

## Abstract

**Objective:** The present study was an attempt to examine the effect of repetitive transcranial magnetic stimulation (rTMS) on the reduction of Behavioral Activation System's activity in right and left dorsolateral prefrontal cortex among methamphetamine abusers. **Method:** In the present study, single subject and multiple baseline research designs were used and repeated measurements observations were also performed. The number of eight methamphetamine users was selected via convenience sampling method from an addiction treatment center and were put in four situations. Two participants received dorsolateral right prefrontal cortex stimulation with frequency of 10 Hz, two of them received dorsolateral left prefrontal cortex stimulation with frequency of 10 Hz, two participants received placebo, and the other two ones were in the control state; all of them were evaluated at the end of the fifteenth session. Then, the research data were analyzed using graphical charts, percentage reduction, and effect size. **Results:** Repetitive transcranial magnetic stimulation (rTMS) led to the significant reduction of Behavioral Activation System's activity in both right and left dorsolateral prefrontal cortex among methamphetamine abusers. **Conclusion:** High frequency rTMS is effective in reducing the activity of BAS in methamphetamine users.

**Keywords:** Repetitive Transcranial Magnetic Stimulation (rTMS); Dorsolateral Pre-Frontal Cortex; Behavioral Approach System (BAS); Methamphetamine

# On the Effect of High Frequency Repetitive Transcranial Magnetic Stimulation (rTMS) on the Reduction of BAS Intensity in Methamphetamine Abusers

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## Introduction

Substance abuse is a serious social issue around the world. The generation of hazardous synthetic and laboratory substances has added to the problems of substance use intervention. One of these hazardous substances is methamphetamine. Methamphetamine is a powerful stimulant that dramatically affects the central nervous system, spinal cord, and sympathetic system (Fetherston & Lenton, 2004). Among amphetamines, methamphetamine brings the most important risk for addiction and mental health problems (Topp, Degenhardt, Kaye & Darke, 2002). The crystallized form of methamphetamine in our country is known as glass, which is one of the main substance that is used by addicts. The consumption of this substance, as a stimulant, is prevalent among young people in many countries. In recent years, drug abuse patterns have undergone considerable changes in Iran with the dramatic escalation of crack, heroin, and methamphetamine (Razzaghi, Rahimi Movaghar, Hosseini, Madani & Chatterjee, 1999).

American Psychiatric Association Diagnostic and Statistical Manual-IV criteria are also applied for dependence and abuse of amphetamines and related substances, as well. Amphetamines dependence can cause a rapid decrease in a person's ability to cope with job stress and family obligations. Methamphetamine abusers usually take increasing doses of this drug to reach the ecstatic state and, thereby, physical and psychological symptoms almost always occur with the continued abuse of this drug (Kaplan & Sadock, 2008). Amphetamines and methamphetamines have a similar activity mechanism and both of them cause the release of monoamine neurotransmitters (dopamine, serotonin, and norepinephrine) and increase the levels of this substance in the extracellular space (Fetherston & Lenton, 2004). The sense of vigilance, wakefulness, increased energy, rush, and decreased appetite are among the effects of methamphetamines. After the initial rush caused by the consumption of methamphetamine, a sense of irritability is activated in the person and may lead to the incidence of aggressive behaviors. Methamphetamines particularly increase the release of dopamine in the striatum. This section includes caudate, putamen, and ventricular striatum and is rich in dopamine receptors. Ventricular striatum entails nucleus accumbens, which is an area of interest in the study of addiction. Research shows that the disruption of nucleus accumbens reduces the risk of relapse in some of the opioids addicts (Gao et al., 2003).

