Effect of Neurofeedback Training Along With Swimming Exercise on the Stress, Anxiety, Depression, Severity of Dependence, and Craving in Methamphetamine-Dependent Patients

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This study investigated whether neurofeedback (NFB) training and swimming exercise (Swim) would reduce the stress, anxiety, depression, severity of dependence, and cravings in patients addicted to methamphetamines. Participants were allocated randomly to four groups: control group, NFB, Swim, and NFB/Swim. All groups completed the study questionnaire before and after treatment. The NFB, Swim, and NFB/Swim groups reported significantly less stress, cravings, and severity of dependence than the control group. The Swim and NFB/Swim groups had significantly lower depression scores than the control group. Also, the NFB/Swim group experienced less anxiety than the control group. However, the NFB/Swim group had lower levels of stress than the Swim group, and lower levels of anxiety and severity of dependence than the NFB group. These findings suggest that NFB training along with swimming exercise was effective in managing methamphetamine-related behavioral disturbances, which may help patients to manage their cravings.

Keywords: methamphetamine dependence, psychological dependence, neurofeedback, physical exercises
Methamphetamine (METH) is one of the most addictive illicit drugs, which dramatically affects the central nervous system (Cherner et al., 2010). Chronic METH abuse may produce long-term changes in the brain structure, function (Cruickshank & Dyer, 2009), and synaptic plasticity (Swant et al., 2010), and cell death via apoptosis and neurotoxicity (Schmued & Bowyer, 1997) in dopaminergic (Yui et al., 2004), serotonergic (Rau et al., 2006), glutamatergic, and noradrenergic pathways (Halpin et al., 2014; Lu et al., 2010). These changes caused by METH abuse may lead to dependence, overdose, withdrawal syndrome, and drug cravings (Danaceau et al., 2007; Stefanski et al., 2002).

Withdrawal from METH could potentially lead to behavioral disorders, such as anxiety, depression, psychotic symptoms, psychosomatic disorders, psychomotor agitation, neuropsychophysiological abnormalities, and cognitive and memory impairments (Glasner-Edwards & Mooney, 2014; McGregor et al., 2005; Rostami & Dehghani-Arani, 2015; Zorick et al., 2010). It has been shown that stress-related psychiatric disorders and drug-associated cues, which may, in turn, activate the reinstatement of compulsive drug-seeking behavior and relapse (Nakama et al., 2008; Sinha et al., 2003), might have significant clinical implications for the prevention of relapse. A number of studies have shown that substance dependence disturbs the normal function of the brain and neural system, which can create abnormalities in the complex interaction of between mind and body (Arani et al., 2010), electrical brain activity, and electroencephalography (EEG; Kalechstein et al., 2009; Newton et al., 2003), which in turn influence risk for initiation and maintenance of addictive behaviors.

Also, previous studies have reported that the EMG changes during METH abstinence were associated with a variety of psychiatric and cognitive abnormalities (Kalechstein et al., 2009; Newton et al., 2003). Therefore, therapeutic approaches should ideally address all mind–brain, psychological, and physical dimensions to provide comprehensive treatment. Neurofeedback (NFB) is an operant conditioning technique, based on electrical brain activity, that trains the mind to improve emotional, cognitive, behavioral, and physical experiences, as well as self-regulation of brain activity (Arani et al., 2010; Rostami & Dehghani-Arani, 2015). The NFB helps to adjust any disruptive wave pattern and restore the normal pattern of brain activity (Thompson & Thompson, 2021), and corrects the brain’s function abnormalities without any lasting side effects (Scott et al., 2005) in substance abuse disorders. Previous studies also indicated that NFB improved the severity of addiction, mental health, and quality of life (Rostami & Dehghani-Arani, 2015), cognitive emotion regulation (Amiri et al., 2020) and craving in METH-dependent patients, as well as abnormalities due to opioid-dependence disorders (Dehghani-Arani et al., 2013).

