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# Repetitive transcranial magnetic stimulation for symptomatic improvement of amphetamine-dependent patients after withdrawal

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***ABSTRACT. Objective:*** *To investigate the effect of repetitive transcranial magnetic stimulation (rTMS) on the symptoms of amphetamine-dependent patients after withdrawal.* ***Method:*** *71 patients with amphetamine-dependent patients were randomly divided into study group and control group. The study group received system rTMS. Treatment, the control group received pseudo-stimulation treatment similar to rTMS, a total of 5 times. At baseline and after the first and fifth treatments, the visual analog scale (VAS) and the amphetamine withdrawal symptom assessment scale were used to assess the patient's psychological craving and symptoms after withdrawal.* ***Results:*** *After one magnetic stimulation treatment in the study group and the control group, the scores were lower than the baseline scores ($p<0.05$). After 5 treatments, the study group scores were lower than the baseline scores ($p<0.05$), and the control group scores and baseline values were not statistically different. After the fifth magnetic stimulation, the study group's symptom scores, emotional disorder scores, physical symptoms scores, and withdrawal scores of the amphetamine withdrawal symptom scale were lower than the baseline scores. There was no statistical difference between the control group scores and the baseline values. Regression analysis showed that the total score of withdrawal symptoms before and after intervention in the study group was positively correlated with baseline VAS values and duration of drug use.* ***Conclusion:*** *rTMS can significantly improve the symptoms of amphetamine-dependent patients after withdrawal, and it is safe and worth promoting.*

***Keywords:*** *Repetitive transcranial magnetic stimulation; amphetamines; amphetamine withdrawal symptoms.*

## 1. Introduction

Amphetamine-type stimulants (ATS) are a group of central nervous system stimulants with similar chemical structures, including amphetamine, methamphetamine , 3,4 - Methylene dioxyamphetamine (MDMA, Ecstasy), etc., has pharmacological and toxicological properties such as hallucinogenic, appetite suppression and sympathomimetic effects. Data indicate that amphetamine-type stimulant dependence and abuse have become a serious social problem. Repetitive trans-cranial magnetic stimulation (rTMS) is a new neuroelectrophysiological technique developed on the basis of TMS. In recent years, it has been widely used in the field of neuropsychiatric diseases, and it has been found that patients who are dependent on some substances can lower the state of craving. In this study, patients with amphetamine-dependent drug dependence were treated by repeated transcranial magnetic stimulation to observe their psychological craving and symptom improvement. The report is as follows.

## 2. Research objects and methods

### *2.1 Research object*

A total of 71 amphetamine-dependent drug dependent patients received compulsory detoxification from the Lion Rock Compulsory Drug Rehabilitation Institute in Hubei Province from July 2016 to July 2017.

Inclusion criteria: (1) compliance with ICD-10 amphetamine-dependent diagnostic criteria; (2) age over 18 years; (3) only amphetamines in the past 12 months; (3) urine drug testing As a result, only amphetamine-type drugs were shown to be positive;

Exclusion criteria: (1) brain organic disease, history of head trauma, obvious mental retardation, history of seizures. (2) Severe physical illness. Such as severe heart disease, liver and kidney diseases. (3) Merger of heroin, marijuana, K powder and other abusers.

All respondents were informed of the study content, volunteered to participate in the study and signed informed consent.

### *2.2 Research tools*

(1) Substance Usage Survey Form: The general socio-demographic data (including name, gender, age, marital status, cultural level, place of residence, etc.) of the study subjects, the number of drug abusers, and the first drug use were collected using a self-made general information questionnaire. Age, duration of drug use, frequency of smoking, dose, smoking or drinking.

(2) Visual Analog Scale (VAS): One end of the horizontal line is "0", indicating that there is no craving; the other end is "10", which means extreme craving; the middle part indicates different degrees of craving. Let the subject choose a value that is representative of their craving from a number from 0 to 10 based on self-perception. The higher the value, the higher the degree of craving.

