Research Paper: Comparing LORETA Z Score Neurofeedback and Cognitive Rehabilitation Regarding Their Effectiveness in Reducing Craving in Opioid Addicts

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ABSTRACT

Introduction: Previous studies have shown that conventional neurofeedback and cognitive modification treatments have numerous psychological benefits for patients with substance use disorders. However, the effectiveness of LORETA (Low-Resolution Brain Electromagnetic Tomography) Z Score Neurofeedback (LZNFB) and cognitive rehabilitation therapy in reducing opioid craving has not been investigated. Thus, the present study aimed to compare the effectiveness of LZNFB and cognitive rehabilitation therapy with Methadone Maintenance Treatment (MMT) in reducing craving in patients with opioid use disorder.

Methods: Thirty patients with opioid use disorder undergoing MMT were randomly assigned into three groups: LZNFB with MMT, cognitive rehabilitation with MMT (as experimental groups), and MMT alone control group. The LZNFB and cognitive rehabilitation groups received 20 and 15 sessions of treatment, respectively. The three groups were assessed using several questionnaires and dot-probe task at pretest, posttest, and one-month follow-up.

Results: The results showed that both experimental groups accomplished a significantly greater reduction in opioid craving than MMT alone group at posttest and follow-up ($P<0.05$). The LZNFB plus MMT group showed a greater decrease in opioid craving than the cognitive rehabilitation plus MMT group. In addition, the cognitive rehabilitation plus MMT group experienced greater improvement in attentional bias towards craving cues than the LZNFB with MMT group at posttest and follow-up. Finally, the LZNFB plus MMT group and cognitive rehabilitation plus MMT group got higher scores on the recovery assessment scale than MMT alone group at posttest and follow-up. According to study results, LZNFB training is more effective than cognitive rehabilitation in decreasing cravings and improving the quality of life in addiction to opioids.

Conclusion: The current study's findings provided preliminary support for the effectiveness of LZNFB and cognitive rehabilitation in reducing opioid craving, improving attentional bias towards craving cues, and the quality of life among Iranian opioid use patients.

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Highlights

- LZNFB training showed higher decrease in opioid craving than the Cognitive rehabilitation in opioid addicts.

- Cognitive rehabilitation group experienced greater improvement on attentional bias towards craving cues than LZNFB.

- LZNFB and Cognitive rehabilitation with MMT group got higher scores on the recovery assessment scale than MMT alone group.

- LZNFB training is more effective than Cognitive Rehabilitation in decreasing of craving in addiction. opioids

Plain Language Summary

Addiction is a chronic relapsing disease that makes many problems for human society. Routine medical treatments are not completely effective and they have relapse. New forms of non-medical treatments such as neurofeedback and cognitive rehabilitation are effective and safe without impressive side effects . This article shows the efficacy of above mentioned interventions for decrease craving and control of this problem.

1. Introduction

About 275 million people (5.6% of the population aged 15-64 years) have used drugs at least once in 2016. According to a 2015 WHO report, 450000 deaths were associated with drug addiction, and 167750 of them were directly caused by drug use, mostly overdoses. Among different drugs, opioids were the most harmful ones, accounting for 75% of drug use death worldwide in 2016 (World Drug Report, 2018).

Craving is an extensive cognitive-emotional construct that is recognized as a contributing factor in improving and preserving drug-related problems in many models of alcohol and drug use (Miller, 2013). Craving is created via learning processes and is associated with classical conditioning and activation of specific reward structures in the brain. The construct consists of significant neurobiological factors that induce a durable desire and perceptual need for the drug. Conscious or indirect distal environmental cues can trigger this condition that happens at any time and place (Association, 2013; Houben, Wiers, & Jansen, 2011).

Despite various treatments suggested for drug addiction (pharmacotherapy and psychotherapy), relapse and craving still exist as the most important and common problems in this field (Sarter, Bruno, Parikh, Martinez, Kozak, & Richards, 2006). Despite the best treatment conditions, the relapse rate is about 95% after six months of abstinence (Yegane, 2007). Empirical evidence shows that patients with Substance Use Disorders (SUD) have poorer response rates to medical and behavioral treatments (Taremian, Nazari, Moradveisi, & Moloodi, 2019). For all the merits and advantages of methadone and buprenorphine therapy, their side effects and high rates of relapse and dependency are remarkable. Recently, several noninvasive non-pharmacologic techniques such as neurofeedback and cognitive rehabilitation have been used to treat SUD (Garland, Boettiger, Gaylord, Chanon, & Howard, 2012; Potenza, Sofuoglu, Carroll, & Rounsaville, 2011; Sarter et al., 2006; Thatcher, 2010). Different studies have shown the effectiveness of neurofeedback and cognitive rehabilitation in controlling craving and relapse in heroin and alcohol addicts (Barrouillet, 2011; De Voogd et al., 2016; Skjærvø, 2010; Thatcher & Lubar, 2014; Wells & Beevers, 2010).

LORETA (Low-Resolution Brain Electromagnetic Tomography) Z Score Neurofeedback (LZNFB) is the latest version of Neurofeedback (NFB) software used to treat some neuropsychological disorders. Robert Thatcher suggested the idea of using real-time Z scores neurofeedback in the 1990s and implemented it in 2006 with an immediate improvement in neurofeedback efficiency. LORETA "is an inverse solution for assessing cortical electrical current density that originates from scalp electrodes to approximation tri-dimensional solution for the cortical electrical activity distribution" (Sokhadze, Cannon, & Trudeau, 2008; Thatcher & Lubar, 2014). The aim is to reinforce movements of consistently deviant brain systems linked to the patient's symptoms (Taremian, 2014; Thompson, 2014). Multi-case studies by Koberda J L in Traumatic Brain Injury (TBI) and Cerebrovascular Accident (CVA) patients showed that 10 sessions of LZNFB training are effective in the rehabilitation of cognitive problems, headache, dizziness, and depression (Koberda, 2015; Lucas Koberda & Stodolska-Koberda, 2014). Also, LZNFB is an effective method in treating alcohol and SUD and can yield even faster and more effective results than traditional or two-channel neurofeedback (Gunkelman & Cripe, 2008; Lucas Koberda & Stodolska-Koberda, 2014).

