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

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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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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