Long-term abuse of amphetamine/methamphetamine can lead to addiction. Research has shown that addiction is a chronic and relapsing disease when it is followed by functional and molecular changes in the brain. In this situation, the person continues search behaviors for drugs despite dangerous and evil consequences awaiting him/her. Methamphetamine increases the degree of release of dopamine- a chemical that leads to feelings of pleasure (International Substance Abuse & Addiction Coalition, 2006). In addition to specific physical

health problems, such as AIDS; addiction brings about mental and psychological problems, as well (Ekhtiari, 2008). Addiction as a brain illness is an approach that has been spread in recent years across the world and is one of the most successful theoretical approaches in this domain.

The World Health Organization and American Psychiatric Association have defined addiction as a chronic disease with a strong urge to drug use and its related problems. The growth of related studies is indicative of the existence of physiological backgrounds for the incidence of clinical problems in the patients affected by chronic substance abuse (Nemati Moghaddam, 2008). In this regard, various studies have been conducted within the framework of different theories. For instance, an extensive related literature has evaluated the relationship of personality factors with substance abuse and the results suggest the key role of psychosis in alcohol and drug abuse. Sensation seeking is another personality structure whose relationship with substance abuse has been widely studied. Sensation seeking, as a personality trait, has neurochemical foundations, which means the need to stimulate the individual. The individuals with high sensation seeking trait are more vulnerable to drug abuse and it is more likely that the reinforcing effects of drugs are more pleasant to these individuals (Gennadij & Knyazev, 2004).

Gray's theory (1970) is also among the leading theories that underlie extremely extensive research on substance abuse, alcohol, and cigarettes (cited in Gennadij & Knyazev, 2004; Knyazev, 2004; Knyazev et al., 2004). In recent decades, research in various fields of psychology has introduced two separate systems that shape human behavior (Carver & White, 2006; Fowles, 1994; Higgins, 1998). Although these approaches have applied different words, the main idea is belief in the existence of two separate but similar brain systems. Here, appetitive system is sensitive to the signs of reward and orient behaviors to the achievement of rewards. In contrast, the aversive system is responsible for punitive stimulations and prevents the behaviors that lead to punishment. Reinforcement sensitivity theory is one of these two-system approaches, which introduces the existence of behavioral approach system (BAS) and behavioral inhibition system (BIS) (Daniel et al., 1994). Reinforcement sensitivity theory is a biologically oriented theory that argues personality differences of people are rooted in the differences in their reward systems. Behavioral inhibition system is responsible for organizing behaviors in response to the stimuli that have been conditioned aversive events. More specifically, this system is related with the punitive stimuli or the stimuli that do not have reward or whose reward is coming to an end or the very intense and severe stimuli or the stimuli that are intrinsically scary (blood, snake). These stimuli can lead to behavioral inhibition (disruption of any type of output behavior), increased levels of stimulation (so that the next behavior will proceed with higher speed and power), and an increase in attention (so that more information can be received) (Gray, 1987; Gray, 1970). This system is the result of the activities of afferent, noradrenergic, and serotonergic

afferent pathways. The neuroanatomy of behavioral punishment system in the septohippocampal system, brainstem, papez circuit, and orbital frontal cortex (Hasani, Bigdelli & Ghooshcian, 2007).

BAS is responsible for organizing the behaviors that respond to pleasant stimuli. This system is sensitive to the unconditioned reinforcing stimuli free of punishment. The sensitivity of this system represents impulsivity (trait impulsivity) and is associated with motivation, extraversion, and sensation-seeking (Gray, 1987). The neuroanatomical basics of this system, which are structurally related with routes of brain dopaminergic system and Cortico-Striato-Pallido-Thalamic (CSPT), are located in the prefrontal cortex, the amygdala, and the basal ganglia (Hasani et al., 2007). BAS, which is sensitive to signs of reward, leads the person to show these behaviors, as we know drug abuse is the combined result of various factors. As the person is involved in the greater number of risk factors, s/he will be exposed to a higher risk of substance abuse because the existence of multiple risk factors are effective both in the onset of substance use and the amount of the following substance use (Minooei & Salehi, 2003; Zuckerman, 1994). Individual differences in behavioral inhibition system and behavioral activation system are indicative of key dimensions of personality. Gray views disorders as the reflection of the hyperactivity and low activity of one of these systems (Pickering & Gray, 2001). The association of high activity of BAS with addictive behaviors has been demonstrated in previous studies (Franken & Muris, 2006; Hundt, Kimbrel, Mitchell & Nelson- Grey, 2008; and O'Connor, Stewart & Watt, 2009).

