

Letters

RESEARCH LETTER

Targeting Withdrawal Symptoms in Men Addicted to Methamphetamine With Transcranial Magnetic Stimulation: A Randomized Clinical Trial

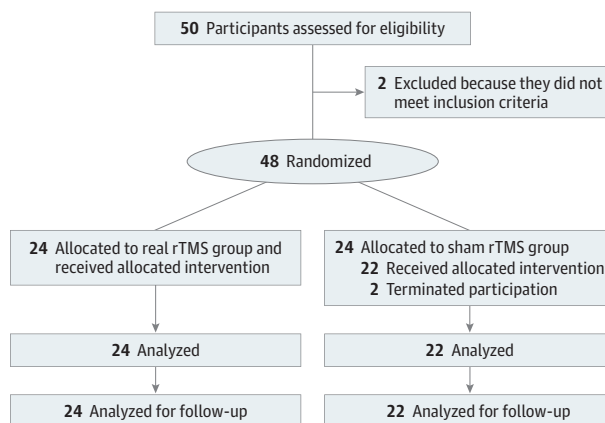
Drug withdrawal is associated with aversive experiences, which promotes relapse.¹ Different neurotransmitters, neuropeptides, signal transduction pathways, and brain regions (especially the nucleus accumbens) have been implicated in the occurrence of withdrawal syndrome during abstinence from addictive drugs.² Withdrawal from methamphetamine results in fatigue, irritability, disturbed sleep, exhaustion, and symptoms of depression and anxiety, which might last for months. Currently, limited pharmaceutical tools are available for detoxification from methamphetamine; vitamins, antidepressants, and antipsychotics have been used to ameliorate withdrawal symptoms in clinical practices.³

In an animal study, optogenetic stimulation of the thalamic-accumbens dopamine D₂ medium spiny neuron pathway alleviated somatic signs induced by opiate withdrawal.⁴ However, it is unknown if noninvasive brain stimulation could facilitate detoxification during the withdrawal period in humans. In this study, we used repetitive transcranial magnetic stimulation (rTMS) targeting the left dorsal-lateral prefrontal cortex (DLPFC) to modulate symptoms of withdrawal from methamphetamine.

Methods | This double-blind, randomized, clinical, parallel-group intervention trial, conducted from August 1, 2017, to February 15, 2018, recruited 50 men with methamphetamine addiction (positive results of urine test; abstinence length, 1-15 days) at Nanjing Shifosi Addiction Rehabilitation Center, Nanjing, China (Figure 1). One man was excluded owing to use of heroin, and another man was excluded owing to use of ketamine. The remaining 48 men (mean [SD] age, 33.3 [9.8] years; range, 18-54 years) were randomly assigned to the real rTMS group (24 men) or sham rTMS group (24 men) by another researcher who did not directly participate in the study. Participants reported no history of head trauma, epilepsy, heart diseases, or metal implants in the body. The study was approved by the ethics committee of Nanjing Normal University and all experimental procedures followed the guidelines of human medical research (Declaration of Helsinki⁵). All participants provided written informed consent. The clinical trial registration was [ChiCTR1800016008060](#). The trial protocol is in the [Supplement](#).

Withdrawal symptoms from methamphetamine were evaluated with a Chinese version of the methamphetamine withdrawal symptom scale, quality of sleep was measured with Pittsburgh Sleep Quality Index, depression was evaluated with the self-rating depression scale, and anxiety was

