LETTER TO EDITOR

CLINICAL AND TRANSLATIONAL MEDICINE

WILEY

The effects of DLPFC-targeted repetitive transcranial magnetic stimulation on craving in male methamphetamine patients

Drug addiction represents severe challenge for global health.[1] Methamphetamine (MA) abuse represents the major drug abuse in China in past decade and the relapse rate remains high. In past decade, there were series of evidences that repetitive transcranial magnetic stimulation (rTMS) could reduce drug craving and intake for a variety of substances.[2,3] Here, we analyzed data on craving changes of 195 MA patients receiving 10 Hz rTMS and 1 Hz rTMS treatment or in control group for 4 weeks, followed up by another 2 months after treatment cession.

The subjects (aged 18–65 years old, DSM-5 diagnosis) were recruited from Hangzhou Gongchen Center of addiction rehabilitation (HZGC) and Longyou Shiliping Center of addiction rehabilitation (SLP) (Table 1). Subjects were excluded for mental disorders, history of epilepsy, or contraindications to TMS (e.g., metal implants in head). The study has been approved by Ethic committee at Nanjing Normal University, Liaoning Normal University, and Shanghai Mental Health Center, and the process was in accordance with the Declaration of Helsinki. All participants provided written informed consent and participated in the study voluntarily. Within all subjects recruited, seven were excluded mixed usage of heroin or co-morbid with severe body diseases. The rest 188 patients were assigned into high-frequency/10 Hz treatment (n = 66), low-frequency/1 Hz treatment (n = 63), or control no-treatment (n = 59) groups (Table 1). In rTMS-treated patients, six chose to opt out for insomnia and headache, and five failed to attend the first posttest. In the untreated control group, four failed to attend first posttest. Finally, 173 patients were included in Day 30 analyses. Craving score was measured as previously described.[4,5] The 10 Hz (100% RMT, 5-second on, 10-second off for 10 min, 2000 pulses) or 1 Hz rTMS (100% RMT, 10-minute on, 600 pulses) was applied to the left DLPFC for 20 days (5 days on, 2 days off).

Linear mixed effect model was employed to understand the longitudinal changes of craving score at four time points. For correlation analyses of craving reduction between the two periods, we employed Spearman's correlation coefficient analysis to estimate the craving rate changes (Δcraving) at day 30 and 90; linear model was used to conform the normality of the changes in craving score. For demographic variable analyses, the history of drug intake in years, dosage per use, dosage per month, and baseline craving is dichotomized at median. The potential differences of treatment efficiency over particular subgroups were identified by fitting with mixed effect models. The statistical analyses were performed with SAS 9.4 (SAS Institute, Cary, NC). A two-sided significance level of $P < .05$ was used.

The piecewise linear mixed effect model suggested that the craving rates significantly decreased during the first 30 days in both 1 Hz and 10 Hz were significantly stronger than the control group (estimate of 1 Hz VS control = −14.25, SE = 4.46, $P < .01$; estimate of 10 Hz vs control = −20.76, SE = 4.38, $P < .0001$). No difference between 10 Hz and 1 Hz was identified (estimate difference = −6.51, SE = 4.34, $P > .05$). In follow-up period (day 30–90), 1 Hz group remain showing significant decrease in craving rate change (estimate = 10.80, SE = 2.95, $P < .001$), but not for 10 Hz group (Figure 1A). The prediction effects of treatment-induced changes on follow-up effects are shown in Figure 1B. The demographic data were stratified by using the medians as cut-off points, and the effects on subgroups were plotted in Figure 1C-F.

There was a marginal decrease in the three groups except the slope of 10 Hz at after day 30, adjusted for center effect. Pairwise comparison revealed that the reduction speeds of the two treated groups were quicker than the control group from baseline to day 30 period (10 Hz: estimate = −21.83, SE = 3.77, $P < .0001$; 1 Hz: estimate = −18.45, SE = 4.00, $P < .0001$), with no difference between the two types of treatments (estimate = −3.37, SE = 3.71, $P > .05$). In the period between day 30 and 90, the 10 Hz group reduced slower than 1 Hz group (estimate = 6.96, SE = 2.26, $P < .01$) and control group (estimate = 7.64, SE = 2.86, $P < .001$).