Furthermore, previous studies have demonstrated that METH-dependent patients have more complex neuropsychophysiological conditions (Rostami & Dehghani-Arani, 2015) and the treatment of these patients is more complicated than those using other types of illicit drugs (Brands et al., 2012). So, it seems that NFB as a stand-alone therapy may have even weaker outcomes for the treatment of METH psychological dependence after treatment. In this regard, some studies have shown that clinical/behavioral outcomes (total abstinence, improved function, and quality of life) of NFB therapy are not clearly established at follow-up.
time points and is not a stand-alone treatment for substance use disorders (Sokhadze et al., 2008). Thus, these patients may need a complementary therapy approach to provide comprehensive treatment.

Previous studies have documented a positive relationship between NFB training and physical activity (Mikicin et al., 2020; Xiang et al., 2018). In line with this assumption, it has been shown that NFB training may be useful in enabling athletes to perform optimally (Dupee et al., 2016) and change EEG power (Xiang et al., 2018), and also, NFB training during swimming exercise was shown to improve and optimize mental/psychomotor performances (Mikicin et al., 2020).

Also, regarding the effectiveness of physical exercise to treat patients addicted to METH, some scattered studies showed that treadmill exercise improved fitness (Dolezal et al., 2013), heart rate (HR) variability, and autonomic balance (Dolezal et al., 2014) and reduced psychological symptoms of depression (Haglund et al., 2015) and relapse (Mooney et al., 2014) among METH-dependent patients. Our previous findings indicated that regular swimming exercise reduced voluntary METH consumption in animal models of relapse by reducing anxiety, obsessive–compulsive disorder, and depression in the METH-withdrawn rats (Damghani et al., 2016).

It is also important to note that, because of the high similarities in brain structures of the laboratory animals (mainly mice and rats) and humans, the experimental findings of animal models can be directly related to the pathology expected in humans (Bryda, 2013). On a further note, unlike other sports, swimming exercise simultaneously activates the greatest number of muscles, delays fatigue, increases the chest movement amplitude (Eider et al., 2014), and the motivation and morale of the patient (Stan, 2012).

Therefore, the results of our previous animal study and also the importance of swimming in the literature support the role of swimming exercise to treat METH-dependent patients. In order to fully elucidate the role that NFB training or physical activity may play to treat METH-dependent patients, the aim of the present study was to investigate the effectiveness of NFB training and swimming exercise, either alone or in combination, on the addiction severity, stress, anxiety, depression, and drug cravings in METH-dependent patients. Combined therapies seem to be an adequate strategy for METH-dependent patients. Therefore, we hypothesized that swimming exercise followed by NFB training would be more effective on the treatment of METH-dependent patients of experiment groups rather than the control.

**Methods and Materials**

**Participants**

The 145 male participants who were undergoing treatment in an addiction treatment camp were enrolled and screened, 31 of whom were unwilling to participate and 62 of which did not match the inclusion criteria. Out of the 52 patients, 12 participants refused to continue the program due to lack of motivation, during the program, and finally, 40 participants aged 25–45 years completed the study between 2020 and 2021. Then, a 2-week screening phase was initiated and
the medical history of the participants, physical examination, and criteria for METH dependence were assessed by the treatment camp’s physician. Inclusion criteria included: (a) participants who met the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition criteria for METH dependence; (b) participants were literate; (c) participants had no history of using pharmacologic treatment during withdrawal; (d) participants had no history of psychiatric drug use; (e) participants had no history of playing professional sports; and (f) participants had no cognitive impairment, head trauma, stroke, cardiovascular, and/or psychiatric disorders. This study was a randomized controlled trial with a pre- and posttest design (Figure 1: Consolidated Standards of Reporting Trials flowchart diagram).

**Procedure**

The camp treatment protocol included a detoxification program, pain relief, psychotherapeutic, counseling, and rehabilitation under the direct supervision of the camp’s physician and clinical psychologist. Then, the eligible participants were evaluated with the Leeds Dependence Questionnaire, the Depression Anxiety Stress Scales, and the Desire for Drug Questionnaire before and after the intervention. We briefly described the intervention programs of the present study, and then, 52 participants were randomly assigned to one of the four groups: control group (Cont; only received the treatment protocol of the camp during their 10-week staying at the camp, and received no NFB training and/or swimming exercise), NFB group (received the NFB training, 3 days/week for 10 weeks), Swim group (received regular swimming exercises, 3 days/week for 10 weeks), and NFB/Swim group (received NFB training and swimming exercise, every other day, each performed 3 days/week and each for 10 weeks).