Figure 1. Study Flowchart and Design



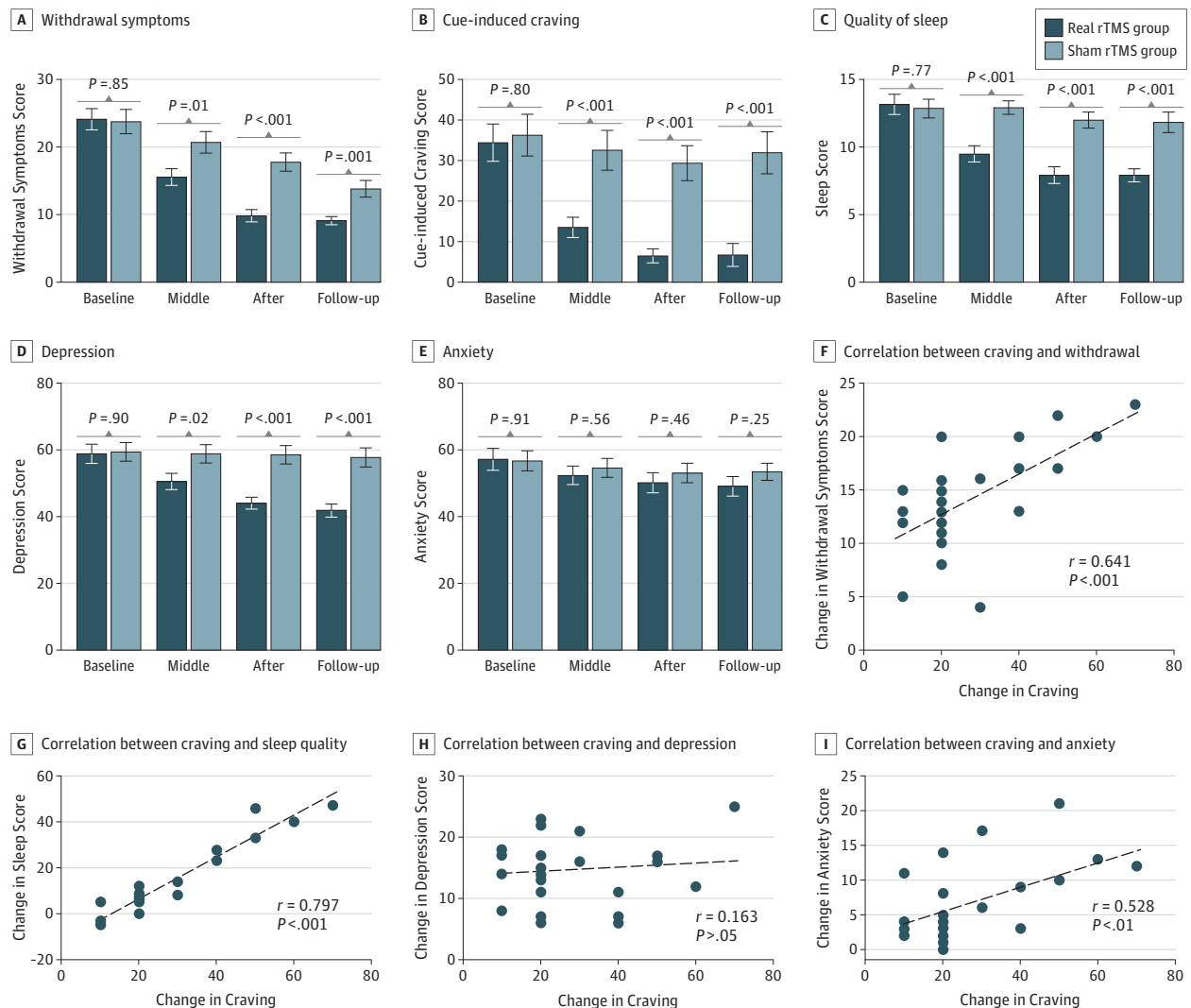
rTMS indicates repetitive transcranial magnetic stimulation.

evaluated with the self-rating anxiety scale. Evaluation of cue-induced craving was performed with a visual analog scale as previously described.⁶ High (10 Hz for 10 minutes) rTMS targeting the left DLPFC was performed as previously described.⁶ The intervention lasts for 10 days, with 2 days rest after the first 5 days (total, 12 days). The data were analyzed with SPSS, version 23.0 (SPSS Inc). Preprotocol analysis was conducted for assessments. Intergroup differences were examined with an independent sample *t* test or χ^2 test. A 2-way repeated-measure analysis of variance was used to assess the main effects of the groups (real rTMS vs sham rTMS) and time (before stimulation, mid-stimulation, and after stimulation). Post hoc *t* tests used Bonferroni adjustments for multiple comparisons; all post hoc tests' level of significance were designated at $P < .05/5 = .01$. All other *P* values were from 2-sided tests and results were deemed statistically significant at $P < .05$.

Results | There were no significant differences between the real rTMS and sham rTMS groups in mean (SD) age (31.8 [1.9] vs 34.4 [2.3] years), educational level (mean [SD], 9.9 [2.9] vs 11.3 [2.1] years), race (ratio of Han Chinese race to other races, 21:3 vs 21:1), mean (SD) body mass index (23.9 [2.9] vs 23.1 [3.9]; calculated as weight in kilograms divided by height in meters squared), mean (SD) length of abstinence (6.5 [4.4] vs 8.5 [4.2] days), mean (SD) duration of methamphetamine use (4.6 [3.0] vs 5.6 [3.3] years), and mean (SD) dose of methamphetamine per day (0.6 [0.3] vs 0.4 [0.3] g).

