Protocol

Targeting withdrawal symptoms in methamphetamine addicts with Transcranial Magnetic Stimulation

Principal investigators: Ying Liang, PHD
Professor in School of Social and Behavioral Sciences, Nanjing University, Nanjing, China

Ti-Fei Yuan, PhD
Professor in Shanghai Mental Health Center, Shanghai Jiaotong University School of Medicine, Shanghai, China

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1. Background

Substance abuse and addiction are one of the major hazards of public health and have attracted wide attention over the world. According to the 2014 World Drug Report, the number of drug users is 243 million, of which approximately 11% are drug addicts. And in 2016, global drug users have increased to 300 million. Drug addiction are associated with adverse psychological and behavioral consequences, such as social anxiety, depression, impulsivity, schizophrenia, or other mental illnesses; it seriously

affected the quality of life of individuals and families, caused huge social and economic burdens, and brought series of social stability problems. Thus, it is vital to develop a valid and non-invasive instrument to treat the drug addiction.

Drug often occurred among recently-abstinent substance users. The duration for methamphetamine withdrawal was generally considered to last from five days to more than two weeks. Drug withdrawal symptoms were associated with aversive experiences, which promotes relapse and incubates craving. Opiate withdrawal leads to activation of selective thalamic-accumbens pathway and potentially mediates the somatic signs. Withdrawal from methamphetamine results in fatigue, irritability, disturbed sleep, exhaustion, depression and anxiety symptoms. With limited pharmaceutical tools available in detoxication from methamphetamine, vitamins, antidepressants and antipsychotics have been employed to ameliorate the withdrawal symptoms. It is yet unknown if non-invasive brain stimulation could facilitate detoxication from methamphetamine.

With a double-blind, randomized controlled, parallel group intervention trial, the purpose of this study is to examine whether 10-Hz Repetitive Transcranial Magnetic Stimulation (rTMS) at Left Dorsolateral prefrontal cortex (L-DLPFC) can reduce the withdrawal symptoms of 50 methamphetamine dependents.

2. Objectives

The overall purpose of this study is to test the effects of 0-Hz Repetitive Transcranial Magnetic Stimulation (rTMS) at Left Dorsolateral prefrontal cortex (L-DLPFC) on the methamphetamine withdrawal symptoms. The specific aims are to conduct a double-blind, randomized controlled, parallel group intervention trial to compare the true rTMS and sham rTMS for the methamphetamine users and assess the comparative effectiveness of true rTMS and sham rTMS on measures of craving, withdrawal symptoms, sleep, depression, and anxiety.

3. Study population

Target population

50 subjects with methamphetamine abuse during acute withdrawal (urine test positive, abstinence length 1-15 days) at Nanjing Shifosi Addiction Rehabilitation Center will be recruited for the study.

Inclusion criteria

(1) met Diagnostic and Statistical Manual of Mental Disorders criteria (DSM-V) criteria for moderate or severe methamphetamine addiction use disorders;
(2) aged of 18-55 years old;
(3) using methamphetamine (purely) for at least 1 year;
(4) intake of drug at least 3 times per week, lasting for at least a month for one period (occasional drug use was not included);
(5) dosage of more than 0.1 gram per use (ranged 0.1 - 1 grams);
(6) urine test confirmation of methamphetamine use upon admission to the rehabilitation center.
(7) Willingness to be randomized and participate in the study

Exclusion criteria

(1) Acute physical or neurological illness that required immediate pharmacological treatment;
(2) other Axis I disorder of DSM-V criteria such as bipolar disorder, schizophrenia, and depression;
(3) neurological diseases such as stroke, seizure, and migraine;
(4) no mix use with other drugs, e.g. heroin;
(5) Significant suicidal risk/ideation requiring immediate referral

Randomization

The study will conduct a double blind, randomized controlled, parallel group intervention trial. The clinical trial registration was ChiCTR-IOR-16008060 at

http://www.chictr.org.cn. 50 subjects will be randomly assigned into real rTMS (25 subjects) or sham rTMS group (25 subjects) by the researcher who donot directly participate in the study. Age, education history, race, body mass index, length of abstinence, drug abuse history should be matched between the two groups. All subjects will be instructed to receive rTMS treatments, but are blind to the treatments assignment until after the follow-up is completed. Blinded researchers, who will not participate in the treatment sessions, conduct the outcome measures.

4. Study design

Study measurement

Cue-induced craving

The subjects will be asked to play with tools of drug use and faked methamphetamine for 5 minutes. Then, their craving will be assessed by visual analog scales (VAS), with 0 mm being “not at all” and 100 mm representing “very likely to use”.

