




Deep magnetic stimulation targeting the medial prefrontal and anterior cingulate cortices for methamphetamine use disorder: a randomised, double-blind, sham-controlled study

Di Zhao ¹, Ningning Zeng,¹ Hang-Bin Zhang,¹ Yi Zhang ¹, Jiatong Shan,² Huichun Luo ¹, Abraham Zangen,³ Ti-Fei Yuan^{1,4}

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For numbered affiliations see end of article.

Correspondence to

Dr Ti-Fei Yuan;
ytf0707@126.com

Craving is a key component of substance use disorders (SUDs).¹ In recent decades, repetitive transcranial magnetic stimulation (rTMS) has emerged as a promising treatment for individuals with SUDs by reducing their drug cravings and drug-associated cues, including methamphetamine, heroin, cocaine, nicotine and alcohol.^{2–7} Recently, the transdiagnostic consistency of the medial prefrontal cortex (MPFC)⁸ and anterior cingulate cortex (ACC)⁹ as neural substrates underlying cue reactivity was proposed. A recent study using high-density, 128-channel electroencephalography (EEG) reported that beta-band (13–30 Hz) activity in the MPFC could serve as a neurophysiological signature for the incubation of cravings in individuals with methamphetamine use disorder (MUD).¹⁰ Previous neuroimaging evidence has shown that the MPFC and ACC are critical neural substrates that generate cravings in patients with MUD.¹¹ Recently, the MPFC and ACC were posited as promising targets for the deep transcranial magnetic stimulation (TMS) treatment of SUD owing to their involvement in reward, emotions and habit formation.^{12 13} However, the potential effects of rTMS to the MPFC and ACC on the cravings of patients with MUD have yet to be elucidated.

Several studies on substance abuse treatment have reported the use of the H7 coil (Brainsway, Jerusalem, Israel), a TMS coil that can selectively target the MPFC and ACC.^{12 13} In the present study, chronic rTMS was delivered via the H7 coil to the MPFC and ACC of subjects with MUD (figure 1A). We hypothesised that modulating the methamphetamine cue-processing circuitry by targeting the MPFC might reduce cue-induced cravings

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous research has established the significance of cravings in substance use disorders (SUDs) and the potential of repetitive transcranial magnetic stimulation (rTMS) in reducing these cravings. Key brain regions, such as the medial prefrontal cortex (MPFC) and anterior cingulate cortex (ACC), are implicated in craving generation, making them promising rTMS targets.

WHAT THIS STUDY ADDS

⇒ This study demonstrates that chronic rTMS targeting the MPFC and ACC significantly reduces cue-induced cravings in individuals with methamphetamine use disorder (MUD) and modulates neural oscillation signatures, specifically reducing MPFC beta oscillation in the 10 Hz group.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study could influence future research and clinical practice by providing evidence for the potential use of rTMS in addiction treatment and highlighting the relevance of neural network changes in addiction pathology.

and investigate the potential changes in the large-scale EEG neural network and neural oscillation signature (eg, MPFC beta oscillation) of cravings that may occur in response to brain stimulation treatment.

The double-blind, sham-controlled, randomised trial was registered at ClinicalTrials.gov (NCT04202926). In accordance with the Declaration of Helsinki, all subjects provided written informed consent and voluntarily participated in the study.

The criteria for inclusion in this study are as follows:

- ▶ Individuals over 18 years of age with a main diagnosis of methamphetamine dependence (*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*) over the last 5 years. Prior to admission into the long-term residential treatment programme, their urine drug screening tests must have been positive. Since then, the subjects with MUD have been in abstinence.
- ▶ No history of major medical illness and severe psychiatric disorders, such as schizophrenia, bipolar disorder and major depression.

The exclusion criteria were only classic contraindications to TMS treatment.

- ▶ A history of epilepsy, brain injury, cardiovascular conditions, or skull implants that can interfere with TMS (eg, a metal implant).
- ▶ Presence of a pacemaker.
- ▶ Concurrent participation in another pharmacotherapy or non-drug therapy.

