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Effects of cognitive restructuring training on neurocognitive functions in opioid addicts

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Summary

Aim: To investigate the effect of cognitive restructuring training on neurocognitive functions related to the prefrontal cortex in opioid addicts and its relationship to relapse prevention.

Method: Thirty opioid addicts who completed a 21-day detoxification program were randomly placed in experimental and control groups. Before and after the training, the subjects underwent urinalysis and were tested on the Addiction-Stroop Task, Iowa Gambling Task, Wisconsin Card Sorting test and Emotion Recognition Scale.

Results: Decision-making and emotion recognition were improved after the training course, but no significant difference was observed in attention bias, cognitive flexibility and relapse.

Conclusions: Cognitive restructuring training and improvement of some neuropsychological functions are not enough to prevent relapse, and attention bias and cognitive flexibility should be adjusted.

cognitive restructuring/neurocognitive function/addiction/relapse

INTRODUCTION

Drug addiction is a persistent substance disorder characterized by impulsion to seek and take the drug, loss of control in intake, and negative emotional states (e.g. dysphoria, anxiety, irritability) when the drug is not taken [1]. It is estimated that there are more than 3 million drug users in Iran and addiction has become the third biggest social problem in the country [2]. Although addiction is associated with several complications, common treatments are not adequately effective [3,4], with annual success rates of the best treatment methods at 30-50%. Studies show that 20-90% of addicts who receive treatment experience relapse [4-6].

One factor that has recently come to the fore in the etiology of addiction, especially the causes of relapse, is the impaired neurocognitive function of the prefrontal cortex [7,8]. Even though the relationship is not clear yet, researchers believe that impaired neuropsychological functions are one cause of addiction; additionally, drug intake *per se* leads to the emergence and/or increase of neuropsychological problems [8]. The neuropsychological functions that play a role in addiction etiology and relapse are decision-making, cognitive flexibility, attention bias, emotion recognition, and response inhibition [8,9].

Scientists believe that psychotherapy affects the functioning and structure of the brain [10]. Beck urges: ‘change your mind to change your brain’ [11]. For example, many medical imaging

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studies have shown that cognitive–behavioral therapies improve high and abnormal metabolism in the prefrontal cortex, anterior cingulate gyrus, and anterior nuclei in people with obsessive–compulsive disorder [10]. Moreover, it has been shown that psychotherapy improves blood circulation and abnormal activity of the prefrontal cortex, anterior cingulate cortex and amygdala in depression, post-traumatic stress, specific phobias and schizophrenia. In other words, studies indicate that psychotherapy optimizes brain performance in areas involved in neurocognitive functions [10,12,13].

In a recent study, Yoshimura et al. [14] used functional magnetic resonance imaging (fMRI) to investigate the effectiveness of cognitive–behavioral psychotherapy on the activities of different brain areas during self-referential processing of negative and positive words in people with depression. After a 12-session therapy course, the activity of the middle prefrontal cortex and anterior cingulate cortex decreased during self-referential processing of negative stimuli, but increased during self-referential processing of positive stimuli. In addition, improvement of depression symptoms was positively correlated with reduced activity of the middle anterior cingulate cortex during self-referential processing of negative words.

None of these studies investigated the brain's functional changes in drug addicts after psychotherapy, and there is no study into the changes of neuropsychological functions in addicts. In addition, all relevant studies have investigated the effects of cognitive–behavioral psychotherapy and ignored the effect of cognitive restructuring training. Therefore, the present study intended to fill these gaps. The second objective, also barely investigated, was to determine the relationship between the improvement of neuropsychological functions and relapse prevention in addicts.

METHOD

Participants

Overall, 30 subjects from the statistical population which included all male opioid users (750 subjects) completed the 21-day detoxification program in 15 addiction recovery camps across the province of Shahrekord, Iran. They were recruited with convenience sampling and randomly placed in two groups of 15 subjects each (the control and experimental groups). The inclusion criteria were male gender, age 18–50, opioid addiction, no current severe psychiatric disorder, and a history of successful medication-free detoxification of 2–4 weeks before the experiment pre-test session. Patients with withdrawal symptoms and those with neurocognitive conditions that affect cognitive-emotional functions were excluded from the study.

