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Title: Comparison of the Efficacy of Matrix Therapy, Transcranial Magnetic Stimulation, and Cognitive Rehabilitation in Attention Bias Modification and Craving Reduction in Stimulant Drug Users

Authors: Sahar Esmaeili[1], Farhad Taremian[1]*, Mazaher Rezaei[1], Nasim Vousooghi[2], Hosein Mostafavi[3]

1. Department of Clinical Psychology and Addiction Studies, Zanjan University of Medical Sciences, Zanjan, Iran.
2. Department of Neuroscience and Addiction Studies, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran.
3. Department of Physiology, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran.

*Corresponding author: Farhad Taremian, Department of Psychology, Zanjan University of Medical Sciences, Zanjan, Iran. E-mail: farhadtaremian@gmail.com

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Abstract

Introduction: Previous studies have shown that Matrix, repetitive transcranial magnetic stimulation (rTMS), and cognitive modification treatments could lead to numerous psychological improvements in patients suffering from substance use disorders. Previous research has shown that other therapeutic interventions could be useful in managing stimulant abuse in addition to Matrix treatment The present study aimed at comparison of the effectiveness of matrix therapy, transcranial magnetic stimulation and cognitive rehabilitation treatments in attention bias modification and craving reduction in amphetamine drug users.

Methods: This study was quasi-experimental with pretest-posttest and three-month follow-up. Forty subjects taking amphetamine were selected by convenient sampling method and were randomly divided into three groups, including the matrix therapy, cognitive rehabilitation and rTMS as intervention groups and control groups (10 subjects in each group). The matrix group received 24 treatment sessions, 3 sessions per week and cognitive rehabilitation group recivied 15 treatment sessions (3 sessions per week). The group with rTMS treatment participated in a total of 10 sessions every other day. Questionnaires and dot-Probe tasks were performed as the cognitive software before and after the therapeutic interventions and one month after the interventions as a follow-up test.

Results: The results showed that the effect of time on craving assessment in three stages was significant in all the study's four groups. In the experimental groups of Matrix, rTMS, and cognitive rehabilitation, the effect of time on the severity of addiction dependence and attentional bias was significantly different in three stages. In the control group, the effect of time in three stages of assessment of addiction severity and attention bias was not significant. Also, there was a significant decrease in the mean of craving in Matrix, rTMS, and cognitive rehabilitation groups from pre-treatment to post-treatment and from pre-treatment to follow-up stages. The mean addiction severity was significantly decreased from pre-treatment to post-treatment and from pre-treatment to follow-up stage in the Matrix, rTMS, and cognitive rehabilitation groups.

Conclusion: The current study's findings indicated that all three interventions effectively reduced amphetamine craving and attentional bias. All three approaches produced positive therapeutic outcomes.

Keywords: Addiction, Amphetamine, Craving, Matrix, Cognitive Rehabilitation, Transcranial

Highlights

1. This study confirms the presence of intense cue-induced craving in response to drug use among methamphetamine addicts.

2. The mean addiction severity was significantly decreased in the Matrix, rTMS, and cognitive rehabilitation groups.

3. The effect of time on the severity of addiction dependence and attentional bias was significantly different in three stages

Plain Language Summary

We studied the efficacy of rTMS, matrix treatment, and cognitive modification in reducing the craving for stimulants. Addiction as a brain disorder can differently affect people due to the different nature of substances and how harmful they are. So, the severity of addiction and its damages could vary depending on the abused substances. Although various kinds of treatments have been suggested for drug addiction, and one of the main goals of these therapies has been to reduce craving and relapse, still craving and relapse exist as the most important and common problems in the field of addiction treatment. Based on this study's findings, Matrix, cognitive rehabilitation, and rTMS treatments could significantly reduce the craving of methamphetamine use and attenuate attentional bias among patients.

1. Introduction

Addiction is a recurrent and chronic brain disease. According to official UN statistics and the book of World Report on Drugs, addiction and its consequences and complications have caused 183,000 deaths in 2012 . It is estimated that 162 to 324 million people worldwide have used at least one type of addictive drugs such as hashish, opium derivatives, cocaine, or amphetamine . Reports from the UN Office on Crime and Materials indicate approximately 12.7 million injectable drug users worldwide . In 2015, according to a WHO report, the deaths resulted from drug addiction were calculated to be 450,000 between 15-64 years (United Nations Office on Drugs and Crime, 2018; Ieong, 2013).

