedial Prefrontal Cortex, iTBS= intermittent theta-burst stimulation; cTBS= continuous theta-burst stimulation.
* p<0.05.

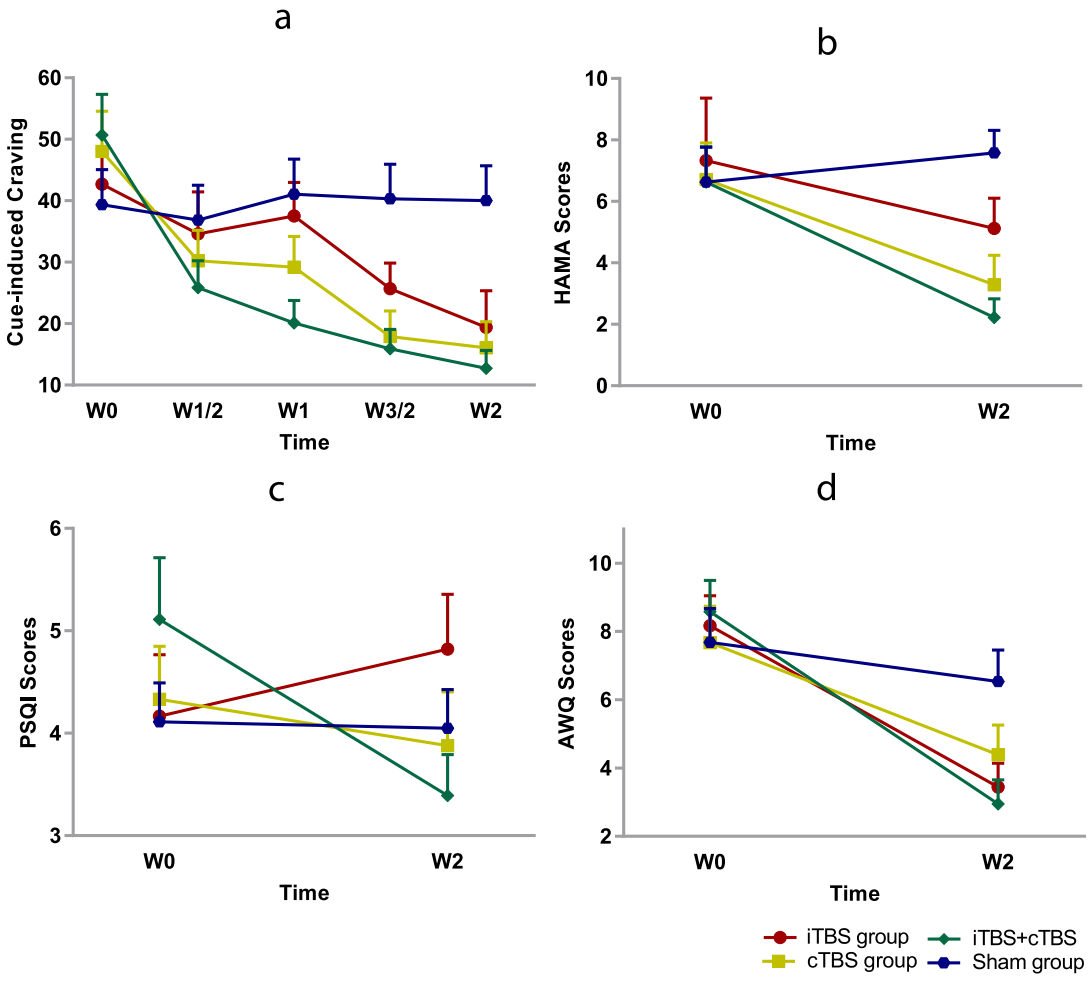


Fig. 1. Clinical outcome of four groups after treatment (n = 74). (a) changes of the cue-induced craving after treatment; (b) changes of the scores of HAMA-14 after treatment; (c) changes of the scores of HAMD-17 after treatment; (d) changes of the scores of AWQ after treatment; (e) changes of the scores of PSQI after treatment. Group *A* = iTBS targeting left DLPFC; Group *B* = cTBS targeting left vmPFC; Group *C* = *a* combination of iTBS targetingleft DLPFC and cTBS targeting left vmPFC. Group *D* = sham TBS group.

shorter period of becoming responder than Group A (χ^2=4.50, corrected p = 0.03) (Fig. 2).