Instruments

Urinalysis

To investigate the accuracy and consistency of patients' reports, the results of urine sample tests and patients' reports were compared; 85% agreement was achieved for the intake of drugs. In this test, the diagnostic strip was placed in the subject's urine on the side determined by an arrow. The results were indicated by the change of color of one or two bands.

Addiction-Stroop Task

This neuropsychological task is used to measure a person's reaction time in recognizing the color of drug-related stimuli as compared with neutral stimuli [15]. In Addiction-Stroop Task Software, substance-related words such as 'lighter', 'crystal meth', 'hangover' and 'opium' are displayed on the screen with different blue, green, red and yellow colors. The person is then asked to select the color of each word, as quickly as possible, using the colored keyboard buttons. The software retest validity has been reported at 0.80–0.91 [16].

Iowa Gambling Task (IGT)

The IGT was designed to simulate real-life decision-making. In this test, the subject will win or lose depending on how they choose their cards. This test relies on gaining maximum wins through optimal card selection, where each card is associated with certain loses and gains. Participants are presented with 4 cards (A, B, C, D). They are told that each time they should choose one card. This process is repeated 100 times. By choosing a card they earn a reward or receive a penalty. These rewards and penalties are not random, rather they follow a certain logic: cards A and B have higher scores, but are also associated with more severe penalties, whereas cards C and D have lower scores and lighter penalties, and thus are safer choices. During the test, the person tries to win as much as possible by selecting the correct cards. At the end, the net score is calculated by subtracting the subtotal score of C and D selections from that of A and B selections. Although there is no study into IGT reliability, it has high face validity for simulating daily decision-making [17,18].

WISCONSIN CARD SORTING TEST (WCST)

This test was developed in 1948 by Berg & Grant [19], and revised by Heaton [20]. It consists of 64 cards with 1 to 4 symbols, which are presented in different colors (red, yellow, blue, and/or green) and shapes (cross, circle, triangle, and/or star); no two cards are the same. WCST is a well-known neuropsychiatric test that measures abstract reasoning, cognitive flexibility, desperation, problem-solving, concept-formation, set change, and attention maintenance. Its retest and internal consistency reliabilities have been reported as 0.92 and 0.94 [19,20].

Emotion Recognition Scale

This facial emotion recognition test was created by Ekman [21]. It consists of 36 images that measure six basic emotions: anger, disgust, fear, surprise, happiness and sadness. The subjects respond to the images presented on a desktop screen. Answers are scored 1 (correct) and 0 (incorrect), and the total score is 0–36 [22]. Test Cronbach's alpha and retest reliability (after 1 week) are 0.71 and 0.85, respectively.

INTERVENTION

The experimental group received six 45-min sessions of Meichenbaum cognitive restructuring training [23]. The method was first introduced by Meichenbaum in 1974, and further developed by Meichenbaum and Cameron in 1983. It is now one of the most comprehensive cognitive–behavioral therapies.

Data analysis

Data analysis was performed by the multivariate analysis of variance (MANOVA) and SPSS 16 ; the significance level of α=0.05 was considered for all hypotheses.

RESULTS

Demographic characteristics of the subjects are presented in Table 1.

Table 1. Demographic characteristics

	Experimental group Mean SD	Control group Mean SD
Age, years	33.60 7.25	35.00 5.33
Education, years	9.26 3.04	8.93 3.05
Intake to year ratio	7.66 4.38	8.86 3.44
Marital status		
Married	12 (80%)	13 (86.7%)
Single	3 (20%)	2 (13.3%)
Employment		
Employed	12 (80%)	11 (73.3%)
Unemployed	3 (20%)	4 (26.7%)

Participants' scores on the neurocognitive tasks, before and after the intervention, are presented in Table 2.

Table 2. Neurocognitive tests' performance pre – and post-intervention

Variable	Experimental group		Control group	
	Pre-intervention Mean SD	Post-intervention Mean SD	Pre-intervention Mean SD	Post-intervention Mean SD
Reaction time (milliseconds)	1005.50 147.8	894.66 157.93	987.97 140.62	904.82 147.10
Decision-making Net score (C+D)–(A+B)	–6.67 7.77	4.26 6.13	–13.60 1178	–10.53 7.61
Perseveration	9.60 4.4	5.06 2.43	8.93 3.61	4.73 2.01
Emotion recognition	21.40 4.23	25.53 2.97	22.06 3.26	23.66 2.19

There was a significant difference between mean pre-intervention and post-intervention scores in both groups in decision-making and emotion-recognition, but no significant difference in cognitive flexibility and attention bias (Table 3).