Addiction as a brain disorder can differently affect people due to the different nature of substances and how harmful they are (Vahabzadeh & Ghassemi Toussi, 2016). So, the severity of addiction and its damages could vary depending on the abused substances. Craving is one of the psychological effects that drug consumers could experience and is one of the most critical issues in addiction treatment (Ieong, 2013; Sofuoglu et al., 2013). It is considered one of the main features of the substance-using disorder in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) . It can be the anticipant of recurrence and reusing phenomenon. Although various kinds of treatments have been suggested for drug addiction, and one of the main goals of these therapies has been to reduce craving and relapse, still craving and relapse exist as the most important and common problems in the field of addiction treatment (Ieong, 2013; Sofuoglu et al., 2013).

As for all types of drugs of abuse, craving is the leading cause of difficulties in the treatment of the users of stimulants, including methamphetamine (Mutumba, 2021). Methamphetamine is a stimulant whose prevalence is 5.2 times higher than other substances that have destructive effects on the central nervous system (Vahabzadeh & Ghassemi Toussi, 2016). Psychological dependence is high in methamphetamine users, so treatment is more difficult (Cruickshank & Dyer, 2009). The principal aim of treatments is to reduce craving and relapse. The approaches include matrix therapy, cognitive rehabilitation techniques, and magnetic stimulation interventions.

Matrix therapy is outpatient psychotherapy whose headlines are based on reinforcing the psychiatric weaknesses of people who use stimulants. In psychotherapy sessions and

individual counseling, one would believe in how drug consumption has created cognitive-behavioral problems (Eghbali et al., 2013; Hemmati Sabet et al., 2015; Seid & Dolatyari, 2015).

In cognitive rehabilitation interventions, one of the common ways is to use computer software to improve cognitive performance in problem-solving, attention, memory, and information processing speed; because these functions are severely impaired in stimulant consumers (Fals-Stewart & Lam, 2010; Ieong, 2013; Potenza et al., 2011). Another approach in the treatment of methamphetamine dependence is to use magnetic stimulation in the brain.

The repetitive transcranial magnetic stimulation (rTMS) as a non-invasive treatment intervention is associated with the regular application of magnetic pulses. Various studies have been done in this field, and various areas of the brain have been stimulated; the most affected site is the lateral-dorsal cortex of the forehead. Of course, different results have been obtained according to the stimulated hemisphere (right or left) and the used frequencies (low frequencies (less than or equal to 1 Hz) vs higher frequencies (more than 1 Hz). Previous studies have shown the efficacy of these therapies in controlling craving and relapse (Bellamoli et al., 2014; De Sousa, 2013; Hone-Blanchet et al., 2015; Pirmoradi et al., 2013). rTMS is a new technique for treating neuropsychological disorders that cause neurobiochemical changes in the brain, and it can lead to releasing neurotransmitters involved in craving reduction such as dopamine (Peter Eichhammer et al., 2003).

Also, Consumption of drugs of abuse causes some neurological harm and damages (Banjara, 2015). One of them is the negative effect on attention (van Hemel-Ruiter et al., 2016). It has been claimed that attentional bias is involved in addiction and plays a crucial role in sustaining drug use. Attention bias means that one selectively focuses on a particular set or sets of environmental stimuli while neglecting other stimuli. Research suggests that there is a bias in drug users toward drug-related stimuli and cues. Mostly, but not always, attentional bias is related to one's motivation and purposeful behaviors. There are several ways to attenuate attention bias (Attwood et al., 2014; Barrouillet, 2011; Garland et al., 2012). One of these methods is the dot Probe task. Evidence suggests that the correction of attentional bias could help treat addiction and reduce drug tendencies (Attwood et al., 2014; Barrouillet, 2011; Garland et al., 2012; Skjærvø, 2010).

Based on the above findings and the literature, since these types of complementary therapies are expected to improve the symptoms of addiction, and reduce the likelihood of recurrence and re-use, we can be optimistic that both prevent and re-infect people with the

disease. The benefits of treatment should be reflected in the individual and social life of the individual and the burden of social and economic pressures caused by this disease on the society should be reduced. Therefore, the main purpose of this study is to study the effectiveness of these treatments in order to achieve these goals. On the other hand, no study has been conducted that simultaneously compares the effectiveness of these three therapeutic interventions and simultaneously measures changes in dopamine receptor gene expression. the present study aimed to compare the effectiveness of Matrix, rTMS, and cognitive rehabilitation interventions in reducing craving and modifying attention bias in methamphetamine users.

