Title: Effect of Neurofeedback Training Along with Swimming Exercise on the Electroencephalographic Changes and Visual Image-Induced Craving in Methamphetamine-Dependent Patients

Running Title: Effects of NFB Training and Swimming Exercise on EEG Changes in Methamphetamine Addicts

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Abstract*:*

***Introduction*:** In this study, we investigated whether neurofeedback (NFB) training and swimming exercise would decrease the electroencephalographic (EEG) changes and visual image-induced craving in methamphetamine (METH)-dependent patients.

Methods: This study was a randomized controlled trial design. 32 METH-dependent patients were allocated randomly to four groups; control, NFB, Swim, and NFB/Swim. The EEG and visual image-induced craving were recorded before and after the intervention in all four groups.

Results: We found that the NFB, Swim, and NFB/Swim groups showed significantly lower absolute power for 4 frequency bands. Also, the swim and NFB/Swim groups had less and greater relative power in the alpha and delta bands, respectively. In addition, NFB/Swim group exhibited an increase in delta/alpha power ratio than the control and the NFB groups. Also, the NFB/Swim group showed a significant reduction in visual image-induced craving score than the control, swim, and NFB groups.

Conclusion: This study provides novel evidence that the NFB training along with swimming exercise during METH-abstinence was effective in the normalization of METH-induced EEG changes, which may help patients to manage their cravings.

Keywords: Methamphetamine, Neurofeedback, Swimming Exercise, Electroencephalography, Craving.

Research highlights:

- Neurofeedback decreased absolute power for 4 frequency bands.
- Swimming decreased absolute power for 4 frequency bands.
- Neurofeedback/Swimming decreased absolute power for 4 bands and METH craving.
- Neurofeedback/Swimming increased delta/alpha power ratio.

Plain Language Summary

Methamphetamine (METH) dependence is associated with behavioral disorders, craving and also abnormal EEG. Neurofeedback (NFB) training during swimming exercise optimized mental/psychomotor performances or brain activity. In the present study NFB, swimming, and NFB/Swimming groups decreased absolute power for 4 frequency bands in methamphetamine (METH)-dependent patients. Also, the NFB/Swimming group decreased visual image-induced craving score in methamphetamine (METH)-dependent patients.

1. Introduction

Methamphetamine (METH) abuse is a widespread issue and a significant public health problem (Burns, 2014), which affects the central nervous system (CNS) (Cherner et al., 2010). METH abuse is associated with dependence, persistent craving, and withdrawal syndrome including depression, anxiety, and cognitive deficits in humans (Dean, Groman, Morales, & London, 2013; McGregor et al., 2005), and animal models (Bigdeli, Asia, Miladi-Gorji, & Fadaei, 2015; Hajheidari, Miladi-Gorji, & Bigdeli, 2015). Also, previous studies have shown that METH abuse makes EEG abnormal (Newton et al., 2004).

The neurotoxic effects of METH persisted even after prolonged abstinence (Ernst, Chang, Leonido–Yee, & Speck, 2000; Hajheidari, Sameni, Bandegi, & Miladi-Gorji, 2017).

Previous studies have shown that METH abuse increased delta and theta band powers after 4 days of abstinence (Newton et al., 2003), and also increased beta band power after 1–3 months of abstinence (Zhao et al., 2021). EEG abnormalities may be related to METH-induced behavioral disorders (Khajehpour et al., 2019; Shafiee-Kandjani et al., 2020). Therefore, it provides a potential insight that therapeutic interventions may occur via modulation of the EEG pattern of brain waves in patients with METH dependence.

Previous studies have shown that neurofeedback training (NFB) normalized or optimized brain activity (LaVaque, 2003), decreased craving for METH (Hashemian, 2015), also demonstrated that the treatment of METH-dependent patients is more complex (Brands et al., 2012).

So, it seems that neurofeedback as a stand-alone therapy may have weaker outcomes for the treatment of METH abuse, and may need the complementary therapy approach to treatment. In this line, previous studies have shown that NFB training during swimming exercise improved and optimized mental/psychomotor performances (Mikicin, Mróz, Karczewska-Lindinger, et al., 2020). In further notes, unlike other sports, swimming exercises simultaneously activate a great number of muscles, delay fatigue, and increase the chest movement amplitude (Eider, Łubkowska, & Paczyńska-Jędrycka, 2014) as well as the motivation and mood of the patient (Stan, 2012), also exercise increases alpha (Schneider et al., 2009) and beta (Moraes et al., 2007) power. Given the high risk of relapse in these patients, it needs a combined treatment to provide comprehensive treatment. Thus, this study aims to investigate the effect of NFB training and swimming exercise, both alone and combined, on the EEG changes and visual image-induced craving in METH-dependent patients.

2. Materials and methods

2.1. Participants

Patients with METH dependence were 32 men, aged 25–45 years, who were staying in an addiction treatment camp (Taybad, Iran), were invited to participate in the study between 2020 and 2021 and then started a two-week screened phase. During the screening, the medical history of the participants, physical examination, and criteria for METH dependence had assessed by the treatment camp's physician. Patients had no history of drug treatment for withdrawal, professional sports, and the use of psychiatric drugs. They had no cognitive impairment, head trauma, stroke, cardiovascular, or psychiatric disorders. The treatment groups were matched concerning their age, education level, and type of drug abuse. Demographic variables including age, educational status, marital status, duration of METH addiction, physical illness history, body mass index (BMI), Vo2 max and Job were evaluated (Table 1). The 114 subjects were enrolled and screened. 31 patients declined to participate and 43 patients didn't match the criteria. Finally, 40 patients met all inclusion. We first informed the patients with a brief description of the study programs and their rights and all participants provided written informed consent. The patients were then randomized into four groups using a pre-test and post-test design; Control (No medication based on the Camp's protocol), NFB training (three days per week, alternate days for 10 weeks) , regular swimming exercises (three days per week, alternate days for 10 weeks), and simultaneous NFB and swimming training (three days swim and three days NFB in alternate days one week for 10 weeks). However, 8 patients showed little motivation to continue and excluded from the analysis finally 32 patients completed the study (Fig.1. Study diagram flowchart). 32 patients were approved by the Ethics Committee guidelines and regulations. EEG and visual image-induced craving were recorded in all 32 patients (Fig.1. Study diagram flowchart). The present study was approved by the Ethics Committee of the Semnan University of Medical Sciences (IR.SEMUMS.REC.1397.308) and received the Iranian Registry of Clinical Trials (IRCT) (IRCT20190703044092N1).