Given that BAS activities push the person to do things that are followed by the probability of receiving reward (without taking into account the possible negative consequences), the sensitivity of this system is considered as a factor in the spread of drug abuse (Patricia, Ilse, Laurence & Walter, 2009). Hence, it seems necessary that the impact of this new therapeutic method, i.e. cranial magnetic stimulation on the decrease of the sensitivity of BAS. In fact, this system is an important factor in the development of addictive behaviors and it seems that the reduction of the sensitivity of this system can lead to the prevention of drug use and reduction of the continuity of drug use.

Transcranial Magnetic Stimulation (TMS) is a powerful and successful noninvasive technique, which is a valuable technique for research and treatment of diseases in the medical profession and psychiatry (Hando, Topp & Hall, 1997). Many studies have shown that RTMS can lead to long-term behavioral changes, including reduced craving for drug use and reduced substance abuse (Wagner, Valero-Cabre & Pascual-Leone, 2007). In this method, a strong electric current creates magnetic fields after passing through the coil that is placed on one's head. These magnetic fields lead to a milder electrical current in the cerebral cortex and, thereby, action potential is stimulated in the nerve tissue. Magnetic stimulation devices are able to produce waves with a frequency of 1 to 100 Hz that can create stimulating or inhibitive effects with respect to the

type of frequency. Although there is not a clear understanding of the action mechanism of this method, evidence attributes the possible changes induced by repetitive magnetic stimulation to the effect on neurotransmitters and neuroplasticity of nerve cells (Ziemann, 2004). Repetitive magnetic stimulation has been introduced as a tool in the study and treatment of addiction disorders due to its effect on the cortical excitability and neurotransmitter dopamine. In previous studies, the effects of RTMS with high frequency on changing the dopamine transporter, rewarding as well as the reinforcing effects of RTMS have been investigated (Camprodon, Martinez-Rega, Alonso, Shih & Pascual-Leone, 2007; Eichhammer et al., 2003; Amiaz, Levy, Vainiger, Grunhaus & Zangen, 2009). Based on the above-mentioned review of literature, the main question of this study is formulated as follows: Can rTMS with the frequency of 10 Hz in 15 sessions of 3,500 pulses reduce the sensitivity of BAS among methamphetamine users?

## **Method**

### **Population, sample, and sampling method**

In this study, a single subject method and multiple baseline research design were used based on the objective and limitations of the study and repeated observations or measures were fulfilled. The population of this study included the methamphetamine abusers who had referred to Atiyeh rehabilitation clinic in Tehran in winter 2010. From this population, eight patients were selected. It is notable that these patients had been diagnosed as methamphetamine abusers by a psychiatrist based on American Psychiatric Association Diagnostic and Statistical Manual-IV criteria. The patients willing to participate in the project were selected by convenience sampling method if they met the inclusion criteria (age range of 18 to 32 years, completion of the informed consent form, treatment test under the supervision of psychiatrists, a fixed amount of methadone or especially Nurofen to the end of the project) and they did not have the exclusion criteria. The exclusion criteria included treatment via rTMS for each disorder, a history of stroke or seizure in the person or his/her family, a history of bipolar disorder or a psychotic symptoms, pregnancy or intention for it, availability of a metal, dentures, and implants in the skull or pacemakers. The eight selected sample units were randomly divided into four states, i.e. two individuals for stimulation on the right dorsolateral prefrontal cortex, two individuals for stimulation on the left dorsolateral prefrontal cortex, and two individuals for the control group. In addition, two participants were randomly selected as the placebo patients and experimental and intervention conditions were the same about them. This means that they received the relevant experiments and went for treatment each session and the virtual coils were set on their cranium without receiving the stimulation similar to the intervention group. Four sessions before rTMS were set as the base line for all the participants. When the person reached

a fixed line, s/he would be put under stimulation for fifteen sessions on a daily basis (except holidays); and the related questionnaire was administered at the end of the first, third, seventh, tenth, thirteenth, and fifteenth sessions.

