Drug and Alcohol Dependence 175 (2017) 84–91

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

High frequency repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex for methamphetamine use disorders: A randomised clinical trial

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ARTICLE INFO

Keywords:
Methamphetamine
Craving
Repetitive transcranial magnetic stimulation
Dorsolateral prefrontal cortex
Cognitive function

ABSTRACT

Background: Repetitive transcranial magnetic stimulation (rTMS) is a brain stimulation and modulation electrophysiological technique, it can change cortical excitability of target brain region, modulate neuron plasticity and brain connections. Previous researches indicated that rTMS could reduce cue-induced craving in drug addiction.

Objective: In this study, we employed real and sham rTMS of the left dorsolateral prefrontal cortex (DLPFC) to test whether it could reduce cue-induced craving for methamphetamine (MA) and influence cognitive function in a randomised clinical trial.

Methods: Thirty MA-addicted patients were randomized to receive 5 sessions of 8 min sham or 10 Hz rTMS to the left DLPFC. Subjects rated their craving at baseline, after exposed to MA-associated cues and after rTMS sessions.

Results: Real rTMS over the left DLPFC reduced craving significantly after 5 sessions of rTMS as compared to sham stimulation. Furthermore, real rTMS improved verbal learning and memory and social cognition in MA-addicted patients.

Conclusions: The present study suggests that 10 Hz rTMS of the left DLPFC may reduce craving and have no negative effects on cognitive function in MA-addicted patients, supporting the safety of rTMS in treating MA addiction.

1. Introduction

Methamphetamine (MA) abuse causes huge public health consequences all over the world (Crime, 2015). It is estimated that there are 3 millions drug users in China and 57.1% of the drug users are amphetamine-type stimulants (ATS) users by the end of 2015 (Committee, 2015). There is no effective medical treatment for ATS addiction until now. Therefore, finding new treatment approaches for MA users is an urgent matter.

Craving reflects an expectation to get drugs and terminate withdrawal symptoms or unpleasant feelings immediately. Both aversive internal and external stimuli can induce craving even after periods of sustained abstinence. Craving has been hypothesized to play an important role in sustained drug use and relapse (Hartz et al., 2001). In a series of prospective studies, it was found to be highly predictive of drug addiction, such as nicotine, heroin and methamphetamine (Bedi et al., 2011; de Jong et al., 2006; Hartz et al., 2001). Furthermore, it has been used primarily as a surrogate outcome measure, with craving reduction interpreted as treatment success. MA craving is mediated largely through a network of interconnected structures, including the ventral tegmental area (VTA), nucleus accumbens (NAc), amygdala, striatum, and prefrontal cortex (PFC) (Degoulet et al., 2013; Li et al., 2015; Morales et al., 2015).

The PFC mainly involved in a variety of cognitive process, including inhibitory control, executive function and craving (Koob and Volkow, 2010). PFC dysfunction will lead to impulse, obsessive-compulsive symptom and attention deficit (Arnsten et al., 2012). Previous studies found that lesions of the frontal cortex and its functionally distinct and interacting sub-regions showed selective deficits in inhibitory control (Solbakk and Lovstad, 2014). Prefrontal dysfunction is also an im-

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http://dx.doi.org/10.1016/j.drugalcdep.2017.01.037
Received 31 October 2016; Received in revised form 14 December 2016; Accepted 26 January 2017
Available online 29 March 2017
0376-8716/

portant cause that leads to losing control of drug addiction (Kasanetz et al., 2013). In a recent functional magnetic resonance imaging (fMRI) study by our group, we reported that MA-addicted patients showed reduced activation in cognitive control related brain regions when they performed a Stroop task (unpublished). Other imaging studies also found that the prefrontal dysfunction was associated with the deficits of response inhibition of MA users (Ersche et al., 2012; Nestor et al., 2011). Furthermore, our group found that MA dependent subjects exhibited a series of impairments in cognitive function, such as verbal memory, problem solving, working memory and social cognition (Zhong et al., 2016). These impairments are supposed to be associated with many important brain functional deficits in areas of anterior cingulated cortex (ACC), dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), striatum and so on (Dean et al., 2013). Among them, DLPFC is an important region that involved in reward, motivation and decision-making, it has great interaction with deep brain area such as striatum and cingulate. It is proposed to play an executive role in controlled response inhibition through its connectivity. Furthermore, most of rTMS studies took the DLPFC as therapeutic target to reduce craving for drug-dependent patients especially cocaine users because cocaine has similar mechanism with methamphetamine, as a result, we chose the DLPFC according to previous experience.