The present study, to our knowledge, is the largest one to investigate the effectiveness of chronic (4 weeks) rTMS treatment on methamphetamine dependence. We demonstrated that prefrontal rTMS at high and low frequency were both
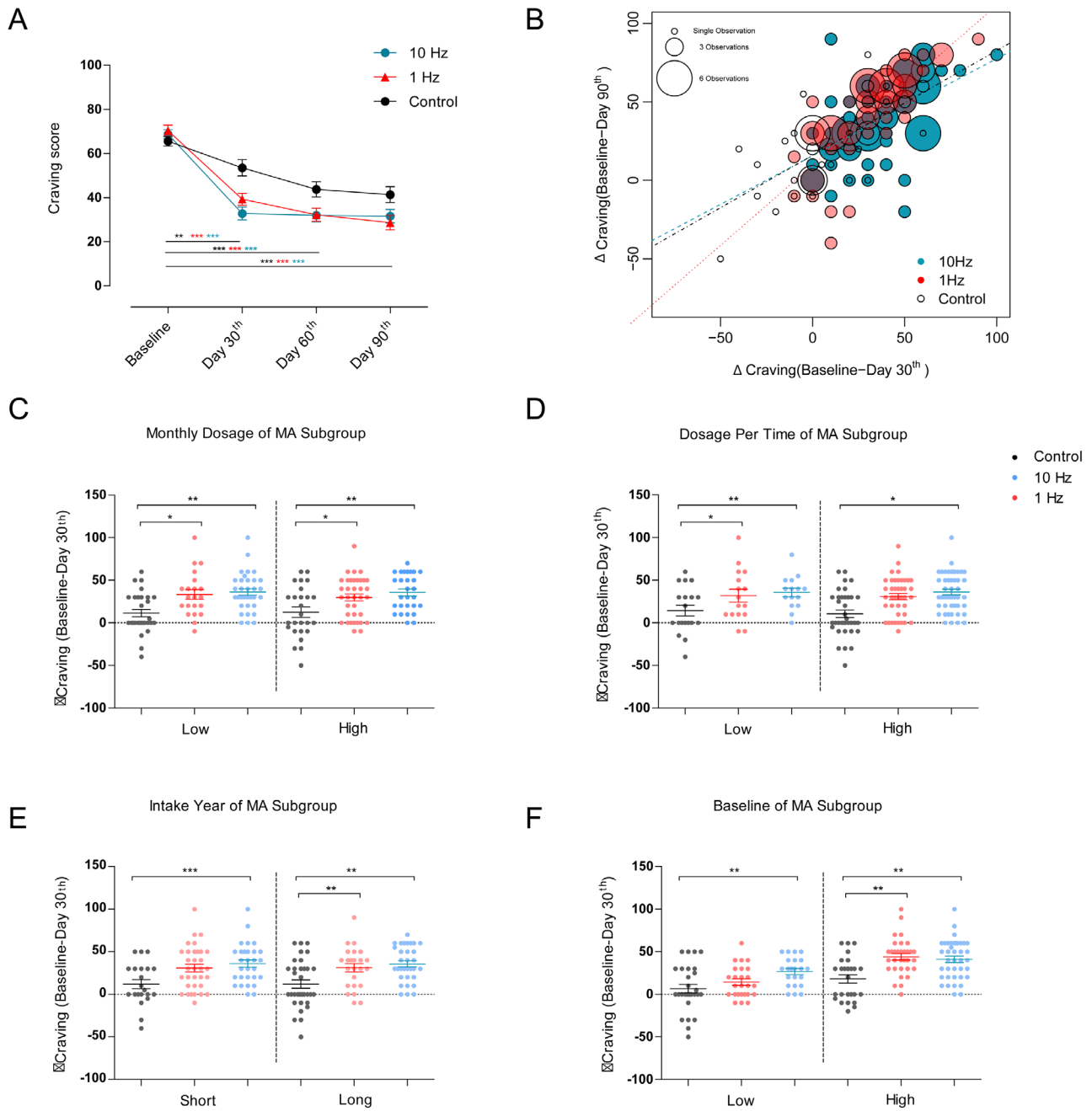
FIGURE 1 A, The craving score of the 10 Hz group (estimate = −35.98 SE = 3.13, $P < .0001$; estimate = −36.72, SE = 3.46, $P < .001$; estimate = −37.07, SE = 3.51, $P < .001$) and the 1 Hz group (estimate = −31.05, SE = 3.24, $P < .0001$; estimate = −38.16, SE = 3.64, $P < .0001$; estimate = −41.85, SE = 3.70, $P < .001$) reduced significantly at day 30/60/90 time points, when compared to baseline. Control group (estimate = −12.00, SE = 3.30, $P = .004$, estimate = −21.26, SE = 3.67, $P < .0001$; estimate = −24.00, SE = 3.71, $P < .0001$) also exhibited decreases at these time points. B, The correlation between delta craving (baseline day 30) and delta craving (baseline day 90) is shown. The size of points in figure stands for the number of observations with same level of craving rates changes. The location of points suggested that craving rate changes after treatment linearly depend on the craving rate changes during the treatment. The regression lines were plotted in respective color. In MA patients, the Spearman's Rho correlation coefficient for the 10 Hz group was 0.55 ($P < .0001$), 0.83 for the 1 Hz group ($P < .0001$), 0.67 for the control group ($P < .0001$). C-F, In the subgroup of monthly dosage ($P < .01$), intake year ($P < .001$), dosage per time ($P < .01$), baseline ($P < .01$), the delta craving (day 30 to day 1) of 10 Hz group was higher than the control group. And the delta craving of 1 Hz group was higher than the wait list group, when dosage each time ($P < .05$) and monthly dosage ($P < .05$) was low. Similarly, it was also found when intake year ($P < .01$), dosage per time ($P < .05$), monthly dosage ($P < .01$), and baseline ($P < .01$) was high, the reduction craving of using 10 Hz was higher than the control with regard to delta craving. When intake year ($P < .01$), monthly dosage ($P < .05$), and baseline ($P < .01$) was high, similar result was observed in the 1 Hz group as compared to the control

