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Research Article

THE EFFECT OF COGNITIVE REAPPRAISAL ON CUE-INDUCED CRAVING IN METHAMPHETAMINE DEPENDANTS

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ABSTRACT
Methamphetamine craving increases the risk of relapse in abstinent individuals and drug seeking. Cognitive Reappraisal is an effective strategy to regulate emotions. Our purpose was investigation of cognitive reappraisal on physiological and cognitive aspects of methamphetamine induced craving. Thirty current methamphetamine dependents equally divided to cognitive reappraisal instructed and control (with no instruction) conditions. Physiological aspect, Heart rate and skin conductance variability recorded at baseline (before watching methamphetamine cue movie) and while watching movie. Also a visual analogue of subjective craving and a desire to drug questionnaire (DDQ) used to assess cognitive craving before and after movie in all subjects. ANCOVA and MANCOVA were used to compare two groups. Cognitive reappraisal inhibits heart rate variability and cognitive craving but had no effect on skin conductance variability. By increasing frontal activity, cognitive reappraisal successfully decreases subjective craving when expose to methamphetamine cue and have low effect on physiological aspect that impaired and have dysfunctions in these individuals.

Keywords: *Cognitive Reappraisal Strategy, Cue-induced Craving, Methamphetamine Dependency*

INTRODUCTION
Methamphetamine (MA) is a highly addictive stimulant substance. According to 2012 statistics in the United States, over 12 million people (4.7 percent of the population) have tried methamphetamine at least once (NIDA, 2012).

Regarding Iran, the prevalence of MA dependence is growing (Shariatirad *et al.,* 2012), which brings legal, social, and serious public health problems (See *et al.,* 2009). Amongst many psychological factors involved in addiction, craving has been known to play an important role in MA abuse (e.g., Galloway *et al.,* 2008; Hartz *et al.,* 2001; Wang *et al.,* 2013).

Craving is commonly reported by heavy drug users and increases drug seeking and risk of relapse in abstinent individuals (Wang *et al.,* 2013).

Neuro-imaging studies have shown higher activities in cingulate gyros and amygdala, and lower activities in frontal cortex related to craving among MA dependent individuals (Baicy & London, 2007; Volkow *et al.,* 2001; Yin *et al.,* 2012).

Low activity in frontal cortex regions associates with low cognitive inhibition and control among cocaine and MA users (Kalivas, 2004; Nestor *et al.,* 2011; Volkow *et al.,* 2010). These deficits in cognitive control of craving and ineffectiveness of pharmacotherapy (Karila *et al.,* 2010) reveal a need for new cognitive interventions in MA dependence.

Due to facilitating and inhibitory effect of emotion regulation in positive and negative emotions (Gross *et al.,* 2006; Gross & Thompson, 2007), it is currently employed against craving for different substances in experimental conditions.

Cognitive Reappraisal (CR) is an antecedent-focused emotion regulation that is defined as interpretation of potentially emotion-relevant stimuli as unemotional (Gross, 1998). Kober *et al.,*(2010) used cognitive emotion regulation strategy to regulate the induced cigarette craving in laboratory. The results of this study showed a significant reduction of craving in participants.

Moreover, Volkow *et al.,* (2010) using Positron Emission Tomography (PET) showed that cocaine cue-inducing movies without cognitive inhibition and control condition can increase cocaine craving. However, cocaine dependents who were instructed to cognitively inhibit and control cue-induced craving had no changes in their craving and showed a decreased metabolism activity in right Orbito-frontal Cortex (OFC) and accumbans and an increased activity in right Inferior Frontal Gyros (rIFG). These studies show the importance of cognitive reappraisal in reducing substance craving and courage to use this emotion regulation strategy in cognitive MA cue-induced craving.

Additionally, craving includes emotional and cognitive aspects with behavioral and physiological states (Merikle, 1999). Since these previous studies have investigated the effect of cognitive reappraisal on cognitive aspect of craving, and these previous studies investigated the effect of cognitive reappraisal on cognitive aspect of craving, there is a gap in our knowledge of emotional and physiological states of MA craving.

The Purpose of this study is to investigate the effects of cognitive reappraisal on both emotional and cognitive aspects of MA craving.

MATERIALS AND METHODS

Thirty men aged 18–45, who only met DSM-IV criteria for methamphetamine dependence within the past six months were eligible to participate. These current users of MA participants were recruited through referrals from local advertisements and snow-balling sampling from September to January 2014 in Sanandaj, west of Iran.