(3) Symptom rating scale after amphetamine withdrawal: This scale was compiled by Xiangya Hospital of Central South University and contains four factors (craving, mood disorder, physical symptoms, psychotic symptoms, 20 items), the internals of the scale The coefficient of agreement is 0.846, and the correlation coefficient between each factor and the total score of the scale is 0.488-0.762; the correlation coefficient between each factor is 0.166-0.409. The letter and validity of the scale are in line with the requirements of psychometrics.

(4) Transcranial magnetic stimulator: CCY-I transcranial magnetic stimulator produced in Wuhan was used.

(5) Biofeedback induction: The biofeedback test process is divided into two phases according to different functions. The first phase is the baseline test. The baseline test time is 2 minutes, the screen plays a picture of neutral stimuli, and the landscape picture. The second stage is clue induction. The time is 2 minutes. First, 30 pictures of drugs or drug-using scenes are presented. Each picture is displayed for 2 seconds. Then, two video clips recording the drug use are played, and each video clip is played for 30 seconds. Scale testing and evaluation were performed immediately after induction.

### *2.3 Research methods*

The subjects were divided into study group and control group by random number

method. VAS baseline assessment and amphetamine withdrawal symptom assessment scale were evaluated before intervention, and VAS assessment was performed immediately after biofeedback induction. The study group underwent transcranial magnetic stimulation. When the patient was treated, the patient was relaxed in the armchair. The marker point, the right anterior dorsolateral region (DLPFC), and the center of the coil were placed vertically above the marker point. The stimulation frequency was 10 Hz. 20 pulses per sequence, 80 sequences per day, sequence interval 10s, magnetic field strength 80% resting threshold. The control group received pseudo-stimulation treatment similar to rTMS, which was the same as the treatment site and method of true stimulation, but the coil used in the stimulation was a pseudo-coil, and only the stimulation sound was emitted during the treatment, and the stimulation was invalid. Once a day for 5 consecutive days. After the first and fifth interventions, the VAS and amphetamine withdrawal symptom assessment scales were evaluated in both groups, and the adverse events that occurred during the intervention were observed and recorded.

### *2.4 Quality control of data collection*

Before the start of the research project, explain the purpose of the study and fill in the requirements, and sign the informed consent form, and the results of all the information concerning the individual are strictly confidential. Before the project begins, the researchers at the drug rehabilitation center will be trained to familiarize themselves with the research process and operational specifications. When conducting investigations, the research items are interpreted in neutral terms without any suggestive words, and empty items are allowed for items that are unclear or unknown. The unified self-assessment questionnaire was completed in a quiet, independent environment. After the data collection was completed, the researchers handed the data to the designated person for quality control of the scale and entered the data, eliminating 12 questionnaires that did not meet the requirements.

### *2.5 Statistical methods*

Statistical analysis was carried out on the research data using SPSS 22.0. The statistical data in accordance with the normal distribution were measured by

parameters (statistical description and t-test). The non-parametric statistics (u-test) were used for the non-parametric statistics. Statistics (test, Z test). $P < 0.05$ indicates that the difference was statistically significant.

## 3.Research results

### *3.1 Demographic characteristics of ATS dependents*

Among the 59 male ATS dependents, the average age was 28.54±4.66 years old. Marital status: 30 unmarried, 17 married, divorced 11 and separated. Cultural level: 49 in junior high school and below, 9 in high school or secondary school, 1 undergraduate and above. The main place of residence: 9 people in rural areas, 15 townships, 31 people in prefecture-level cities, and 4 in large cities such as provincial capitals. Forty-five people were attracted and 14 were relapsed. The average age of the first intake: 22.05 ± 4.07 years old. The average duration of drug use: 5.96 ± 3.44 years. Frequency of smoking: 12 people use almost every day, 33 people 3-5 days a week, 9 people once a week, 5 people 1-3 times a month. The average dose was taken daily: 0.55 ± 0.32 g. All 59 people combined with smoking, and 37 of them also combined drinking. There were no significant differences in age, marital status, education, place of residence, frequency of smoking, etc. between the two groups.