Table 3. Results of MANOVA in experimental and control groups

Dependent variable	SS	df	MS	F	p
Emotion recognition	48.113	1	48.113	8.251	0.008
Cognitive flexibility	0.833	1	0.833	0.193	0.712
Decision-making	464.133	1	464.133	8.988	0.006
Attention bias	5733.711	1	5733.711	0.153	0.669

Table 4. Results of chi-square test for determining the effectiveness of cognitive restructuring in relapse prevention

Group	Experimental	Control	Total
	Frequency (%)		
Abstinence	11 (73.33)	7 (46.47)	18 (60)
Relapse	4 (26.67)	8 (53.44)	12 (40)
Total	15 (100)	15 (100)	30 (100)

$\chi2$= 2.20, df= 1, p=0.264

As shown in Table 4, χ^2 is not significant at the level of 0.05 – therefore, there is no significant difference between the two groups in terms of relapse prevention. Although relapse in the experimental group was lower than in the control group, the difference was not significant.

DISCUSSION

The present study aimed to investigate the effectiveness of cognitive restructuring in emotion recognition/processing and cognitive impairments in drug addicts. Although cognitive–behavioral therapy for substance abuse is considered to develop adaptive skills, many active components of cognitive–behavioral therapy exert their effect through the empowerment of some aspects of executive control over behavior [24]. For example, one probable reason for long-term effect of cognitive–behavioral therapy is its focus on the following general strategies: exercise of cognitive control over some over-learned patterns of substance intake through functional behavioral assessment (e.g. identification of the prodromal periods of drug use and its results); reduction of an impulsive response to substance-dependent cues through craving control strategies (regulation of craving and negative emotions); improvement of decision-making and problem-solving skills; and identifying, challenging and exerting control over substance intake-related cognitions [25].

Following this reasoning and considering the studies in the field of medical imaging showing that psychotherapy, and especially cognitive–behavioral treatment, improves blood circulation (functional dimension of the brain) and adjusts gray matter of the brain (structural dimension) in different disorders, it may be concluded that such therapies alleviate neurocognitive dysfunctions.

Our results showed that teaching the cognitive restructuring method to drug addicts does not reduce attention bias towards substance-dependent stimuli. These findings are inconsistent with the discovery by Calamaras et al. [26] that cognitive–behavioral therapy for social anxiety reduces attention bias towards social threatening cues. This inconsistency can be attributed to two facts. First, according to cognitive models, attention bias in anxiety is due to a comparison or confirmation of the self-image by social stimuli; whereas in addiction attention bias is due to substance abuse that causes damage to some parts of the brain. Therefore, it is possible that areas of the brain required for the modification of attention bias are damaged by drug intake. Second, inconsistency of results in the present study with Calamalas et al. is due to the use of different attention bias assessment methods (Addiction-Stroop Task vs. Dot Probe Task). Recently, researchers have used attention bias modification as an adjuvant therapy for cognitive–behavioral addiction treatment and shown that it was more effective than the common treatment method [25]. This indicates that attention bias has unique therapeutic mechanisms that are not directly affected by traditional cognitive–behavioral addiction therapy.

Our study suggests that cognitive restructuring training greatly improves decision-making. Indeed, it can be said that a cognitive recognition course reduces the risk of bad choices made by the addicts. This finding is consistent with previous studies, where psychotherapy, especially cognitive–behavioral therapy, improved blood flow to ventromedial prefrontal cortex, which is most closely associated with decision-making [12,27]. We also established that cognitive restructuring improved subjects' capability in emotion recognition from facial expressions. Studies have shown that emotional information processing is performed by the amygdala and ventromedial prefrontal cortex. As psychotherapy optimizes brain activity in these areas in such disorders as depression, post-traumatic-stress specific phobia and schizophrenia, the hypothesized effectiveness of psychotherapy in increasing emotion recognition capability is very probable [12,28-30]. Moreover, our findings are consistent with those of Yoshimura et al. [14], who used fMRI to show that cognitive–behavioral psychotherapy in people with depression reduced the activities of medial prefrontal and anterior cingulate cortex when processing negative stimuli.