2. Materials and methods

2.1. Participants

This study was quasi-experimental with pretest-posttest and three-month follow-up. This study's participants were selected by convenient sampling method from the clients of authorized drug addiction clinics in Tehran and Karaj in 2019-2020. Forty-sixth participants were selected from outpatients addicted to methamphetamine diagnosed by a physician and psychologist based on standard clinical interviews. The number of participants in the study was selected according to previous researches and related literature (Hyman, et al 2008, sousa, 2013), and it was 36 subjects who were equally and randomly divided into three experimental groups including the matrix therapy, cognitive rehabilitation and rTMS as intervention groups (12 subjects in each group). Ten other subjects were also involved as a control group with no treatment. Six subjects (2 subjects in each group) were excluded entirely from statistical analysis due to long absences, incomplete responses to scales and not performing the software's tests and evaluations. Finally, statistical analysis was performed on 40 subjects. Inclusion criteria were: being in the age range of 20 to 65 years, History of at least 1 year of amphetamine use, High score on the craving scale, satisfaction to participate in research. patients were not included in the study if: patients treated with non-methadone medications (such as buprenorphine, opium tincture, or sedatives to control withdrawal symptoms), had an any serious and current other psychiatric disorder, previous participation in a similar intervention program and absence of more than two sessions.

This study was approved by the vice-chancellery for research of the Zanjan University of Medical Sciences (ZUMS.RES.1396.96). All candidates gave their written informed consent in accordance with the research format of the Zanjan University of Medical Sciences. Ethical conditions, including patient privacy and confidentiality, were respected at all stages of the study.

Participants were informed about the study's aim and were instructed to sleep well and relax before each training session. We separately implemented the interventional sessions in 24 sessions for the matrix group, 15 sessions for the cognitive rehabilitation group, and five sessions for the rTMS candidates. We used some questionaries as pre-tests demonstrated in bellow paragraphs and were repeated after final training sessions as post-tests for all candidates.

2.2.Instruments

All candidates were evaluated via paper- and computer-based tests, which served as the pre-tests. In both experimental and control groups, the Desire for Drug Questionnaire (DDQ) was used as a craving assessment test, Substance Dependence Severity Scale (SDSS) was completed as an assessment of dependence, and Dot-Probe tasks were done to evaluate attention bias.

2.2.1. The Desire for Drug Questionnaire (DDQ)

The Desire for Drug Questionnaire (DDQ) is designed to measure instant craving. It includes three subscales: (a) drug use desire (7 question), (b) negative reinforcement (4 question), and (c) a distinguished control over drug use (3 question). The range of subscales of the DDQ is from 1 to 10. (Deady, 2009; Franken et al., 2002). Internal consistency for each factor was reported to be 0.81, 0.84 and 0.79, respectively (Franken et al., 2002). Internal consistency of DDQ have been reported acceptable in Iranian population (Hassani-Abharian et al., 2016).

2.2.2Substance Dependence Severity Scale (SDSS)

Substance Dependence Severity Scale (SDSS) is a semi-structured interview questionnaire designed based on the DSM-IV and ICD-10 drug and alcohol dependence definitions that show the intensity and frequency of the dependence over the past 30 days. The questionnaire consists of 11 questions with a maximum score of 42 (Miele, 2000). The alpha coefficient was 0.77 and the correlation between test and retest results showed a high correlation coefficient (0.97) which confirmed the reliability. Construct validity was assessed by a cross-check against General Health Questionnaire (GHQ) and the results were in favor of its validity (Motlaq et al., 2009).

2.2.3.Dot-probe task (DPT)

We used the dot-probe task as a pre- and post-training assessment to measure attentional bias towards stimulants' craving-related cues. DPT is a computerized task in which

two pictures appear concurrently at different locations on a computer screen. After the pictures or cues disappear, a dot appears in the monitor. Participants are needed to respond to a feature of the probe as fast as possible. According to attentional bias to craving-related cues of the stimulant drug, reaction to these cues is faster than that of neutral pictures, which is vice versa in normal people. When subjects selectively pay more attention to the craving-related cues, they respond quicker than neutral ones (Begh et al., 2013; De Voogd et al., 2016; Lancee et al., 2017).