### *3.2 Comparison of VAS scores between baseline and after treatment in both groups*

After the biopsy-induced clue induction in the study group and the control group, the VAS score was higher than the baseline score ($p<0.05$). After a magnetic stimulation treatment, the scores of the study group and the control group were lower than the baseline score ($p<0.05$). After 5 treatments, the study group scores were lower than the baseline scores ($p < 0.05$). See Table 1.

*Table 1 Comparison of VAS scores between baseline and after treatment in both groups*

| Time | Study group (n=31) | Control group (n=28) | T value | P value |
|---|---|---|---|---|
| Baseline | 3.35±1.94 | 3.79±1.64 | -0.915 | 0.364 |
| After induction | 3.90±2.07* | 4.75±1.92* | -1.624 | 0.110 |
| After the first treatment | 2.90±1.72* | 3.50±1.64* | -1.359 | 0.180 |
| After the fifth treatment | 2.23±1.56* | 3.64±1.47 | -3.574 | 0.001 |

Note: compared to baseline * $p<0.05$

### *3.3 Comparison of symptom scores of amphetamine withdrawal syndrome at baseline and after treatment in both groups*

After the fifth magnetic stimulation, the study group's thirst, emotional, physical, and withdrawal scores were lower ($p<0.05$) than the baseline scores after the amphetamine withdrawal symptom rating scale; see Table 2.

*Table 2 Comparison of the scores of symptom scores between the two groups at baseline and after treatment with amphetamine withdrawal syndrome*

| Time | Withdrawal scale | Study group (n=31) | Control group (n=28) | T Value | P Value |
|---|---|---|---|---|---|
| Baseline | thirst score | 1.23±0.81 | 1.18±0.72 | 0.236 | 0.814 |
| | Emotional Disorders score | 3.87±3.12 | 3.61±2.91 | 0.335 | 0.739 |
| | Somatic symptoms score | 5.03±2.68 | 6.21±3.18 | -1.550 | 0.127 |

| | | | | | |
|---|---|---|---|---|---|
| | Total withdrawal points | 10.13±5.27 | 11.00±5.93 | -0.598 | 0.552 |
| After the first treatment | thirst score | 1.03±0.84 | 1.39±1.13 | -1.400 | 0.167 |
| | Emotional Disorders score | 3.03±2.82 | 3.39±2.38 | 0.902 | 0.371 |
| | Somatic symptoms score | 4.97±2.43 | 5.21±2.43 | -0.390 | 0.698 |
| | Total withdrawal points | 9.03±4.92 | 10.54±3.89 | 0.254 | 0.800 |
| After the fifth treatment | thirst score | 0.45±0.57* | 1.46±0.51 | -2.294 | 0.025 |
| | Emotional Disorders score | 1.29±1.24* | 2.79±1.79 | -3.753 | 0.000 |
| | Somatic symptoms score | 3.81±2.51* | 5.89±2.01 | -1.602 | 0.115 |
| | Total withdrawal points | 5.61±3.32* | 9.96±3.37 | -3.350 | 0.001 |

Note: compared to baseline * $p<0.05$

### *3.4 Analysis of factors influencing the scores of the total points of the withdrawal syndrome scale of the study group*

The study group withdrawal symptom scale total score improvement score (baseline value - the fifth post-treatment score) was the dependent variable, and the independent variables were age, initial drug use age, drug use duration, daily drug use dose, and VAS baseline value. 5 consecutive numerical variables, and whether to

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drink (yes, no = 0), whether to relapse (relapse = 1, initial absorption = 0) two two-category dummy variables. The coefficient of determination of the regression analysis was 0.374, F=1.239, p<0.05. The duration of drug use and the VAS baseline had an effect on the score of the total score of the withdrawal symptom scale. See Table 3.