We first informed participants with a brief explanation of the study procedure and described the informed consent process and their rights, and then, informed consent was obtained from all participants before the subdivision process began. To motivate participants to attend the study, all participants were visited by the treatment camp’s physician and clinical psychologist, and family members of the participants were supported by a psychiatric social worker. The treatment groups were matched concerning their age, education level, and type of drug abuse. The present study was approved by the research ethics committee of Semnan University of Medical Sciences (IR.SEMUMS.REC.1397.308) and received the Iranian Registry of Clinical Trials (IRCT20190703044092N1). Demographic variables including age, educational status, marital status, duration of METH addiction, physical illness history, body mass index, maximal oxygen uptake, and job were evaluated (Table 1).

**NFB Training Method**

The NFB training protocols lasted 10 weeks, 3 days per week (alternate days), each session 30 min, using the Thought Technology Pro Comp 2 system, which was administered by the well-trained clinical psychologist, as previously described by Dehghani-Arani et al. (2013) in the Iranian population. In brief, this protocol in each session focused on sensory-motor rhythm (SMR) training in the central brain cortex.
Figure 1 — A flowchart diagram showing the study design. LDQ = Leeds Dependence Questionnaire; DASS = Depression Anxiety Stress Scales; DDQ = Desire for Drug Questionnaire.
## Table 1  Demographic Information

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cont ($n = 10$)</th>
<th>NFB ($n = 10$)</th>
<th>Swim ($n = 10$)</th>
<th>NFB/Swim ($n = 10$)</th>
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<tr>
<td>Age (years; mean ± SD)</td>
<td>35.10 ± 8.07</td>
<td>31 ± 5.37</td>
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<td>1 (10)</td>
<td>1 (10)</td>
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<td>7 (70)</td>
<td>7 (70)</td>
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<td>3 (30)</td>
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<tr>
<td>Duration of METH addiction (years; mean ± SD)</td>
<td>7.70 ± 2.21</td>
<td>7.30 ± 3.02</td>
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<td>BMI (kg/m; mean ± SD)</td>
<td>22.80 ± 3.11</td>
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<tr>
<td>VO$_2$max (mean ± SD)</td>
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<td>39.20 ± 4.63</td>
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<td>Unemployed</td>
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Note. ANOVA = analysis of variance; BMI = body mass index; Cont = control; NFB = neurofeedback; METH = methamphetamine.

$^a$One-way ANOVA. $^b$Chi-square.
(Cz region) and alpha–theta in the parietal cortex (Pz region). In this protocol, the active, reference, and grand electrodes were placed in the Cz, left, and right ear, respectively. A protocol was designed to reinforce the SMR band (12–15 Hz) and suppress the alpha (8–12 Hz), theta (5–8 Hz), delta (2–5 Hz), and high beta (18–30 Hz)—according to a previous study (Kober et al., 2015)—showing that the NFB training provided visual feedback for increasing SMR power while keeping other frequencies low. A visual threshold-dependent protocol was used as reward stimuli for the participants (e.g., a computer game). Participants were advised to focus on feedback to find the most successful mental strategy and to get as many rewards as possible. When the EEG frequencies were within the defined thresholds, the participants obtained the reward, and the image was changed. If the participant could not adjust to the thresholds, the image would remain unchanged. In this study, if the participant was able to increase the SMR wave by 80% of the time and decrease the delta, theta, and high beta by 20% of the time, received many rewards of visual feedback. Feedback in the alpha–theta training protocol on the Pz area was presented only in an auditory format. In this protocol, the participants closed their eyes and only listened to the sound being played to them. The active, reference, and grand electrodes were placed in the Pz, left, and right ears, respectively, and two distinct tones of sounds were used to amplify alpha and theta under eyes-closed conditions. If the delta wave was increased, the system could prevent the participant from falling asleep by using a special sound. In this session, if the theta/beta ratio would have decreased, voice feedback was provided as a reward stimulus, which consisted of continuing to play the music.