2.2.Experimental protocol:

2.2.1. NFB training method:

Patients underwent the NFB protocol for 10 weeks which was three interval sessions per week, and each session lasted 30 minutes using the Thought Technology ProComp 2 system, as previously described in the Iranian population (Dehghani-Arani, Rostami, & Nadali, 2013; Kober et al., 2015). This protocol in every session was focused on sensory-motor rhythm (SMR) training in the central brain cortex (Cz region), and alpha-theta in the parietal cortex (Pz region). This protocol consists of placing the active, reference, and grand electrodes in the Cz, left, and right ears, respectively. The main purpose of our protocol design was 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). A visual threshold-dependent protocol in the form of a computer game was used as reward stimuli for the patients. Patients 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 patient obtained the reward, and the image was changed. If the patient could not adjust to the thresholds, the image would remain unchanged. In this study, if the patient 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 patients 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 patient 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.

2.2.2. Swimming Protocol:

The swimming training protocol was done for 10 weeks with 3 sessions per week, and 60 minutes per session. This was conducted in the swimming pool (Taybad, Iran) under the supervision of an experienced exercise trainer. To start, we calculated the maximum heart rate (HRmax) with the formula (220- Age) (Bragada, Pedro, Vasques, Tiago, & Vítor, 2009; Gellish et al., 2007). We used average HRmax to approximate the exercise intensity, which was determined at a moderate intensity (60-70% heart rate [HR] reserve -12 beats/min). Each swimming session included three parts; the first was 10 min warm-up, then there was a 40 swim, and the last part was the 10 minutes cool down (Karapolat et al., 2009). In this study, the water temperature was about 32^{oC}.

2.2.3. ***EEG Protocol:***

All EEG recordings were carried out after completing a neuropsychological test between 12 noon and 4 pm, under laboratory-controlled sound and light conditions, as previously described (Choi et al., 2013). EEG recording lasted for 10 min and included the following conditions: 5 min with eyes closed, 5 min with eyes open. EEG recordings were obtained from the scalp using SynAmps2 with a 19-channel Quik-Cap and a NeuroScan system. The signals were recorded at a sampling frequency of 500 Hz and electrode impedance was below 5 kiloohms (kΩ). The EEG was band-pass filtered at 0.1–60 Hz using the signal processing software of the NeuroScan system for spectral analysis in 32-bit file format, and 19 electrode sites of 19 channels were driven by the NeuroGuide montage set as follows: FP1, F3, F7, Fz, FP2, F4, F8, T3, C3, Cz, T4, C4, T5, P3, O1, Pz, T6, P4, and O2. Artifacts were eliminated using the artifact detection of the NeuroGuide software. Here we analyzed the eyes closed EEG in resting conditions. Accepted epochs of EEG data for absolute (uV^2) power were calculated using fast Fourier transforms and averaged by NeuroGuide's spectral analysis system in four frequency bands: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), and beta (12–30 Hz). The activity at 19 sites was divided into five regions: frontal, parietal, temporal, central, and occipital. Relative power was calculated as a percentage of the total power for each frequency band. Also, the delta/alpha ratio was computed as the ratio of mean scalp delta to alpha power.

2.2.4. ***Visual image-induced Craving***

Participants were asked to rate their craving intensity and their subjective desire for methamphetamine, induced by each picture on the self-report Visual Analogue Scale (VAS) from 0 to 100 (Ekhtiari, Alam-Mehrjerdi, Nouri, George, & Mokri, 2010). The time interval of each picture exposure in the task was between 15-20 seconds. In each category of pictures, there were 2 pictures as follows: METH outside or inside the package without instruments (2 pictures), METH with instruments (2 pictures), instruments (2 pictures), cues accompanied by drug use (2 pictures), an act of abuse without a seen instrument (2 pictures), and neutral pictures (2 pictures).

2.3. Statistical analysis:

We used the Kolmogorov-Smirnov test to evaluate the normality of the data. Demographic data between groups were compared using the Chi-square test and One-Way ANOVA, as required. The Multivariate Analysis of Covariance (MANCOVA) was used to determine whether pre-testing participants influenced their post-test scores on the dependent measures with the Post Hoc Bonferroni test. Results are expressed as mean± SEM and SD. Differences were considered statistically significant at $P<0.05$.

EEG data were processed with custom-made scripts using MATLAB version R2012a. First, data from the resting-state measurements were imported into EEGLAB, bandpass filtered between 1-40 Hz, and inspected for gross movement artifacts that were then manually removed. Subsequently, epochs of 4 seconds in length were created. Epochs containing amplitudes exceeding ±100 μV at any scalp electrode and/or epochs containing abnormally distributed data (joint probability or kurtosis >5 SD from expected mean values) were rejected. Because absolute EEG power data are skewed, data were log-transformed before analysis. We then utilized several procedures to reduce the likelihood of type-1 error. To identify EEG bands of interest for further analysis, we calculated a grand mean of 19 electrodes for each frequency band, thus providing an overall index of power for each band. The grand mean power in each group was compared by the MANCOVA test. Power at each electrode site was subsequently examined using MANCOVA.

3. Results:

3.1. Demographic variables

Patients revealed no significant differences in any of the demographic variables. All of the 32 participants were male and 65% of the population were married and 35% were single with a mean age of 33 years. The majority of participants were employed (64%) and from Secondary school (37%). The mean duration of METH use was 7 years. More than half of the participants reported physical illness history (52%). ANOVA showed no statistically significant difference between groups in the mean age ($F_{3, 28}=1$, P=NS), duration of METH use ($F_{3, 28}=0.15$, P=NS), BMI ($F_{3, 28}=0.72$, P=NS), and Vo2 max ($F_{3, 28}=1.66$, P=NS) in

METH addicts. The mean BMI and Vo_2 max in groups were 22.37 and 39.93, respectively (Table 1).

