Neuroscience Letters 781 (2022) 136672

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Effects of acute exercise on craving and cortical hemodynamics under drug-cue exposure in MA-dependent individuals

Liping Qi [a,*], Zhi-Hao Tian [a], Yin Yue [a], Shuo Guan [a], Lei Tang [b], Guijun Dong [c,*]

[a] School of Biomedical Engineering, Dalian University of Technology, Dalian 116024, China
[b] Compulsory Isolation Drug Rehabilitation Center of Shandong Province, Zibo 255311, China
[c] Quzhou University, Quzhou 324000, China

ARTICLE INFO

Keywords:
Brain networks
Drug-cue reactivity task
Functional near-infrared spectroscopy
General linear model
Graph theory
Virtual reality enhanced exercise

ABSTRACT

Background: Methamphetamine (MA) dependent individuals who want to break free of their drug habit or guard against a relapse often find it hard to overcome cravings induced by drug-related cues they are bound to encounter. The purpose of this study was to investigate the effects of acute virtual reality (VR) enhanced physical exercise on cue-induced cravings in MA-dependent individuals.

Methods: Thirty MA-dependent individuals performed a drug-cue reactivity task both before and after a 10 min VR-enhanced competitive cycling exercise. Functional near-infrared spectroscopy (fNIRS) was recorded during the pre- and post-exercise drug-cue reactivity tasks.

Results: MA dependent individuals show higher hemodynamic responses in prefrontal cortex (PFC) to drug-related cues than to neutral cues. After acute exercise, hemodynamic responses in PFC, including bilateral dorsolateral prefrontal cortex and orbitofrontal cortex, were attenuated under the same drug-related cues exposure. Acute exercise also affected the functional connectivity between PFC and motor cortex in response to drug-related cues versus neutral cues.

Conclusions: These results suggest that a single session of VR-enhanced competitive cycling exercise facilitates MA-dependent individuals' self-control over their cue-induced cravings by modulating cortical activations and brain functional networks.

1. Introduction

Methamphetamine (MA) is a powerful and addictive psychostimulant. At this point there is no approved pharmacological treatments for MA addiction [1]. The success of any other treatment is invariably in jeopardy when abstaining patients experience powerful cravings that are triggered by drug-related cues similar to the cravings for other addictive drugs, such as methamphetamine, nicotine or heroin [2–4]. A growing body of studies have been investigated the effect of acute physical exercise on the control of MA cravings [5–9]. Exercise has been proposed as a treatment for drug addiction at different phases of the addition process including the initiation of use, the transition to addiction, withdrawal, and relapse. Individuals in recovery turn to exercise as either a substitute for drug use or to help maintain abstinence [10]. It appears that acute exercise is also an effective intervention to control craving and cognitive process in MA-dependent individuals [6,7]. Exercise programs have had positive clinical outcomes, such as a lessening of self-reported craving, improved emotions, and enhanced cognitive functions [6,11]. In addition, virtual reality (VR) has been proposed as a way to improve exercise enjoyment [12]. Previous studies have shown that VR-enhanced exercise training can improve physical performance, emotion regulation, and exercise engagement [13,14]. In the present study, we designed a VR-enhanced competitive cycling exercise program in the hopes of increasing the chances of long-term exercise adherence and to provide a sense of challenge and regulated competition, which may result in a more enjoyable exercise experience for the MA-dependent individuals.

A growing number of neuroimaging studies and *meta*-analyses concerning addiction have revealed cue-related responses in several brain areas, including frontal orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC), visual, and parietal cortical and subcortical areas [15]. More recently, preclinical and clinical studies have started to clarify the role of the prefrontal cortex (PFC) in addiction [16,17]. The PFC is of particular interest because of its key role in top-down

* Corresponding authors at: A1220 Innovation Building, Dalian University of Technology, Liaoning 116024, China (L. Qi).
E-mail addresses: lipingqi@dlut.edu.cn (L. Qi), dongguijun@sdpei.edu.cn (G. Dong).

https://doi.org/10.1016/j.neulet.2022.136672
Received 4 March 2022; Received in revised form 27 April 2022; Accepted 28 April 2022
Available online 30 April 2022

regulation and executive functions underlying drug addiction [18]. Previous functional magnetic resonance imaging (fMRI) studies have shown that several PFC regions, such as OFC, DLPFC, and anterior cingulate cortex (ACC), are activated in response to the presentation of drug-related cues relative to neutral cues in cigarette smokers [19] and abstinent alcoholics [20,21]. The DLPFC response to drug cues was positively correlated with craving, and the information about drug availability was encoded in the DLPFC during self-control of cigarette craving [16,22]. Functional near-infrared spectroscopy (fNIRS) studies have also suggested abnormal activation of the PFC, OPC, and ACC among long-term MA users [23,24].