Transcranial magnetic stimulation (TMS) is a brain stimulation and modulation technique. It generates electrical currents by projecting a pulsatile electromagnetic field through the skull into brain and modulates neuronal excitability immediately (Kluger and Triggs, 2007; Rossini and Rossi, 2007). As a noninvasive electrophysiological technique, repetitive TMS (rTMS) could increase or decrease cortical excitability of target brain region, enhance neuron plasticity and brain connections, and increase cerebral cortex inhibition function. Nowadays, rTMS has become a new physical approach for psychiatric diseases (Hovington et al., 2013). The main effect of rTMS is to modulate cortical excitability: low frequency (< 1 Hz) rTMS reduces neuronal activity and cortical excitability, while higher frequency (> 5 Hz) rTMS increases neuronal activity and cortical excitability and increases relative regional cerebral blood flow (Chen et al., 1997; Pascual-Leone et al., 1994). rTMS could stimulate not only local but related far cortical and subcortical function, and the biological effect will continue for a time after the stimulation stops, it is a good tool for reconstructing partial or whole neural function network (Li et al., 2011). In recent years, rTMS has been widely used in the treatment of substance use disorders, it can significantly reduce craving, improve emotional problems and cognitive function, improve withdrawal rate for alcohol, nicotine, cocaine (Bellamoli et al., 2014; Camprodon et al., 2007; Ceccanti et al., 2015; Del Felice et al., 2016; Dunlop et al., 2016; Gorelick et al., 2014; Terraneo et al., 2016; Trojak et al., 2015). Previous studies supported that high frequency (> 5 Hz) rTMS over the DLPFC could reduce craving level in drug-dependent patients. According to previous review, we found that the high frequency 10 Hz is the most used in the treatment of substance addiction, especially cocaine addiction (Gorelick et al., 2014). A recent study showed that high frequency rTMS (10 Hz) over the left DLPFC transiently decreased cue-induced craving in heroin-dependent patients by using CCY-I TMS instrument (Shen et al., 2016), so we chose 10 Hz for our study.

Considering prefrontal dysfunction and cognition impairments has been observed in patients with methamphetamine use disorder and the effectiveness of rTMS for other psychiatric disease, we assume that high frequency rTMS maybe a potential treatment for MA use disorder. The purpose of this study was to test whether high frequency (10 Hz) rTMS of the left DLPFC would modulate cue-induced craving in MA-addicted patients in a randomized, single blind, sham-controlled way. Furthermore, we want to find whether high frequency rTMS would influence cognitive function by using a detailed CogState Battery of standardized neuropsychological tasks. We hypothesized that DLPFC-rTMS would not produce significant cognitive adverse effects in MA-addicted patients.

2. Methods and materials

2.1. Experimental design

This study is one part of the randomized, double blind and controlled clinical trail: Novel Intervention for Amphetamine-type Stimulants Addiction, which has been registered on the ClinicalTrials.gov (ID: NCT02713815). All subjects were instructed to be treated by rTMS, but would be blind to the individual group assignment. All outcome measures were assessed by blinded researchers who had no access to the treatment sessions.

2.2. Participants

Thirty male individuals from Shanghai Compulsory Rehabilitation Center who met Diagnostic and Statistical Manual of Mental Disorders criteria (DSM-V) criteria for moderate or severe MA use disorders participated in this study. The inclusion criteria were: (1) more than 9 years of education; (2) aged of 18–49 years old; (3) normal vision and audition; (4) receive no medications during treatment. The exclusion criteria were: (1) serious physical or neurological illness that required pharmacological treatment affecting cognitive function (e.g., stroke, seizure, or severe head injury); (2) other Axis I disorder of DSM-V criteria such as bipolar disorder, schizophrenia, depression); (3) neurological diseases such as stroke, seizure, migraine, head trauma (4) substance dependence other than nicotine, within the past 5 years (see CONSORT flowchart in Fig. 1).

The data of twenty healthy controls come from our previous database, which were recruited from local community. The controls matched with the MA groups in gender, age and education.

Written consent was obtained from all subjects. The study was approved by the institutional review board and the ethics committee of Shanghai Mental Health Center. All participants are Han Chinese according to their identification card.

2.3. Data collection and measurements

Each subject was interviewed by one psychiatrist and completed a self-administrated case report form, which included socio-demographic characteristics (age, education, marriage, jobs, weight, height, etc.), drug use history (age of onset, total duration of MA use, dose, reason, etc.).