3.2. Effect of NFB training and swimming exercise on the EEG power changes in METH-dependent patients.

The MANCOVA revealed a significant interaction effect from pre- to post-treatment in absolute power (Wilks' Lambda=0.039, F=11.22, P=0.0001, Partial η2=0.66). There was no significant difference in pre-treatment of the absolute power between groups. We observed significant differences among the three treatment conditions for the absolute power in alpha (F=68.04, P=0.0001), beta (F=7.25, P=0.001), theta (F=6.62, P=0.002), and delta (F=5.1, P=0.007) frequency bands.

Comparing the absolute power across for posttreatment between groups showed that the alpha band in the NFB, swim and NFB/Swim groups had lower absolute power than the control group (P=0.0001, for all comparisons), also the NFB/Swim group showed lower alpha power than the swim group (P=0.0001). Comparing the absolute power for posttreatment between groups showed that the beta band in the NFB (P=0.041), Swim (P=0.021), and NFB/Swim (P=0.001) groups had lower absolute power than the control group, also the NFB/Swim group showed lower absolute power than the NFB (P=0.044) and swim (P=0.049) groups. Comparisons between groups in the theta band showed that the NFB (P=0.005), swim (P=0.003), and NFB/Swim (P=0.014) groups had lower absolute power than the control group. Also, comparisons between groups in the delta band showed that the NFB (P=0.042), swim (P=0.032), and NFB/Swim (P=0.006) groups had lower absolute power than the control group (Fig. 2A to D).

The MANCOVA revealed a significant interaction effect from pre- to post-treatment in relative power (Wilks' Lambda=0.214, F=5.51, P=0.0001, Partial η2=0.41). There was no significant difference in pre-treatment of the relative power between groups. We observed significant differences among the three treatment conditions for the relative power in alpha (F=12.21, P=0.0001) and delta (F=4.1, P=0.017) frequency bands.

Comparing the relative power across for posttreatment between groups showed that the alpha band in the swim (P=0.002) and NFB/Swim (P=0.0001) groups had lower power than the control group, also the NFB/Swim group showed lower relative power than the NFB group (P=0.001).

Comparing the relative power for posttreatment between groups showed that the delta band in the swim (P=0.022) and NFB/Swim (P=0.029) groups had greater relative power than the control group (Fig. 3A to D).

The MANCOVA revealed a statistically significant interaction effect from pre- to post-treatment in the delta/alpha power ratio (Wilks' Lambda=0.551, F=7.35, P=0.001, Partial η2=0.449). There was no significant difference in pre-treatment of the delta/alpha power ratio between groups. We observed significant differences among the three treatment conditions for the delta/alpha power ratio (F=7.61, P=0.001). Comparing the delta/alpha power ratio for posttreatment between groups showed that

NFB/Swim group had greater ratios than the control (P=0.0001) and the NFB (P=0.024) groups (Fig. 4).

The reduction of the spectral powers was more evident in the frequency bands of alpha, beta, and theta following NFB/Swim training in METH-dependent patients, which are shown in blue on the spectral topography mapping of absolute power (Fig. 5).

3.3. Effect of NFB training and swimming exercise on the visual image-induced craving in METH-dependent patients.

The MANCOVA revealed a significant interaction effect from pre- to post-treatment in visual image-induced craving (Wilks' Lambda=0.25, F=11.07, P=0.0001, Partial η2=0.50). There was no significant difference in pre-treatment of the visual image-induced craving score between groups. We observed significant differences among the three treatment conditions for the visual image-induced craving score (F=20.51, P=0.0001) and reaction time in response to the visual image-induced craving (F=4.41, P=0.01).

Comparisons between groups in the visual image-induced craving showed that the NFB/Swim group (P=0.0001) had lower craving score than the control, swim, and NFB groups (P=0.0001, for all comparisons) (Fig. 6A). Also, comparisons between groups showed that the swim (P=0.004) and NFB/Swim (P=0.0001) group had faster reaction times in response to the visual image-induced craving than the control group (Fig. 6B).

4. *Discussion:*

We found no significant difference in the pre-treatment scores of the absolute and relative powers in frequency bands between groups in METH-dependent patients. Here we found the greater power for 4 frequency bands for pre-treatment in METH-dependent patients.

In accordance with our findings, a previous study has shown an increased EEG power in the delta and theta for all areas of the brain after 4 days of METH abstinence and EEG was abnormal in a majority of 64%patients (Newton et al., 2003). In line with our findings, a previous study showed that whole brain metabolism in the METH abusers was 14% higher, as a sensitive indicator of brain dysfunction (Volkow et al., 2001).

The increase in the power of all 4 frequency bands in the present findings suggests increased cortical activation in resting conditions, impaired inhibitory function, and loss of neural efficiency that may indicate a "noisy" brain (Prashad, Dedrick, & Filbey, 2018), which in turn led to the interruption of the cognitive-affective-behavioral processes, including depression, psychosomatic disorders, psychomotor agitation, neuro-psycho-physiological abnormalities, encephalopathy, cognitive and memory impairments (Begić et al., 2011; Glasner-Edwards & Mooney, 2014; Kalechstein et al., 2009; Zorick et al., 2010). Also, it has been shown that increased delta and theta EEG activity may reflect the rewarding properties of drug use, whereas the increased alpha power may be associated with anxiety and nervousness (Reid, Flammino, Howard, Nilsen, & Prichep, 2006), as it observed in the patients of the current study.

Our findings have shown that the NFB training, swimming exercise, and the combination of NFB and swimming exercise for 10 weeks reduced EEG absolute power for 4 frequency bands. While the combination of NFB and swimming exercise (NFB/Swim group) was significantly more effective in reducing EEG absolute power for alpha and beta frequency bands in METH-dependent patients during withdrawal.