Behaviour assessment

Withdrawal symptoms

Withdrawal symptoms from methamphetamine were evaluated using a Chinese version of methamphetamine withdrawal symptom scale, which is a 14-item self-reported questionnaire to measure the severity of withdrawal. Each item was rated on a four-point Likert scale, ranging from “0” = never to “3” = very often. The total score is the summary of all items, ranging from 0 to 60.

Sleep

Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI), which is a self-report questionnaire that assesses sleep quality and quantity.

Depression

We will use the Self-rating Depression Scale (SDS) to assess the depression, which is a 20-item self-reported questionnaire to measure the severity of depression symptoms.

Each item was rated on a four-point Likert scale, ranging from “1” = never to “4” = very often. The total score is the summary of all items, ranging from 20 to 80.

Anxiety

We will use the Self-rating Anxiety Scale (SAS) to assess the depression, which is a 20-item self-reported questionnaire to measure the severity of depression symptoms. Each item was rated on a four-point Likert scale, ranging from “1” = never to “4” = very often. The total score is the summary of all items, ranging from 20 to 80.

Assessment timeline

Before the treatment, the subjects will be scheduled for a baseline assessment. Thereafter, subjects will receive the first 5 days treatments. Then these subjects who remain eligible will be instructed to receive behavior measurements for a mid-term assessment. With 2 days rest after the first 5 days, another 5 days intervention will be conducted. And post-treatment assessment will be made after all the treatments are completed. All the subjects will be asked to complete 3-month follow-up assessments. Those with insufficient treatment response at Post-treatment will be withdrawn.

TMS procedures

High (10 Hz) rTMS at 100% MT will be applied over the left DLPFC with a CCY-I TMS instrument (Yiruide Co., Wuhan, China) lasting for 10 days. The round coil (external diameter = 125 mm, internal diameter = 20 mm) will be used, and the size of estimated magnetic field was 52.5 mm and stimulation depth is 1.5-3.0 cm. For 10 Hz stimulation, each session will consist of 5 seconds on and 10 seconds off for 10 min with 2000 pulses in total. Motor threshold will be 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 produce five motor-evoked potentials responses of at least 50 mV in 10 trials. The intensity will be set at 100% of the individual’s resting motor threshold. For sham rTMS, the coil will be turned for 90 degrees to prevent the magnetic field entrance and therefore the brain activation. The

intervention will last for 10 days, with 2 days rest after the first 5 days (totally 12 days).

Adverse experience assessment

We will evaluate the adverse experience at every treatment session. The self-administrated rTMS treatment form will be made to record spontaneous adverse events such as seizure, headache, and dizziness.

5. Data analysis

The data will be analyzed with SPSS 23.0 (Chicago, US). $P<0.05$ was considered as statistically significant. Preliminary data analyses will include descriptive statistics and exploratory graphing such as frequencies, means, standard deviations, box and whisker plots, stem and leaf diagrams, and scatter plots to assess the normality of the data in terms of the presence of skew and/or outliers for both the outcomes and adherence scores. The inter-group differences were examined with independent sample t test or Chi-Square test. A two-way repeated measure ANOVA was used to assess the main effects of groups (real rTMS vs. sham rTMS) and time (before, mid, and after stimulation).

6. Risk

The risks to the subjects include the discomfort of revealing personal information on the behavior assessments, as well as during treatment sessions, and the potential risk for treatment ineffectiveness. Within the scope of rTMS and assessment, subjects may feel discomfort when disclosing personal information to the therapist or assessor. In addition, some cases in previous trials have reported that the rTMS might cause serious adverse events, such as seizures. However, most studies reported that rTMS would not produce significant adverse effects in patients. Thus, as long as the operation of rTMS is standardized, we could prevent these adverse effects.

7. Benefit

Several benefits will be presented to participation in this study: 1) subjects will get comprehensive psychiatric and medical assessments; 2) participants will have carefully monitored intervention and no financial cost; 3) subjects may experience greater improvement in their symptoms of craving, withdrawal, sleep, depression, and anxiety.

8. Confidentiality

Confidentiality will be scrupulously maintained by standard procedures including the use of participant numbers/codes instead of names, the storage of all data including audiotapes in locked cabinets or rooms, and the withholding of all participant information from release without the express written consent of the individual. Data will be entered into Microsoft Access screens which are password protected. All research staff will be trained strictly, and no patient names will be used on research forms that are transmitted to the University.

9. Informed Consent Process

All the subjects will sign the informed consent before the baseline assessment. The subjects will read over the form and have the opportunity to ask questions. The research assistants will be available to answer these questions. Once the participants have signed the consent form, he will be given a copy of it to keep for his records. The research assistant will make it clear that participation is voluntary. Over the course of participation in the study, the research assistant will check in with the subject (during assessments) to ensure the subject's participation is going well and that the subject wishes to continue.