2.3. Interventions

2.3.1. Matrix treatment

The Matrix group received twenty-four 45-minute sessions of intervention (3 sessions per week). Their treatment was based on a matrix pattern. Matrix is an outpatient psychotherapy that has been introduced as a practical approach to treat stimulant users (Matrix Institute on Addictions, 2012).

2.3.2. Dot-probe task (DPT)

We used pictures instead of words as stimuli to make the test reasonable for patients from various educational backgrounds. For choosing the craving-related pictures of stimulant abuse, 100 craving related pictures taken from the International Affective Picture System and picture collection of SINA institute in Tehran were selected. The selected pictures were shown to twenty stimulant abusers who were not included as the main study participants. The abusers were said to select the most stimulant pictures based on the degree of craving they made . Then, we paired 40 target pictures with neutral ones similar in composition, size, and color. Each trial began with a 500-msec black fixation cross (8 mm* 8 mm) located in a white screen center. Next, the fixation of two pictures, including a neutral one on one side and a stimulant one (craving-related picture) on the other side, was simultaneously presented for 1000-msec. After the 1000-msec duration, the picture pair were randomly replaced with a target or dot (3 mm in diameter) either on the right or left side for 500-msec. In 50% of the trials, the target appeared in the presence of the neutral picture. The participants were asked to indicate the dot's direction by pressing the matching button on the computer keyboard. Participants were instructed that the dot would appear in one of the two pictures' right or left locations and were required to pay attention to pictures and dots and perform the task as quickly and correctly as possible. In this case, both speed and accuracy were considered as essential factors. The task involved the participants in 160 dot-probe trials because each of the 40 picture pairs was displayed four times. The distance of the participants 'eyes from the screen was 50 – 70 cm. The session duration was about 5-7 min (Begh et al., 2013; De Voogd et al., 2016; Lancee et al., 2017).

2.3.3. Dot-Probe Attention Bias Modification Training (ABMT)

Dot-probe training was used as an intervention for the cognitive rehabilitation group. This training task engaged the participants in 480 Dot-probe trials for each session. Each of the 40 picture pairs was presented 12 times (12 * 40). Among all trials, 90% of the targets appeared at the neutral picture position and 10% at the craving-related picture position (Hakamata et al., 2010).

2.3.4. Repetitive transcranial magnetic stimulation method (rTMS):

The treatment protocol included ten sessions for each subject, which was performed every other day. The dorsal-lateral area of the left prefrontal cortex was the site that was repeatedly stimulated by the coil at a frequency of 10 Hz. Each session's total duration was eight minutes, and the protocol was set out at 5 seconds of rTMS at 1200 pulses in the area. The stimulation was then stopped for 15 seconds (Su et al., 2017).

2.4.Data Analysis

To evaluate and compare the effectiveness of matrix treatment, rTMS, and cognitive intervention in pre-treatment, post-treatment, and follow-up states, repeated-measures ANOVA was used. LSD post hoc test was used to compare the pairwise time steps in the dependent variables. Furthermore, due to the Eta coefficient's limitations in estimating the therapeutic effects in three different time steps and pairwise comparisons, Hedges' effect size was used to estimate the effect size more accurately. The formula for estimating the effect size of hedges is given below. Due to the lack of homogeneity of the studied groups in demographic variables of age, consumption rate, and pre-treatment in the dependent variables, in order to compare the effectiveness of different treatment methods in the dependent variables by controlling for the primary differences in pre-treatment craving, age, and consumption rate as covariance, One-way analysis of covariance (ANCOVA) was used. P-values under 0.05 were considered significant. Data were analyzed using SPSS-23 software.

$$hedges'g = \frac{M1 - M}{SD\ Pooled}$$

$$SD\ Pooled = \sqrt{\frac{(s1^2) + (s2^2)}{2}}$$

3.Results

The age of the subjects was 38.50 ± 6.40 years (mean ± standard deviation) in the matrix treatment group, 31.80 ± 5.22 years in the cognitive modification group, 31.60 ± 6.02 years in

the rTMS subjects, and 31.50 ± 5.48 years in the control group. In terms of marital status, 10% were single, 80% married, and 10% divorced in the matrix treatment group, 30% single, 60% married, and 10% divorced in the cognitive modification group, 60% single, 20% married, and 20% divorced in rTMS subjects, and 40% single, 50% married, and 10% divorced in the control group. The type of abused substance in all four groups was methamphetamine. The mean amount of drug usage was 3.6 g/day in the matrix treatment group, 3.55 g/day in the cognitive modification treatment group, 4.05 g/day in the rTMS subjects, and 8 g/day in the control group. The chi-square test results showed no significant differences between the groups regarding their marital variables (P> 0.05). However, one-way ANOVA showed that the mean age of the matrix group was significantly higher than the cognitive modification, rTMS, and control groups (F=3.51, P = 0.025).