The exclusion criteria included a history of using other substances during six months ago or current psychotic disorder, bipolar affective disorder, and major depressive disorder requiring antidepressant pharmacotherapy or psychotherapy.

The Subjects suffering current severe anxiety disorders including panic disorder, posttraumatic disorder, or generalized anxiety disorder were excluded due to potential interference with the measurement of dependent variables. The current treatment using any psychiatric drugs, Opioid agonists, psycho-stimulants, or any other agents known to interfere with heart rate and skin conductance monitoring was exclusionary.

The subjects with history of head trauma with loss of consciousness greater than 30 minutes and current medical illness or neurological disease were also excluded. All the subjects were required to maintain abstinence from methamphetamine, alcohol, and all other drugs of abuse except nicotine as confirmed by urine drug screening on the test day.

The participants provided written consent after being fully informed of potential risks of participation. The study was approved by medical ethics committee of Shahid Beheshti University of medical sciences.

Study Design

The exclusion criteria were checked by Structured Clinical Interview for DSM Disorders (SCID) and Addiction Severity Index (ASI) for MA dependence (McLellan *et al.,* 1995; Sharifi *et al.,* 2009). Other substance use and medical illness tested by urine drug screening and physician examination. Written informed consent was obtained from all the subjects. The participants were equally divided into two groups.

In end of execution and assessment, because of deficit in physiological assessment and questionnaire, five participants were being omitted (2 in control group and 3 in experimental group).

Related movies and pictures to MA use and smoking show increased craving in MA dependents (Price *et al.,* 2010; Tolliver *et al.,* 2010).

The MA-cues movie produced from local and portraying scenes that simulated smoking of MA from beginning to the end. In a pilot study, collecting scenes present to a fifteen MA dependent to select more craving ones.

The main movie includes 7 minutes of the scenes. After randomly dividing, participants to control (CC) and Cognitive Reappraisal Conditions (CR) were assessed in two stages as pretest-posttest. All the subjects watched the produced MA-cue movie for the first time. CC individuals (13 remained) watched the MA-cue movie without any instruction, just were told to them:

‘‘We will soon show you a short clip about someone who is smoking MA. It is important to watch movie carefully. If you are ready, let’s go?’’

But, CR individuals (12 remained) instructed about 15 minutes in cognitive reappraisal strategy and discussion about CR.

The participants in CR were asked to use cognitive reappraisal while watching the movie. Instructions of cognitive reappraisal were modeled from Gross (1998) and prior researches in cognitive reappraisal, cocaine, and cigarette (e.g., (Gross & John, 2003; Kober *et al.*, 2010; Ochsner & Gross, 2005; Volkow *et al.*, 2010). To CR subjects were told:

‘‘We will soon show you a short clip about someone who is smoking MA. It is important to watch movie carefully. But, you try to see it with two points that you should know: 1- the person that you see in movie was asked to play role of a real MA dependent. The substance that were be used is not MA and is something similar electro smoke that just smoke and nothing else, but exactly similar to MA pattern using. If you are ready, let’s go?’’

We asked the subjects to repeat what we was said and discussed about something were told to them for about 15 minutes. After watching movie, participants in this condition were asked to rate a question from 1 (strongly unsuccessful) to 10 (strongly successful), when I was watching movie, I used the thoughts that were told me about movie. Participants was successful in using CR (n= 12, M= 8.75, SD= 1.2).

Craving Scales

To assess the subjective experience of craving used, a visual analog scale (1–100) for self-reports of MA craving, the subjects were asked to rate craving with 0 being “no craving at all” to 100 representing “the most craving I have ever had” and a Self-report instruments for basic levels of craving. Desire for Drug Questionnaire (DDQ) examines drug craving in addicted patients in the present time (Franken *et al.*, 2002).

DDQ has also consisted of three main elements including desire and intention to abuse, negative reinforcement and control. In Iran, these have been validated for DDQ for Methamphetamine abusers (Maarefvand *et al.*, 2012). These tools presented to all subjects before showing MA-cue movie and immediately after it.

Physiological Responding

Changes in heart rate (HR) and skin conductance (SC) have been included in craving studies and these measures have less vulnerability to conscious control and used to detect craving (Baker & Brandon, 1990).