In emotion aspect, after the two-week TBS treatment, a significant difference for time effect (F = 12.17, df=1, p < 0.01) and time-by-group effect (F = 2.15, df=3, p = 0.03) was found on HAMA-14 scores. HAMA-14 scores were significantly different in four group (p = 0.03) from T0 to T2 (Table 2). Post-hoc analysis identified that Group C had significantly decreased in HAMA- 14 scores compared with Group D (p = 0.04), while no differences were found among Group A, Group B, and Group C.

For sleep quality and withdrawal symptom aspects, a significant time-by-group effect (F = 2.79, df=3, p < 0.05) was recorded on the PSQI scores. In addition, there was significant time (F = 46.55, df=1, p < 0.01) and time-by-group effect (F = 3.31, df=3, p = 0.03) on AWQ scores. It was also demonstrated that changes of PSQI scores (p<0.05) and AWQ scores (p = 0.03) were different among four groups (p < 0.05) (Table 2). Post-hoc analysis suggested that Group C had significantly decreased in AWQ scores compared with Group D (p = 0.03), while no difference was found between other groups. Besides, Group C had significantly decreased in PSQI scores than Group A (p = 0.04) when performing the post-hoc analysis.

3.3. Correlations between craving and other secondary outcomes

Pearson's correlation demonstrated significant positive correlations between changes of craving scores and changes of HAMA-14 scores (r = 0.37, corrected p = 0.02). Significant positive correlations between changes of craving scores and changes of AWQ scores (r = 0.38, corrected p = 0.01) were also recorded.

However, there were no significant correlations between changes in craving scores and other variables (i.e. HAMD-17, PSQI scores, and Cogstate battery).

3.4. rTMS response prediction

Multiple linear regression (F = 2.45, $df_{regression}$=15, $df_{residual}$=54, p = 0.01) presented that longer accumulated years of drug use (t=−2.11, df=54, p = 0.04) predicts lower percent of craving changes after two weeks of treatment. Besides, higher baseline HAMD scores (t = 2.69, df=54, p = 0.01) and CPAL scores (t = 2.53, df=54, p = 0.01) predict higher percent of craving changes. Patients in real TBS treatment group have higher percent of craving changes than the sham TBS group (t=−4.28, df=54, p < 0.01). The other variables were insignificant, including age, education, age at first methamphetamine use, baseline cue-induced craving, and scores of HAMA-14, PSQI, TWOB, GML, ISL, SEC.

Logistic regression (AUC=0.82, 95%CI=0.71−0.92; Sensitivity=0.71; Specificity=0.80) showed that baseline HAMD-17 scores (OR=1.16), baseline CPAL scores (OR=1.02), and TBS treatment group (i.e. Group A vs Group D: OR = 32.70; Group B vs Group D: OR = 27.24; Group C vs Group D: OR=48.08) significantly predicted the treatment responders after the two-week TBS treatment (Table 3).

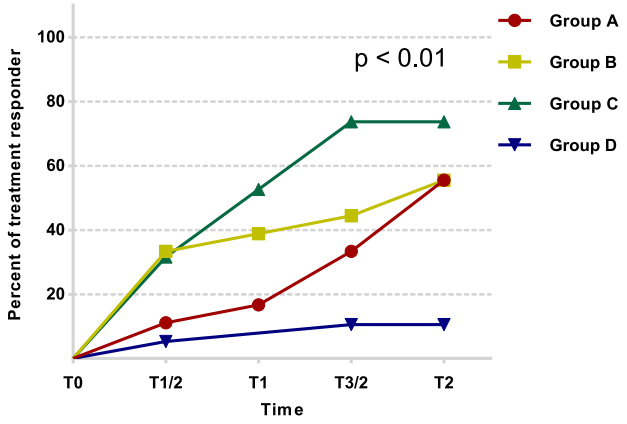
Table 2
Changes of treatment outcomes in four groups (n = 74).