(1) Cue-induced craving: The cue exposure presentation consisted of 80 MA-related (drug-use materials, person and situation) pictures. Participants were instructed to pay close attention to the pictures and rate their level of craving after watching these pictures and recalling the last time they engaged in MA use. Craving was assessed by visual analog scales (VAS), with 0 mm being “no craving” and 100 mm representing “most craving ever experienced for MA”. VAS was conducted before and after real rTMS or sham stimulation as well as pre experiment baseline. 40 pictures were presented each time for 5 min (Fig. 2).
(2) Cognitive function: We assessed cognitive function using the Chinese version of the CogState Battery, which is a repeatable and sensitive computerized cognitive test with good validity and reliability. We selected five tasks according to our previous positive findings (Zhong et al., 2016): International shopping list task (ISLT, 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 score of ISLT is defined as the total number of correct responses. The scores of TWOB and SEC tasks are the proportion of correct responses, denoting the accuracy of performance. The scores of CPAL and GML tasks are the total

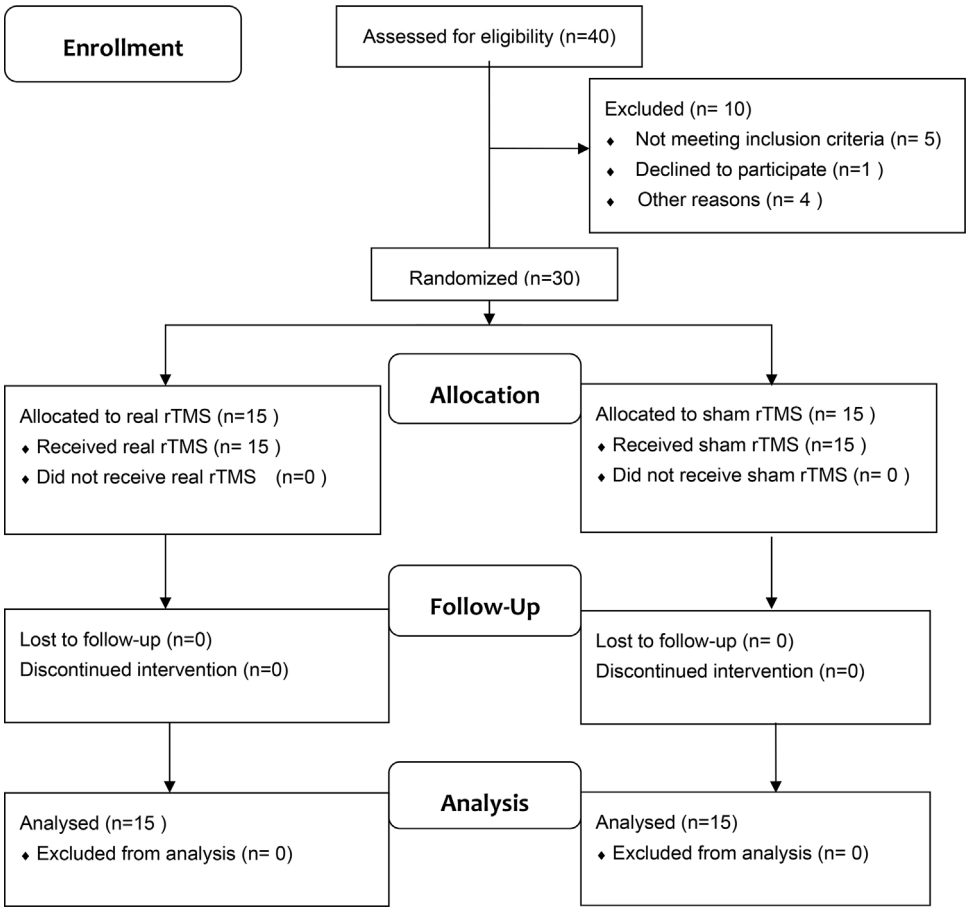

Fig. 1. CONSORT flowchart of the study. 20 participants were planed to be enrolled in each group, however, 10 were excluded because of not meeting inclusion criteria for rTMS, or declining to participate or other reasons.

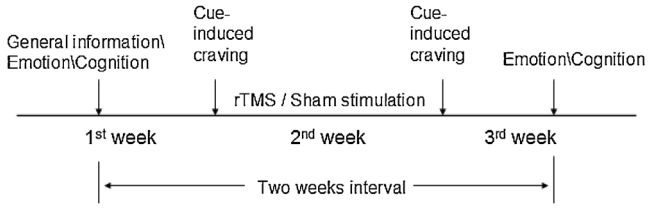

Fig. 2. The design of the study. Depression, anxiety, sleep and cognition were evaluated at 1st week and 3rd week, the interval was two weeks. Cue-induced craving were evaluated at the baseline before stimulation and at 1st day and 5th day after the rTMS or sham stimulation.

number of errors. These tasks were displayed on a green screen, along with standardized instructions before the start of each task. We uploaded the results of the CogState Battery to a secure account on the CogState server site (http://www.Cogstate.com), where data were calculated and normalization was transformed.