Mean, standard deviation, and repeated measure ANOVA results to evaluate the effectiveness of matrix therapy, rTMS, and cognitive modification in reducing craving, the severity of addiction dependence, and attentional bias from Pre-treatment to Post-treatment and follow-up in each group is reported separately in Table 1.

As the primary assumption of repeated measurement, Mauchly's test of sphericity showed that the spherical hypothesis for craving variables in the matrix treatment group and cognitive modification treatment was not observed in the group's addiction severity variable (P < 0.05). Therefore, Huynh-Feldt correction was used to interpret the assumption of homogeneity of the bias variances in the mentioned variables.

Repeated measure ANOVA results showed that the effect of time in three stages of craving assessment was significant in all four studied groups (P < 0.05). In the matrix, rTMS, and cognitive modification groups, treatment significantly affected the severity of addiction dependence and attentional bias in three assessment time points (P < 0.05). In the control group, the effect of time in three stages of assessing the severity of addiction and attention bias was not significant (P > 0.05). The Eta coefficient results for estimating the variation of dependent variables by different treatment conditions are also reported in Table 1.

Table 1. Descriptive statistics and result of repeated measure ANOVA for dependent variables

Measure and group	Pre-treatment	Post-treatment	Follow-up	Tests of within-subjects effects		
	Mean ± SD	Mean ± SD	Mean ± SD	F	P-value	Eta
<u>Craving</u>						
Matrix treatment	72.20 ± 27.77	46.70 ± 17.46	40.10 ± 24.00	12.57	0.003**	0.54
Cognitive modification	65.90 ± 20.94	42.70 ± 25.27	38.10 ± 28.15	3.42	0.049*	0.27
rTMS	61.90 ± 24.09	30.10 ± 12.05	28.60 ± 12.36	13.94	0.003**	0.61
Control	112.10 ± 14.62	92.00 ± 12.25	107.80 ± 13.65	11.82	0.001**	0.57
<u>Severity of addiction dependence</u>						
Matrix treatment	25.20 ± 3.01	15.20 ± 5.18	15.40 ± 8.50	17.21	<0.001***	0.66
Cognitive modification	26.00 ± 1.83	18.20 ± 7.00	14.10 ± 8.70	13.20	<0.001***	0.60
rTMS	25.60 ± 3.10	13.50 ± 3.21	11.40 ± 5.40	35.91	<0.001***	0.80
Control	26.20 ± 5.67	25.20 ± 6.73	25.90 ± 5.32	0.30	0.620	0.03
<u>Attention bias</u>						
Matrix treatment	-199.10 ± 196.24	238.30 ± 173.03	-9.80 ± 73.68	16.12	<0.001***	0.64
Cognitive modification	-28.10 ± 179.11	92.50 ± 213.38	-70.30 ± 133.93	5.66	0.012*	0.39
rTMS	-47.70 ± 218.49	180.00 ± 161.03	16.30 ± 59.30	5.90	0.011*	0.40

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Control	-95.60 ± 110.48	- ±173.40	213.90 95.90	-131.30 ±	1.75	0.201	0.14

SD: Standard deviation

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

LSD test results by the pairwise comparing of the time steps showed a significant decrease in craving in Matrix treatment, rTMS, and cognitive modification groups from pre-treatment to post-treatment and from pre-treatment to follow-up ($P < 0.01$). In the control group, mean craving decreased significantly from pre-treatment to post-treatment ($P < 0.05$). The mean severity of addiction decreased significantly from pre-treatment to post-treatment and from pre-treatment to follow-up in the matrix, rTMS, and cognitive modification groups ($P < 0.01$). In the rTMS group, the mean severity of addiction significantly decreased from post-treatment to follow-up ($P = 0.05$). The mean attentional bias in the matrix treatment group was significantly increased from pre-treatment to post-treatment and from pre-treatment to follow-up ($P < 0.05$) and significantly decreased from post-treatment to follow-up ($P = 0.006$). In the rTMS, there was a significant decrease in the time aspect of attentional bias from the post-treatment phase to follow-up ($P = 0.002$). There was a significant increase from pre-treatment to post-treatment in the cognitive modification group and a significant decrease from post-treatment to follow-up ($P < 0.05$).