TABLE 1 Democratic characteristics of the study participants (mean ± SEM)

Variable	10 Hz	1 Hz	Control	F/chi	P
Age	33.33 ± 0.81	34.4 ± 1	35.89 ± 1.02	1.860	.159
Intake year	7.05 ± 0.55	6.28 ± 0.43	7.1 6 ± 0.46	0.967	.382
Dosage per time (g)	0.71 ± 0.06	0.73 ± 0.07	0.63 ± 0.07	0.693	.501
Monthly dosage (g)	11.8 ± 1.17	13.48 ± 1.24	11.23 ± 1.95	0.624	.537
Baseline	68.77 ± 2.03	70.35 ± 2.49	65.55 ± 2.1	0.187	.308
Abstinent time (day)	70.67 ± 6.84	80.63 ± 6.62	80.8 ± 6.82	0.754	.472
Center					
HZGC	36 (35.6%)	33 (32.7%)	32 (31.7%)		.205
SLP	25 (34.7%)	24 (33.3%)	23 (31.9%)		

F-value is for age and chi value is for intake years, dosage each time, monthly dosage, and baseline craving, abstinent time (day).

effective and well tolerated at reducing cue-induced craving for MA patients, with lasting effects for at least 60 days. These results suggested that chronic rTMS is practical strategy for treatment of craving for MA patients, and potentially reduce their relapse finally.

The neural mechanism underlying the rTMS efficacy on craving reduction remains to be elucidated. First, in MA patients, the altered prefrontal cortical functions accompany reduced executive control and the expression of craving.[6,7] rTMS treatments result in restoration of the prefrontal functioning, and might disrupt the neural substrate for craving expression even when drug-associated cues are present. Second, cortical rTMS treatments activate striatal regions and induce dopamine accumulation,[8] which could reduce the craving as well. Third, rTMS at DLPFC might trigger network changes (both global connectivity and local excitability),[3] such as the parietal circuits and eliminate the attention bias induced by cues. All these possibilities warrant future investigations on mechanism and potential new target for drug-dependent treatment.

