

# The Effect of High-frequency Repetitive Transcranial Magnetic Stimulation on Reducing Depression and Anxiety in Methamphetamine Users

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## Original Article

### Abstract

**Background:** Methamphetamine use has been associated with higher rates of depression and anxiety. The mesocorticolimbic dopaminergic reward system seems to play a crucial role in inducing depression and anxiety in methamphetamine users. High-frequency repetitive transcranial magnetic stimulation (rTMS) has been shown to alter dopaminergic neurotransmission considering the acute rewarding and reinforcing effects in the subcortical structure. The aim of this study was to investigate the efficacy of rTMS in reducing depression and anxiety symptoms in methamphetamine users.

**Methods:** In a single-subject method with concurrent multiple baseline designs, in 2017, in Iran, eight methamphetamine users were included, which compared 15 days of active versus placebo stimulation and control group. Two subjects received rTMS on the right dorsolateral prefrontal cortex (DLPFC) and two subjects received rTMS on the left DLPFC. We carried out the measurement using the Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI) before, during, and after 15 and 30 days of the procedure.

**Findings:** Right and left DLPFC stimulation significantly reduced depression and anxiety, but the reduction of depression and anxiety by the right DLPFC stimulation was noticeable in this study.

**Conclusion:** High-frequency rTMS is useful for the treatment of depression and anxiety in methamphetamine users.

**Keywords:** Transcranial magnetic stimulation; Depression; Anxiety; Methamphetamine

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## Introduction

It is estimated that 275 million people have used illicit drugs such as amphetamines.<sup>1,2</sup> Among amphetamines, methamphetamine is the most influential and it carries a higher risk of dependence and mental disorders.<sup>3</sup> Methamphetamine is a lipophilic molecule which exhibits potent action on the sympathetic and the central nervous system (CNS).<sup>4</sup> Despite the fact that a few studies that strictly explore the epidemiological quality assessment of the relationship between psychiatric disorders and methamphetamine dependence have been performed, it has been reported that the majority (~70%) of every convenience sample of methamphetamine users have depression. The use of methamphetamine has a relation to dopaminergic, serotonergic, and noradrenergic transmission and the involvement of a person's mood.<sup>5</sup> Studies of methamphetamine users involved in treatment showed that the symptoms of anxiety and depression were self-reported by two-thirds of the total number of users. Likewise, a survey of 200 amphetamine users demonstrated that anxiety (63%), depression (64%), paranoia (74%), hallucination (28%), panic attacks (21%), and suicidal thoughts (19%) were common psychological symptoms.<sup>6</sup> The available treatment options for addictive behaviours remain limited to date. Furthermore, the long-term success rates are poor.<sup>7</sup>

Transcranial magnetic stimulation (TMS) is a powerful and non-surgical brain stimulation technique. In addition, it has been proven that TMS is valuable for research and therapeutic applications within the field of psychiatric medicine.<sup>8</sup> Repetitive TMS (rTMS), in which trains of several TMS pulses are delivered using various stimulation patterns, is applied to induce long-lasting alterations, facilitation, or functional disruptions.<sup>9</sup> According to the long-term neurophysiological effects of rTMS, significant and long-lasting behavioural alterations can be induced to specifically bring about reduction of craving and drugs consumption.<sup>10</sup>

The brain reward system consists of fundamental neural pathways, which are involved in motivational and rewarding experiences. In addition, the impaired function of the brain reward system is implicated in both drug addiction and depressive behaviour. Furthermore, studies have

reported comorbidity between these two states in both human beings and animals.<sup>8,11</sup> Similarly, associations among neuronal activity increase in the mesocorticolimbic dopamine (DA) system; the acute rewarding and reinforcing effects of addiction have been established in neurobiological studies of drug abuse.<sup>8</sup> It has also been found that stimulant drugs (such as cocaine and amphetamines) induce a direct increase in DA levels within the mesocorticolimbic circuitry.<sup>12,13</sup> The mesocorticolimbic circuitry includes DA projections from the cell bodies in ventral tegmental area (VTA) to limbic structures, for instance, from the nucleus accumbens (NAc),<sup>14</sup> the amygdala,<sup>15</sup> and the hippocampus<sup>16</sup> to the cortical areas such as the orbitofrontal cortex (OFC) and the anterior cingulate.<sup>17</sup> The primary hypothesis on depression that has been proposed in the last three decades shows that the main symptoms of depression are due to the functional deficiency of the brain's monoaminergic transmitters' DA.<sup>18</sup> In the same way, certain research and clinical tests have proved that the impaired functionality of integrated neural pathways (linking select cortical, subcortical, and limbic sites with their related molecular mediators) may be derived from depression.<sup>19</sup> The effects of rTMS on dopaminergic neurotransmission and cortical excitability show that such a tool can be employed in the research and treatment of DA activity and altered cortical excitability in conditions such as depression<sup>20,21</sup> and addiction.<sup>22,23</sup>