**Swimming Protocol**

The swimming training protocol lasted 10 weeks, 3 days per week (alternate days), each session 60 min, in the swimming pool (Taybad, Iran) under the supervision of an experienced exercise trainer. First, we determined the maximum HR based on the formula (220–Age; Bragada et al., 2009; Gellish et al., 2007). Mean maximum HR was used to estimate exercise intensity, which was determined at a moderate intensity (60%–70% HR–12 beats/min). Each swimming session included a 10 min warm-up followed by 40 min of swimming and a min cooling down afterward (Karapolat et al., 2009). During this period, patients’ pulses were detected manually; then, every 10 min, patients were told to increase the number of swimming laps and/or swimming velocity. The water temperature was approximately 32 °C throughout the study.

**Measures**

**Leeds Dependence Questionnaire**

The Leeds Dependence Questionnaire is a 10-item self-report scale, designed to measure dependence upon a variety of substances and the degree of dependency from mild to severe. Each item is scored from zero to three giving a maximum score of 30. Cronbach’s alpha and test–retest reliability were .94 and .95, respectively (Rabiey et al., 2019). In this study, we used the validated Persian version (Iranian language) of the original questionnaire (Massah et al., 2019).
The Depression Anxiety Stress Scales

The Depression Anxiety Stress Scales questionnaire was a 42-item self-reported test for measuring depression, anxiety, and stress. Scores for depression, anxiety, and stress scales are determined by summing the scores for the relevant 14 items. Each question has a 4-point Likert scale from never to completely, and the scores of each question are calculated by summing the scores of the questions. Cronbach’s alpha was computed at .966 for the total score, .947 for the depression scale, .897 for the anxiety scale, and .933 for the stress scale (Lovibond & Lovibond, 1995; Rabiey et al., 2019). We used the validated Persian version (Iranian language) of the original questionnaire (Pooravari et al., 2017).

Desire for Drug Questionnaire

The Desire for Drug Questionnaire was designed by Franken et Al. (Franken et al., 2002; Hassani-Abharian et al., 2016), to assess drug cravings of a variety of substances on a 7-step Likert scale scored from 1 to 7 (Rabiey et al., 2019). The Desire for Drug Questionnaire constitutes 14 items for three main craving components, desire and intention to drug use, negative reinforcement for drug use, and drug abuse control. The Cronbach’s alpha was reported as .89 and .85 for the general credit questionnaire (Franken et al., 2002; Hassani-Abharian et al., 2016; Rabiey et al., 2019). We used the validated Persian version (Iranian language) of the original questionnaire (Akhavan-Behbahany et al., 2020).

Statistical Analysis

We used the Kolmogorov–Smirnov test to evaluate the normality of the data. The study variables indicated a normal distribution ($p > .05$). Demographic data were compared using the chi-square and one-way analysis of variance. We conducted a repeated-measures analysis of covariance to assess whether the average scores of the choice criteria differed using pre- and posttreatment measurements as time points for within-subject factors, and three treatment conditions as between-subject factors. Also, the patterns of METH use, incarceration history, and economic status were included as the covariate variables. Bonferroni correction test was used for post hoc pairwise comparisons. We expressed results as mean ± SEM and SD. Differences were considered statistically significant at $p < .05$. We used SPSS to analysis the data. Partial eta-squared ($\eta^2$) was used for effect size calculations in this study.

Results

Demographic Variables

Participants in the four groups did not differ on any of the examined demographic variables ($p > .05$, Table 1). Out of the 40 participants, all were male, 70% were married, and 30% were single, with a mean age of 33 years. The majority of the participants had a middle school education (40%). Most of the participants were employed (60%). The mean duration of METH use was 7 years. Nearly half of the participants reported a history of physical illness (50%). Results of analysis of
variance showed no statistically significant difference in the mean age ($F[3, 36] = 0.99, P > .05$ [not significant]), duration of METH use, $F(3, 36) = 0.09, P > .05$ (not significant), body mass index, $F(3, 36) = 0.65, P > .05$ (not significant), and maximal oxygen uptake, $F(3, 36) = 2.1, P > .05$ (not significant), in METH-dependent patients between groups. The mean body mass index and maximal oxygen uptake were 22.67 and 40.45, respectively.