### **Instrument**

**BIS/BAS:** In this research, Carver & White's questionnaire (1994) was used. This questionnaire contains 24 items that are scored using Likert scale. Seven items out of these 24 ones belong to BIS and 13 items pertain to BAS. Behavioral activation system scale (BAS) consists of three subscales, namely drive (4 items), fun seeking (4 items), and reward responsiveness (5 items). In addition, four statements are misleading that are not scored. Cronbach's alpha coefficients of .77, .73, .76, and .71 were reported for BIS, drive, fun seeking, and reward responsiveness, respectively (Carver & White, 1994). The device of treatment parameters was used for the application of magnetic stimulation according to international guidelines that were passed for optimal parameters in 1996 (George, Wassermann & Kimbrell, 1997). In this regard, the frequency of 10 Hz, 5 seconds of stimulation, 14 second-interval between each stimulation, and the intensity of 110% incipient motion were determined. In total, 3500 pulses were considered for each participant in each session. Since this study is an interventional research, the ethical criteria and conditions of the American Psychological Association and also the ethical and moral criteria of Psychology and Counseling Organization of Iran were observed (Hosseini, 2006). In this study, a written consent was also developed according to the above criteria and the participants delivered a completed written consent about participating in the research project and sufficient explanation on the magnetic stimulation and treatment processes they were supposed to undergo. Then, the treatment process and the potential risks were fully described to them.

### **Results**

In the following table, the descriptive statistics relating to demographic variables are presented.

**Table 1. Descriptive statistics of demographic variables for each group**

<i>Patients</i>	<i>Gender</i>	<i>Age</i>	<i>Education</i>	<i>Marital status</i>	<i>Groups</i>
<b>1. N.M.</b>	Male	34	Secondary school	Single	Experimental left DLPFC
<b>2. A.Z.</b>	Male	28	Associate's degree	Single	Experimental left DLPFC
<b>3. A.A.</b>	Male	25	Associate's degree	Single	Placebo left DLPFC
<b>4. M.S.H.</b>	Male	27	Diploma	Single	Experimental right DLPFC
<b>5. B.A.</b>	Male	31	Diploma	Single	Experimental right DLPFC
<b>6. A.K.</b>	Male	27	Associate's degree	Single	Placebo right DLPFC
<b>7. K.S.H.</b>	Male	22	Diploma	Single	Control
<b>8. M.V.</b>	Male	26	Bachelor's degree	Single	Control

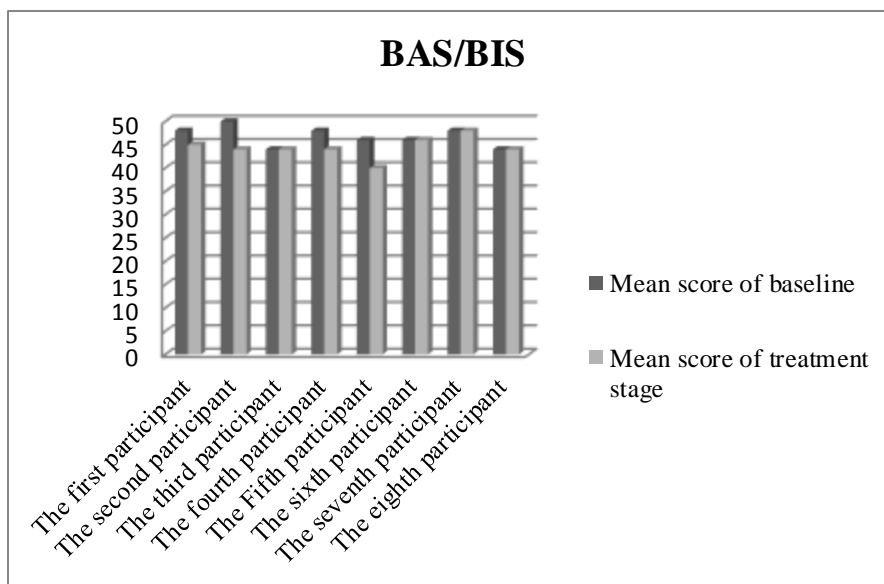
In the table below, the variations in the questionnaire scores have been presented in the form of mean of baseline scores and mean scores at the time of stimulation for the 8 patients participating in the study. Moreover, the reduction percentage and effect size of the treatment stage have been compared with those of the stimulation and baseline stages.