(3) Mood and sleep status: we assessed depression by Hamilton depression scale-17 (HAMD-17). Anxiety was evaluated by Hamilton anxiety scale-14(HAMA-14). Sleep was evaluated by Pittsburgh Sleep Quality Index (PSQI).

The CogState Battery, HAMD, HAMA and PSQI were assessed at before and after rTMS stimulation (Fig. 2).

2.4. rTMS procedure

Thirty participants were randomly assigned into a real rTMS group and a sham rTMS group (n = 15 in each group) by another researcher who was not directly involved in this study by using the simple random-sampling method (random number table). Motor threshold was determined in both groups over the left motor cortex, by finding the lowest intensity that produced a motor response in the right abductor pollicis brevis muscles (APB), which produced five motor-evoked potentials responses of at least 50 mV in 10 trials. During the treatment, the coil was placed over the left prefrontal area at a point 5 cm anterior to the scalp position at which the motor threshold was determined. Subjects in real rTMS group received 5 days, high frequency (10 Hz) rTMS at 80% resting motor threshold (rMT), 5 s on and 15 s off for 8 min with 1200 pulses over the left DLPFC, while sham TMS group received same parameters except that the coil was turned away from the skull for 90°. We used a figure-8-shaped coil for accurately targeted stimulation by the CCY-I TMS instrument (Yiruide Co., Wuhan, China). At the beginning, the rMT was set as 100%, however, many subjects reported a scalp discomfort, so we down-regulated it to 80% for all of the 30 participants. The participants and psychiatrists who assessed outcomes were both blind to the randomization, only the therapist knew the real rTMS and sham rTMS. The therapist had no access to the study design (double-blind). Those healthy control participants did not receive any rTMS/sham treatment.

2.5. Safety

Safety was assessed at every treatment session by a self-administrated rTMS treatment form by recording spontaneous adverse events such as seizure, headache, and dizziness.

2.6. Data analyses

The data were analyzed using SPSS, version 16.0. Group differences

Table 1
Demographic and drug use characteristics.

Characteristics	rTMS group (N = 15)	sham group (N = 15)	F/x^2	p
Age (years)	31.85 ± 5.25	32.84 ± 4.79	0.290	0.594
Education (years)	10.93 ± 3.31	10.13 ± 1.73	0.690	0.413
Marriage			3.319	0.219
Married	3 (20%)	5 (33.3%)		
Divorced	3 (20%)	6 (40%)		
Never	9 (60%)	4 (26.7%)		
Employment			0.136	0.713
Yes	6 (40%)	7 (46.7%)		
Body mass index (BMI)	23.77 ± 3.34	23.97 ± 2.41	0.037	0.849
Age of onset (years)	25.67 ± 5.52	26.13 ± 4.88	0.060	0.808
Abstinence (months)	3.00 ± 1.56	2.80 ± 1.70	0.113	0.739
Duration of MA use (months)	40.33 ± 32.04	60.80 ± 41.40	2.293	0.141
Dose of MA use per day (g)	0.49 ± 0.34	0.49 ± 0.32	0.001	0.999
Frequency			1.624	0.792
Every day	4 (26.7%)	3 (20%)		
3–5 times a week	2 (13.3%)	4 (26.7%)		
Once a week	4 (26.7%)	2 (13.3%)		
1–3 times a month	5 (33.3%)	6 (40%)		

were compared using Student *t*-test or analysis of variance (ANOVA) for continuous variables and chi-square test for categorical variables. Multivariate linear regression was done with craving changes in 5 days as the dependent factor and age, education, age of onset, total duration of MA use, frequency, rTMS groups (active or sham), and HAMD-17, HAMA-14, PSQI baseline scores as independent factors. Repeated-measure ANOVA was used to assess the main effects of groups (real rTMS vs. sham rTMS) and time (before and after stimulation). The alpha level were reported with $p < 0.05$ (two-sided tests) treated as statistically significant.

3. Results

3.1. Demographic and drug use information

Demographic characteristics and drug use were shown in Table 1. The average ages of the participants were 32.35 ± 4.96 years old. There were no differences between the real rTMS and sham rTMS group in terms of average age, education years, marriage, employment, and Body Mass Index (BMI). No differences were found between two groups in terms of onset age, abstinence period, duration of MA use, MA use dose and frequency.