In the case of addiction, the selection of the addiction network is the main Region of Training (ROT) in LZNFB (Thatcher & Lubar, 2014). "The addiction network is a reward network in which the moment to moment positive valence of environmental stimuli, and internal demonstrations create pleasure"(Brodmann areas: 13, 24, 25, 32, 34, 44, 45, 46, and 47) (Cox, Fadardi, Intriligator, & Klinger, 2014; Fals-Stewart & Lam, 2010; Mokri, Ekhtiari, Edalati, Ganjgahi, & Naderi, 2008; Sofuoglu, 2010; Thatcher, 2016).

Some experts believe that LZNFB is more effective than conventional NFB (standard one- or two-channel neurotherapy) based on the number of sessions and training of more brain parts. They argue that the large numbers of hubs, Brodmann area, and networks are Regions of Interest (ROI) that can be selected for training in LZNFB—something not possible in conventional NFB (Thatcher, 2010). In LZNFB, contrary to conventional NFB, the aim is not just to suppress and reinforce amplitudes. The minimum number of sessions to obtain reasonable results is 40 in conventional NFB and 20 in LZNFB (Lucas Koberda & Stodolska-Koberda, 2014; Peniston & Kulkosky, 1989; Thatcher & Lubar, 2014).

Significant attentional bias effects have been found in several studies and for various substances (Garland et al., 2012; Thatcher, 2010). The two main cognitive factors that have been known to prompt relapse in addicted people are a) diminished response inhibition toward these cues and b) attentional biases toward drug-related cues, which increase the desire to use and make resistance to temptation more problematic for addicted individuals (Campanella, 2016; Fadardi, Cox, & Rahmani, 2016; Potenza et al., 2011; van Hemel-Ruiter, Wiers, Brook, & de Jong, 2016). Some hypotheses suggest that the basic cognitive processes are involved in addiction and cue-reactivity and attentional bias factors. Nestor et al. registered fMRI activity in response to an attentional bias task. They suggested that the registered activity indicated an increased "bottom-up" control and a decreased "top-down control" in nicotine addiction and concluded that cognitive control might have a central role in the reactivity or response selectivity towards nicotine-related cues. As a kind of top-down treatment, several models of cognitive rehabilitation modify behaviors and cognitions via an improved prefrontal cortical function that is responsible for executive control, as mentioned in recent addiction methods of treatment (Potenza et al., 2011). The Attentional Bias Modification (ABM) training was provided using an adapted version of the dot-probe task (Barrouillet, 2011; De Voogd et al., 2016; Skjærvø, 2010; Thatcher & Lubar, 2014; Wells & Beevers, 2010). Based on the evidence mentioned above, attentional bias modification towards drug-related cues is highly relevant for the continued development and improvement of treatment therapies in addiction.

According to the findings mentioned above and research papers about these two treatment methods, we hypothesized that LZNFB plus Methadone Maintenance Treatment (MMT) and cognitive rehabilitation plus MMT might decrease the craving of opioids addicts and increase the degree of recovery in patients more than in the MMT alone group. Also, the efficacy of LZNFB is more than cognitive rehabilitation in opioid addicts.

The current study aimed to investigate and compare the effects of LZNFB and cognitive rehabilitation in decreasing craving and relapse in opioids addicts. Improving the brain's ability to control and reduce craving through non-pharmacological treatments such as conditional NFB learning and cognitive rehabilitation can help opioid addicts. However, most previous researchers in LZNFB conducted case studies in this respect.

2. Methods

Study participants

In the present study, 36 opioids addicts referred to clinics and MMT centers in Zanjan City, Iran, were purposefully chosen. We considered only male participants because female addicts rarely refer to MMT clinics. Opioid addiction diagnosis was based on the SUD criterion delineated in the DSM-5. Patients were randomly divided into LZNFB, cognitive rehabilitation intervention groups, and the control group. Group allocation was kept confidential by assigning a unique code to each participant. Six participants dropped out of the study due to their failure in completing the instructions or training procedures in the experimental groups. Thus, the final sample included 30 opioids addicts.

Table 1. Chi-square test analysis in terms variables before methadone therapy

Variables	Mean±SD			F	P
	LNFB	Cog. Reh.	Control		
Age (y)	34.70±6.90	36.00±6.32	36.90±6.74	0.276	0.701
Amount of consumption (g)	2.40±1.43	1.90±0.99	2.10±0.99	0.472	0.629
Duration of consumption (mon)	108.60±68.02	84.20±27.53	74.80±32.22	1.421	0.259

LNFB: LORETA Neurofeedback; Cog.Reh.: Cognitive Rehabilitation.

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Demographic characteristics

All three groups included male subjects from 24 to 51 years (36.03±6.89 years). More specifically, the age range in the groups was as follows: LZNFB group: 24-49 (34.70±6.89 years), cognitive rehabilitation: 29-51 (36.00±6.325 years), control group: 27-48 (36.90±6.740 years). There were no statistically significant differences regarding age variable between the groups: ($F_{37,2}$=0.276, P=0.701). Tables 1 and 2 show demographic data regarding age, marital status, education, amount, and duration of drug consumption. There were no significant differences among groups with regard to the variables mentioned above.

The inclusion criteria involved the male patients who used just opioids and now are under the Methadone Maintenance Treatment (MMT) aged 20-60 years.

We excluded female subjects, alcohol, and multi-drug abuse users, other substance use patients, those under other medical treatments such as buprenorphine, opium tincture, tranquilizers, and those with severe psychiatric and medical problems such as psychosis, bipolar, antisocial, personality disorders, or borderline patients.

This study was approved by the Vice-Chancellery for research of the Zanjan University of Medical Science. All candidates gave their written informed consent following the research format of the Zanjan University of Medical Science.