*Table 3 Multiple regression analysis of the scores of the total points of the withdrawal symptom scale*

| Model | | Unnormalized coefficient | | Normalization coefficient | t | Significant |
|---|---|---|---|---|---|---|
| | | B | Standard error | Beta | | |
| 1 | (constant) | -6.898 | 5.669 | | -1.217 | .229 |
| | Whether to drink | 1.173 | 1.504 | .108 | .780 | .439 |
| | Whether to relapse | 1.720 | 1.666 | .139 | 1.033 | .307 |
| | Age | -.530 | .447 | -.463 | -1.184 | .242 |
| | Age of first drug use | .703 | .442 | .538 | 1.592 | .118 |
| | Drug abuse lasts for several years | .534 | .451 | .346 | 1.185 | .032 |
| | Daily dose | 1.315 | 2.205 | .080 | .596 | .554 |
| | VAS baseline | .678 | .423 | .230 | 1.600 | .046 |

a. Dependent variable: Withdraw progress, only case b with group = 1

## 4. Discussion and analysis

### *4.1. Progress in the study of amphetamine-based drugs after withdrawal symptoms*

Methamphetamine is a highly dependent psychoactive substance. If repeated abuse can cause serious psychological dependence, once the dependent person interrupts the consumption of methamphetamine, it can cause severe withdrawal reaction, mainly manifested by anxiety and strong psychological craving. And symptoms of physical discomfort. According to the theory of opposing processes, the researchers believe that amphetamine-only withdrawal symptoms are a compensatory response to euphoria, energy, and behavior after taking it. Amphetamine-type stimulants can enhance euphoria, pleasure, and fatigue by enhancing the release of presynaptic dopamine in the brain and preventing re-uptake. When the efficacy disappears, drug withdrawal symptoms such as lack of interest, fatigue, and anxiety will appear,the longer the withdrawal time, the more severe the withdrawal symptoms will be and will gradually weaken after several weeks. At the same time, most of the long-term use of amphetamines have symptoms of acute or chronic brain damage, or combined with physical damage. Therefore, after the abortion of amphetamines, the clinical manifestations of dependent patients may be far more than the simple amphetamine ring. Symptoms, in general, the symptoms appear after amphetamine withdrawal are more complicated, to be carefully evaluated and choose an effective treatment plan [1] [2] [3].

In 1994, DSM set the diagnostic criteria for symptoms after amphetamine withdrawal as a large and continuous use of amphetamine. After discontinuation or reduction, emotional disorders and two (or more) of the following physiological changes: fatigue; clear, unpleasant Dream; excessive insomnia or sleep; increased appetite; mental retardation or agitation. After domestic factor analysis by Yang Liu and Wei Hao, the symptoms of amphetamine withdrawal were divided into the following four factors: first, physical symptoms, mainly insomnia; slow movement; strong appetite; fatigue; increased sleep; inattention Short-term memory loss. The second is emotional disorders, mainly characterized by anxiety; irritability; impulsivity; irritability; depression; lack of interest. The third is psychiatric disorders, lack of self-awareness; hallucinations; sloppy thinking; suspicion; delusion. The fourth is psychological craving.

Studies have shown that the strong psychological cravings and physical and mental symptoms of amphetamine-type stimulants after withdrawal are important causes of relapse. Therefore, effective interventions for symptoms after withdrawal from amphetamines are needed to reduce relapse rate and reduce drug use. Social harm is of great significance.

### *4.2. rTMS improves the craving caused by amphetamine-dependent drug dependence and its mechanism*

There is currently no specific treatment for post-withdrawal symptoms caused by the abuse of amphetamine-type stimulants. rTMS (repetitive transcranial magnetic stimulation) is a non-invasive, non-invasive physical therapy developed at home and abroad in recent years, and has been widely used in the treatment of substance addiction. rTMS mainly generates magnetic fields on the coils according to the principle of electromagnetic exchange. The magnetic field penetrates the skull into the cerebral cortex, and triggers local small electric currents in the cerebral cortex to change the local bioelectrical activity of the cerebral cortex, thereby playing a therapeutic role. [4].