3.2. The effect of rTMS on craving

Compared with the baseline (10.33 ± 20.52 in rTMS group and 13.87 ± 29.12 in sham group, no difference between two groups ($p > 0.05$)), the craving rating increased significantly after MA cue exposure in both two groups ($p < 0.05$), leading to a craving score of 27.53 ± 27.22 in the rTMS group and 34.00 ± 35.35 in the sham group, and there is no difference between real rTMS group and sham group ($p > 0.05$). In the first day of rTMS treatment, the craving scores only had a decreasing tendency with 15.80 ± 21.44 in the rTMS group ($p > 0.05$ compared with baseline) and 26.60 ± 34.22 in the sham group, respectively ($p > 0.05$ compared with baseline). However, after 5 days of rTMS treatment, cue-induced craving decreased significantly in the rTMS group, with the craving score at 5.67 ± 6.62 ($p = 0.008$ compared with day 1 baseline), in contrast to 22.27 ± 34.36 in the sham group ($p > 0.05$ compared with day 1) (Fig. 3).

Multivariate linear regression demonstrated that age ($t = 4.082$; $p < 0.001$), education ($t = -2.768$; $p = 0.010$) and rTMS group ($t = -2.317$; $p = 0.029$) could better predict craving changes.

3.3. Depression, anxiety and cognitive function

Depression scores decreased significantly after both rTMS and sham stimulation group ($p < 0.05$), but there was no between-group effect ($p > 0.05$), while anxiety scores reported no significant changes after rTMS or sham stimulation. No significant difference was found in PSQI after rTMS or sham stimulation (Table 2) (Fig. 4).

In the test of CogState Battery, ISL scores increased significantly after real rTMS, while the sham group reported no changes, and there is a significant effect between two groups ($p = 0.005$). SEC scores increased significantly after real rTMS ($p = 0.023$), while the sham group reported no changes ($p > 0.05$). GML, TWOB and CPAL scores reported no significant changes after rTMS or sham stimulation ($p > 0.05$) (Table 2) (Figs. 5 and 6).

3.4. Safety

Two patients experienced mild insomnia for 1 day during the real rTMS session. Some patients experienced mild scalp discomfort, temporary headache and nausea in real rTMS sessions, but didn't last long and could tolerate. No subject reported seizures or other serious adverse events. Interestingly, two participants reported that they dreamed a lot at night and recalled long-term memory decades ago.

4. Discussion

Previous studies revealed that rTMS over the DLPFC reduced craving of drug-dependent patients, such as cocaine, nicotine, heroin and alcohol (Amiaz et al., 2009; Camprodon et al., 2007; Li et al., 2013a; Mishra et al., 2010; Politi et al., 2008; Shen et al., 2016). In this preliminary study, we found that high frequency rTMS of left DLPFC could significantly reduce craving for MA-addict subjects with no serious side effects. The only one rTMS research for MA reported that low frequency rTMS (1 Hz) of the left DLPFC transiently increases cue-induced craving (Li et al., 2013b). Previous evidence generally indicated that low frequency rTMS has inhibitory effect of excitability, while high frequency rTMS increase cortical excitability, so our results did not conflict with this research.

Animal and human studies provided us several potential mechanisms of rTMS for cue-induced craving in MA. The basic principle of TMS is that most neuronal axons that receive magnetic stimulation would become electrically excited, trigger action potentials and change synaptic plasticity. It has been observed rTMS with frequencies of 5 Hz and higher had excitatory effect on human neurons in the stimulated cortex (Lee et al., 2006). This effect was believed to reflect synaptic facilitation changes, most likely through mechanisms of long term potentiation (Huerta and Volpe, 2009). Furthermore, this effect could persist for long-lasting, even trigger synaptic plasticity in deep brain regions such as hippocampus, suggesting that rTMS protocols that induct LTP would be successful in modifying synaptic plasticity in the reward system in humans (Esslinger et al., 2014).

The second mechanism is that rTMS could modulate several important neurotransmitters involved in addiction-related processing, including dopamine and GABA (Barr et al., 2011). Brain imaging studies demonstrated that rTMS over the DLPFC increased extracellular dopamine levels, and modulates dopamine release in anterior cingulate cortex (ACC) and orbitofrontal cortex (Cho and Strafella, 2009). Furthermore, rTMS has been shown to enhance GABA neurotransmission (Dubin et al., 2016).