Following NFB training, patients learn to voluntarily modulate their own electrical brain activity, which has beneficial effects on cognitive functions (Kober, Witte, Ninaus, Neuper, & Wood, 2013) and is already used as a therapeutic tool to treat different types of disorders. The NFB helps to adjust any disruptive wave patterns and restore a normal pattern of brain activity and corrects abnormal brain function without any lasting side effects (Scott, Kaiser, Othmer, & Sideroff, 2005) in substance use disorders. In this regard, previous studies have shown that NFB training as a mood-enhancing and energizing experience (Raymond, Varney, Parkinson, &

Gruzelier, 2005), can induce neural plasticity in the dorsal anterior and mid-cingulate (Lanius et al., 2012; Yamashita, Hayasaka, Kawato, & Imamizu, 2017), involved in the cognitive functioning and emotional processing. Also, NFB-induced brain and neural plasticity is a phenomenon that has been considered as a basic mechanism for behavioral changes (Rostami & Dehghani-Arani, 2015).

The interesting finding of our study was that NFB/Swim and swim reduced the relative power of alpha and increased the relative power of delta. Our study also showed that NFB/Swim caused a significant increase in the delta/alpha power ratio for posttreatment in METH-dependent patients. In this regard, previous experience has shown that delta and alpha oscillations are reciprocally related to each other (Gennady G Knyazev, 2007).

Previous studies have shown that functionally delta oscillations may be involved in the integration and synchronization of cerebral activity with homeostatic processes, including autonomic functions, and motivational and cognitive processes (Harmony, 2013; Gennady G Knyazev, 2007, 2012). For example, increases in delta power were also reported during semantic tasks, cognitive (Franke et al., 2022), and motivation (Gennadij G Knyazev, Savostyanov, & Levin, 2004) processing. Delta inhibitory oscillations would modulate the activity of those networks that should be inactive to perform the task (Harmony, 2013).

Another potential explanation of our results could be the use of relative EEG power as a sensitive and stable measure to provide a useful neurophysiological biomarker to determine psychotic disorders and age-related changes in EEG (Howells et al., 2018; Jelic et al., 2000) in patients. A previous study has shown that regional cerebral blood flow (rCBF) decreases when delta power increases (Dang-Vu et al., 2005). Another study has shown that detoxified methamphetamine abusers had significantly lower rates of metabolism in the thalamus and striatum (Volkow et al., 2001). This finding emphasizes the importance and presence of an extra-thalamic delta rhythm (Dang-Vu et al., 2005), including the cortex (Steriade, Nunez, & Amzica, 1993) in METH-dependent patients. It seems the brain of METH-dependent patients following the NFB training along with swimming exercise in the present study, is calm and relaxed. This thereby produces more delta (Dunn, Hartigan, & Mikulas, 1999).

The increased delta/alpha power ratio following the NFB training along with swimming exercise may be a reflection of decreased cortical activation and increased neural efficiency and reduced effort in METH-dependent patients who had a "noisy" brain and stressful before treatment. Our finding indicates that the brain of METH-dependent patients following the NFB training along with swimming exercise was quiet and calm in a relaxed state with lower anxiety. Maybe this reduced effort in a calm brain caused a decrease in the visual image-induced craving score in METH-dependent patients following the NFB training along with swimming exercise. These patients also had faster reaction times in response to the visual image-induced craving in NFB/Swim and swim groups. In accordance with our findings, previous studies have shown that exercise reduced METH (Wang, Zhou, Zhao, Wu, & Chang, 2016) and cannabis (Buchowski et al., 2011) cravings.

A previous study has shown that the craving in substance-dependence patients is almost all related to abnormalities in alpha and beta, particularly in the parietal and central lobes of the brain (Sokhadze, Cannon, & Trudeau, 2008), as observed in our study of patients before treatment. Although there is some evidence that the greater delta power increased ratings of cocaine craving (Reid et al., 2006). Thus, a more important question would be whether the increase in delta/alpha power ratio could decrease the visual image-induced craving for METH after abstinence in NFB/Swim group. This question cannot be answered by our present data and requires a different experimental protocol.

Therefore, the neurofeedback training along with swimming exercise (NFB/Swim group) may more effectively reduce the craving for METH after abstinence. Previous studies have documented associations between NFB training and physical activity. In this regard, it has been shown that the NFB training may be useful in enabling athletes to perform optimally (Dupee, Forneris, & Werthner, 2016), and also NFB training during swimming exercise improved and optimized mental/psychomotor performances (Mikicin, Mróz, Karczewska, et al., 2020).