Effect sizes (Standardized Gain, ESsg) were calculated to determine the magnitude of changes during three assessment time points (Table 2). Hedges reported an effect size of 0.2, 0.5, and 0.8 as small, medium, and large, respectively.

Table 2. Within-group effects on self-report measures for groups at each assessment

Measure and group	Pre- to post-treatment	Pre-treatment to follow-up	Post-treatment to follow-up
Craving			
Matrix treatment	1.12	1.23	0.31
Cognitive modification	1.00	1.12	0.17
rTMS	1.62	1.74	0.12
Control	1.49	0.30	-1.22
Severity of addiction dependence			
Matrix treatment	2.36	1.54	-0.03
Cognitive modification	1.52	1.89	0.52
rTMS	3.83	3.22	0.47
Control	0.16	0.05	-0.11
Attention bias			
Matrix treatment	-2.31	-1.28	1.79
Cognitive modification	-0.63	0.22	0.79
rTMS	-1.19	-0.40	1.35
Control	0.81	0.34	-0.59

The results of ANOVA disclosed that there was a significant difference in the pre-treatment craving variable ($P < 0.01$). Due to the lack of homogeneity of the groups of study in demographic variables of age and drug consumption as well as pre-treatment craving variable, to compare the effectiveness of Matrix therapy, rTMS, and cognitive modification in reducing craving, the severity of the addiction, and attentional bias, One-way intra-group analysis of covariance (ANCOVA) was used to control for differences between groups in pre-treatment, craving, age, and consumption rate as covariates. Adjusted means and ANCOVA results are reported in Table 3.

The main assumptions of analysis of covariance including the relativity of scale of dependent variables, normality of variables distribution based on Kolmogorov-Smirnov test in studied groups ($P > 0.05$), homogeneity of variables' variance in studied groups based on

Levene test (P > 0.05), implementation of pre-treatment before treatment, the linearity of correlation between the pre-treatment and independent variables (P < 0.01) and homogeneity of regression slope in the dependent variables (P > 0.05) were all observed in this study. The results of ANCOVA indicated that after controlling for the effects of pre-treatment, age, and consumption rate as covariates, there was a significant difference between the means of the dependent variables in the study groups in both the post-treatment and follow-up stages (P < 0.05). LSD test results by the pairwise comparison of groups revealed no significant difference between the three groups in matrix, rTMS, and cognitive modification treatment in the dependent variables in post-treatment and follow-up (P > 0.05). The mean of craving, the severity of addiction dependence, and attentional bias were significantly decreased in three Matrix, rTMS, and cognitive modification groups than the control group in post-treatment and follow-up phases (P < 0.01). The Eta coefficient results are reported in Table 3 to estimate the dependent variables' variation by the differences in the studied groups.

Table 3. Descriptive statistics and ANCOVAs of the dependent variable

Stage	Dependent variable	Adjusted means				Tests of between-subjects effects		
		Matrix treatment	Cognitive modification	rTMS	Control group	F	P value	*Eta*
		Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD			
Post-treatment								
	Craving	47.27 ± 6.47	46.63 ± 6.34	37.73 ± 6.34	82.87 ± 9.55	4.53	0.009	0.29
	Severity of addiction dependence	15.24 ± 2.00	18.02 ± 1.85	13.60 ± 1.81	25.23 ± 2.23	5.44	0.004	0.33
	Attention bias	249.65 ± 68.95	85.25 ± 62.82	172.43 ± 61.08	-210.44 ± 75.02	6.60	0.001	0.37
Follow-up								
	Craving	34.44 ± 7.46	40.65 ± 7.31	31.24 ± 7.31	108.28 ± 11.01	9.45	<0.001	0.46
	Severity of addiction dependence	14.58 ± 2.38	15.31 ± 2.20	12.64 ± 2.15	24.26 ± 2.64	3.70	0.021	0.25
	Attention bias	5.85 ± 34.66	-84.35 ± 31.57	6.45 ± 30.70	-123.05 ± 33.71	3.50	0.026	0.241