Previous studies demonstrated that rTMS not only had effect on stimulated region, but it also induced changes of cortical and subcortical functional connectivity. For example, the prefrontal-striatum neural circuit is an important cognition control center and plays a dominant role in behavior inhibition, impulsivity control and decision-

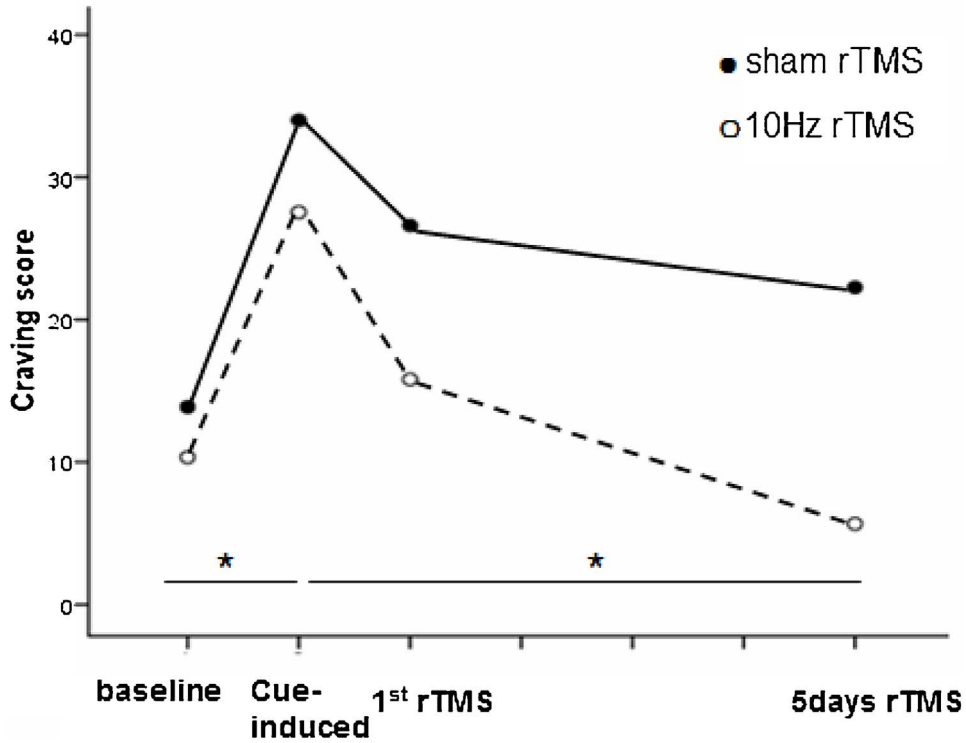

Fig. 3. The craving score after cue-induced and rTMS or sham stimulation. The cue-induced craving score reported no significant decreases after 1st session in rTMS group, but decreased significantly after 5 sessions ($p = 0.008$), while the sham group reported no changes along with 5 sessions ($p > 0.05$).

Table 2
Emotion, sleep and Cogstate battery scores before and after intervention.

	rTMS group			Sham group		
	before	after	p	before	after	p
HAMD	10.40 ± 7.79	8.40 ± 7.11	0.012*	11.50 ± 5.02	7.40 ± 4.38	0.003*
HAMA	9.80 ± 9.05	8.20 ± 11.83	0.421	8.90 ± 8.68	8.00 ± 8.57	0.496
PSQI	16.60 ± 10.15	12.27 ± 6.34	0.057	16.00 ± 6.67	13.40 ± 8.41	0.179
ISL	20.40 ± 2.82	23.27 ± 5.04	0.030*	20.2 ± 4.33	20 ± 5.71	0.593
GML	50.60 ± 15.65	49.87 ± 16.63	0.823	51.07 ± 13.49	54.2 ± 18.61	0.498
TWOB	1.10 ± 0.15	1.15 ± 0.27	0.328	1.07 ± 0.22	1.11 ± 0.24	0.319
CPAL	81.33 ± 45.08	82.27 ± 56.91	0.935	89.6 ± 36.84	109.2 ± 60.1	0.113
SEC	0.89 ± 0.24	1.02 ± 0.16	0.023*	0.97 ± 0.21	1.04 ± 0.12	0.071

HAMD(Hamilton depression scale), HAMA(Hamilton anxiety scale), PSQI (Pittsburgh Sleep Quality Index), ISL (verbal memory), TWOB (working memory), GML (error monitoring), SEC (social emotional cognition) and CPAL (visual spatial working memory).
* $p < 0.05$.