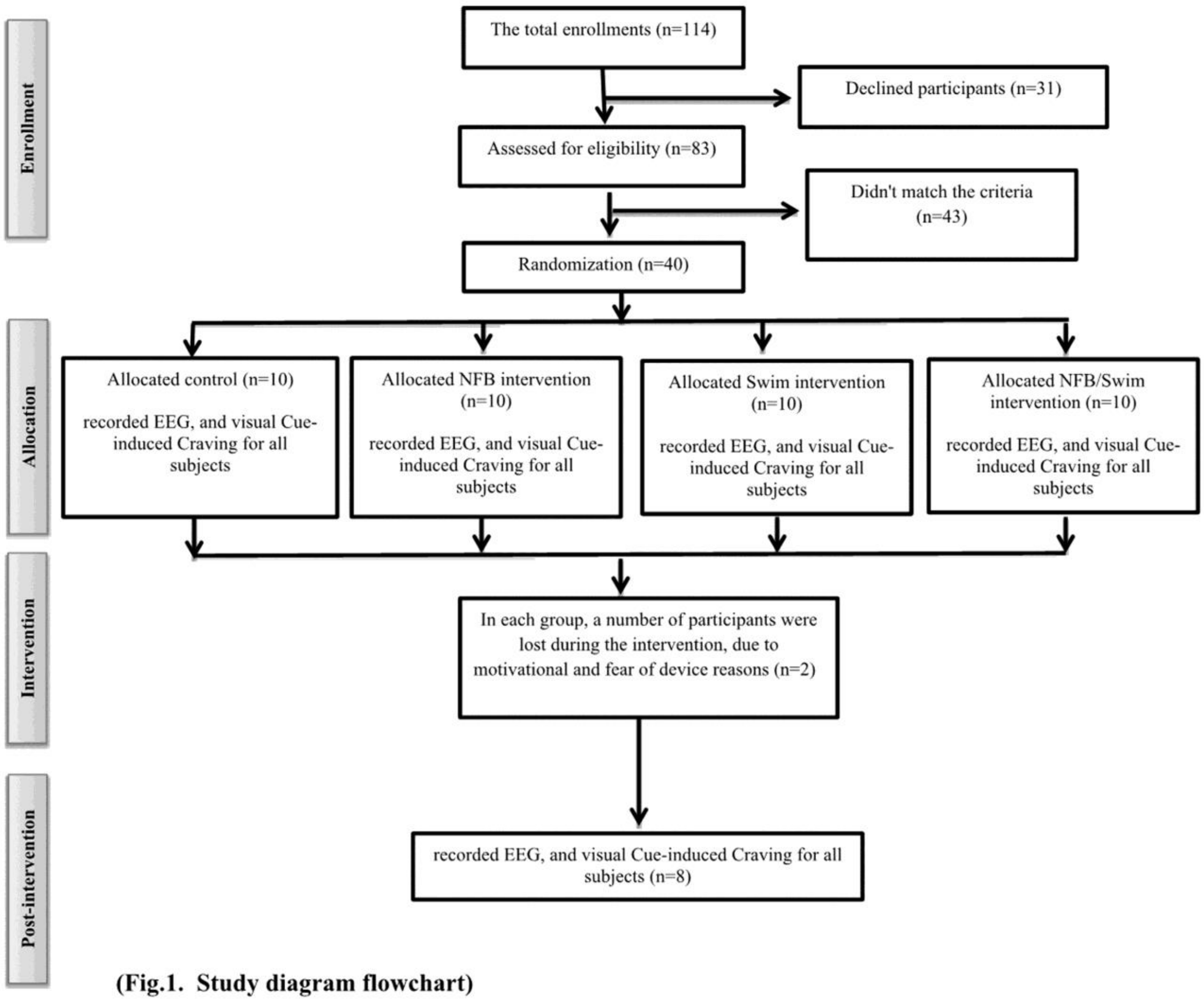
At present, the neurobiological mechanisms to reduce EEG absolute power for 4 frequency bands and METH craving following the effectiveness of swimming exercise combined with NFB training are still unknown. It may be due to an ability to self-regulate dopaminergic neurons of the substantia nigra/ventral tegmental (Sulzer et al., 2013), the endogenous release of key neuromodulators (Ros et al., 2021), the regulation of serotonin (Konareva, 2006), and β-endorphin (Akbari, Dolatshahee, & Rezaee, 2016) following NFB training. Also, the regulation of the above-mentioned key neuromodulators following swimming exercise might have enhanced the effects of NFB. Future studies need to examine the neurobiological mechanisms induced by NFB training and swimming exercise.

5. Limitations: This study also had some limitations. Larger sample sizes in future studies increase power and decrease estimation error and increase the ability to further evaluate subgroup differences. It is suggested to use different types of exercise and also other protocols of NFB in the treatment of METH-dependent patients.

6. Conclusion:

This study provides novel evidence that the NFB training along with swimming exercise during METH-abstinence could decrease EEG absolute power for 4 frequency bands and the relative power of alpha while increased the relative power of delta and the delta/alpha power ratio. Also, our findings have shown that the NFB training along with swimming exercise decreased the visual image-induced craving score in METH-dependent patients. Our results could suggest the application of the NFB training along with swimming exercise as a useful therapeutic strategy for the treatment of METH use disorder with follow-up studies that utilize a larger number of samples and the most suitable type and intensity of exercise (voluntary, treadmill, and swimming).

Legends:



(Fig.1. Study diagram flowchart)

Fig. 1. A flowchart diagram showing the study design.

Table 1. Demographic information.

Variables	Groups				P-value
	Cont (n = 8)	NFB (n=8)	Swim (n = 8)	NFB/Swim (n=8)	
Age (years) (Mean ± SD)	35.87 ± 4.79	31.12±4.99	32± 5.75	34.62±8.27	0.646[a]
Educational status N (%)					0.708[b]
Primary school	2 (25) %	3 (37.5) %	2 (25) %	3 (37.5) %	
Guidance school	3 (37.5) %	4 (50) %	3 (37.5) %	2 (25) %	
Diploma	2 (25) %	1 (12.5) %	2 (25) %	1 (12.5) %	
Higher education	1 (12.5) %	0 (0) %	1 (12.5) %	2 (25) %	
Marital status N (%)					0.946[b]
Married	5 (62.5) %	5 (62.5) %	6 (75) %	5 (62.5) %	
Single	3 (37.5) %	3 (37.5) %	2 (25) %	3 (37.5) %	
Duration of METH addiction (years) (Mean ± SD)	7.62 ± 2.61	7±3.33	7.75 ± 2.71	7.87±2.41	0.948[a]
Physical illness history N (%)					0.740[b]
No	5 (62.5) %	3 (37.5) %	4 (50) %	3 (37.5) %	
Yes	3 (37.5) %	5 (62.5) %	4 (50) %	5 (62.5) %	
BMI[c](kg/m) (Mean ± SD)	21.62 ± 2.19	22.37±2.13	23.37 ± 2.13	22.12±3.13	0.485[a]
Vo_2 max (Mean ± SD)	41.12 ± 2.98	39.25±5.23	38 ± 3.29	41.37±1.59	0.615[a]
Job N (%)					0.948[b]
Unemployed	1 (12.5) %	1 (12.5) %	2 (25) %	2 (25) %	
Employed	7 (87.5) %	6 (75 %	5 (62.5) %	4 (50) %	
Unknown	**0 (30) %**	**1 (12.5) %**	**1 (12.5) %**	**2 (25) %**	

