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

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Craving is a key component of substance use disorders (SUDs). 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. Recently, the transdiagnostic consistency of the medial prefrontal cortex (MPFC) and anterior cingulate cortex (ACC) 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). Previous neuroimaging evidence has shown that the MPFC and ACC are critical neural substrates that generate cravings in patients with MUD. 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. 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. 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 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. 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). 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. 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 index; 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_{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_{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_{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.
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.

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Figure S1 Large-scale EEG neural network changes in response to 10Hz TMS over MPFC and ACC in different carrier bands (A. Theta band: 4-8Hz; B. Alpha band: 8-13Hz; C. Beta band: 13-30Hz; D. Gamma band: 30-50Hz). The horizontal axis represents 31 brain regions in different functional networks from source localization as follows: 1. VIS Visual Network: Left Visual Area 1 (LV1), Right Visual Area 1 (RV1); 2. SMN Somatosensory Network: Left Somatosensory Cortex (LSMC), Right
Somatosensory Cortex (RSMC); 3. DAN Dorsal Attention Network: Left Inferior Frontal Junction (LIFJ), Right Inferior Frontal Junction (RIFJ), Left Intraparietal Sulcus (LIPS), Right Intraparietal Sulcus (RIPS), Left Frontal Eye Fields (LFEF), Right Frontal Eye Fields (RFEF), Left Supplemental Eye Fields (LSEF), Left Supplemental Eye Fields (LSEF); 4. DMN Default Mode Network: Posterior Cingulate Cortex (PCC), Medial Prefrontal Cortex (MPFC), Left Angular Gyrus (LANG), Right Angular Gyrus (RANG); 5. FPN Frontoparietal Control Network: Left Posterior Middle Frontal Gyrus (LPMFG), Right Posterior Middle Frontal Gyrus (RPMFG), Inferior Parietal Lobule (LIPL), Right Inferior Parietal Lobule (RIPL), Left Orbital Gyrus (LORB), Right Orbital Gyrus (RORB), Left Middle Temporal Gyrus (LMTG), Right Middle Temporal Gyrus (RMTG); 6. VAN Ventral Attention Network: Left Anterior Middle Frontal Gyrus (LAMFG), Right Anterior Middle Frontal Gyrus (RAMFG), Left Insula (LINS), Right Insula (RINS), Dorsal Anterior Cingulate Cortex (DACC), Left Supramarginal Gyrus (LSUP), Right Supramarginal Gyrus (RSUP). The vertical axis represents the significance of changes in brain regions before and after 10Hz MPFC and ACC intervention (dashed line: p=0.05, uncorrected).