The HR and SC variability recorded by physiology suite of BioGraph Infiniti and the scores converted to $\log^{10} + 1$ to correct for non-normality. Physiological responses collected in two phases, before watching MA-cue movie for five minutes with eye-open and without thought anything and any movement condition, while participants were watching the MA-cue movie.

Statistical Analysis

To compare two conditions in demographic variables, chi square and independent t-test were used. The post measures in the two conditions compared with univariate and multivariate analysis of covariance (ANCOVA and MANCOVA).

ANCOVA was used for comparing scores of HR and SC variability and MANCOVA was used for three subscales of DDQ and one score of VAS in post-test.

RESULTS AND DISCUSSION

Results

Demographic variables and substances used patterns in two conditions are given in table 1. It shows that none of variables have statistically significant differences between two groups.

Table 1: Compare demographic variables and use pattern in two conditions

Variables	CR (cognitive reappraisal) n= 12		CC (control condition) n= 13		p
	frequency	percentage	frequency	percentage	
Marriage status					p>0.05
Single	7	58.3	4	30.8	
Married	3	25	2	15.4	
Separated/Divorced	2	16.7	7	53.8	
Employment					p>0.05
Employed	6	50	5	31.5	
Unemployed	6	50	8	68.5	
Use start drug					p>0.05
Cannabis	3	25	5	38.5	
Alcohol	6	50	4	30.8	
Opium	2	16.7	3	23.1	
Heroin or MA	1	8.3	1	7.7	
Jail history					p>0.05
Yes	5	41.7	5	38.5	
No	7	58.3	8	61.5	
Nicotine use					p>0.05
Yes	11	91.3	11	85.6	
No	1	8.7	2	14.4	
Heroin use					p>0.05
Yes	3	25	5	38.5	
No	9	75	8	61.5	
	Mean ± Standard deviation		Mean ± Standard deviation		
Age	31.8 ± 5.9		34.5 ± 6.7		p>0.05
Use start age	18.1 ± 2		17.9 ± 1.5		p>0.05
Education	9.4 ± 1.7		9.5 ± 1.6		p>0.05
Duration of MA use	6.5 ± 2.5 (Years)		5.8 ± 2.4 (Years)		p>0.05
Daily use amount	12600 ± 3200 (Toman)		12200 ± 4100 (Toman)		p>0.05
Last MA use	11.2 ± 4.4 (Hours Ago)		9.9 ± 3.5 (Hours Ago)		p>0.05

Effects of Cognitive Reappraisal on Hr and Sc Variability

Mean and standard deviation of base line and while watching MA-cue movie in HR and SC variability are given in table 2. ANCOVA shows that in while watching MA-cue movie (post test), CC individuals experience more HR variability than instructed individuals with cognitive reappraisal ($F= 12.4$, $\eta= 0.36$, $p<0.01$). In other words, cognitive reappraisal can reduce HR variability in comparison with control condition (Figure 1).

Table 2: Pretest and post test HR and SC variability scores in study groups

Variable	CR (cognitive reappraisal) n= 12 Mean (Standard deviation)	CC (control condition) n= 13 Mean (Standard deviation)
HR variability (log^{10} +1)		
Base line	1.92 (0.42)	1.87 (0.37)
While watching movie	1.89 (0.39)	2.14 (0.33)
SC variability (log^{10} +1)		
Base line	2.52 (0.31)	2.48 (0.26)
While watching movie	2.54 (0.19)	2.64 (0.27)

As you see in Figure 1, there were no differences between cognitive reappraisal and control conditions in SC variability post test scores (F= 1.13, η= 0.05, p>0.05). So, the cognitive reappraisal had no effect on SC variability in comparison with control condition.