With respect to the phenomenon of high-frequency rTMS altering dopaminergic neurotransmission, the acute rewarding and reinforcing effects in the subcortical structure have been shown. Whether or not 10-Hz rTMS in 15 sessions with 3500 pulses is able to reduce depression and anxiety in methamphetamine users has to be investigated. Do these effects last one month after treatment? In addition, does stimulation over the right or the left dorsolateral prefrontal cortex (DLPFC) have different results in decreasing depression and anxiety in methamphetamine users?

## Methods

We studied eight right-handed men with a mean age of 27.5 years (range: 18-35 years) in 2017, in Iran, fulfilling the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criterion for methamphetamine dependence.

Patients with a history of neurological disease, on medication, on abnormal physical examination, having experienced seizures, having brain damage, having bipolar disease, possessing psychotic symptoms, having metal implants, being pregnant or potentially pregnant, and those who failed to meet the published criteria for TMS safety<sup>24</sup> or those who experienced rTMS treatments previously were excluded from this study.

Each session consisted of 3500 total pulses. The frequency was 10 Hz, the duration was five second, and the intensity was 110% of the individual’s motor threshold with coil 8, with five working days "on" and two weekend days "off" design. The safeties of these parameters have been previously described in psychiatric populations.<sup>25</sup> Our study was a single-subject method with concurrent multiple baseline designs. Eight subjects were assigned randomly: two subjects underwent right DLPFC stimulation, two subjects underwent left DLPFC stimulation, two subjects were exposed to placebo stimulation, and two subjects were in the control group. These areas were located using the 10-20 system.

The patients were asked to complete the Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI) for the four sessions at baseline before rTMS. When the score results were stable, the patients had 15 sessions of rTMS. Each of the BAI and BDI inventories was completed after 1, 3, 7, 10, 13, and 15 sessions, and followed up after 15 and 30 days following the completion of rTMS. The outcome measurements were analysed separately for the left, the right, the placebo, and the control groups with descriptive statistics including charts as well as analysis methods based on the Reliable Change Index (RCI) and the effect size. No side effects were reported during the study and the follow-up.

### Results

Table 1 contains the demographic characteristics

**Table 1.** Demographic characteristics

Case	Gender	Age (year)	Job	Education	Single/married	Group
1	Male	34	Unemployed	Secondary school	Single	Experimental left DLPFC
2	Male	28	Unemployed	Associate's degree	Single	Experimental left DLPFC
3	Male	25	Unemployed	Associate's degree	Single	Placebo left DLPFC
4	Male	27	Unemployed	Diploma	Single	Experimental right DLPFC
5	Male	31	Unemployed	Diploma	Single	Experimental right DLPFC
6	Male	27	Unemployed	Associate's degree	Single	Placebo right DLPFC
7	Male	22	Unemployed	Diploma	Single	Control
8	Male	26	Unemployed	Bachelor's degree	Single	Control

DLPFC: Dorsolateral prefrontal cortex

of the patients. Tables 2 and 3 contain the score results of eight patients, which have been extracted from the BDI and the BAI. More specifically, the baseline scores, the scores during rTMS stimulation, and the follow-up scores were extracted. Moreover, RCI or the difference between the last rTMS session and the baseline was calculated. In addition, RCI for the comparison of the final baseline with the scores extracted in the next month were demonstrated.

It is clear that the efficacy percentages in the placebo and the control groups with the calculations of RCI are in reverse. On the other hand, the advantages in the experimental groups for recuperation, i.e., 24% to 60% in depression and 9% to 84% in anxiety, were demonstrated.

As shown in tables 4 and 5, the descriptive statistical results were calculated with the effect size. The changes of the effect size of baseline-treatment stage and the effect size of treatment stage-follow up, citing the BDI and the BAI for the first, second, fourth, and fifth subjects, were significant.

Participants were satisfied and informed consent was obtained from all participants included in the study. The written informed consent was obtained from the patients for publication of this study.