Our study suggested that training in cognitive restructuring did not significantly improve cognitive flexibility. Similar to other neuropsychiatric functions, there is not much information on the effectiveness of cognitive–behavioral therapy in the improvement of cognitive flexibility, and all relevant studies are into specific phobias and schizophrenia. In the current study blood flow and metabolism in anterior-lateral parts, which are both involved in cognitive flexibility, were improved during psychotherapy [31-33]. However, this is inconsistent with previous research, which is due to the differences in samples, damaging effect of substance abuse on brain structure, and therapy techniques. It is worth noting that the studies cited here are performed at the medical imaging level and have not looked at subjects' performance in the test and whether any post-therapeutic changes were observed. This gap should be filled in future studies.

Results of the chi-square test showed that post-treatment prevalence of opioid avoidance was higher in the cognitive–restructuring group than in the control group, but this difference was not significant. Relapse reduction in the treatment group is consistent with previously obtained results, for example of Marlatt & George [3], looking at the effectiveness of cognitive–behavioral strategy in relapse reduction, and of Marques & Formigoni [34], investigating the effectiveness of cognitive–behavioral therapy in treatment and prevention of relapse in drug-dependent patients. In explaining these findings it can be said that the most critical predictor of relapse is people's capability in using an effective coping strategy when faced with high-risk situations, low self-confidence, and wrong attitudes towards substance abuse. Cognitive–behavioral therapy can help prevent relapse by providing the required coping strategies, changing one's attitude towards substances, and improving self-confidence [35].

On the other hand, cognitive restructuring training did not significantly prevent relapse in our sample, which is inconsistent with the findings of previous studies. This lack of significance may be attributed to the low number of therapeutic sessions – a 6-session course is not long enough for a cognitive–behavioral therapy. For example, Siegle et al. [36] proposed a 16-session therapy. The other reason may be the confounding effect of participation in other training courses such as self-help groups, especially among the control group.

According to Kiluk et al. [24,37], teaching coping skills and their acquisition by addicts is a very important factor in the determination of the effectiveness of cognitive–behavioral addiction therapy. Learning these skills depends on being highly motivated, having a positive attitude to therapy, and the absence of cognitive dysfunctions that would intervene with treatment. Thus, the insignificant effect of cognitive restructuring therapy in relapse prevention may be attributed to the fact that the subjects who participated in educational sessions had highly disturbed cognitive functions, which inhibited them from acquiring the required skills. In addition, they might lack the required motivation for learning the skills or a positive attitude towards the therapy [25]. On the other hand, studies have maintained that although cognitive–behavioral therapy is associated with median and higher impact on many psychiatric disorders, its effectiveness in addiction therapy is low [38].

IQ level is another factor that affects the effectiveness of cognitive–behavioral therapy in addicts with impaired cognitive processing capability. In fact, the success of cognitive–behavioral therapy depends on the patient's IQ. Therefore, one reason why cognitive–behavioral therapy may fail is that the subjects did not have the required IQ level [37].

In addition, the reason for insignificant relapse prevention may be the fact that all important neuropsychiatric functions have not been modified by the cognitive restructuring training at the onset of addiction, its maintaining and relapse. Attention bias and cognitive flexibility, important factors in the maintaining and relapse of addiction, were not modified in this study, which *per se* can be a cause of relapse. For example, the mind of a cured addict who still has attention bias towards drug cues is easily engaged with them. In addition, lack of high cognitive flexibility inhibits the patient from shifting their mind to other mental activities. Although their emotion processing and safe decision-making processes are improved, this improvement is not enough for coping with the craving that may arise and preventing relapse. Accordingly, adjuvant therapies such as attention bias modification should also be provided to the addicts to prevent relapse.