**Table 2. Score variations of the subjects on the pretest, posttest, and reduction percentage, and effect size based BIS/BAS questionnaire**

<i>Patients</i>	<i>Variables</i>	<i>Mean</i>		<i>Decrease percent</i>	<i>SD</i>		<i>Effect size</i>
		<i>Baseline</i>	<i>Treatment period</i>		<i>Baseline</i>	<i>Treatment period</i>	
<b>1. N.M.</b>	BAS	48	45	.57	6.25%	1.82	3
	BIS	22	22	0	-	0	-
<b>2. A.Z.</b>	BAS	50	44	.81	12%	1.52	6
	BIS	20	20	0	-	0	-
<b>3. A.A.</b>	BAS	44	44	0	-	0	-
	BIS	22	22	0	-	0	-
<b>4. M.S.H.</b>	BAS	48	44	.81	8.33%	2	2
	BIS	22	22	0	-	0	-
<b>5. B.A.</b>	BAS	46	40	1.48	13%	2	4
	BIS	23	23	0	-	0	-
<b>6. A.K.</b>	BAS	46	46	0	-	.5	-
	BIS	23	23	0	-	0	-
<b>7. K.S.H.</b>	BAS	48	48	.5	-	0	-
	BIS	22	22	0	-	0	-
<b>8. M.V.</b>	BAS	44	44	0	-	0	-
	BIS	25	25	0	-	0	-

Plots, effect size, and percentage of decrease (when reduction of the behavior is aimed) were used to analyze the collected data. For data analysis, chart and graphical analyses were employed. In addition to chart and graphical analyses of the data, percentage of recovery (and percentage of decrease) was also used to evaluate the clinical significance of changes and the analysis of single-case experimental data. The effect size has been calculated in this study by using a method that is based on the mean and standard deviation (d Cohen) (Cohen, 1992).

The following chart shows the mean scores in the baseline and treatment stages for all eight participants.



**Chart 1: Mean of treatment and baseline scores for the eight participants**

### Discussion and Conclusion

The aim of this study was to investigate the effect of repetitive transcranial magnetic stimulation (rTMS) on the reduction of Behavioral Activation System's activity in right and left dorsolateral prefrontal cortex among methamphetamine abusers. The results showed that rTMS with frequency of 10 Hz is effective in the reduction of activity of this system among methamphetamine abusers. According to the results of this study, the reduced percentages for the first participant, the second participant, the fourth participant, and the fifth participant were equal to 6.25%, 12%, 8.33%, and 13%, respectively. As per the data obtained in table 2, it can be claimed that the variations and changes (i.e., effect size of the treatment) are very high for all the four participants in the intervention group who received stimulation in both right and left dorsolateral prefrontal cortex. There was a higher decline percentage in the fourth and fifth subjects who received stimulation in the right prefrontal cortex than the first and second subjects who received stimulation in the left prefrontal cortex area.