**Effect of NFB Training and Swimming Exercise on Stress, Anxiety, and Depression in METH-Dependent Patients**

The repeated-measures analysis of covariance results demonstrated significant within-subject effects for the time from pre- to posttreatment for stress, $F(1, 36) = 312.48, p < .0001$, Partial $\eta^2 = .89$, anxiety, $F(1, 36) = 453.02, p < .0001$, Partial $\eta^2 = .92$, and depression, $F(1, 36) = 358.98, p < .0001$, Partial $\eta^2 = .90$.

We observed significant differences among the three treatment conditions for stress, $F(3, 36) = 15.11, p < .0001$, Partial $\eta^2 = .57$, anxiety, $F(3, 36) = 6.41, p = .001$, Partial $\eta^2 = .35$, and depression, $F(3, 36) = 9.18, p < .0001$, Partial $\eta^2 = .43$. Also, this analysis revealed a significant interaction of Time $\times$ Treatment group for stress, $F(3, 36) = 5.56, p = .037$, Partial $\eta^2 = .317$, anxiety, $F(3, 36) = 3.04, p = .05$, Partial $\eta^2 = .22$, and depression, $F(3, 36) = 3.89, p = .048$, Partial $\eta^2 = .29$.

Comparing the stress scale for posttreatment showed that the NFB ($p < .0001$), Swim ($p = .046$), and NFB/Swim ($p < .0001$) groups experienced lower levels of stress compared with the Cont group. Also, the NFB/Swim group had lower stress levels than the Swim group ($p = .007$; Figure 2). Assessment of the anxiety scale showed that the NFB/Swim group experienced lower levels of anxiety than the Cont ($p = .008$) and NFB ($p = .002$) groups (Figure 3). Also, NFB ($p = .06$), Swim ($p = .008$), and NFB/Swim ($p < .0001$) groups had significantly lower depression scores than the Cont group (Figure 4). This finding indicates that the scores for

![Figure 2](image-url)  
*Figure 2* — Effect of NFB training and swimming exercise on stress in METH-dependent patients. There is no significant difference between the four groups in the pretest stress score. NFB, Swim, and NFB/Swim groups had significantly lower stress scores than the Cont group for posttest. ***$p < .0001$ and *$p = .046$ versus Cont. ^$p = .007$ versus Swim. Cont = control; NFB = neurofeedback; METH = methamphetamine.
depression, anxiety, and stress were lower after treatment during the posttest in METH-dependent patients who received both NFB training and swimming exercise.

**Effect of NFB Training and Swimming Exercise on the Severity of Dependence and Instant Craving in METH-Dependent Patients**

The repeated-measures analysis of covariance results demonstrated significant within-subject effects for the time from pre- to posttreatment for the severity of dependence, $F(1, 36) = 667.66, p = .0001$, Partial $\eta^2 = .95$, and instant craving, $F(1, 36) = 1,264.51, p = .0001$, Partial $\eta^2 = .97$.

(Ahead of Print)
We observed significant differences among the three treatment conditions for the severity of dependence, \( F(3, 36) = 14.02, p = .0001 \), Partial \( \eta^2 = .54 \), and instant craving, \( F(3, 36) = 11.07, p = .0001 \), Partial \( \eta^2 = .48 \). Also, this analysis revealed a significant interaction of Time \( \times \) Treatment group for the severity of dependence \( F(3, 36) = 13.65, p = .0001 \), Partial \( \eta^2 = .53 \), and instant craving, \( F(3, 36) = 23.71, p = .0001 \), Partial \( \eta^2 = .66 \).