The sample size in this study was determined through a rigorous power analysis conducted prior to data collection. After the screening, the patients were randomised and classified into two groups: one receiving 10 Hz rTMS and the other receiving sham stimulation. The random allocation sequence was generated through a computerised randomisation procedure. Twenty-three male subjects who completed the pre-test and post-test were included in the analysis (figure 1B). Adherence to the treatment protocol was consistent between the two groups. No significant differences in adherence rates were observed during the study, minimising the potential influence of adherence on the results. The demographic and clinical characteristics of the subjects are summarised in table 1. The baseline demographic and clinical data did not indicate statistically significant distinctions between the study groups. An overview of the study design is shown in figure 1C. High-frequency rTMS (10 Hz, 100% resting motor threshold, 3 s ON and 17 s OFF for 16.67 min; 1500 pulses) or sham TMS (a sham coil) was applied to the MPFC and ACC with a Magstim Rapid² stimulator (Magstim Company, Whitland, UK) using the H7 coil (Brainsway). The treatment consisted of five active or sham sessions per week over a period of 3 weeks. During treatment, the coil was positioned 5 cm anterior to the motor spot of the leg to target the MPFC and ACC. The inactive sham coil replicated the noise and head sensations of the active coil. The subjects were assigned a coded magnetic card that determined the type of coil being activated (active/sham) in a blinded manner via an interactive web-based randomisation system. In the pre-test and post-test, cue-induced craving measures were administered as in our previous study, with subjects rating their cravings after watching a 5-minute video of methamphetamine consumption.¹⁰ Resting-state EEGs were collected using the 128-channel EEG Geodesic Net Amps system (Electrical Geodesics, Eugene, Oregon, USA; www.egi.com). No adverse effects were reported in the study.

The primary endpoint is the change in cue-induced cravings from baseline to week 4, following 15 treatments

administered over 3 weeks. Secondary endpoints include changes in the MPFC global functional connectivity at 10 Hz (alpha band) and MPFC beta (13–30 Hz) oscillations from the pre-test to the post-test. The Brainstorm toolbox (<http://neuroimage.usc.edu/brainstorm>) and Fieldtrip toolbox (<https://www.fieldtriptoolbox.org>) were used for source localisation. Using the minimum norm estimation approach, we performed source localisation analyses using the same head model and lead-field matrix as in our previous study. We filtered the current density in the source space and calculated the spectral power for different carrier bands: theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz) and gamma (30–50 Hz).¹⁰ For each subject, the current source density for the beta band was extracted from the cortical clusters. We also computed the global connectedness of the MPFC, which reflected the average connectivity between the MPFC and all other brain parcellations.^{14 15} All statistical analyses were performed using SPSS V.25 and R V.4.1.2. Statistical significance is defined as a two-sided $p < 0.05$.

Twenty-three subjects completed 3 weeks of treatment (10 Hz group, $n=12$; sham group, $n=11$). For cue-induced cravings, the significant effects of group ($F_{(1, 21)}=9.736$, $p < 0.001$), time ($F_{(1, 21)}=16.65$, $p < 0.001$) and group×time interaction across subjects with MUD ($F_{(1, 21)}=5.662$, $p=0.027$) were observed. Craving scores significantly decreased from the pre-test to post-test in the 10 Hz group ($n=12$; Wilcoxon matched-pairs signed-rank test: $p=0.008$; figure 1D), while no improvement was observed in the sham group ($n=11$; Wilcoxon matched-pairs signed-rank test: $p=0.125$; figure 1E). The secondary outcome was the EEG activity of the MPFC (functional connectivity: weighted phase-lag index¹¹; current source density at the source level). For MPFC connectedness (global connectivity), the significant effects of time ($F_{(1, 20)}=10.91$, $p=0.003$) and group×time interaction across subjects with MUD ($F_{(1, 20)}=13.93$, $p=0.001$) were observed. Only the active rTMS-induced modulation of MPFC connectedness in the alpha band was significant (10 Hz group: Wilcoxon matched-pairs signed-rank test, $p=0.003$; sham group: Wilcoxon matched-pairs signed-rank test, $p=0.234$).

The activity of MPFC beta oscillations significantly decreased in the 10 Hz group ($n=11$; one subject was excluded owing to excessive artefacts; Wilcoxon matched-pairs signed-rank test: $p=0.007$), while the change in the MPFC beta activity of the sham group was insignificant ($n=11$; Wilcoxon matched-pairs signed-rank test: $p=0.425$). Moreover, in the 10 Hz group, the baseline MPFC synchronisation for the beta band was positively correlated with the percentage change in the cue-induced craving score ($r=0.658$, $p=0.028$) (figure 1G). The changes in beta activity in the MPFC were positively correlated with the percentage changes in the cue-induced craving scores (change percentages: $r=0.913$, $p < 0.001$, figure 1H; change: $r=0.866$, $p=0.001$, figure 1I).