Among the limitations of this study is a lack of control over the effects of comorbid psychiatric disorders which might affect neurocognitive functions, although this issue was addressed by not including subjects suffering from severe psychiatric disorders and random assignment of participants into the experimental and control groups. In future studies it may be beneficial to recruit addicts with similar psychiatric disorders. Other limitations were a lack of follow-up to investigate the long-term effects of therapy, and heterogeneity in the history and amount of drug intake among the subjects (which was also addressed by using random assignment). Future studies assessing the long-term effects of cognitive restructuring therapies are called for.

REFERENCES

1. Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology. 2010; 35(1): 217–238.
2. Moghanibashi-Mansourieh A, Deilamizade A. The state of data collection on addiction in Iran. Addiction. 2014; 109(5): 854.
3. Marlatt GA, Donovan DM. Relapse Prevention: Maintenance Strategies in the Treatment of Addictive Behaviors. Guilford Press; 2005.
4. Shumaker, Sally A. (Ed); Schron, Eleanor B. (Ed); Ockene, Judith K. (Ed); McBee, Wendy L. (Ed), (1998). The handbook of health behavior change (2nd ed.)., (pp. 33-58). New York, NY, US: Springer Publishing Co.
5. CARN P, Cheryl Anderson PhD R. Exploring the factors influencing relapse and recovery among drug & alcohol addicted women. J Psychosoc Nurs Ment Health Services. 2000; 38(7): 8.