4. Discussion

The purpose of this study was to compare the efficacy of matrix therapy, rTMS, and cognitive modification in reducing the craving for stimulants. The effects of the Matrix treatment model on amphetamine users and their craving symptoms have been studied previously. In 2018, Mohammadi and Kargar Shaker stated that 12 matrix sessions once a week for 12 sessions reduced methamphetamine reduces craving, increases hardiness and increases psychological well-being in methamphetamine-dependent abusers (Mohammadi & Kargar Shaker, 2018). Research conducted by Hemmati and colleagues in 2015 showed that this

treatment could reduce methamphetamine consumption and decrease anxiety (Hemmati Sabet et al., 2015). Eghbali and colleagues also demonstrated that Matrix treatment could increase methadone maintenance therapy's efficacy and reduce relapse in addicted subjects (Eghbali et al, 2013). Both studies' results are in line with our found data in the present resear.

The effects of transcranial magnetic stimulation on decreasing craving and attentional bias were significant during treatment and follow-up. These findings regarding craving decrease are consistent with a previous study showing significant craving decrease after rTMS treatment in the lateral-dorsal region of the cortex's (Luigjes et al. 2019; Su et al. 2020). This finding was also observed years after by Lee et al. studying methamphetamine users (Rostami et al., 2013). The rTMS has also been investigated in alcohol abusers, and it was found that cognitive performance improved during the executive control task, and commission error decreased. This treatment was performed in a single session in the lateral-dorsal part of the prefrontal cortex in the right hemisphere (Herremans et al., 2013). In another study conducted by Rostami and colleagues in 2013, it was shown that rTMS in methamphetamine abusers could reduce craving. Twenty subjects participated in the mentioned study. The treatment was performed in the right hemisphere in the lateral-dorsal part of the prefrontal cortex with 10 Hz and the left hemisphere in the same site with 1 Hz for 20 sessions / 30 minutes each time. The results of the mentioned studies are in line with our research (Rostami et al., 2013).

Cognitive modification therapy is a general term that uses various techniques and methods to rehabilitate and modify neurological skills (Bowirrat et al., 2012; Campanella, 2016). It can benefit from using computerized exercises. This tool was first performed on alcohol abusers, called the alcohol avoidance method. It was found that people who performed the exercises had a lower recurrence rate than the control group one year after follow-up. The study involved 509 subjects receiving cognitive-behavioral treatment. Before and after the treatment with the alcohol avoidance approach, the unconscious attention approach was measured. Half of the participants were enrolled in the experimental group, and half were put in the control group. A significant decrease in recurrence was observed in the experimental group after one year of follow-up (Bickel et al., 2014).

A recent approach for treatment and rehabilitation of substance dependents is a paper and pencil cognitive rehabilitation package called NECOREDA (Neurocognitive Rehabilitation for Disease of Addiction), which targets the cognitive impairments and patients' educational needs. The pilot study was carried out on ten opiate and methamphetamine-dependent patients for three months on an outpatient basis. The NECOREDA method included a series of brain exercises and tasks called "Brain Gym" and psycho-learning frameworks

called "Brain Treasures" conducted in 16 training sessions followed by 16 review sessions. Due to the importance of attention disorders in these patients, 11 stages of training were focused on different types of attention, such as fixed and selective attention, split attention, and attention shift. It was found that this cognitive treatment method had a significant effect on the quality of the patients' lives and was effective in healing the patients and avoiding substances (Rezapour et al., 2015). The results of this study are in line with the findings of our research.

In 2010, Stewart and colleagues conducted a study to evaluate cognitive modification's relative efficacy as a treatment for substance misuse. They selected 160 adults with substance misuse problems included in the 12-step treatment plan. They were then randomly divided into two groups (Stewart et al , 2010). One group received standard treatment together with CACR computerized cognitive modification (a program designed to improve cognitive performance in areas including problem-solving, attention, memory, and information processing speed), The second group received an equally intensive attention control condition consisted of standard treatment with computer-assisted typing training (CATT). Both groups participated in 3 sessions of 50-minute weekly cognitive modification. Cognitive assessments were made at baseline, during treatment, after treatment, and at 3, 6, 9, and 12 months of follow-up. The results showed that those who participated in the CACR program had a higher participation treatment index than the CATT group. They also had a higher commitment to treatment, with longer days of remaining in it (129 days vs. 109 days). Also, they completed the treatment more than the control group (55% vs. 38%). A year later, the CACR group showed a marked improvement in assessments related to substance use and its problems, legal issues, and social-family relationships. They also spent more than 12 months without alcohol and drugs (71% vs. 54%) (Fals-Stewart & Lam, 2010).