[a] One Way ANOVA [b] Chi-Square

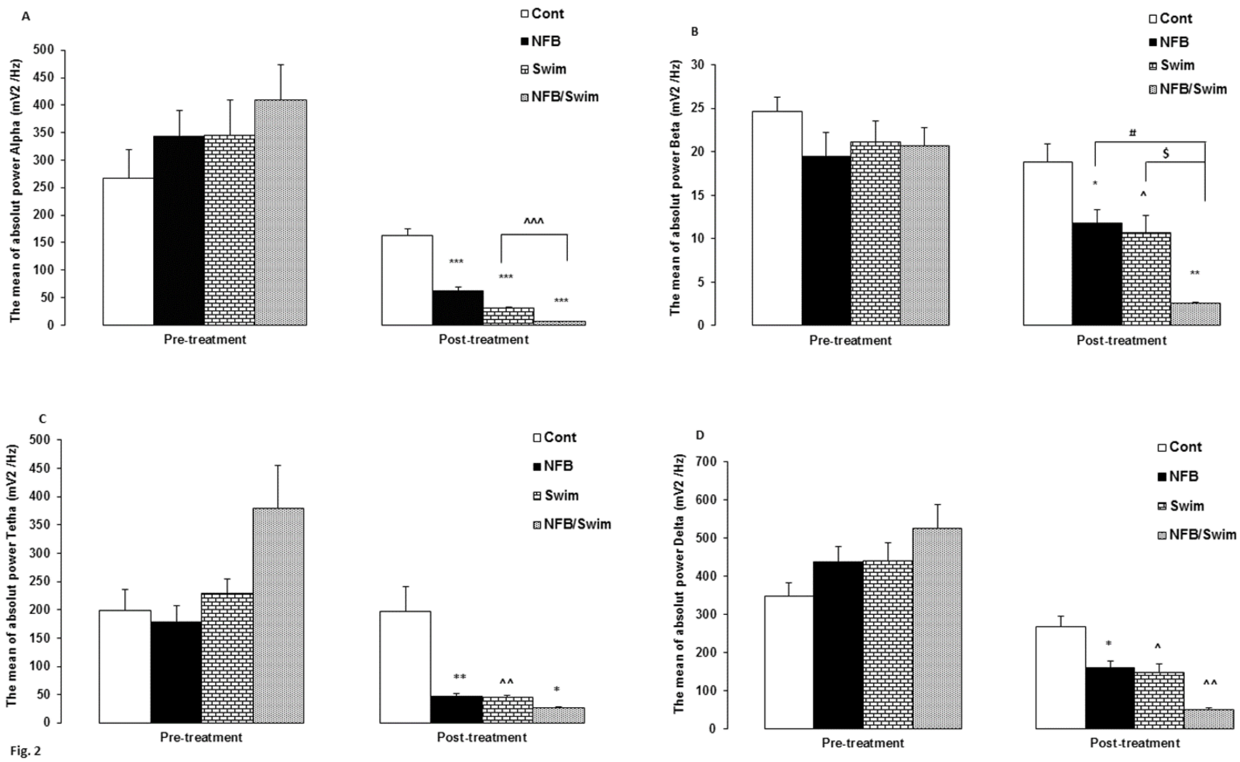


Fig. 2. Effect of neurofeedback training and swimming exercise on the absolute power in any frequency band in METH-dependent patients. There was no significant difference in pre-treatment of the absolute power between groups. Swim and NFB/Swim groups had significantly lower absolute power than the control group in any frequency band and NFB/Swim group had significantly lower absolute power than the swim group in the alpha and beta frequency bands for the post-test. A) ***P = 0.0001 vs. Cont; ^^^P=0.0001 vs. Swim. B) *P = 0.041, $^{\wedge}$P = 0.021 and **P = 0.001 vs. Cont; $^{\#}$P=0.044 vs. NFB; $^{\#}$P=0.049 vs. Swim. C) **P = 0.005, $^{\wedge\wedge}$P = 0.003 and *P = 0.014 vs. Cont; D) *P = 0.042, $^{\wedge}$P = 0.032, **P = 0.005 vs. Cont.