The results demonstrated significant changes in withdrawal symptoms, craving, quality of sleep, and mood status (depression and anxiety) after 10 days of rTMS treatments (Figure 2). Withdrawal symptoms showed a significant difference for time ($F_{3,32} = 198.18$; $P < .001$; $\eta^2 = 0.81$) and the descriptive data showed that withdrawal symptoms decreased.

Figure 2. Repetitive Transcranial Magnetic Stimulation (rTMS) Intervention Effects on Withdrawal Symptoms, Craving, Quality of Sleep, and Depression and Anxiety Scores



A, Withdrawal symptoms showed a significant difference for time ($F_{3,132} = 198.18$; $P < .001$; $\eta^2 = 0.81$) and for a time \times group interaction effect ($F_{3,132} = 20.27$; $P < .001$; $\eta^2 = 0.31$). Post hoc t tests (with Bonferroni correction for multiple comparisons) showed that withdrawal symptoms were significantly reduced for both the real rTMS group ($t_{23} = 13.21$; $P < .001$) and the sham rTMS group ($t_{21} = 9.53$; $P < .001$). B, Cue-induced craving showed a significant difference for time ($F_{3,132} = 50.52$; $P < .001$; $\eta^2 = 0.53$) and for a time \times group interaction effect ($F_{3,132} = 22.93$; $P < .001$; $\eta^2 = 0.34$). Post hoc t tests (with Bonferroni correction for multiple comparisons) showed that the craving score was significantly reduced for the real rTMS group ($t_{23} = 8.59$; $P < .001$) but not for the sham rTMS group ($t_{21} = 2.40$; $P = .046$) after applying Bonferroni correction for multiple comparisons. C, Quality of sleep showed a significant difference for time ($F_{3,132} = 32.76$; $P < .001$; $\eta^2 = 0.42$) and for a time \times group interaction effect ($F_{3,132} = 22.59$; $P < .001$; $\eta^2 = 0.33$). Post hoc t tests (with Bonferroni correction for multiple comparisons) showed that sleep difficulties were significantly reduced for the real rTMS group ($t_{23} = 8.85$; $P < .001$) but not for the sham rTMS group ($t_{21} = 1.08$; $P = .290$). D, Depression scores showed a significant difference for time ($F_{3,132} = 83.43$; $P < .001$; $\eta^2 = 0.65$) and for a time \times group interaction effect ($F_{3,132} = 63.77$; $P < .001$; $\eta^2 = 0.59$). Post hoc t tests showed that depression was significantly reduced for the real rTMS group ($t_{23} = 11.97$; $P < .001$) but not for the sham group ($t_{21} = 1.86$; $P = .076$). E, Anxiety scores showed a significant difference for time ($F_{3,132} = 25.59$; $P < .001$; $\eta^2 = 0.36$) and for a time \times group interaction effect ($F_{3,132} = 4.560$; $P = .01$; $\eta^2 = 0.03$). Further analyses (paired-samples t tests, 5% level) showed that anxiety was significantly reduced for the real rTMS group ($t_{23} = 5.28$; $P < .001$) but not for the sham rTMS group ($t_{21} = 2.35$; $P = .03$) after applying Bonferroni correction for multiple comparisons. F, Correlation between reduced craving was positively associated with reductions in withdrawal symptoms ($P < .001$). G, Correlation between reduced craving was positively associated with improvements in sleep ($P < .001$). H, Correlation between reduced craving was not positively associated with the depression score ($P = .45$). I, Correlation between reduced craving was positively associated with decreased severity of anxiety ($P = .007$).

There was also a significant time \times group interaction effect ($F_{3,132} = 20.27$; $P < .001$; $\eta^2 = 0.31$) and post hoc t tests (with Bonferroni correction for multiple comparisons) showed that withdrawal symptoms were significantly reduced for both the rTMS group ($t_{23} = 13.21$; $P < .001$) and for the sham group

($t_{21} = 9.53$; $P < .001$). For craving, the analysis indicated a significant difference for time ($F_{3,132} = 50.52$; $P < .001$; $\eta^2 = 0.53$) and the descriptive data showed that craving decreased. There was also a significant time \times group interaction effect ($F_{3,132} = 22.93$; $P < .001$; $\eta^2 = 0.34$) and post hoc t tests (with

Bonferroni correction for multiple comparisons) showed that the craving score was significantly reduced for the real rTMS group ($t_{23} = 8.59$; $P < .001$), but not for the sham rTMS group ($t_{21} = 2.40$; $P = .046$) after applying Bonferroni correction for multiple comparisons. Quality of sleep showed a significant difference for time ($F_{3,132} = 32.76$; $P < .001$; $\eta^2 = 0.42$) and the descriptive data showed that sleep difficulties decreased. There was also a significant time \times group interaction effect ($F_{3,132} = 22.59$; $P < .01$; $\eta^2 = 0.33$) and post hoc t tests (with Bonferroni correction for multiple comparisons) showed that sleep difficulties were significantly reduced for the real rTMS group ($t_{23} = 8.85$; $P < .001$) but not for the sham rTMS group ($t_{21} = 1.08$; $P = .29$).