Ethical considerations were observed before, after, and during the research procedure and encompassed privacy rights, confidentiality, no publicity in written descriptions, personal information, including names, photographs, and no harms and risks during the intervention or side effects after the treatment. Candidates read the research contract in advance and signed two copies of it.

The participants were informed about the study objectives. All training sessions were done in the afternoons. The participants were instructed to sleep well and relax before each training session. If they lacked the criteria mentioned above, the session was postponed. We separately implemented the interventional sessions in 20 hours (20 sessions) for the LZNFB group and 5 hours (15 sessions) for the cognitive rehabilitation group. We used some questionnaires as pretests demonstrated in the below paragraphs and were repeated after final training sessions as posttests for all candidates. Figure 1 shows the consort flow diagram.

Study instruments

All candidates were evaluated via paper- and computer-based tests, which served as the pretests. In the two experimental and control groups, we collected demographic information. We used the Leeds Dependence Questionnaire (LDQ), the Desire for Drug Questionnaire (DDQ), and the Obsessive-Compulsive Drug Use Scale question (OCDUS) as craving assessment tests. In addition, we used the Recovery Assessment Scale (RAS) and self-report questionnaire as well as dot-probe tasks as the computer-based tests. The tests were repeated after the interventions in both groups and 1 month after the interventions. In the control group, the tests were administered twice at the one-month interval.

Craving assessment:

The DDQ is designed to measure instant craving and includes three subscales: (a) drug use desire, (b) negative reinforcement, and (c) a distinguished control over drug use. The subscales of the DDQ scores range from 1 to 10 that measure instant craving (Deady, 2009; Franken, Hendriks, & van den Brink, 2002). LDQ contains ten items and assesses substance dependence. In addition to measuring consumption and physically dependent symptoms, this test assesses the severity of dependence via embracing broader views of psychological dependence. According to the preliminary analyses, the instruments enjoy acceptable internal consistency

Table 2. Frequency and percentage of marital status and education and the Chi-square test results

Variables		No.(%)			Ch	P
		Control	Cog. Reh.	LNFB		
Marital status	Single	3(30)	3(30)	4(40)	0.623	0.296
	Married	7(70)	7(70)	6(60)		
	Divorced	0(0)	0(0)	1(10)		
Education	Elementary	2(20)	3(30)	0(0)	0.349	0.545
	Intermediate	2(20)	3(30)	0(0)		
	High School	5(50)	3(30)	4(40)		
	Postgraduate	1(10)	1(10)	1(10)		
	Bachelor	0(0)	0(0)	3(30)		
	Master	0(0)	0(0)	1(10)		

LNFB: LORETA Neurofeedback; Cog.Reh.: Cognitive Rehabilitation.

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(the Cronbach α=0.94) and test-retest reliability (r=0.95) and concurrent, discriminant, and convergent validity in case of alcohol and opiate addiction. Finally, the OCDUS targets general craving (within a week). It includes scales ranging from 1 to 6, containing three subscales: (a) thoughts concerning drugs, (b) control and desire to use drugs, and (c) resistance to thoughts and intentions to use drugs (Deady, 2009; Franken et al., 2002).

The Recovery Assessment Scale (RAS) is an outcome tool that tests for empowerment, coping ability, and quality of life. The RAS is a 22-item survey rated on a 5-point scale. In a study of 35 inpatients, the RAS was found to have good test-retest reliability (r=0.88) and good internal consistency (the Cronbach α=0.93). The scale showed that recovery is positively associated with self-esteem, empowerment, social support, and quality of life, indicating good concurrent validity. It was inversely associated with psychiatric symptoms suggesting discriminant validity. These findings suggest that RAS has good construct validity for assessing the recovery processes (Deady, 2009).

Dot-Probe Task (DPT)

For measuring attentional bias toward opioid craving-related cues, we used the dot-probe task as a pretest and posttest assessment. This 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 presence of two pictures. Participants should respond to a probe feature as fast as possible.

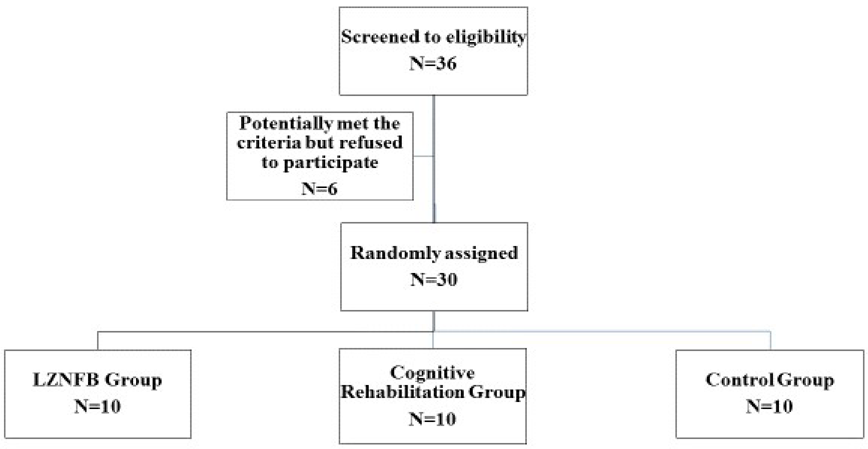

Figure 1. CONSORT flow diagram to illustrate the progress of patients through the trial

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According to attentional bias to opioid craving-related cues, reaction time for these cues is faster than neutral pictures; however, the reaction is the opposite for normal people. When subjects selectively pay more attention to the opioid craving-related cues, they are quicker in responding than neutral ones are (Begh et al., 2013; De Voogd et al., 2016; Lancee, Yasiney, Brendel, Boffo, Clarke, & Salemink, 2017).