### Discussion

The main objective of this study was to consider the efficacy of rTMS in reducing depression and anxiety symptoms in methamphetamine users. In addition, the effect of rTMS on both the left and the right DLPFC was regarded.

The experimental results demonstrated that a high-frequency (10 Hz) rTMS led to desirable effects in decreasing depression and anxiety in methamphetamine users. Clearly, previous research results are supported by the consequences of the proposed approach.<sup>10,22,26,27</sup>

**Table 2.** Descriptive analyses of Beck Depression Inventory (BDI)

Case	Baseline			rTMS						Follow-up		RCI (%)	
	Before rTMS	Before rTMS	Before rTMS	After 1 session of rTMS	After 3 sessions of rTMS	After 7 sessions of rTMS	After 10 sessions of rTMS	After 13 sessions of rTMS	After 15 sessions of rTMS	Follow-up (15 days)	Follow-up (30 days)	Between last baseline and session 15 of rTMS	Between last baseline and follow-up (30 days)
1	29	26	25	25	19	20	19	24	19	19	10	10	24
2	25	20	25	27	25	24	27	25	26	14	13	13	48
3	52	53	50	51	53	60	48	48	51	51	51	51	-
4	13	27	26	26	18	25	18	18	14	14	12	12	46
5	18	21	26	26	26	25	20	18	14	14	14	14	46
6	40	40	40	40	42	39	27	39	40	40	41	40	-
7	26	25	27	28	30	28	32	34	32	31	32	31	-
8	27	26	26	27	26	25	27	25	27	27	26	27	-

rTMS: Repetitive transcranial magnetic stimulation; RCI: Reliable Change Index

**Table 3.** Descriptive analyses of Beck Anxiety Inventory (BAI)

Case	Baseline			rTMS						Follow-up		RCI (%)	
	Before rTMS	Before rTMS	Before rTMS	After 1 session of rTMS	After 3 sessions of rTMS	After 7 sessions of rTMS	After 10 sessions of rTMS	After 13 sessions of rTMS	After 15 sessions of rTMS	Follow-up (15 days)	Follow-up (30 days)	Between last baseline and session 15 of rTMS	Between last baseline and follow-up (30 days)
1	23	15	15	15	11	8	11	17	11	10	10	9	9
2	11	4	3	2	3	4	4	6	4	2	2	66	66
3	13	19	18	7	6	6	17	11	25	10	15	-	-
4	35	30	10	6	3	4	3	6	3	2	2	76	84
5	10	12	15	7	8	8	10	10	8	8	8	73	73
6	26	16	17	18	20	20	19	20	20	18	18	-	-
7	25	12	20	25	26	25	20	20	20	25	25	-	-
1	23	15	15	15	11	8	11	17	11	10	10	9	9

rTMS: Repetitive transcranial magnetic stimulation; RCI: Reliable Change Index

**Table 4.** Effect size on decrease of depression scores

Case	Average of baseline scores	Average of treatment stage scores	Average of follow-up scores	SD of baseline scores	SD of treatment stage scores	SD of follow-up scores	Effect size of baseline-treatment stage	Effect size of treatment stage-follow up
1	26.25	20.00	10.00	1.89	2.00	0	3.08	5.00
2	24.25	23.50	13.00	2.98	4.76	0	0.33	2.62
3	51.50	51.83	51.00	1.29	4.44	0	-	-
4	23.00	17.83	12.00	6.68	4.02	0	1.20	1.20
5	22.75	19.50	14.00	3.69	5.20	0	0.75	1.00
6	40.00	37.83	40.50	0	5.41	0.70	-	-
7	26.50	31.16	31.50	1.29	2.04	0.70	-	-
8	26.50	26.16	26.50	0.57	0.98	0.70	-	-

SD: Standard deviation

**Table 5.** Effect size on decrease of anxiety scores

Case	Average of baseline scores	Average of treatment stage scores	Average of follow-up scores	SD of baseline scores	SD of treatment stage scores	SD of follow-up scores	Effect size of baseline-treatment stage	Effect size of treatment stage-follow up
1	16.00	12.16	10.00	5.03	3.25	0.70	1.00	0.66
2	6.00	3.83	2.00	3.55	1.32	1.41	1.50	1.00
3	14.75	12.00	12.50	4.64	7.64	10.60	-	-
4	22.00	4.16	2.00	12.35	1.47	0.70	2.57	2.00
5	16.75	8.50	8.00	9.06	1.22	0	1.60	0
6	18.25	19.50	18.00	5.31	0.83	1.41	-	-
7	19.75	22.66	25.00	5.50	2.90	3.53	-	-
8	23.75	26.00	25.50	2.80	1.60	0.70	-	-