For depression, a significant difference was seen for time ($F_{3,132} = 83.43$; $P < .001$; $\eta^2 = 0.65$) and the descriptive data showed that the depression score decreased (Figure 2). There was also a significant time \times group interaction effect ($F_{3,132} = 63.77$; $P < .001$; $\eta^2 = 0.59$) and post hoc t tests showed that depression was significantly reduced for the real rTMS group ($t_{23} = 11.97$; $P < .001$) but not for the sham rTMS group ($t_{21} = 1.86$; $P = .08$). For anxiety, a significant difference was seen for time ($F_{3,132} = 25.59$; $P < .001$; $\eta^2 = 0.36$) and there was a significant time \times group interaction effect ($F_{3,132} = 4.560$; $P = .01$; $\eta^2 = 0.03$); further analyses (paired-samples t tests, 5% level) showed that anxiety was significantly reduced for the real rTMS group ($t_{23} = 5.28$; $P < .001$) but not for the sham rTMS group ($t_{21} = 2.35$; $P = .03$) after applying Bonferroni correction for multiple comparisons. The reduced craving score was correlated positively with reductions in withdrawal symptoms ($r = 0.641$; $P < .001$), improvements in sleep ($r = 0.797$; $P < .001$), and decreased severity of anxiety ($r = 0.528$; $P < .01$), but not the depression score ($r = 0.163$; $P = .44$).

Discussion | Repetitive transcranial magnetic stimulation treatments have been shown to reduce craving to drug-associated cues in individuals who are addicted to different substances, including heroin, cocaine, methamphetamine, and nicotine.^{6,7} This study further proved that rTMS acts as a prospective tool against withdrawal syndrome; therefore, the application of rTMS to patients in different stages of addiction may be expanded. Stimulation targeting the left DLPFC leads to increased dopamine release, enhanced cortical activity, and reorganized cortical networks, which might trigger substantial changes in the nucleus accumbens and alleviate withdrawal symptoms. Further mechanistic and longer follow-up studies are required to elucidate the long-term effects of rTMS on addiction.

In conclusion, high-frequency rTMS targeting the left DLPFC could facilitate methamphetamine detoxification. The potential value of the procedure should be tested in larger clinical trials and to prevent relapse from addiction.

Ying Liang, PhD
Lei Wang, MSc
Ti-Fei Yuan, PhD

Author Affiliations: School of Social and Behavioral Sciences, Nanjing University, Nanjing, China (Liang, Wang); Shanghai Key Laboratory of Psychotic Disorders, Shanghai Mental Health Center, Shanghai Jiaotong University School of Medicine, Shanghai, China (Yuan); Co-innovation Center of

Neuroregeneration, Nantong University, Nantong, Jiangsu, China (Yuan); Guangdong-Hongkong-Macau Institute of CNS Regeneration, Ministry of Education CNS Regeneration Collaborative Joint Laboratory, Jinan University, Guangzhou, China (Yuan); School of Psychology, Nanjing Normal University, Nanjing, China (Yuan).

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Corresponding Author: Ti-Fei Yuan, PhD, Shanghai Key Laboratory of Psychotic Disorders, Shanghai Mental Health Center, Shanghai Jiaotong University School of Medicine, Shanghai, China (ytf0707@126.com).

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Concept and design: Liang, Yuan.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Liang, Yuan.

Critical revision of the manuscript for important intellectual content: Wang, Yuan.

Statistical analysis: All authors.

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COMMENT & RESPONSE

Disturbing Lack of Early Intervention Studies in Bipolar Disorder

To the Editor The recent meta-analysis of the positive effects in 10 studies of early intervention in early-phase psychosis (ie, prodromal schizophrenia) by Correll et al¹ is a highly significant advance for the field and for individuals with early-phase psychosis. However, at the same time, its publication emphasizes the enormous disparity in allocation of research resources for the study of early psychosis vs early prodromal bipolar disorder, where there are almost no studies. This lack is occurring despite the fact that bipolar disorder in children is more common, car-