Study procedure

Electroencephalography (EEG) and Quantitative Electroencephalography (QEEG)

For the LOZNFB group, Electroencephalography (EEG) collection was recorded for 5-min in an eyes-closed condition and 19 scalp locations using the left ear lobe as a reference. Mitsar amplifier 201 was used for EEG recording amplifier and signal calculation. We used NeuroGuide software version 2.9 and ICA EEG caps in different sizes, too, as other necessary instruments for LZNFB training. There are many variables in EEGs of candidates as pretest, posttest, and one-month follow-up, but we did not consider them in this article.

LORETA Z Score Neurofeedback (LZNFB) training

We implemented the LZNFB in experimental group one. First, the distance between the nasion and inion was measured to identify the suitable EEG cap size. The head was measured and marked before each session to ensure reliability. The ears and forehead were cleaned by a mild abrasive alcohol recording to remove any oil and dirt from the skin. Electro-Gel was used for electrode injection, and the prepared impedance between each electrode and ear was found to be less than 5 KΩ. The LZNFB training was conducted using the 19-leads of the standard international 10/20 system with linked ears as reference leads and mid line front-parietal zone (FPZ) as a ground reference. The data were collected and stored utilizing the Mitsar-201 amplifier system with a sample rate of 500 per second. We use standard 9-mm tin cup ear electrodes. Each training session lasted approximately 60 minutes and consisted of eight 5-minute training rounds with a 30-s pause between the rounds. Totally, 43 minutes of training on addiction networks were implemented in 2 to 4 sessions per week for every candidate. During each session, to reduce extra-cranial artifacts, the participants were trained to relax and control their eye movements, eye-blinks, tongue, and muscle activity of the forehead, neck, and jaws. Through the treatment periods, the Methadone Maintenance Treatment (MMT) was implemented in both experimental and control groups, but the LZNFB group received 20 sessions of treatment.

ROI in this research is an addiction network selected in NeuroGuide (NG) software during NFB training for the participants. Audio-visual feedback options for individuals were selected based on their interest and included movies, animations, and Central Zone (CZ) displays with piano, guitar, or flout sound, which was changeable to each other intra- or inter-sessions. In the first five sessions, we used the “Z tune method” and then the “all or none method” as the purest operant conditioning method for NFB training in the remaining sessions. The “all-or-none” method means that 100% of the selected metrics must be equal to or less than the Z score threshold during the selected time window before a feedback signal is delivered. The “Z tune method” requires that at least 70% of the metrics meet the all-or-none criteria and then calculates the 10-s history of the 30% that fail to meet the all-or-none criteria. They are called outliers or extreme metrics, and if the slope of the outliers is in the direction of Z=0, then a feedback signal is delivered (Thatcher, 2010).

Dot-Probe Task (DPT)

We used pictures instead of words as stimuli to make the project reasonable for addicts from various educational backgrounds. For choosing the opioid craving-related picture, first, 100 craving-related pictures were selected from the International Affective Picture System and picture collection of SINA institute in Tehran. The pictures were shown to 20 non-participant opioids addicts to select the most stimulant pictures based on the degree of craving they made. Then, we matched 40 target pictures with neutral ones that must be compatible in composition, size, and color. Each trial began with a 500-ms black fixation cross (8×8 mm) located in the center of a white screen. Next, the fixation of two pictures, including a neutral on one side and a stimulant (opioids craving-related picture) on the other side, was simultaneously presented for 1000 ms. The height and vertical distance of each picture were 50 and 60 mm, respectively. After 1000 ms, the picture pair was randomly replaced with a target or dot (3 mm in diameter) either on the right or left side for 500 ms. In 50% of the trials, the target appeared in the presence of a neutral picture. The participants were asked to indicate the direction of the dot by pressing the matching button on the computer keyboard. The participants were orally instructed that the dot would appear in one of the right or left locations of the two pictures, and they were required to pay attention to the pictures and dots and perform the task as quickly and correctly as possible. In this case, both speed and accuracy were considered important factors. This task involved the participants in 160 dot-probe trials. Each of the 40 picture pairs was displayed 4 times (4*40). The distance of the participants' eyes from the screen was 50 to 70 cm. The session lasted about 5-7 min (Figure 2).

4-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 opioid craving-related picture position. Participants received 1520 min training per session over two weeks (one or two sessions, mostly every day, and overall 15 sessions for each participant).

3. Results

As the preliminary finding confirmed, all three groups were matched in age and education. Therefore, all groups were comparable as a result of a random assignment. One-sample Kolmogorov-Smirnov test was used to check the sampling distribution of all pretests. The results showed that all variables in the study had normal distribution in the pretests, and there were no statistical differences among the participants. For all pretests, the Kolmogorov-Smirnov Z>0.44 and P>0.05 were considered, suggesting that attrition did not systematically bias the results.

The pre-treatment vs post-treatment phases and one-month follow-up in the experimental and control groups were analyzed by SPSS software v. 22. One-sample Kolmogorov-Smirnov test, Analysis of Covariance (ANCOVA), repeated measures, and Bonferroni or post hoc tests were used as the statistical data analysis models. ANCOVA is used when we want to statistically control for the possible effects of an additional confounding variable (covariate). This test is useful when we suspect that our groups differ on some variables that may influence the effect that our independent variables have on our dependent variable. ANOVA is helpful too, but ANCOVA is statistically more powerful. So, we used ANCOVA to evaluate the effects of LZNFB and cognitive rehabilitation on the craving, attentional bias, and recovery assessment scale. The ANCOVA test results showed the significant impacts of the treatment on these variables (Table 3). In the dot-probe test, the response time in the groups, F=7.055 and P=0.001 were found. The treatment was 37% effective, and the observed power (0.967) indicates that 33 times of ineffectiveness could occur among 1000 times of trials. The changes among cognitive rehabilitation, control, and normal groups are significant (P=0.002).

In this study, the craving was measured by three tests of DDQ, LDQ, and OCDUS. Between-subjects effects and pairwise comparisons between intervention and control groups in all craving tests were significant. Thus, treatments were significantly effective (P<0.001) in decreasing craving. The effectiveness of treatment or Eta squared was 79% for DDQ, 72% for LDQ, and 75 % for OCDUS.