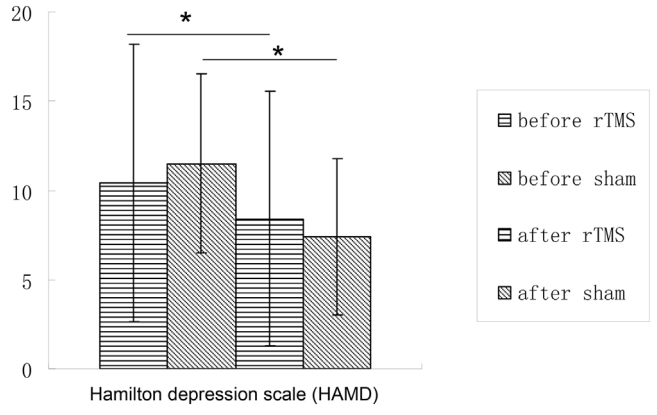

Fig. 4. Depression was evaluated by Hamilton depression scale (HAMD). Depression scores decreased significantly after rTMS and sham stimulation, but there was no between-group effect ($p > 0.05$).

making (Behan et al., 2015). It was reported that 10 Hz rTMS over the left DLPFC reduced the connectivity between DLPFC and left caudate compared to the sham group in major depressive patients (Kang et al., 2016). Besides, 5 Hz rTMS to the right DLPFC provoked a significant decrease in seeded functional connectivity of the right DLPFC and left hippocampus (Bilek et al., 2013). Alcohol dependent patients had higher connectivity within the left fronto-parietal cognitive control network (FPn) and the left fronto-striatal motivational network than health controls, and 10 Hz rTMS to right DLPFC further increased the connectivity within the left FPn (Jansen et al., 2015). These TMS/fMRI findings support the idea that rTMS of the DLPFC induces functional changes in cortical and subcortical regions, especially the reward system.

Moreover, rTMS seems to affect regional cerebral blood flow and blood oxygenation. Obeso et al. combined rTMS with positron emission tomography (PET) scans and found that rTMS over the pre-supplementary motor area increased regional cerebral blood flow (rCBF) in brain regions that related to response inhibition (Obeso et al., 2013). High frequency rTMS delivered to prefrontal cortex increased blood oxyge-

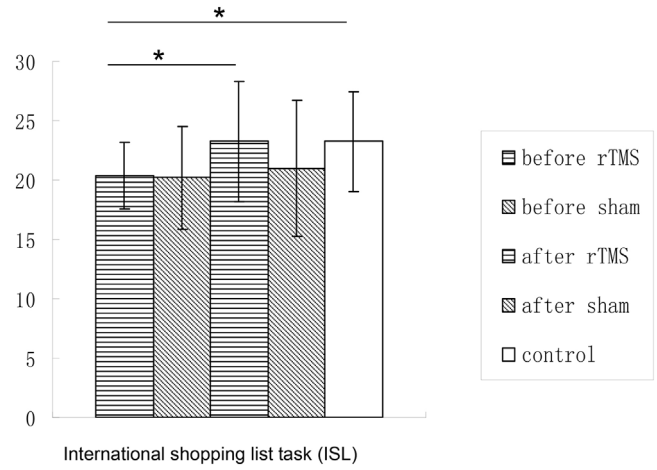

Fig. 5. Verbal learning and memory was evaluated by International shopping list task (ISL). ISL scores increased significantly after rTMS, while the sham group reported no changes, and there is a significant effect between two groups ($p = 0.005$).

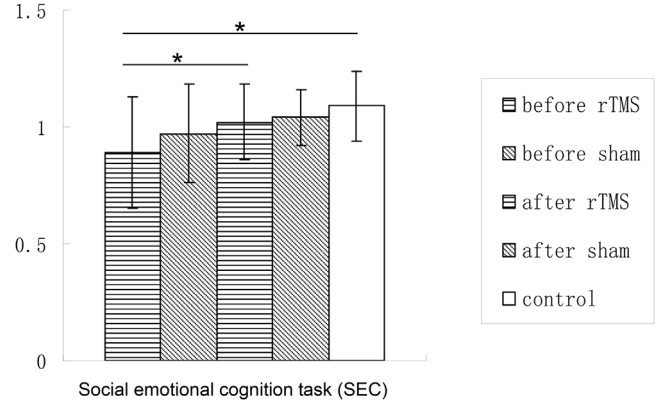

Fig. 6. Social cognition was evaluated by Social emotional cognition task (SEC). SEC scores increased significantly after rTMS ($p = 0.023$), while the sham group reported no changes ($p > 0.05$).

nation in healthy participants (Cao et al., 2013). Besides, TMS might have consequences on other neuronal processes, such as genetic and protein regulation. It has been reported that TMS can trigger the expression of brain-derived neurotrophic factor (BDNF) (Shang et al., 2016), and genetic mutations that affect cortical excitability, such as the BDNF gene polymorphism and serotonergic gene polymorphism, showed different response to rTMS (Hwang et al., 2015; Malaguti et al., 2011).