Comparisons between groups for the severity of dependence showed that the Swim \((p = .002)\) and NFB/Swim \((p = .0001)\) groups reported significantly lower scores in the severity of dependence than the Cont group. Also, the NFB/Swim group had lower severity of dependence than the NFB group \((p = .0001)\); Figure 5). Comparisons between groups for the instant craving scale showed that NFB \((p = .001)\), Swim \((p = .001)\), and the NFB/Swim \((p = .0001)\) groups experienced less craving than the Cont group (Figure 6), indicating that METH-dependent patients who received the NFB training along with swimming exercise displayed less dependence and drug craving in the posttreatment period.

**Discussion**

**The NFB Training and Swimming Exercise Decrease Stress, Anxiety, and Depression in METH-Dependent Patients During Withdrawal**

We found significant within-subject effects for the time from pre- to posttreatment scores for stress, anxiety, and depression in the treatment of METH-dependent patients. A comparison of posttest scores of treatment groups showed that the
combination of NFB training and swimming exercise for 10 weeks reduced the level of stress, anxiety, and depression. The levels of stress, anxiety, and depression were lower in NFB/Swim group than in single NFB or swimming groups. Therefore, the NFB training along with swimming exercise (NFB/Swim group) might more effectively reduce stress, anxiety, and depression in METH-dependent patients during withdrawal. In this regard, previous studies have shown that NFB training can induce neural plasticity, including the dorsal anterior and mid-cingulate (Loriette et al., 2021), involved in the processing of emotional information and cognitive performance (Lanius et al., 2012; Yamashita et al., 2017). A previous study suggested that alpha/theta NFB is a mood-enhancing and energizing experience (Raymond et al., 2005). NFB-induced brain and neural plasticity is a phenomenon that has been considered as a basic mechanism for behavioral changes (Rostami & Dehghani-Arani, 2015). Thus, the alpha/theta NFB enabled in subjects’ ability to cope more effectively with stress and anxiety (Moradi et al., 2011; Plotkin & Rice, 1981; Scott et al., 2005), particularly in METH-dependent patients during the early phases of recovery. A study showed that NFB decreased self-reports on depression and stress scores among cocaine users (Horrell et al., 2010). Our findings also showed that swimming exercise improved the effectiveness of NFB training in reducing stress, anxiety, and depression in the treatment of METH-dependent patients. Our results are consistent with previous animal and clinical studies, indicating that exercise reduces anxiety and depression levels in the METH-dependent rats (Damghani et al., 2016) and individuals (Haglund et al., 2015). At present, the neurobiological mechanisms to reduce stress, anxiety, and depression levels following the effectiveness of swimming exercise combined with NFB training are still unknown and mostly based on animal studies. It may be due to an increased brain-derived neurotrophic factor level (Duman & Monteggia, 2006; Pietropaolo et al., 2008; Sigwart et al., 2011) and the normalization of brain.

Figure 6 — Effect of NFB training and swimming exercise on the instant craving in METH-dependent patients. There is no significant difference between the four groups in the pretest instant craving score. The NFB, Swim, and NFB/Swim groups experienced less instant craving than the Cont group for posttest. \( ** p = .001, ^{\wedge\wedge} p = .001, ^{***} p = .0001 \) versus Cont. Cont = control; NFB = neurofeedback; METH = methamphetamine.
neurotransmitters, such as serotonin (Greenwood et al., 2003), noradrenalin (Stranahan et al., 2009), and dopamine (Meeusen & De Meirleir, 1995) following swimming exercise, emphasizing the need for further research. Also, previous studies have shown that exercise increased striatal D2/D3 receptor availability in METH abstinence (Morais et al., 2018), stimulated adult hippocampal neurogenesis (Inoue et al., 2015), and the defensive mechanisms of antioxidants (Camiletti-Moiron et al., 2013). Therefore, it seems that exercise prevents certain allostatic changes in the brain reward and stress systems and brain-derived neurotrophic factor modifications that may contribute to the mood corrections (Morais et al., 2018) seen in METH-dependent patients.