To assess the living outcome and wellbeing of patients after the intervention, we used the recovery assessment scale questionnaire. Statistical data for this test demonstrated significant changes. Between-subject effects for the group (F=12.746, P<0.001, partial Eta squared = 0.522) indicate that the treatment improved the recovery assessment scale in the intervention groups compared with the control group with 52% effectiveness, P<0.001, and observed power=0.999. This number indicates that there was just one-time ineffectiveness after 1000 times of trials.

Bonferroni or post hoc test was used to compare between-group variables. Table 4 presents that the changes among cognitive rehabilitation and control groups for the dot-probe test are significant (P=0.002). For all craving tests, changes among all groups are significant (P<0.001), and for the RAS test, changes between all groups are significant too (P<0.01).

We evaluated the effects of both pieces of training in three steps (pretest, posttest, and one-month follow-up), then the repeated-measure ANOVA model was used instead of the paired t test. Repeated-measures ANOVA models were used to examine training effects on dependent variables through pretest, posttest, and one-month follow-up. The results showed that both treatments were effective during the time (P<0.001 in all variables) for decreasing craving, improving attentional bias, and the recovery assessment scale (Table 5). Intervention participants showed greater reductions in craving, attentional bias, and increases in RAS than controls, suggesting the effectiveness of the treatment. Comparing all these variables, we found that the effectiveness of LZNFB was more than that of cognitive rehabilitation (Sample plot for DDQ is depicted in Figure 3).

4. Discussion

This study aimed to investigate the effectiveness of LZNFB and cognitive rehabilitation in decreasing craving compared to the MMT control group. Opioid addicts can relieve withdrawal symptoms and inhibit lapses via

Table 3. Tests of between-subjects effects, dependent variable: post tests

Variables Source		SS	df	MS	F	P	Eta	Observed Power
Dot. Res	Res.Time. Pre	782.010	1	782.010	3.109	0.087	0.082	0.403
	Group	5322.928 3	177	4.309	7.055	0.001	0.377	0.967
	Error	8802.79035		251.508				
DDQ	DDQ.Pre	1548.286	1	1548.286	17.871	<0.001	0.407	0.982
	Group	8546.309	2	4273.155	49.321	<0.001	0.791	1.000
	Error							
LDQ	LDQ.Pre							
	Group							
	Error							
OCDUS	OCDUS.Pre							
	Group							
	Error							
RAS	RAS.Pre							
	Group							
	Error							

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SS: Sum of Squares; MS: Mean Square; LNFB: LORETA Neurofeedback; Cog.Reh.: Cognitive Rehabilitation; DDQ: Desire for Drug Questionnaire, LDQ: Leeds Dependence Questionnaire, OCDUS: Obsessive Compulsive Drug Use Scale Question, RAS: Recovery Assessment Scale.

methadone use; however, they are incapable of resisting opioids when exposed to drugs cues (Thatcher & Lubar, 2014). This study may reflect the importance of bottom-up and top-down intervention models in treating the dark side of the addiction associated with prolonged and threatening cravings with advanced neurofeedback protocol (LZNFB) and cognitive rehabilitation. Using QEEG-guided LZNFB, the clinician can use the patient's symptoms in line with the dysregulated networks and modules related to those symptoms (Thatcher, 2016; Thatcher & Lubar, 2014). We can conclude that LZNFB training in the addiction network produces craving reduction and improves recovery.

Our findings showed the effectiveness of LZNFB and cognitive rehabilitation treatments in decreasing craving and attentional bias toward drug cues and improving wellbeing, which is consistent with previous studies (Begh et al., 2013; Campanella, 2016; Cox et al., 2014; DehghaniArani, Rostami, & Nadali, 2013; Fals-Stewart & Lam, 2010; Hashemian, 2015; Heidari, Taremian, & Khalatbari, 2017; Passini, Watson, Dehnel, Herder, & Watkins, 1977; Peniston & Kulkosky, 1989; Potenza et al., 2011; Ross, 2013; Saxby & Peniston, 1995; Schoenmakers, de Bruin, Lux, Goertz, Van Kerkhof & Wiers 2010; Scott, Kaiser, Othmer, & Sideroff, 2005; Skjærvø, 2010; Taremian, 2014; Thatcher, 2010; van Hemel-Ruiter et al., 2016; Wiers, Houben, Fadardi, Van Beek, Rhemtulla, & Cox 2015).

Several previous studies conducted by the pioneers of NFB therapy in SUD, Elmer and Alyces Green and Eugene Peniston, showed its efficiency in reducing the craving. Similar to our findings, some studies on alcohol dependence patients by Passini et al., Bodehnamer & Callaway, Burkett et al. Raymond et al. established progressions via comparing the treatment and control groups. Scott et al. concluded that neurofeedback treatment enhanced psychological health in mixed substance addicts (Bodenhamer-Davis & Callaway, 2004; Burkett, Cummins, Dickson, & Skolnick, 2004; Hashemian, 2015; Passini et al., 1977; Peniston, 1994; Peniston & Kulkosky, 1991; Raymond, Varney, Parkinson, & Gruzelier, 2005; Ross, 2013; Saxby & Peniston, 1995).

Table 4. Bonferroni or Post Hoc

Variables	Group I	Group J	Mean Difference (I-J)	Std. Error	P
Dot-probe posttest	LNFB	Cog.Reh.	-18.068	8.604	0.046
	LNFB	Control	10.562	8.489	0.224 0.002
DDQ posttest	Cog.Reh.	Control	28.630	8.156	<0.001
	LNFB	Cog.Reh.	-20.773	4.197	
	LNFB	Control	-41.837	4.213	<0.001
	Cog.Reh.	Control	-21.063	4.164	<0.001
LDQ posttest	LNFB	Cog.Reh.	-4.577	1.173	0.002
	LNFB	Control	-9.447	1.150	Control
OCDUS posttest	LNFB	Cog.Reh.	-10.916	2.408	<0.001
	LNFB	Control	-21.609	2.431	<0.001
	Cog.Reh.	LNFB	10.916	2.408	<0.001
RAS posttest	LNFB	Cog.Reh.	6.039	1.758	
	LNFB	Control	10.504	1.757	<0.000
	Cog.Reh.	Control	4.466	1.754	0.017

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LNFB: Loreta Neurofeedback, Cog.Reh: Cognitive rehabilitation, DDQ: Desire for Drug Questionnaire, LDQ: Leeds Dependence Questionnaire, OCDUS: Obsessive Compulsive Drug Use Scale Question, RAS: The Recovery Assessment Scale.