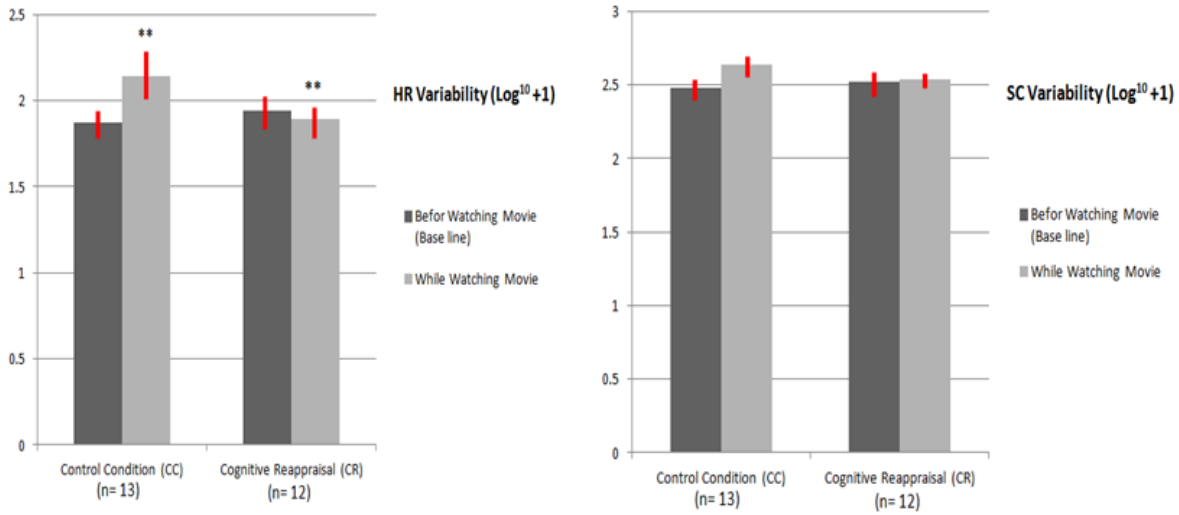

Figure 1: Comparisons of HR and SC variability in Cognitive reappraisal and Control Conditions by ANCOVA (p< 0.01)**

Effects of Cognitive Reappraisal on Cognitive Craving

Mean and standard deviation of base line and while watching MA-cue movie in three subscales of DDQ and VAS scores are shown in table 3.

Table 3: Base line and posttest DDQ subscales and VAS scores in study groups

Variable	CR (cognitive reappraisal) n= 12 Mean (Standard deviation)	CC (control condition) n= 13 Mean (Standard deviation)
Visual Analogue Scale (VAS)		
Base line	63.33 (13.37)	58.46 (16.12)
After watching movie	66.46 (18.86)	84.23 (17.18)
DDQ- Intention to abuse		
Base line	4.76 (1.06)	4.55 (1.30)
After watching movie	4.83 (1.23)	5.93 (1.15)
DDQ- Negative reinforcement		
Base line	4.30 (1.77)	4.27 (1.35)
After watching movie	4.15 (1.48)	5.41 (1.47)
DDQ- Control		
Base line	4.31 (1.37)	4.44 (0.97)
After watching movie	4.04 (1.45)	4.90 (0.99)

MANCOVA revealed instruction of cognitive reappraisal can control craving while watching MA-cue movie comparing with another group (Wilks' Lambda value= 0.561, F= 6.90, η= 0.63, p<0.01, Observed power= 0.967). As seen in Figure 2, All four scores increased in control condition individuals which shows increasing craving while watching MA-cue movie (DDQ- intention to use, F= 10.84, p= 0.004, η= 0.36, Observed power= 0.88; DDQ- Negative Reinforcement, F= 15.64, p= 0.001, η= 0.45, Observed power= 0.96; DDQ- Control, F= 7.52, p= 0.018, η= 0.28, Observed power= 0.74; and VAS, F= 22.58, p= 0.001, η= 0.54, Observed power= 0.99).