	A DLPFC iTBS	B vmPFC cTBS	C DLPFC iTBS + vmPFC cTBS	D Sham	F/χ^2	df_{factor}	df_{error}	P	Group Difference
n	18	18	19	19					
Main outcome									
% △Cue-induced craving, (SD)	50.25% (53.58%)	65.01% (36.80%)	70.64% (28.94%)	−1.30% (55.70%)	9.50	3	70	**0.00002****	A,B,C>D
Responders (%, Week 2)	10 (55.60%)	10 (55.60%)	14 (73.70%)	2 (10.50%)	16.51	3[α]	–	**0.0009****	A,B,C>D
Second outcomes									
Cognitive functions									
△TWOB (SD)	−0.04 (0.39)	−0.06 (0.20)	−0.15 (0.27)	−0.14 (0.23)	0.66	3	66	0.58	
△GML (SD)	3.67 (18.16)	9.00 (18.16)	1.22 (21.53)	3.67 (17.83)	0.49	3	66	0.69	
△ISL (SD)	0.22 (3.92)	0.13 (5.73)	−1.17 (4.83)	0.72 (4.10)	0.54	3	66	0.66	
△SEC (SD)	0.06 (0.15)	−0.02 (0.17)	−0.01 (0.10)	−0.02 (0.23)	0.87	3	66	0.46	
△CPAL (SD)	−6.11 (36.47)	−16.38 (41.05)	−12.83 (53.02)	6.67 (46.22)	0.90	3	66	0.45	
Emotion									
△HAMA, mean(SD)	2.35 (8.10)	4.13 (6.44)	4.56 (5.77)	−0.95 (3.03)	3.15	3	66	**0.03***	C>D
△HAMD, mean(SD)	1.82 (6.66)	−0.31 (4.45)	2.39 (3.65)	0.58 (3.56)	1.14	3	66	0.34	
Sleep Quality									
△PSQI, mean (SD)	−0.47 (2.40)	0.29 (1.96)	1.72 (3.27)	0.05 (1.47)	2.79	3	67	**0.05***	C>A
Withdrawal symptom									
△AWQ, mean (SD)	4.72 (4.17)	3.28 (5.27)	5.63 (4.00)	1.16 (5.08)	3.31	3	70	**0.03***	C>D

[†] F value (ANOVA) was for the variable list in the table (%△cue-induced craving, △TWOB, △GML, △ISL, △SEC, △CPAL, △HAMA-14, △HAMD-17, △PSQI, and △AWQ). Chi-squared value was for responders.
[α] degrees of freedom for the chi-square test.
TWOB= Two back task, GML= Groton maze learning task, ISL= International shopping list task, SEC= Social emotional cognition task, CPAL=Continuous paired association learning task, HAMA-14= Hamilton Anxiety Scale-14, HAMD-17= Hamilton Depression Scale-17, PSQI= Pittsburgh Sleep Quality Index, AWQ= Amphetamine Withdrawl Questionnaire, DLPFC=Dorsolateral Prefrontal Cortex, vmPFC= Ventromedial Prefrontal Cortex, iTBS= intermittent theta-burst stimulation; cTBS= continuous theta-burst stimulation.
* p<0.05.
** p<0.01.

3.5. Safety outcomes

No serious adverse events were reported in the present study. All reported side effects were tolerable and mild and ameliorated gradually during the treatment duration. The side effect emerging in patients included headache, insomnia, and dizziness. No significant differences, like headache (p = 1.00), insomnia (p = 0.54), and dizziness (p = 0.61), were identified in four groups, respectively (Table S2).



Treatment responder

Group A	0	2	3	6	10
Group B	0	5	6	8	10
Group C	0	6	10	14	14
Group D	0	1	1	2	2

Fig. 2. Kaplan–Meier and Breslow analysis for response of four treatment groups (n = 74). Group A = iTBS targeting left DLPFC; Group B = cTBS targeting left vmPFC; Group C = a combination of iTBS targetingleft DLPFC and cTBS targeting left vmPFC. Group D = sham TBS group.

4. Discussion

To our knowledge, this is the first randomized controlled study comparing the efficacy of TBS treatment targeting on DLPFC and/or targeting on vmPFC. Our results showed that TBS treatment targeting on DLPFC and/or vmPFC is well-tolerated for patients with MUD. The iTBS treatment on DLPFC, cTBS treatment on vmPFC, as well as a combination of both iTBS and cTBS treatment produced a significant craving decrease than sham group. Patients in Group C experienced the highest response rate of 73.7% than other three groups. Baseline depression symptoms, spatial working memory, and assigned treatment group were significant predictors of treatment response of TBS treatment.