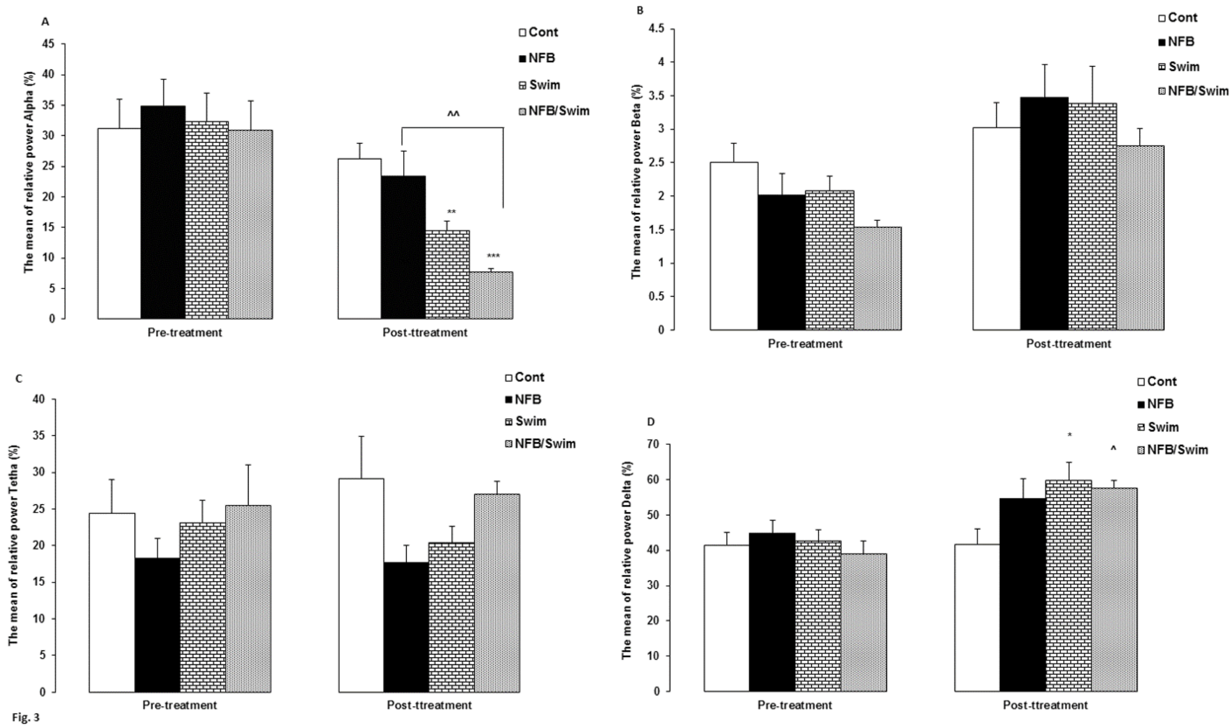


Fig. 3. Effect of neurofeedback training and swimming exercise on the relative power in any frequency band in METH-dependent patients. There was no significant difference in pre-treatment of the relative power between groups. Swim and NFB/Swim groups had significantly lower and greater relative power than the control group in the alpha and delta frequency bands, respectively for post-treatment. A) **P = 0.002, ***P=0.0001 vs. Cont; ^^P=0.001 vs. NFB. D) *P = 0.022, ^P=0.029 vs. Cont.

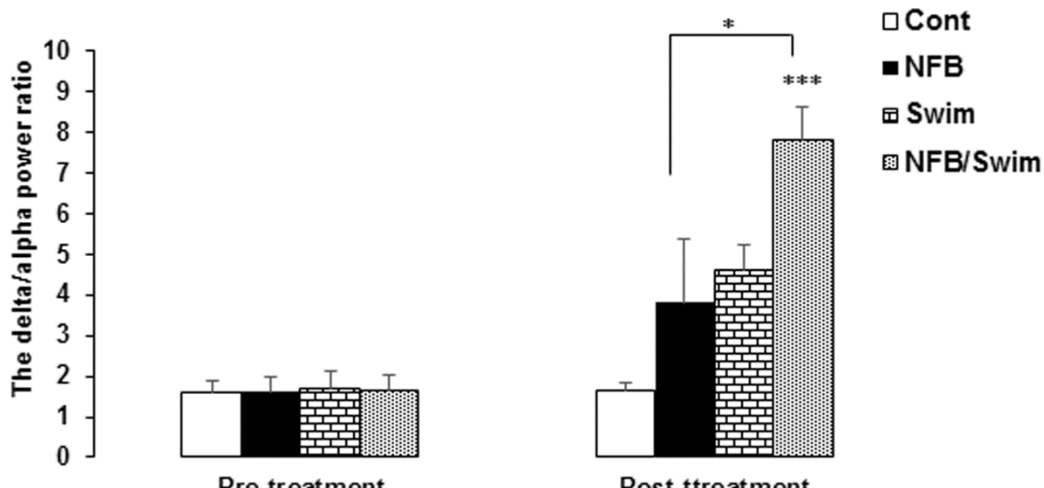


Fig. 4

Fig. 4. Effect of neurofeedback training and swimming exercise on the delta/alpha power ratio in METH-dependent patients. There was no significant difference in pre-treatment of the delta/alpha power ratio between groups. NFB/Swim group had significantly greater ratios than the control and NFB groups for post-treatment. ***P=0.0001 vs. Cont; *P=0.024 vs. NFB.

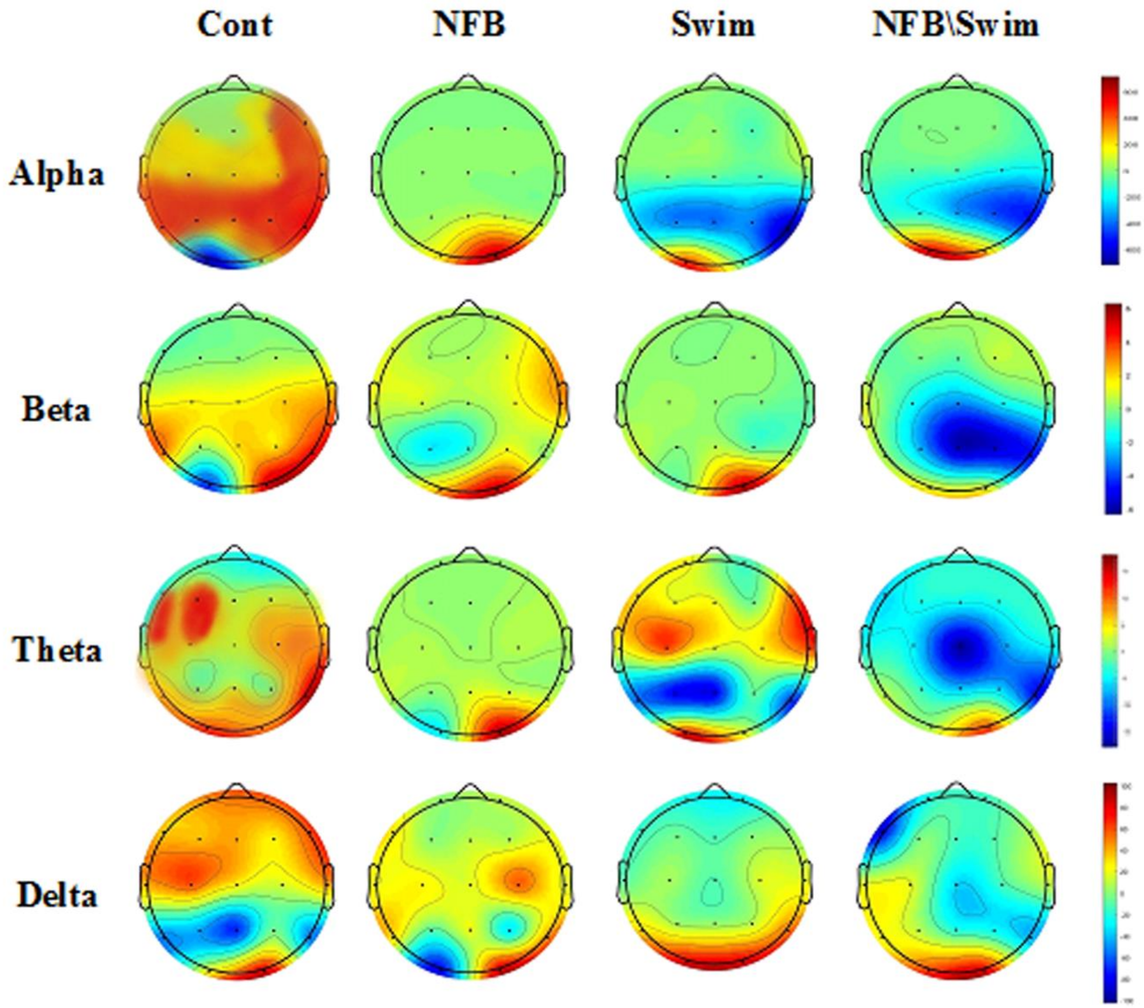


Fig. 5.