In summary, our findings show that rTMS with a midline prefrontal target (ie, MPFC) significantly

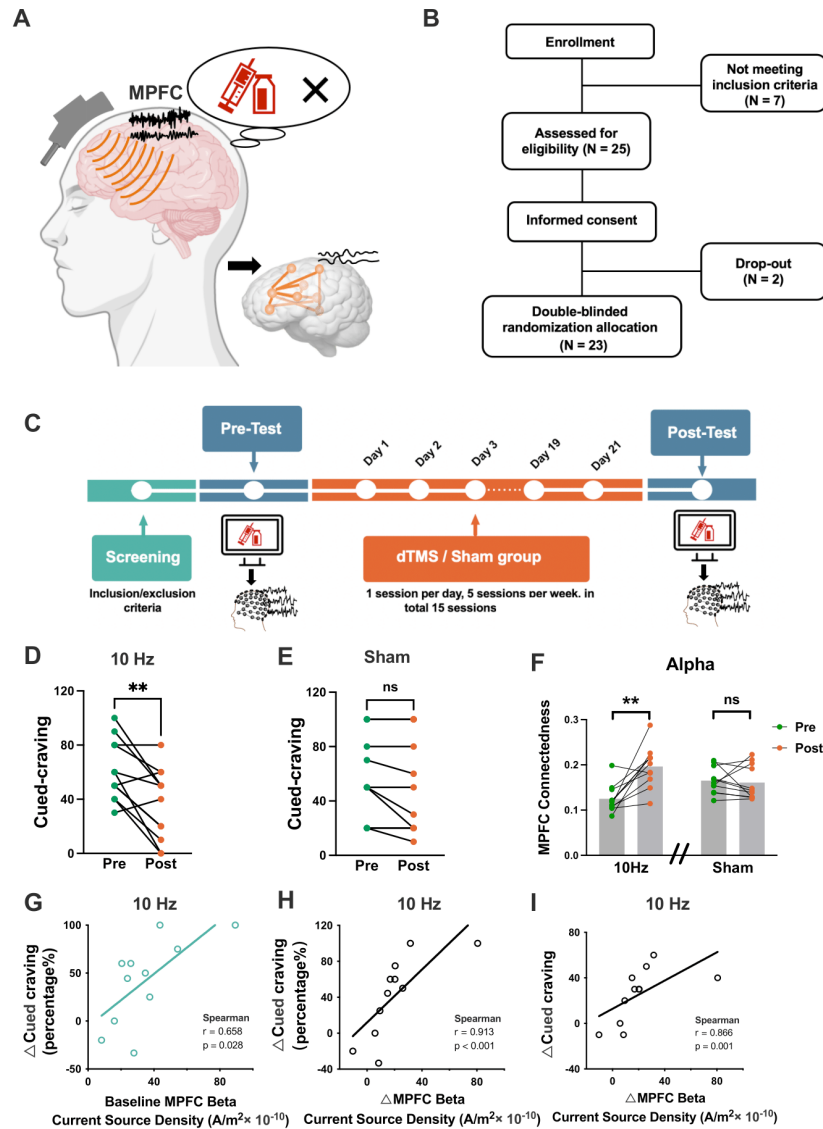


Figure 1 (A) Schematic illustration of rTMS with an H7 coil targeting the MPFC and anterior cingulate cortex in individuals with methamphetamine use disorder. (B) Flow diagram of the enrolment and eligibility of subjects. Seven subjects did not meet the inclusion criteria: two failed to make contact after the screening visit, three were excluded because they failed the metal safety screening and two were currently taking prescription medications. (C) Study timeline and assessments. Cue-induced craving and resting-state, 128-channel EEG recordings were collected during the pre-test and post-test. High-frequency rTMS (10 Hz, strength at 100% resting motor threshold, 3 s ON, 17 s OFF for 16.67 min; 1500 pulses) or placebo rTMS (using a sham coil to produce similar acoustic and scalp sensations) was used to stimulate the MPFC. The active or sham treatments were administered five times per week over a period of 3 weeks. (D) The cue-induced craving scores significantly decreased in the 10 Hz group ($n=12$; Wilcoxon matched-pairs signed-rank test: $p=0.008$ (** $p<0.01$)). (E) The changes in cue-induced craving scores in the sham group were insignificant ($n=11$; Wilcoxon matched-pairs signed-rank test: $p=0.125$). (F) High-frequency (10 Hz) rTMS targeted the MPFC-induced modulation of the MPFC network connectivity in the alpha band (10 Hz group: Wilcoxon matched-pairs signed-rank test, $p=0.003$; sham group: Wilcoxon matched-pairs signed-rank test, $p=0.234$) (** $p<0.01$). (G) Higher pre-test MPFC beta activity predicted a greater cue-induced craving decrease in the 10 Hz group ($r_{\text{spearman}}=0.658$, $p=0.028$). (H) The percentage changes in the MPFC beta activity were positively correlated with those of cue-induced craving scores in the 10 Hz group ($r_{\text{spearman}}=0.913$, $p<0.001$). (I) Changes in MPFC synchronisation for the beta band were positively correlated with changes in the 10 Hz group ($r_{\text{spearman}}=0.866$, $p=0.001$). The authors were permitted to reuse the figure. dTMS, deep transcranial magnetic stimulation; EEG, electroencephalography; MPFC, medial prefrontal cortex; ns, no significance; rTMS, repetitive transcranial magnetic stimulation.