One of the core challenges in treating substance use disorder is the high risk to relapse. Studies have shown that one possible mechanism of relapse is a strong desire for drugs triggered by drug-related cues or background [34]. Clinical studies have also shown that cue-induced cravings, electrophysiological changes, and imaging changes are important indicators in predicting relapse in substance-dependent patients [35-37]. The present study found that Group A significantly decreased cue-induced craving after a two-week treatment, which is consistent with our previous study [27]. Interestingly, Group B has a better but non-significant craving decrease effect compared with Group A. Previous study indicated that cTBS targeting vmPFC diminished the evoked BOLD signal in vmPFC and insula, regions correlated with drug cue reactivity [24]. It may partially explain the treatment effect of vmPFC cTBS on craving. The possible interpretation for this better but not significant effect on craving decrease may attribute to the theoretical basis that vmPFC is one direct region involving in formation of cue-induced craving, while DLPFC is the region within the executive network [38, 39]. We also found that Group C exhibited the highest response rate and patients in Group C had the shortest periods of becoming the responder. Unlike the paradigm applying on a single region, stimulating the regions of two neural networks (i.e. executive network and limbic network) may bring a cumulative effect on patients' symptoms. Specifically, the impairment of the executive control function is common in patients

Table 3
Logistic regression factors potentially predicting treatment efficacy of 2-week theta-burst treatment on craving in methamphetamine-dependent patients.

	B	S. E	Wald	df	P-value	OR	95% CI for OR	
							Lower	Upper
Accumulated years of drug use	−0.15	0.09	2.62	1	0.11	0.86	0.72	1.03
Baseline HAMD-17 scores	0.15	0.07	434	1	**0.04***	1.16	1.01	1.33
Baseline GML scores	−0.02	0.01	2.96	1	0.09	0.98	0.95	1.00
Baseline CPAL scores	0.02	0.01	4.88	1	**0.03***	1.02	1.00	1.03
Groups (Reference: Sham group)			12.34	3	**0.01****			
DLPFC iTBS vs. Sham	3.49	1.14	9.44	1	**0.002****	32.70	3.53	302.48
vmPFC cTBS vs. Sham	3.30	1.14	8.39	1	**0.003****	27.24	2.91	254.87
DLPFC iTBS+ vmPFC cTBS vs. Sham	3.87	1.13	11.76	1	**0.001****	48.08	5.26	439.74

GML= Groton maze learning task, CPAL=Continuous paired association learning task, HAMD-17= Hamilton Depression Scale-17, DLPFC=Dorsolateral Prefrontal Cortex, vmPFC= Ventromedial Prefrontal Cortex, iTBS= intermittent theta-burst stimulation; cTBS= continuous theta-burst stimulation.
* p<0.05,.
** p<0.01.

with MUD due to the neurotoxic effect of methamphetamine [40]. DLPFC rTMS had been proved to improve executive functions, and changes in executive function were associated with craving [21]. These facts may interpret why Group C had the relatively higher but not significantly effective impact on craving in the three real treatment groups. Better efficacy of Group C may also due to dose-effect (1800 pulse/session in Group C and 900 pulse in other groups) [41]. However, it should also be noted that the stimulation effect could be reversed by prolonging the treatment duration [42]. Overall, whether the combined treatment effect of vmPFC cTBS and DLPFC iTBS is better than the single treatment protocol, and whether the combined treatment effect is related to the cumulative effect of the two neural network activities or only depends on the effect of dose remain unknown and worthy of further study .

No difference among four groups was found in all five aspects of cognitive function (verbal learning, problem-solving, working memory, spatial working memory, and social cognition) in present study. It is known that DLPFC is the key area involving in cognition. On the other hand, medial prefrontal cortex also participates in emotion processing, working memory maintenance, and performance monitoring [43, 44], which may be the reason for comparable effect of DLPFC iTBS and vmPFC cTBS. Group C were significantly more effective in anxiety improvement than Group D, while Group A are comparable to Group B. Normally, a complex network including vmPFC, anterior, amygdala, and several other related brain regions regulate the emotion [45]. Increasing activity of vmPFC was correlated with severer emotion disruption [46, 47], thus decreasing bold activity of vmPFC by vmPFC cTBS can bring the amelioration of emotional symptoms. For DLPFC, existing studies have already identified the anti-anxiety effect of rTMS targeting DLPFC [48]. Therefore, Group C had the relatively better anti-anxiety effect than Group D and the other two real TBS groups (Group A and Group B) were comparable. Changes in anxiety scores and withdrawal symptoms scores after treatment were positively associated with changes in craving. This result is not surprising, as many theoretical frameworks have emphasized the role of emotions and withdrawal symptoms in formation and development of addiction [49-51].