In the present study, the dot-probe task and the dot-probe training were used to evaluate the attentional bias to drug cues and modify this bias toward neutral stimuli for craving reduction. Attentional bias toward drug-related cues is the central cognitive aspect of addiction, which increases the impulse desire for drug use. There is considerable evidence to support this kind of cognitive bias in addicted individuals. A previous study found a significant difference in response rate to stimuli between heroin users and control individuals in terms of accuracy of their reaction when responding to the dot-probe task (Nejati et al., 2014). The results of this study were in line with the findings of current research. In 2008, a dot-probe test conducted by Garousi and colleagues indicated that there was a relationship between the duration of drug use and drug withdrawal and attention bias to the stimuli related to the words presented during the speech for a thousandth of a second such that with the increase in the duration of use, opioid

addicts were more attentive to bias, and their reaction time was longer. Also, with increasing the duration of abandonment in individuals who have quitted the drug usage, attention bias was decreased, and their reaction time was shorter than the opioid-dependent group (Garousi et al., 2008). The results of these studies are also in line with the data of current research.

Overall, it can be concluded that individuals involved in cognitive rehabilitation exercises participate deeper in treatment, have more treatment reliability, and complete the treatment programs better. Because of these effects, in a one-year follow-up, they show better results. Improvements may also be observed in areas related to one's life.

In a randomized controlled experimental study on alcoholic addicts, the individuals were trained five sessions to disengage attention from alcohol-related stimuli (ABM condition). The control group was trained on an irrelevant reaction-time test (control condition). They measured the effects of ABM on the visual-probe task. The Desires for Alcohol Questionnaire (similar to DDQ) was employed to assess the level of craving. The follow-up data were collected up to three months after the treatment to evaluate the treatment's overall effects and relapse times. The results illustrated that ABM effectively enabled the participants to avoid alcohol-related cues (Eberl et al., 2013).

Using the addiction severity questionnaire, it was also found in the present study that therapeutic approaches significantly reduced the severity of the addiction. Although data regarding the relationship between severity of dependence and craving are limited, the current study found that treatments significantly reduced both the severity of dependence and craving. Therefore, these two can be considered closely together.

In summary, there was no significant difference between the three groups in Matrix, rTMS, and cognitive rehabilitation treatment in the dependent variables, both at the post-treatment and follow-up stages. The mean of craving, the severity of addiction dependence, and attentional bias were significantly decreased in the three groups compared to the control subjects in both post-treatment and follow-up phases.

Based on this study's findings, Matrix, cognitive rehabilitation, and rTMS treatments could significantly reduce the craving of methamphetamine use and attenuate attentional bias among patients from pre-test to post-test and follow-ups. The findings of this study should be interpreted with great care. Although the researchers have attempted to control the situation as much as possible, it is difficult to control all the conditions regarding psychological treatment in all human subjects. Further studies are warranted while addressing the limitations of this study.

There are different kinds of cognitive rehabilitation training. We recommend comparing the ABM method with other cognitive rehabilitation approaches such as Captains Log, online attentional bias modification, and NECOREDA (Neurocognitive Rehabilitation for Disease of Addiction). However, further studies are needed to illuminate the nature of cue-reactivity differences among those dependent on stimulant drugs such as methamphetamine. This study confirms the presence of intense cue-induced craving in response to drug use among methamphetamine addicts.

One of the limitations of this study was that it was difficult to find people who were only users of stimulant drugs because most people were multi-drug abusers. On the other hand, because they did not receive any medication to treat their addictive illness, there was an urgent need for continuous follow-up in the research process. Also, the lack of medication had some effect in reducing subjects' motivation to participate in the study.

On the other hand, the present study compared the effectiveness of treatments among male groups. Further researchers are suggested to compare the effects among female patients as well. Also, this study only used a one-month follow-up. It would be more reliable to follow participants' improvements in a more extended period, such as 6-12 months, and regularly track treatment effects. Further research could gather more data using a larger number of participants and more behavioral data.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered in this article. The participants were informed about the purpose of the research and its implementation stages; they were also assured about the confidentiality of their information; moreover, they were free to leave the study whenever they wished, and if desired, the research results would be available to them.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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