Foreign meta-analysis indicates that rTMS stimulates drug-addicted patients in the dorsolateral prefrontal (DLPFC) region, which plays an important role in the impulse suppression loop and the reward loop, for nicotine, alcohol, cocaine, codeine, methamphetamine The degree of craving for abusers has been improved to varying degrees [5]. Recent studies in China have also shown that rTMS has a certain therapeutic effect on schizophrenia, depression, multiple tic disorder in children, and chronic alcoholism [6] [7] [8] [9]. Zhu et al.'s research shows that rTMS has an improved effect on anxiety and psychological craving symptoms of methamphetamine dependent patients [10].

After the induction of biofeedback in this study, the psychological cravings of the study group and the control group were successfully awakened, and the VAS score was increased. After the first 8000 pulses of right-sided DLPFC high-frequency repetitive transcranial magnetic stimulation treatment, the study group and the VAS score of the control group was reduced, but after 5 times (40,000 pulses) of repetitive transcranial magnetic stimulation, the VAS score and the

baseline score of the study group were statistically significant, while the control group had no statistical comparison with the baseline. Learning meaning. Further examination of the symptom scores after amphetamine withdrawal test also confirmed that after 5 times of rTMS treatment, the study group's craving score was statistically different from the baseline score, while the control group was not statistically significant. The results suggest that high frequency (10 Hz) rTMS treatment can effectively reduce the psychological craving of patients with amphetamine-dependent patients.

### *4.3. rTMS improves brain damage caused by amphetamine-dependent drug dependence and its mechanism*

Studies at home and abroad have shown that amphetamines cause brain damage, long-term abuse can lead to neuronal cell death in the striatum, hippocampus and frontal cortex, and progress to acute and chronic recurrent encephalopathy, making the addicts a series of characteristics Brain dysfunction, manifested as psychotic symptoms such as hallucinations, mental personality, paranoid personality, impulsive personality and other personality changes, memory loss, decreased concentration of attention, etc. [12].

Neurophysiological studies have found that the dorsolateral prefrontal cortex (DLPFL) is highly correlated with the limbic brain region and plays an important role in mood regulation. At the same time, high frequency rTMS (10-20 Hz) facilitates local neuronal activity. Increased cortical excitability. In recent years, it has been found that different cortical regions stimulated by PET and MRI can excite deep nuclear nuclei in the brain, causing changes in neurotransmitters, hormones, brain-derived neurotrophic factors, blood flow and metabolism, and regulating brain function through various mechanisms. [13].

The sample of this study was from the strong clinic. Among the 59 male ATS dependent patients, the average duration of drug abuse was 5.96±3.44 years, the frequency of smoking was 12 people used almost every day, and 33 people used 3-5 times a week. Nine people once a week, 5 people 1-3 times a month, the average daily dose was 0.55 ± 0.32g, indicating that the sample of this study is a long-term large number of people taking amphetamines. The duration of drug use in this study

and the VAS baseline had an effect on the score of the total score of the withdrawal symptom scale. The regression analysis of this study showed that the duration of drug use and the VAS baseline had an effect on the score of the total score of the withdrawal symptom scale, indicating that the longer the drug use time, the higher the baseline craving score, the more obvious the improvement of symptoms after withdrawal. It is indicated that high-frequency rTMS treatment of the dorsolateral prefrontal cortex (DLPFL) can effectively improve the symptoms of brain damage in patients taking amphetamines for a long time. This finding is also consistent with the neurophysiological findings mentioned above.

This study found that none of the patients in the experimental group found complaints of discomfort, indicating that high-frequency rTMS is safe and has no side effects. In general, rTMS can effectively improve the psychological craving, anxiety and depression of amphetamine abusers, improve symptoms such as impaired attention, memory loss, decreased emotional control, and other symptoms of impaired brain function and withdrawal symptoms, high security , which is worth further promotion.

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