Taremian and Heydari showed the efficacy of conventional NFB (alpha-theta protocol) in decreasing craving in opioid addict patients. They trained the experimental group for 20 sessions and compared the results with the control group by evaluating their craving with the DDQ test (similar to our research craving tests). The results showed that in comparison to the control group, the modified alpha-theta protocol is more effective in decreasing the intensity of craving (d=18, P<0.0001) (Heidari et al., 2017).

Dehghani Arani and Rostami studied the effectiveness of the conventional NFB method for treating 20 opioid addicts that received buprenorphine or methadone as the maintenance treatment. Compared to the control group, the NFB group improved in somatic symptoms, desire to use opioids, the total score in general mental health,

Table 5. Tests of within-subjects effects

Variables	Source	SS	df	MS	F	P
Dot-probe	Factor 1 * group Error (factor1)	5916.883 15906.800	6.000 72.000	986.147 220.928	4.464	<0.001
DDQ	Factor 1 * group Error (factor1)	7744.333 3947.800	2.291 30.922	3381.046 127.670	26.483	<0.001
LDQ	Factor 1 * group Error(factor1)	399.778 218.400	2.408 32.507	166.027 6.719	24.712	<0.001
OCDUS	Factor 1 * group Error (factor1)	2039.111 1035.800	2.616 35.321	779.373 29.326	26.577	<0.001
RAS	Factor 1 * group Error (factor1)	595.683 790.267	4.903 58.834	121.498 13.432	9.045	<0.001

SS: Sum of Squares; MS: Mean Square; LNFB: LORETA Neurofeedback; Cog.Reh.: Cognitive Rehabilitation.

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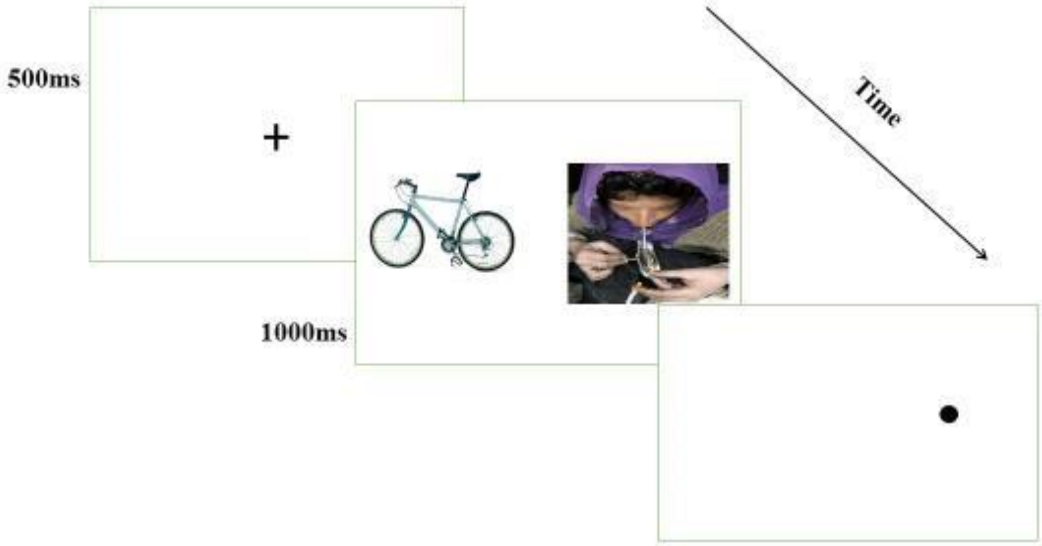

Figure 2. The display in the dot-probe task

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After a fixation cross, two pictures appeared simultaneously side by side, one stimulant picture (here on the left) and one neutral picture (right). Then a dot replaced one of the pictures, and the participant was asked to respond based on the location of the dot (i.e., left or right)

positive outcome, depression, and withdrawal relief from craving (Dehghani-Arani et al., 2013). There were no differences between methadone and buprenorphine maintenance treatments in this study compared to our research. Some experts claim that LZNFB is more effective than the conventional one according to the number of sessions. It is suggested that, in LZNFB, the regions of interest are more than those in the conventional NFB, notifying no suppression and reinforcement on upper and lower amplitudes of bands.

Hashemian studied 20 male patients with methamphetamine dependency in two groups. One group received real neurofeedback therapy, while the other group was treated with non-real neurofeedback (sham) therapy. Ten sessions of 30 minutes neurofeedback training were implemented for each patient. Alpha-theta training was carried out in the PZ region using a unipolar protocol in the two groups. DDQ was used for evaluating the level of craving. The results showed that, in the real neurofeedback group, the craving for methamphetamine use reduced significantly, whereas, in the second group, the change was not significant (Di Chiara, 1999). This study did not use the follow-up of relapse. It seems that 10 training sessions of conventional NFB may be inadequate for maintaining valuable results, and modulation might not completely occur to protect the future relapses. It can be postulated that the previous studies implemented long-term neurofeedback training; however, the present study achieved similar results within a shorter time.