RTMS on the neurotransmitter OF dopamine leads to long-term changes and this can be the reason for the beneficial results obtained in methamphetamine abusers. Dorsolateral prefrontal cortex is one of the most important areas of stimulation for addiction (Strafella, Paus, Barrett & Dagher, 2001). Different mechanisms have been described for the effect of repetitive transcranial magnetic stimulation on the prefrontal cortex. First, stimulation in this area can lead to the drop of dopamine in the subcortical caudate nucleus (Fitzgerald,



Brown, Daskalakis, Chen & Kulkarni, 2002). Second, this can result in the direct stimulation of target areas and the impact of stimulation on the opposite hemisphere cortex increases and subcortical activity is stimulated in the neural network connected to the areas. In addition, studies have reported repetitive magnetic stimulation to be associated with positron emission tomography in trans-cortical stimulation and 10 Hz extracellular dopamine in areas of the prefrontal cortex (Fitzgerald et al., 2002). Therefore, prefrontal cortex was considered as the stimulation area. Based on research findings, high-frequency repetitive transcranial magnetic stimulation on left prefrontal cortex increases the dopamine secretion in the caudate nucleus of the same side (Berman et al., 2000; Loo et al., 1999).

Fowles suggest that substance abuse is the result of the dominance of BAS over BIS and this relationship has been highly confirmed in research. He states that the dominance of BAS over BIS creates impulsive mood and leads one to positive reinforcing changes regardless of the subsequent negative results of drugs (Fowles, 2001). Gray (1993) suggests that the dopamine released in the nucleus accumbens has a very close relationship with the emotional zenith of alcoholics and drug abusers. In other words, people with behavioral active system are more susceptible to get engaged in situations with a high probability of reward (Carver, 1994; Dawe & Loxton, 2004). The effect of rTMS on cortical stimulation depends on stimulation parameters, including identification of the position, magnetic field, stimulation with single pulse or repeated pulse, stimulation frequency, the number of pulses, intensity and direction of stimulation (George et al., 1997; Grunhaus et al., 2000). In the present study, the conduct of 15 successive treatment sessions can be one of the reasons for the effectiveness of rTMS in sensitivity reduction of BAS. It is possible that this factor has made probable long-term changes in nerve cells (Klein, Kreinin & Chistyakov, 1999; Menkes et al., 1999). The intensity of stimulation is among the other effective factors in rTMS (Erhardt et al., 2004). Due to the important role of rTMS in making long-term changes in cortical excitability, the intensity of 110% incipient motion was applied in this study wherein motor evoked potential is created. Indeed, it is more likely to produce positive results. The use of control or case group and also placebo group is one of the advantages of this research in that the findings revealed that the group who received stimulation experienced higher treatment effects than the control or placebo group. In fact, the advantage of this method was shown by placebo since treatment results were not obtained in the placebo group. Today, the studies that have been conducted on the usefulness of brain stimulation for behavioral modification and neurochemical changes related to drug abuse have led to the findings consistent with that of the present study (Gershon, Dannon & Grunhaus, 2003; Loo et al., 2003; Ernst, 2002). In the present study, rTMS in both the left and right dorsolateral prefrontal cortices has led to the decrease of BAS activity in methamphetamine abusers. However, the remarkable thing in this study is the

fact that the effect of rTMS may depend on reduced methamphetamine abuse in a complex way and reduced methamphetamine use leads to a decrease in anxiety, depression, sensation seeking, and craving for drug use; or the fact that rTMS results in a reduction in the activity of this system by itself (Mansouriyeh, Mahmoud Alilou, Rostami & Hashemi, 2012). Generally, the resolution of this issue is complex and the exploration of these relationships require further research in this field. The consideration of the environmental and neurologic infrastructure can be a step towards improving the treatment of substance abuse. In addition, the identification of the exact neurological routes by means of advanced new systems, such as FMRI and PET can assist to determine the effectiveness of this method. The small sample size, the exclusive use of male participants, and the use of self-assessment test are among the limitations of this study.

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