6. McKay JR, Franklin TR, Patapis N, Lynch KG. Conceptual, methodological, and analytical issues in the study of relapse. Clin Psychol Rev. 2006; 26(2): 109–127.
7. Verdejo-Garcia A, Benbrook A, Funderburk F, David P, Cadet J-L, Bolla KI. The differential relationship between cocaine use and marijuana use on decision-making performance over repeat testing with the Iowa Gambling Task. Drug Alcohol Dependence. 2007; 90(1): 2–11.
8. Fernández-Serrano MJ, Pérez-García M, Verdejo-García A. What are the specific vs. generalized effects of drugs of abuse on neuropsychological performance? Neurosci Biobehav Rev. 2011; 35(3): 377–406.
9. Verdejo-García AJ, López-Torrecillas F, Aguilar de Arcos F, Pérez-García M. Differential effects of MDMA, cocaine, and cannabis use severity on distinctive components of the executive functions in polysubstance users: a multiple regression analysis. Addict Behav. 2005; 30(1): 89–101.
10. Barsaglini A, Sartori G, Benetti S, Pettersson-Yeo W, Mechelli A. The effects of psychotherapy on brain function: A systematic and critical review. Progress Neurobiology. 2014; 114: 1–14.
11. Beck AT, Wright FD, Newman CF, Liese BS. Cognitive Therapy of Substance Abuse. Guilford Press; 2011.
12. Buchheim A, Viviani R, Kessler H, Kächele H, Cierpka M, Roth G, et al. Changes in prefrontal-limbic function in major depression after 15 months of long-term psychotherapy. PloS One. 2012; 7(3): e33745.
13. O'Neill J, Gorbis E, Feusner JD, Yip JC, Chang S, Maidment KM, et al. Effects of intensive cognitive-behavioral therapy on cingulate neurochemistry in obsessive–compulsive disorder. J Psychiatr Res. 2013; 47(4): 494–504.
14. Yoshimura S, Okamoto Y, Onoda K, Matsunaga M, Okada G, Kunisato Y, et al. Cognitive behavioral therapy for depression changes medial prefrontal and ventral anterior cingulate cortex activity associated with self-referential processing. Soc Cogn Affect Neurosci. 2014; 9(4): 487–493.
15. Stroop JR. Studies of interference in serial verbal reactions. J Experiment Psychology. 1935; 18(6): 643.
16. Brewer JA, Worhunsky PD, Carroll KM, Rounsaville BJ, Potenza MN. Pretreatment brain activation during Stroop Task is associated with outcomes in cocaine-dependent patients. Biol Psychiatry. 2008; 64(11): 998–1004.
17. Bechara A, Damasio AR, Damasio H, Anderson SW. Insensitivity to future consequences following damage to human prefrontal cortex. Cognition. 1994; 50(1): 7–15.
18. Bechara A, Damasio H. Decision-making and addiction (part I): impaired activation of somatic states in substance dependent individuals when pondering decisions with negative future consequences. Neuropsychologia. 2002; 40(10): 1675–1689.
19. Grant DA, Berg E. A behavioral analysis of degree of reinforcement and ease of shifting to new responses in a Weigl-type card-sorting problem. J Experiment Psychology. 1948; 38(4): 404.
20. Heaton R, Chelune G, Talley J, Kay G, Curtiss G. Wisconsin Card Sorting Test Manual: Revised and Expanded. Odessa, Florida: Psychological Assessment Resources. Inc; 1993.
21. Ekman P. Facial expressions of emotion: New findings, new questions. Psychological science. 1992;3(1):34-8.
22. Young AW. Facial Expressions of Emotion: Stimuli and Tests. Thames Valley Test Company; 2002.
23. Michenbaum D. Stress Inoculation Training: A Preventative Treatment Approach. Principles and Practice of Stress Management; 2007.
24. Kiluk BD, Nich C, Babuscio T, Carroll KM. Quality versus quantity: acquisition of coping skills following computerized cognitive–behavioral therapy for substance use disorders. Addiction. 2010; 105(12): 2120–2127.
25. Sofuoglu M, DeVito EE, Waters AJ, Carroll KM. Cognitive enhancement as a treatment for drug addictions. Neuropharmacology. 2013; 64: 452–463.
26. Calamaras MR, Tully EC, Tone EB, Price M, Anderson PL. Evaluating changes in judgmental biases as mechanisms of cognitive-behavioral therapy for social anxiety disorder. Behav Res Ther. 2015; 71: 139–149.
27. Yamanishi T, Nakaaki S, Omori IM, Hashimoto N, Shinagawa Y, Hongo J, et al. Changes after behavior therapy among responsive and nonresponsive patients with obsessive-compulsive disorder. Psychiatry Res Neuroimaging. 2009; 172(3): 242–250.
28. Fu CH, Williams SC, Cleare AJ, Scott J, Mitterschiffthaler MT, Walsh ND, et al. Neural responses to sad facial expressions in major depression following cognitive behavioral therapy. Biol Psychiatry. 2008; 64(6): 505–512.
29. Goldin PR, Gross JJ. Effects of mindfulness-based stress reduction (MBSR) on emotion regulation in social anxiety disorder. Emotion. 2010; 10(1): 83.
30. Kircher T, Arolt V, Jansen A, Pyka M, Reinhardt I, Kellermann T, et al. Effect of cognitive-behavioral therapy on neural correlates of fear conditioning in panic disorder. Biol Psychiatry. 2013; 73(1): 93–101.
31. Haut KM, Lim KO, MacDonald A. Prefrontal cortical changes following cognitive training in patients with chronic schizophrenia: effects of practice, generalization, and specificity. Neuropsychopharmacology. 2010; 35(9): 1850–1859.
32. Paquette V, Lévesque J, Mensour B, Leroux J-M, Beaudoin G, Bourgouin P, et al. "Change the mind and you change the brain": effects of cognitive-behavioral therapy on the neural correlates of spider phobia. Neuroimage. 2003; 18(2): 401–409.
33. Wykes T, Brammer M, Mellers J, Bray P, Reeder C, Williams C, et al. Effects on the brain of a psychological treatment: cognitive remediation therapy functional magnetic resonance imaging in schizophrenia. Br J Psychiatry. 2002; 181(2): 144–152.

34. Marques ACP, Formigoni MLO. Comparison of individual and group cognitive-behavioral therapy for alcohol and/or drug-dependent patients. Addiction. 2001; 96(6): 835–846.
35. Lazarus RS. Psychological Stress and The Coping Process. New York: McGraw-Hill; 1966.
36. Siegle G, Carter C, Thase M. Use of FMRI to predict recovery from unipolar depression with cognitive behavior therapy. Am J Psychiatry. 2006; 163(4): 735–738.
37. Kiluk BD, Nich C, Carroll KM. Relationship of cognitive function and the acquisition of coping skills in computer assisted treatment for substance use disorders. Drug Alcohol Depend. 2011; 114(2): 169–176.
38. Hofmann SG, Asnaani A, Vonk IJ, Sawyer AT, Fang A. The efficacy of cognitive behavioral therapy: a review of meta-analyses. Cogn Ther Res. 2012; 36(5): 427–440.