Multiple linear regression showed that age had a significant positive correlation with craving changes and education correlated negatively with craving changes. These results demonstrated that the older the age, the lower the education had better response to rTMS treatment. However, the correlation between age and response is still a controversial issue and there is no strong evidence to date. Pallanti et al. found a greater response in younger patients with treatment-resistant depression and an inverse correlation between age and treatment response. They also reviewed several articles and made three explanations: stimulation parameters (stimulation intensity and frequency, duration of treatment), differences in rTMS effects on neuroplasticity in older vs. younger, and a combination of the both (Pallanti et al., 2012). Further research is needed to clarify the relationship between age, education and rTMS response.

In this study, we found that 5 sessions of 10 Hz rTMS over DLPFC could improve verbal learning and memory and social emotional cognition in MA-addicted subjects. There is some evidence from brain imaging and behavioral studies showing that noninvasive rTMS to cortex has effect on cognitive performance after stimulation. Wang et al. found that multiple-day rTMS targeted to cortical-hippocampal network regions improved arbitrary face-word pairings memory and hippocampal-cortical functional connectivity, and these effects could last at least 15 days (Wang et al., 2014; Wang and Voss, 2015). Some randomized, double blind, controlled clinical trails currently also proved rTMS could improve memory function in schizophrenia, depression, Alzheimer's Disease (Fitzgerald et al., 2009; Guse et al., 2013; Lee et al., 2016). The role of rTMS on social emotion cognition has been proven in healthy subjects and schizophrenia patients. 10 Hz rTMS over pre-motor cortex reduced error rates and response times in a conscious and unconscious face recognition task (Balconi and Bortolotti, 2013). High frequency rTMS to left DLPFC also improved facial affect recognition in schizophrenia patients who had social cognitive impairments (Wolwer et al., 2014). The mechanism of high frequency rTMS on cognitive function is still unclear, more rTMS approaches combined fMRI with cognitive tasks are needed.

This study has several limitations. First, the relatively small sample of subjects (15 each group) limited us to highlight differences between the two groups, especially concerning the high amplitude of variation in craving scores, but our data was in accordance with normal distribution and homogeneity of variance (except for the craving score at baseline). Secondly, given the increased risk of seizure during high frequency rTMS, we were careful about the intensity of stimulation and the number of TMS pulses and only applied 80% rMT and 1200 pulses each day in MA-dependent subjects. This may be related to the power output of the CCY-I machine. Most rTMS trials have been completed with a higher intensity stimulation (e.g., 100%–120% rMT). Because there is a large distance from coil to cortex over prefrontal cortex compared to motor cortex, high intensity stimulation requires prefrontal treatment. These may be a reason why the effect of rTMS was not so obvious. Higher intensity stimulation (100% rMT) or more daily pulses per session (2000 above) or total rTMS sessions (20 above) may have more marked changes in cortical excitability and may have been more effective to reduce craving. Also, more proper stimuli may be warranted in future craving studies, as the participants reported that the effect of drug related instrument (bottle, straw, tinfoil, etc.) was better than pictures. Furthermore, we used the "5 cm rule" to locate the DLPFC of patients and did not take into consideration the shape and size of a person's head. MRI-guided neuronavigation may achieve both better accuracy and superior efficacy for locating the DLPFC. In this study, there was no significant difference on improving emotion and sleep in rTMS group compared to control group, it may be related that emotion scores of the subjects at baseline was not remarkable. For example, only 60% (9/15 participants) were found to have mild to moderate depressive symptom in true rTMS group and 53.3% (8/15 participants) in sham group. Finally, we should remember that not all the participants had good response to rTMS, a response rate may be considered in rTMS treatment.

The results of this preliminary study demonstrated that high frequency rTMS of the left DLPFC could decrease cue-induced craving in MA-addicted subjects. This finding suggests that high frequency rTMS may increase prefrontal cortex functions. Future studies will focus on electrophysiological changes and fMRI combined with frontal activation tasks to find the mechanisms of rTMS, and need to be examined with longer treatment and follow-up period.

Contributors

Min Zhao was responsible for the study concept and design. Na Zhong, Haifeng Jiang and Jijun Wang helped design the study. Hang Su, Hong Gan, Hui Han, Tianzhen Chen, Xiaotong Li, Xiaolu Ruan, Youwei Zhu acquired the clinical data. Hang Su did the rTMS intervention, conducted the data analysis and drafted the manuscript. All authors provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved final

version for publication.

Conflict of interest

All authors declare that they have no conflicts of interest.

Acknowledgements

The authors are supported by the National Nature Science Foundation (81271468, 81130020, 81501148, U1502228), Shanghai Municipal Health and Family Planning Commission (2014ZYJB0002, 2013SY011) and the Shanghai Key Laboratory of Psychotic Disorders (13DZ2260500). The funders have no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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