Fig. 5. The spectral topography mapping of absolute power in any frequency band of post-treatment in METH-dependent patients. Each dot represents an electrode. Colors represent high (red) or low (blue) power. The reduction of the spectral powers was more evident in the frequency bands of alpha, beta, and theta following NFB/Swim training in METH-dependent patients.

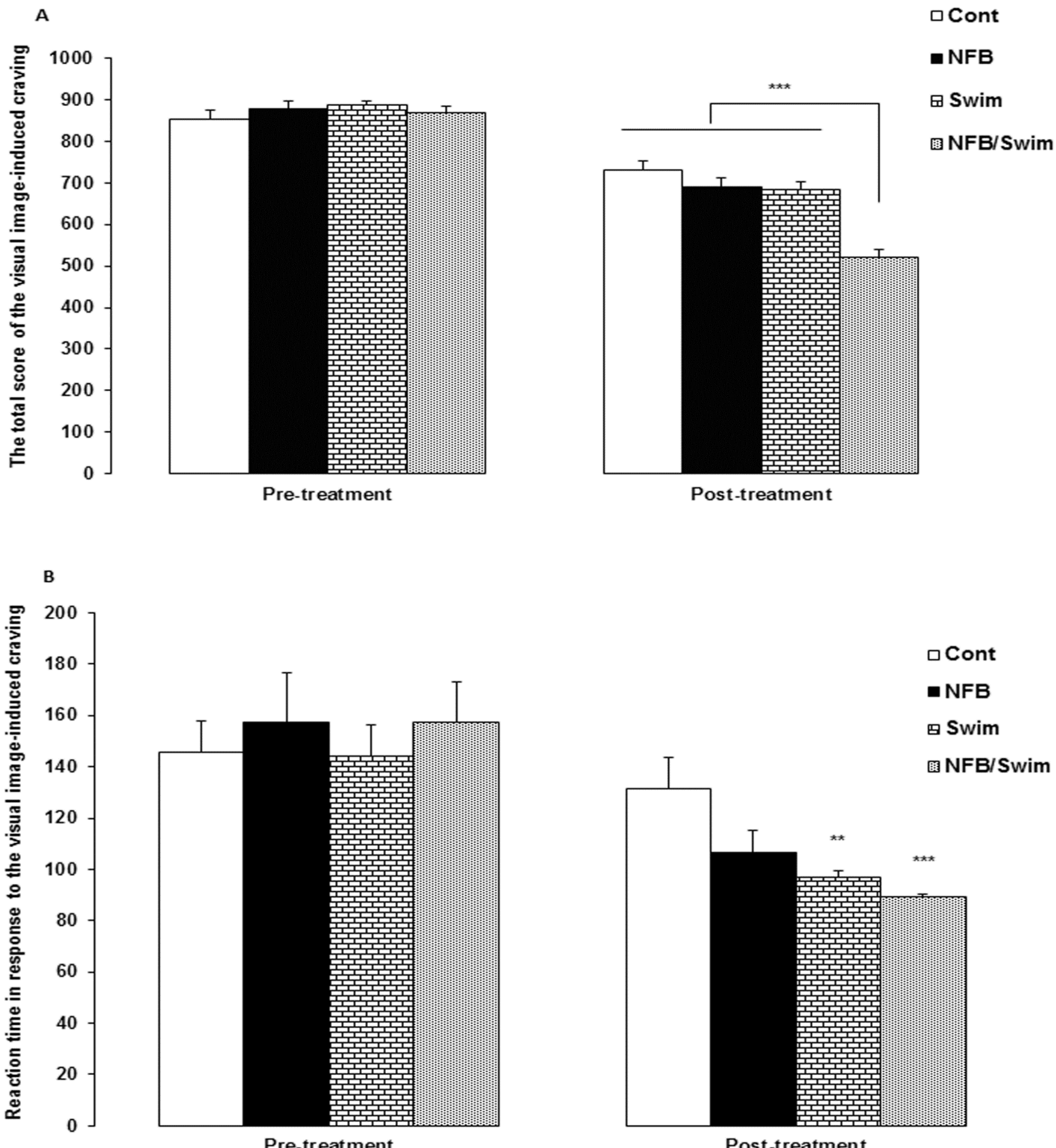


Fig. 6

Fig. 6. Effect of neurofeedback training and swimming exercise on the visual image-induced craving in METH-dependent patients. There was no significant difference in pre-treatment of the visual image-induced craving score between groups. NFB/Swim group had significantly lower craving scores and faster reaction times in response to the visual image-induced craving than the control for post-treatment.

A) ***P = 0.0001 vs. Cont, NFB and Swim. B) **P = 0.004, ***P=0.0001 vs. Cont.

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Ethical Considerations Compliance with ethical guidelines

All procedures performed in studies involving human participants were following the ethical standards of the Ethics Committee of the Semnan University of Medical Sciences (IR.SEMUMS.REC.1397.308) and with the 1964 Helsinki declaration. Also, we received the Iranian Registry of Clinical Trials (IRCT) (IRCT20190703044092N1). The questionnaire and methodology for this study were approved by the Human Research Ethics committee of the Semnan University of Medical Sciences.

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Authors contributions

All authors contributed in preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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