Table 1 Descriptive statistics of the study participants

	10 Hz group (n=12)	Sham group (n=11)	P value
Age (years)	41.3 (7.5)	40.9 (7.2)	0.890
Male/female	12/0	11/0	NA
Education (years)	8 (3.3)	9.7/3.2	0.898
DSM-5	9.7 (1.6)	7.3 (2.7)	0.129
Total years of methamphetamine use	9.5 (3.7)	9.5 (4.2)	0.898
Age of methamphetamine initiation	32.8 (9.3)	29.6 (7.8)	0.626
Duration of current abstinence (days)	396 (236)	342 (183)	0.626
Methamphetamine use before abstinence (g/month)	17.2 (13.5)	16.6 (10.8)	0.898

Values are presented as mean (SD).

Mann–Whitney test was used to compare age, education, total years of methamphetamine use, age of methamphetamine initiation, duration of current abstinence and amount of methamphetamine use before abstinence.

DSM-5: number of criteria met by symptoms diagnosed.

DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; NA, not applicable.

reduced the cue-induced craving for methamphetamine. Using a high-density EEG and source localisation analysis approach, we found that stimulating the MPFC increased the global connectedness for the alpha band (10 Hz), indicating the efficacy of the treatment from a network perspective. These findings also indicate the involvement of large-scale functional network modulation (online supplemental figure S1) in the MUD pathology and TMS mechanism of action, as the MPFC beta activity was selectively altered in patients with MUD with decreased cue-induced craving. As a result of 10 Hz rTMS, the MPFC beta activity decreased, which was associated with reduced cravings. The high-definition EEG (HD-EEG) source imaging results should be interpreted with caution owing to the small number of subjects in which altered MPFC activity was observed; however, these are compelling at a mechanistic level. Accordingly, increased MPFC connectivity could reflect top-down control over drug-seeking¹⁶ and indicate the strengthened influence of inhibition over methamphetamine craving and use. Future randomised controlled clinical trials with larger sample sizes, female subjects and long follow-up periods are required to evaluate the application of this technique in the addiction community.

Author affiliations

¹Shanghai Key Laboratory of Psychotic Disorders, Brain Health Institute, National Center for Mental Disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China

²Department of Arts and Sciences, New York University Shanghai, Shanghai, China

³Department of Life Sciences, Ben-Gurion University, Beer Sheva, Israel

⁴Co-Innovation Center of Neuroregeneration, Nantong University, Nantong, China

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Competing interests None declared.

Patient consent for publication Obtained.

Ethics approval This study involves human participants and was approved by the Research Ethics Board and the local safety monitoring board (2019-04R). Participants gave informed consent to participate in the study before taking part.

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ORCID iDs

Di Zhao <http://orcid.org/0000-0002-6830-8920>

Yi Zhang <http://orcid.org/0000-0002-2643-067X>

Huichun Luo <http://orcid.org/0000-0002-7833-1358>

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Di Zhao is an associate researcher at Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine (2021–present) in China. She obtained her doctoral degree through a joint program between East China Normal University in China (2013–2015) and the University of California, San Francisco, USA (2015–2017). She completed her postdoctoral training at the School of Medicine, Shanghai Jiao Tong University in China (2018–2021). She currently serves as the Deputy Secretary-General of the Cognitive Science Society of China, Cognitive and Brain Regulation Sub-Association. Her main research interests include uncovering abnormalities in the brain's circuitry associated with various psychiatric conditions, utilising both extracranial and intracranial neurophysiological data. In the clinical realm, she employs non-invasive brain stimulation techniques (transcranial magnetic stimulation/transcranial electrical stimulation) to specifically target cognitive functions and devise personalised interventions for individuals in clinical populations.