Most previous studies in LZNFB were case studies, but they had similar results to our research. The findings of our study can be best supported by Rex Cannon and Joel Lubar's study entitled "LORETA Neurofeedback for Addiction and the Possible Neurophysiology of Psychological Processes Influenced". Their case was a 28-year-old heroin addict that received 25 sessions of LZNFB training in the ROI. The present study confirms that the region of training influences addicts' behaviors, demonstrating the possible neural mechanisms involved in the negative self-reference related to addiction even after an abstinence period, and possibly offers insights to precursors on how to start SUDs (Thatcher, 2015).

In another case study by Wesley D. Center, LZNFB treatment was conducted to explore the effectiveness of this training in a 55 years old alcoholic male addict. The treatment was implemented during 27 sessions of LZNFB with minimal intrusion into his life. Similar to the present study, the researchers selected the addiction reward networks as week systems and main areas for treatment, and Z tunes were selected as the treatment method in which real-time Z scores foster the EEG resonant frequencies and network functioning via reinforcing the movement of the trained Z scores toward 0 (Thatcher, 2010). As a result, the training method moved Z scores toward 0, which reduced and eliminated the patient's drinking problems and improved mood stability, duration, quality of sleep, and short-term memory. The method we used had some differences from Wesley's study. We implemented 5 sessions of Z tune training and

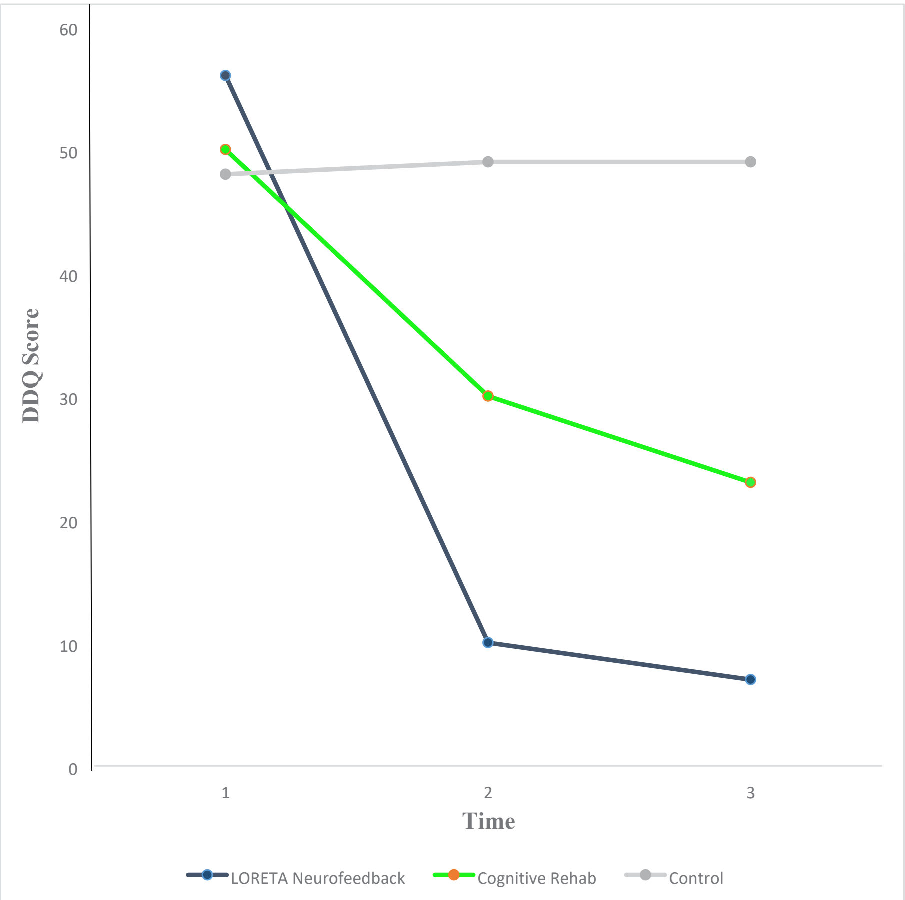

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Figure 3. The sample plot for DDQ test in pretest, posttest, and follow-up between the four groups, 1: pretest, 2: posttest, 3: follow-up

15 sessions of the "all or none" method as the purest operant conditioning training model of NFB; however, the results were similar in craving reduction and outcome improvement (Thatcher, 2015).

In the present study, the dot-probe task and the dot-probe training were used to evaluate the attentional bias to drugs cues and modify this bias toward neutral stimuli for reducing craving. One of the main cognitive aspects of prompt relapse in addicts is an attentional bias toward drug-related cues, which increases the impulse desire for drug use. There is considerable evidence to support this kind of cognitive bias in addicted individuals (Fadardi et al., 2016; van Hemel-Ruiter et al., 2016).

MacLeod, Rutherford, Campbell, Ebsworthy, and Holker used non-clinical participants to influence their emotional susceptibility using a dot-probe task administered through a computer and arranged to respond to negative stimuli via selective attention modulation (Garland et al., 2012). Wiers et al. examined the practicality of different varieties of CBM (attention control training and approach-bias retraining) in a fully automated web-based way and investigated their roles in reducing addiction in self-selected drinking addicts. Candidates enrolled via online advertising, and ultimately 136 subjects took part in a pretest, four computerized training sessions, and a posttest. As a result of training, the participants in all conditions reduced their drinking. The case analyses illustrated persistent improvements in self-efficacy due to approach-bias retraining after one and three months of follow-up (Wiers et al., 2015). In comparison with our study, similar results were obtained regarding craving reduction and outcome wellbeing.

On the other hand, despite the two-fold nature of the number of sessions, our sample was smaller due to some limitations. First, the dropout level was high in the present study, as half of the participants left the training after a few sessions. Second, the training did not seem attractive to some candidates despite the use of LZNFB. This problem can be resolved using interventions such as a free one-month methadone prescription which may motivate the participants.