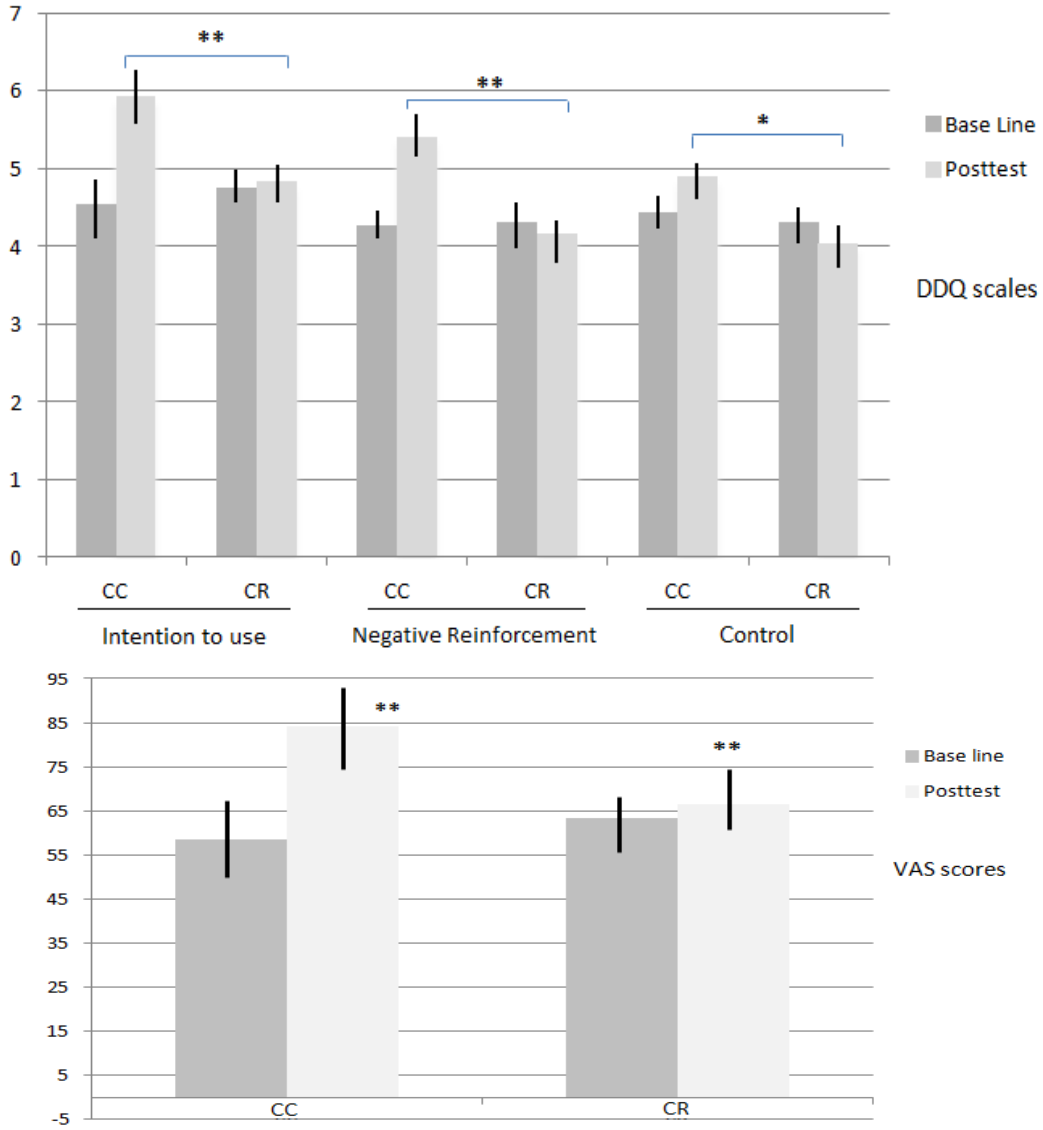

Figure 2: Comparisons of DDQ sub scales and VAS in Cognitive reappraisal and Control Conditions by MANCOVA (* p< 0.05, ** p< 0.01)

Discussion and Conclusions

The present study investigated the effects of cognitive reappraisal on Heart Rate Variability (HRV) and Skin Conductance (SC) as physiological changes in induced MA craving. The findings suggest that cognitive reappraisal decreases HRV but has no effect on SC in MA dependents while watching MA-cue movies. In contrast to HRV, SC is not associated with a specific stimulus onset rather changes into SC happens over longer periods of time (Mendez, 2009). HRV is a reliable and sensitive measure which reflects balance of sympathetic and vagal neural influences on HR (Acharya *et al.*, 2006). Previous studies have shown autonomic nervous system dysfunction, as determined through diminished HR variability among the deleterious stimulant substances such as cocaine (e.g., Vongpatanasin *et al.*, 2004) and MA (e.g., Henry *et al.*, 2012). While acute MA use stimulates the sympathetic nervous system, resulting in increased heart rate, the chronic MA use induces autonomic nervous system (ANS) dysfunction (Kaye *et al.*, 2007). These deficits in stimulant substances has to do with the increased HR variability reacting to craving-cue movies and pictures (Culbertson *et al.*, 2010; Tolliver *et al.*, 2010;

Volkow *et al.,* 2010). Contrary to this finding, Volkow *et al.,* (2010) showed that cognitive inhibition had no effect on HR means comparing with control group in cocaine dependents. This study and our present one show that the cognitive reappraisal has no effect on SC variability. Also, the partial eta square (0.36) of the HRV was weak which can be attributed to sympathetic nervous system dysfunctions in MA dependants (Henry *et al.,* 2012; Kaye *et al.,* 2007) or disconnected physiological response to psychological stimulus (Ooteman *et al.,* 2006). As Tolliver *et al.,* (2010) suggest, physiological cue reactivity correlates poorly with cue induced craving. This heterogeneity may emerge from a lack of observable differences (Newton *et al.,* 2005).