SD: Standard deviation

The long-term effects of rTMS on dopaminergic neurotransmission and cortical excitability suggest that such a tool can be used on methamphetamine users. DLPFC has been identified as the main target for stimulation in depression<sup>28</sup> and addiction.<sup>8</sup>

There are several mechanisms that have been proposed for explaining the effects of rTMS on the DLPFC. Firstly, the stimulation of the DLPFC can induce releases of DA in the subcortical structure and the caudate nucleus.<sup>29,30</sup> Secondly, the effect of brain stimulation can extend beyond directly-targeted areas, including cross-hemispheric cortical and subcortical activity in remote neural networks connected to the stimulated regions.<sup>27</sup> Furthermore, a study using combined rTMS/positron emission tomography (PET) reported an elevation in the extracellular DA concentration, following the 10-Hz rTMS administered to the DLPFC.<sup>30</sup> Associations between methamphetamine users and increased levels of depression are known.<sup>5,31</sup> In this regard, rTMS has shown great promise for medication-resistant patients who suffer from depression<sup>21,28</sup> and substance use disorder (SUD).<sup>22,26,27</sup>

The effects of TMS on cortical excitability are immensely dependent on stimulation parameters. Variations in stimulation parameters include the following: the orientation of the magnetic field, single or repetitive stimulation and the frequency of stimulation, the number of pulses, and the intensity and the site of stimulation.<sup>32</sup> In previous studies, the positive effects of rTMS on depression have been reported. Likewise, the current research demonstrated that 10-Hz rTMS had desirable effects on depression in methamphetamine users. Stimulation intensity is another fundamental parameter in rTMS, which has been reported as a key parameter of the occurring long-term potential (LTP) in most studies.<sup>33</sup> Owing to the significant functionality of rTMS in making long-term alterations in cortical excitability and better treatment probability, in this study, the stimulation intensity is assumed as 110% of patient's motor threshold, in which the motor-evoked potential (MEP) is used. In addition, the lasting treatment effects of rTMS are considered. The experimental results demonstrated that these effects lasted beyond a month. Obviously, following up the lasting effects had some limitations and was, therefore, impossible. Long-term follow-up with more

instances is thus necessary.

Including the control and the placebo groups is the most considerable advantage of the current research, in which, the experimental groups had better treatment effects in comparison to the placebo and the control groups. An important factor that can influence rTMS treatment is handedness, so right-handed men were elected. Owing to the variety of cortical anatomy types and the various viewpoints about the stimulation area, the effects of rTMS over the right and the left DLPFC on depression, anxiety, and addiction (methamphetamine users) reduction are studied in this research.

Several studies applied high-frequency (10-20 Hz) rTMS on the left prefrontal cortex (PFC). Consequently, their efficacy in depression treatment has already been demonstrated.<sup>34</sup>

On the other hand, the right DLPFC rTMS induced significant changes in conditions of anxiety and happiness over time. However, the left DLPFC stimulation induced significant changes in sadness over time.<sup>22</sup> In addition, it has been demonstrated that low-frequency (1 Hz) rTMS in the right DLPFC is applicable for depression.<sup>27</sup> Functional imaging suggests that the right PFC serves a critical function in risky-behaviour regulation.<sup>35</sup> Further studies showed that increasing happiness enhanced risky-behaviour regulation after right PFC rTMS.<sup>36</sup> In addition, several human studies have begun to evaluate the effects of rTMS protocols employed on the PFC in regard to drug craving, and nicotine- and cocaine-dependent groups.<sup>8</sup>

Despite the fact that high-frequency rTMS of the left DLPFC reduced drug consumption, the craving levels remained fixed.<sup>27</sup> It also has been empirically proved that a single session of high-frequency rTMS can significantly reduce cocaine craving when applied to the right, but not the left PFC. Moreover, anxiety was significantly reduced after right-sided stimulation. Furthermore, happiness was increased after right- and sadness was increased after left-sided stimulation.<sup>27</sup> In contrast, other rTMS had no effect on depression<sup>37</sup> and addiction<sup>27</sup> or the effects were undesirable.