Cox et al. examined the role of attentional bias modification in modifying addicts' behaviors. In this article, the researchers explored the techniques designed to help people overwhelm their alcohol attentional bias, drugs, smoking-related stimuli, or harmful food. Also, they prepared some techniques adapted for mobile use and let the candidates with addictive behavior use the attentional training in privacy whenever needed. The method was inexpensive, enjoyable, and flexible to use. They reported that the training techniques were effective in reducing both attentional bias and drug use and changing candidates' uncontrolled behavior (Cox et al., 2014). The dot-probe training is cheap and advantageous to be used after the treatment. Patients should be familiarized with this treatment and install the program on their personal computer or mobile phone for their use at home or outdoors and mostly in case of strong craving. It is a good way to reduce critical cravings.

Using the first double-blind, randomized controlled experiment, Begh et al. attempted to examine the effects of retraining in terms of attentional bias on cigarette smokers trying to stop smoking. Adult smokers attended a 7-session weekly stop-smoking program that involved modified visual probe tasks implemented through attentional retraining or placebo training. Training started one week before the abstinence day and was planned to be implemented during 5 sessions weekly. Both groups received 21 mg transdermal nicotine patches for 8–12 weeks, and withdrawal orientated behavioral support for 7 sessions. Results showed that the reaction time of attentional bias changed, and the desire to smoke was reduced (Begh et al., 2013). In line with the present study results, Begh et al. demonstrated that dot-probe training reduces craving and stops smoking. Another notable similar finding is the similarity of mechanisms in "nicotine patch" and "methadone maintenance". In the case of withdrawal from drugs or cigarettes, it would be challenging to keep the patients concentrated during the training sessions. Methadone and nicotine modulate withdrawal and create disgusting symptoms that annoy candidates during task completion. Hence, there can be more reliable results in the case of maintenance therapy.

Finally, using a randomized controlled experimental study, Schoenmakers examined the impacts of modification training of attentional bias on alcoholic addicts. The individuals were trained for five sessions on their disengaged attention from alcohol-related stimuli (ABM condition), and 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. To examine the overall effects of the treatment and the amount of relapse, the follow-up data were collected up to three months after the treatment. The results illustrated that ABM effectively enabled the participants to avoid alcohol-related cues. Besides, it was found that ABM was effective among alcohol-dependent patients (Schoenmakers et al., 2010). Similar to the present study, DAQ measurement confirmed the effective training treatment. However, we practiced with candidates using more sessions. Although the follow-up interval was short in our study, five training sessions were noticeable. ABM method is economically efficient, easy to do, and can be more useful if patients desire to use it.

5. Conclusion

According to the study results, LZNFB is more effective than cognitive rehabilitation and the MMT control group in decreasing craving. Also, it is more effective than conventional NFB, too, based on the fewer sessions and more training parts of the brain by selecting more than one interesting network, for example, craving, addiction, and anxiety network altogether. However, comparing these two kinds of NFB needs another separate study. Many hubs, Brodmann areas, and networks are selected for training in LZNFB, which is not possible in conventional NFB. Another advantage is the minimum number of sessions to obtain good results. For example, this number is 40 in conventional NFB and 20 in LZNFB (Barrouillet, 2011; Sarter et al., 2006; Saxby & Peniston, 1995; Thatcher, 2010; Thatcher, 2015). However, we recommend other independent studies to confirm this conclusion by comparing these two methods using similar sessions. Using LZNFB, we hypothesize that significant learning would require more than 20 sessions and at least 10 sessions after 3-6 months of booster training. Besides, future researchers should conduct lengthier studies (1, 6, and 12 months) with larger samples to explore the long-term changes caused by LZNFB and address the exact mechanism underlying this effect. More specifically, one group should receive LZNFB without pharmacotherapy. Additionally, a placebo group is required to eliminate the possible intervening roles of the therapist and the technologically induced context involved in LZNFB treatment. Furthermore, comparing the sham and LZNFB groups will result in more reliable and valid effects of LZNFB while excluding the effects related to prompting, technology, etc.

The technique of dot-probe training is simpler and cheaper than LZNFB but not as acceptable as LZNFB and sometimes was boring for our patients. There are different kinds of cognitive rehabilitation training. We recommended comparing this ABM method with the other cognitive rehabilitation training such as Captain's log, online attentional bias modification, paper and pencil cognitive rehabilitation package called NECOREDA (Neurocognitive Rehabilitation for Disease of Addiction), and even conventional neurofeedback. To evaluate the durability of dot-probe training, we need 3 and 6 months follow-ups. However, further studies are needed to illuminate the nature of differences in cue reactivity among those who are dependent on heroin and other opioids. This study confirms the presence of strong cue-induced craving in response to drug use among opioid addicts. Moreover, it is advisable to train the female group and other substance dependencies and even non-drug types of addiction via LZNFB and cognitive attentional bias modification.

Study limitations

First, the present study compared the effectiveness of neurofeedback and cognitive rehabilitation among male groups. We suggest other researchers compare the effects of these therapeutic approaches among female patients as well. Second, this study only used a 1-month follow-up. It is more reliable to follow participants' improvements over a longer period, such as 6 to 12 months, and track treatment effects at regular intervals. Third, larger studies, blinding and real RCT, longer duration, with larger samples scrutinize sources of hidden bias. Fourth, due to the moderate sample size, the researchers could not fully discover the impacts of the treatment. Thus, we recommend that future researchers employ larger sample sizes in their studies. Despite several limitations, the present study was an attempt to discover the impacts of LZNFB and cognitive rehabilitation treatment in the case of opioid dependence.

Ethical Considerations

Compliance with ethical guidelines

This study was registered in and received research code from the Iranian Registry of Clinical Trials (https://www.irct.ir, Code: ZUMS.REC.1396.97), Zanjan University of Medical Sciences.

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Authors' contributions

Conceptualization: Alireza Faridi, Farhad Taremian; Methodology: Farhad Taremian, Robert W Thatcher; Software, Validation, Formal Analysis: Mohsen Dadashi, Farhad Taremian, Reza Moloodi; Original Draft Preparation: Alireza Faridi; Writing - review & editing: Farhad Taremian; Visualization, Supervision: Robert W Thatcher.

Conflict of interest

The authors declared no conflict of interest.

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