In a review study, Fowles (1980) suggested that HR is strongly associated with Gray's Behavioral Activation System (BAS) activity and SC associated with Behavioral Inhibition System (BIS) activity. According to Gray's two factors learning theory (1982), BAS initiates behavior in response to conditioned stimuli for reward (approach) or for relieving non-punishment (active avoidance) and BIS inhibits behavior in response to cues for punishment (passive avoidant) or frustrating non-reward (extinction). Moreover, BAS sensitivity emerges as a significant predictor of reactivity to substance and craving (Bijttebier *et al.,* 2009) to the extent that substance related disorders include a reward deficit syndrome as possible contributing factor to the development of substance use disorder (Blum *et al.,* 2000). Reversely, BIS's results are not clear and are indicating a heterogeneity in substance use (Bijttebier *et al.,* 2009) which related to SC variability. Thus, this issue needs more investigation in MA dependence in the future.

Our findings suggest that cognitive reappraisal had strong effect on cognitive and subjective aspects of craving. Exposure to MA-cue movies increases VAS and three subscales of DDQ scores in comparison with cognitive reappraisal condition. In this regard, MA addicts had high brain activation in cingulate cortex and low activation in frontal lobe while watching MA-cue pictures, demonstrating that MA addicts may have emotion-related brain activation abnormalities (Yin *et al.,* 2012). MA addicted individuals when exposed to conditioned drug-cues usually show an intense desire for the drug (Culbertson *et al.,* 2010; Tolliver *et al.,* 2010). According to Somatic Marker Theory (SMT) in addiction, the amygdala (key structure in impulsive neural system) detects or recognizes the environmental features that are potential sources of immediate pleasures, or satisfaction of homeostatic needs. Craving triggers responses in other brain areas that may become translated into feelings of desire, anticipation, and urges to seek the drug right at that moment (Verdejo-Garcia, & Bechara, 2009).

The chronic MA abuse associates with a disruption of fronto-striatal function as well as deficits in cognitive control (Salo *et al.,* 2009). As Volkow *et al.,* (2010) reported, the increased activity in nucleus accumbens involved with reward and prediction of reward, associated with the drug-seeking behavior following an exposure to conditioned-cues. Nucleus accumbens modulated by OFC which signals the motivational value of the conditioned stimuli, amygdala and ventral hippocampus. Dysfunction in frontal regions may associate with increased craving and drug taking in stimulant substances such as cocaine and MA. In Volkow *et al.,* (2010) reports, as cocaine abusers purposefully inhibit craving while exposed to conditioned drug-cue, decreases in right NAcc were correlated with changes in right IFG. This is a crucial brain region for inhibitory control. Reducing cue craving by cognitive reappraisal might be a strategy to prevent relapse and treat MA dependence.

Moreover, Li *et al.,* (2013) suggested that suppression of the left dorsolateral prefrontal cortex by low frequency repetitive Transcranial Magnetic Stimulation (rTMS) reduces inhibitory control, which in turn leads to enhancing cue-induced cravings for drugs such as MA. They reported that the Ventral Tegmental Area (VTA), and connected brain structures involved with reward (e.g., nucleus accumbens) and cognitive control (e.g., prefrontal cortex), appears to be a critical substrate of drug craving.

As one may notice in the findings, the lowest partial eta square (0.28) belongs to control subscale. Maarefvand *et al.,* (2012) have reported that "control" concept could not be well understood by drug addicts in Persian language in the DDQ questionnaire. But "desire and tendency" toward drug abuse is the main factor which receives the same score in the same question of the original version of DDQ. This instrument feature associated with low cognitive reappraisal effect in this sub scale.

In general, cognitive reappraisal seems to neutralize the effects of MA-cue movies in subjective craving of MA dependents but this does not happen in physiological changes. These may indicate that MA craving have two different aspects among which cognitive one is stronger than physiological (Newton *et al.*, 2005).

The cognitive aspect of craving powerfully can be controlled by cognitive reappraisal strategy and can have important implications for psychological intervention in MA dependents.

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