## Conclusion

In contrast with these disputed studies' results which are mentioned above, rTMS over both the right and the left DLPFC caused a reduction of

depression and anxiety in methamphetamine users. The outstanding feature of the current study was the significant effect of 10-Hz rTMS on the right DLPFC in reducing depression and anxiety in methamphetamine users.

It is apparent that there is a direct relationship between craving and drug use; therefore, decreasing craving will reduce drug use. As a consequence, a reduction in craving will enhance social communication and self-confidence, through which, a person's happiness and his depression level will be, respectively, increased and decreased. On the other hand, high-frequency rTMS on the right DLPFC may reduce depression. It is thus suggested that the reason behind decreasing depression should be considered in further research. Further studies will expand the knowledge of the neuro-anatomical structure of methamphetamine users. Consequently, the effective elements of the pathophysiological mood process of these patients will be discovered.

**Limitations:** In this study, self-reporting questionnaires were used to collect information; as such, this method of information collection can affect the generalization of the results. A sample of a city is selected, which is suggested to be similar to study in cities and other examples used to enhance the overall nature of the findings.

### Conflict of Interests

The Authors have no conflict of interest.

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### Authors' Contribution

Conceptualization, data curation, data analysis funding, investigation, methodology, software, data curation, supervision, writing-original draft, writing, review and editing: NM; supervision: MMA; adviser, head of the rTMS clinic: RR.

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# بررسی کاهش افسردگی و اضطراب به وسیله تحریک مکرر مغناطیسی فراقشری با فرکانس بالا در مصرف کنندگان مت‌آمفتامین

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## مقاله پژوهشی

## چکیده

**مقدمه:** مصرف مت‌آمفتامین با میزان بالای افسردگی و اضطراب مرتبط است. به نظر می‌رسد سیستم پاداش دوپامینرژیک مزوکورتیکولیمبیک نقشی اساسی در ایجاد افسردگی و اضطراب در مصرف کنندگان مت‌آمفتامین دارد. تحریک مکرر مغناطیسی فراقشری با فرکانس بالا با توجه به اثرات شدید پاداشی و تقویت کننده در ساختار زیر قشر، انتقال عصبی دوپامینرژیک را تغییر می‌دهد. هدف از انجام پژوهش حاضر، تأثیر تحریک مکرر مغناطیسی فراقشری در کاهش علائم افسردگی و اضطراب در مصرف کنندگان مت‌آمفتامین بود.

**روش‌ها:** در یک روش تک آزمودنی با خط پایه چندگانه هم‌زمان در سال ۱۳۹۵، در ایران، ۸ مصرف کننده مت‌آمفتامین شامل ۱۵ جلسه تحریک گروه آزمایش و گروه دارونما و گروه دارو کنترل‌نما، مورد بررسی قرار گرفتند. دو نفر تحریک مکرر مغناطیسی فراقشری در ناحیه قشر پیش‌پیشانی پشتی جانبی راست و دو نفر تحریک در ناحیه قشر پیش‌پیشانی پشتی جانبی چپ را دریافت کردند. اندازه‌گیری‌ها با استفاده از پرسش‌نامه اضطراب Beck (Beck Anxiety Inventory یا BAI) و پرسش‌نامه افسردگی Beck (Beck Depression Inventory یا BDI) قبل، طی تحریک و پس از ۱۵ و ۳۰ روز انجام شد.

**یافته‌ها:** تحریک مکرر مغناطیسی فراقشری در دو ناحیه قشر پیش‌پیشانی پشتی جانبی راست و چپ، به طور معنی‌داری افسردگی و اضطراب را کاهش داد، اما کاهش افسردگی و اضطراب توسط تحریک در ناحیه قشر پیش‌پیشانی پشتی جانبی راست قابل توجه بود.

**نتیجه‌گیری:** تحریک مکرر مغناطیسی فراقشری با فرکانس بالا برای درمان افسردگی و اضطراب در مصرف کنندگان مت‌آمفتامین مفید است.

**واژگان کلیدی:** تحریک مغناطیسی فراقشری؛ افسردگی؛ اضطراب؛ مت‌آمفتامین

**ارجاع:** منصوریه نسترن، محمود علیلو مجید، رستمی رضا. بررسی کاهش افسردگی و اضطراب به وسیله تحریک مکرر مغناطیسی فراقشری با فرکانس بالا در مصرف کنندگان مت‌آمفتامین. مجله اعتیاد و سلامت ۱۳۹۹؛ ۱۲ (۴): ۸۶-۲۷۸.

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