The predictors of the response rate were also investigated in our study. At present, rTMS is mostly applied in patients with higher clinical severity according to the FDA recommendation. For example, FDA approved rTMS for treatment-refractory depression and obsessive-compulsive disorder. Our multiple linear regression indicates that accumulated years of methamphetamine use are negatively associated with changes of craving. That is to say, a long period of methamphetamine use history was associated with worse treatment results, and it may suggest that the severity of SUD is a significant predictor for better TBS responses. This result is inconsistent with recommendations of the FDA, but similar results have also been found in previous studies [52]. Therefore, it is necessary to further analyze the mechanism, which is significant to help clinicians make the optimal therapeutic schedule. Besides, we also found that patients with higher HAMD-17 scores were more likely to be responsive in this study. However, our previous study suggested that MUD patients with milder emotional symptoms were more likely to appear in the responder group after DLPFC iTBS treatment [21]. Since both Group B and Group C (63% of all recruited patients) in this study involved vmPFC cTBS treatment setting, it may prompt us that vmPFC region is more sensitive to substance-dependent patients (e.g. methamphetamine) accompanied by severe emotional symptoms, while DLPFC iTBS is more useful for patients with mild emotion symptoms. In fact, emotional symptoms are closely associated with abnormal hyperactivation of vmPFC [53]. It is worth noting that all subjects included in this study did not meet the diagnostic criteria for depression. The average HAMD score of the sample is not high (i.e. average score is less than 8). Therefore, this study cannot determine the therapeutic response of the real TBS stimulation in the treatment of methamphetamine-dependent individuals with severe depressive symptoms. In addition, the depressive symptoms of the patients may be related to the existence of withdrawal symptoms and psychological distress [54, 55]. Taking these factors together may help to find effective predictors more accurately. Before the definite conclusion, more clinical and basic research on substance-dependent patients with different symptom clusters (e.g. cognitive and emotion) will be demanded in the future.

There are inevitably some limitations to this study. First, future study is needed for combining functional brain imaging technologies to further verify activities in brain area of executive control network and limbic circuit before and after treatment, which is lacking in our study. Secondly, this study evaluated the outcomes over a short period of time. Future work should be applied to investigate the durability of efficacy under different stimulation paradigm given to chronic and repeating feature of MUD. Thirdly, we used 10−20 EEG system to locate the DLPFC and vmPFC of patients without incorporating shape and size of individuals' heads into thinking; however, previous studies have suggested the feasibility to locate the stimulation area through the 10−20 EEG System [56]. MRI-guided neuronavigation can help positioning the frontal region with better accuracy and efficacy. Finally, A major limitation was that the sham condition our study adopted was not the optimal choice. We did not directly ask patients about their guesses about their group neither. We have tried to decrease the potential deviation such as informing patients not to discuss the details of treatment with each other and improving the therapeutic comfort by several methods. Although we have done several steps to optimize the blinding method, this study still has a common problem in the rTMS clinical trials, which is the mild pain and discomfort of treatment may weaken the blinding method. In the

future, it is significant to carry out multicenter clinical studies with more comprehensive blinding methods and larger sample sizes.

In conclusion, our study indicated that both DLPFC iTBS and vmPFC cTBS treatment were tolerable and safe. Comparing to the single DLPFC iTBS treatment protocols, the rTMS protocols involving vmPFC cTBS are potential to be the optimized paradigms. The spatial memory performance and depression indicators were significant predictors of TBS treatment on vmPFC and/or DLPFC in MUD patients.

Contributors

TZC, HS, HFJ, XTL, QYW, HYT, JYZ, and HJG performed research; TZC, HS, NZ, JD, and HFJ analyzed data; MZ, TZC, HS designed research. TZC and HS drafted of the manuscript together. All authors have contributed to the interpretation of data, critically revised the manuscript, and approved the final version of the manuscript.

Data sharing statement

The original data are available from the corresponding author on reasonable request and with consent from the Institutional Review Board (IRB).

Declaration of Competing interest

All authors declared no competing interests for this work.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ebiom.2020.103027.

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