The NFB Training and Swimming Exercise Decrease the Severity of Dependence and Instant Craving in METH-Dependent Patients During Withdrawal

We found significant within-subject effects for the time from pre- to posttreatment scores of the severity of dependence and instant craving in the treatment of METH-dependent patients. However, a comparison of posttest scores of treatment groups showed that both NFB training and swimming exercise and the NFB training along with swimming exercise for 10 weeks can reduce the severity of dependence and instant craving. Also, the severity of dependence was lower in NFB/Swim group than in the NFB group. Therefore, the NFB training along with swimming exercise (NFB/Swim group) might be more effective in reducing the severity of dependence during METH withdrawal among dependent patients. In this regard, previous studies have shown that NFB decreased the craving for METH (Hashemian, 2015) and opioid use (Arani et al., 2010), and produced more improvements in the severity of addiction, mental health, and quality of life in crystal METH-dependent patients (Rostami & Dehghani-Arani, 2015). Our findings also showed that swimming exercise improved the severity of dependence and craving in METH-dependent patients, which were consistent with previous animal (Damghani et al., 2016; Engelmann et al., 2014; Sobieraj et al., 2016) and clinical (Morais et al., 2018; Wang et al., 2015, 2016, 2017) results, showing that aerobic exercise program decreased METH-seeking behavior and associated craving. Thus, swimming exercise may recruit a common brain pathway and decrease the rewarding effects of METH, which can be explained at least in part, by the anti-anxiety and antidepressant effect of exercise during METH withdrawal. Also, we found that the NFB/Swim group had lower severity of dependence than the NFB group. Thus, the NFB/Swim group was more effective in reducing the severity of dependence for METH. Therefore, by reducing psychological symptoms, negative emotional states, and cognitive disorders, exercise may serve to complement NFB training to behavioral changes induced by METH. In this regard, a study showed that the improvements in better mental performance following the NFB training affect the optimization of psychomotor reactivity in the swimming group (Mikicin et al., 2020). This means that the combination of mental effort (brain–computer interface training using NFB) and physical exercise (creeping and swimming activities) may lead to changes in brain activity. The neurobiological mechanisms of exercise to reduce METH-induced craving seem to reflect an
interplay of several agents, including neurochemicals, oxidative stress, neurogenesis, and glycogenesis (Morais et al., 2018). Further studies are suggested and warranted to confirm the effectiveness of NFB training along with a variety of other exercises to treat neuropsychological disorders induced by METH dependency.

**Strengths and Limitations**

One of the strengths of this study was the use of nonpharmacological combination therapy as a new treatment approach; however, our study also has some limitations. Despite a large effect size in the present study, a larger sample size increases power and decreases estimation error, and increases the ability to further evaluate subgroup differences, which is suggested for further studies. Also, a more important question would be whether the effects of exercises and NFB could be sustained over the weeks following the discontinuation of training. This question cannot be answered by our findings because it requires a 6-month and 1-year prospective follow-up study.

**Future Research**

The swimming protocol in this study was based on the old method to estimate exercise intensity; it is suggested to use new methods in future research. It is suggested to use different types of exercise as well as other protocols of NFB in the treatment of METH-dependent patients. In the present study, physiological parameters such as laboratory data or blood samples should be measured to control the placebo and the expected effects and to evaluate the mechanisms of action of the combination therapy, which was one of the limitations of our study and suggested for future research. Future studies should investigate the effects of NFB training and swimming exercise in opiate-dependent men and women.

**Conclusions**

This study provided novel evidence that regular swimming exercise and NFB training during METH withdrawal can decrease the severity of stress, anxiety–depression, dependence, and craving for METH dependent patients. Our findings may have a potential therapeutic application for the treatment of METH-induced psychological dependence and relapse in addicts. For most behavioral measures, the effectiveness of the combination of NFB and swimming exercise was more favorable. The findings of this study suggest that swimming exercise may complement NFB training in behavioral changes induced by METH. According to the results of this study, the application of the NFB training along with swimming exercise can be an effective therapeutic strategy for the management of METH withdrawal in addicts with follow-up studies that utilize a larger number of samples, and the most suitable type, and intensity, of exercise (voluntary, treadmill, and swimming).

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