There are limitations for this study. First, the subjective craving is important to predict relapse,[9,10] but it will be helpful to include relapse examination and examining the drug intake frequency with urine test. Second, the study did not include a sham rTMS-treated group, and placebo effects might partly contribute to the effects we observed. Third, here we report slight difference in 1 Hz and 10 Hz group only at follow-up period, and it will be necessary to understand if there is any potential neural mechanism underlying this.

In conclusion, the present study supported that a course of rTMS over left DLPFC is efficacious in reducing craving in methamphetamine dependents. The finding contributes to further treatment designed for drug cessation treatment.

Xiaoli Liu[1,2,3,4]*
Xiwen Zhao[5]*
Ying Shen[6]*
Ting Liu[1,3]
Qingming Liu[1,3]
Li Tang[7]
Hui Zhang[8]
Wenbo Luo[9,10]
Ti-Fei Yuan[1,3]

[1]Shanghai Key Laboratory of Psychotic Disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[2]Ningbo Key Laboratory of Sleep Medicine, Ningbo Kangning Hospital, Ningbo, Zhejiang, China
[3]School of Psychology, Nanjing Normal University, Nanjing, China
[4]Co-innovation Center of Neuroregeneration, Nantong University, Nantong, China
[5]Yale Center for Analytical Sciences, School of Public Health, Yale University, New Haven, Connecticut
[6]Rehabilitation Medicine Center, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China
[7]Department of Biostatistics, St. Jude Children's Research Hospital, Memphis, Tennessee

[8]*Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois*
[9]*Research Center of Brain and Cognitive Neuroscience, Liaoning Normal University, Dalian, China*
[10]*Key Laboratory of Brain and Cognitive Neurosience, Dalian, Liaoning Province, China*

Correspondence

Ti-Fei Yuan, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China.
Email: ytf0707@126.com
Wenbo Luo, Research Center of Brain and Cognitive Neuroscience, Liaoning Normal University, Dalian, China.
Email: luowb@lnnu.edu.cn

*These authors contributed equally to this work.

REFERENCES

1. Everitt BJ, Robbins TW. Drug addiction: updating actions to habits to compulsions ten years on. *Annu Rev Psychol*. 2016; 67: 23-50.
2. Diana M, Raij T, Melis M, Nummenmaa A, Leggio L, Bonci A. Rehabilitating the addicted brain with transcranial magnetic stimulation. *Nat Rev Neurosci*. 2017; 18(11): 685-693.
3. Ekhtiari H, Tavakoli H, Addolorato G, et al. Transcranial electrical and magnetic stimulation (tES and TMS) for addiction medicine: a consensus paper on the present state of the science and the road ahead. *Neurosci Biobehav Rev*. 2019; 104: 118-140.
4. Liu T, Li Y, Shen Y, Liu X, Yuan TF. Gender does not matter: add-on repetitive transcranial magnetic stimulation treatment for female methamphetamine dependents. *Prog Neuropsychopharmacol Biol Psychiatr*. 2018; 92: 70-75.
5. Shen Y, Cao X, Tan T, et al. 10-Hz Repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex reduces heroin cue craving in long-term addicts. *Biol Psychiatry*. 2016; 80(3): e13-e14.
6. Volkow ND, Koob GF, McLellan AT. Neurobiologic advances from the brain disease model of addiction. *N Engl J Med*. 2016; 374(4): 363-371.
7. Goldstein RZ, Volkow ND. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nat Rev Neurosci*. 2011; 12(11): 652-669.
8. Strafella AP, Paus T, Barrett J, Dagher A. Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. *J Neurosci*. 2001; 21(15): RC157.
9. Sinha R. The clinical neurobiology of drug craving. *Curr Opin Neurobiol*. 2013; 23(4): 649-654.
10. Kosten TR, Scanley BE, Tucker KA, et al. Cue-induced brain activity changes and relapse in cocaine-dependent patients. *Neuropsychopharmacology*. 2006; 31(3): 644-650.