Measuring cue-induced brain activations with non-invasive and portable neuroimaging techniques, such as fNIRS, provides a promising tool for the understanding of the neurobiological mechanisms of cue-induced craving, treatment development, as well as for the assessment of treatment effectiveness. As an invasive way of measuring the changes in the concentration of oxygenated hemoglobin (oxy-Hb) and deoxygenated hemoglobin (deoxy-Hb), fNIRS is used to quantify the effects of exercise on cerebral oxygenation and hemodynamics [25]. The method has been used to investigate the positive effect of exercise on brain function in the case of MA dependent individuals [26–28]. The purpose of the present study was to examine the effects of acute VR-enhanced exercise on cue-induced craving among MA-dependent individuals. Our hypothesis was that MA-dependent individuals would show enhanced hemodynamic responses in the PFC to the drug-related cues relative to the neutral cues, and the VR enhanced exercise intervention would reduce the drug-cue conditioned responses in the PFC. We tested this hypothesis using a within-subject design of drug-cue paradigm and fNIRS measurements before and after acute bouts of VR-enhanced exercise. This pilot project investigates cortical hemodynamic fluctuations during exposure to drug-related cues in order to establish an exercise program preventing drug dependency relapses in clinical populations. Identification of craving-related neutral correlates and effective regulation of craving through exercise are needed to advance MA addiction exercise treatment.

2. Materials and methods

2.1. Participants

Thirty male MA-dependent participants (32.4 ± 3.7 years of age, 176.5 ± 6.2 cm height, and 79.1 ± 6.8 kg weight) were recruited from the compulsory isolation drug rehabilitation center of Shandong Province, China. The physical characteristics of the participants are shown in Table 1. The average duration of abstinence is 13.4 ± 3.6 months. They have met the criteria of DSM-IV for MA dependence, and they have no history of neurological, psychiatric, and musculoskeletal diagnosis. The study was approved by the ethics committee of Shandong University of Sports (Ethics Approval Number: 2019006). The study conformed to the ethical requirements of the latest version of the Helsinki Declaration. Prior informed written consent was obtained from each participant.

2.2. Procedures

2.2.1. Drug-cue reactivity task

A block design drug-cue paradigm was used in the present study. The advantage of blocked designs is that they offer greater sensitivity and thus a greater chance of detecting the effects of interest, particularly in brain regions in which these effects may be more subtle. To accommodate the typically delayed variations in MA- cravings, we used a 24-second block design. Each 24-second block is made up of 4 individual images (either drug-cues or neutral images), each displayed for approximately 6 s. The drug cue blocks are specific to MA (i.e., MA crystal, plastic bottle, and tinfoil, etc.). The neutral control blocks are non-drug-related cues such as everyday objects or scenes. Then a 15-s rest was given to the participants with a crosshair on the computer screen. A total of 24 drug-cue pictures and 24 neutral images were presented during the fNIRS recording. The order of the blocks and the images within each blocks were randomized. The study design and procedures are shown in Fig. 1.

Table 1
Physical characteristics of participants (mean ± SD).

Characteristics	Mean ± SD
Age (years)	32.3 ± 3.8
Height (cm)	176.2 ± 6.0
Weight (kg)	78.9 ± 6.5
BMI (kg/m^2)	25.4 ± 1.7
Education (years)	10.8 ± 3.0

2.2.2. Virtual reality enhanced exercise intervention

VR-enhance competitive cycling was used as an exercise intervention. Two participants were asked to compete with each other as fast as they comfortably could at 1.5kp workload for 10 min after a warm-up cycling session on the cycle ergometers (EB200, Huixiang Fitness Equipment Inc., Shandong, China). The two participants were situated in virtual surroundings (120-inch screen) and were represented by virtual selves able to interact and compete with each other (VRoad, ilodo Inc., Beijing, China). Participants can check the performance of their virtual selves in the VR environment. Heart rate (HR) was monitored by a Polar H10 monitor (Polar Electro, Inc., Finland) during exercise and rest. One hour rest period was given each participant to ensure their heart rate return to baseline before they performed the second round of drug-cue reactivity task.

2.3. fNIRS measurement

A multichannel fNIRS system (Nirsmart; Danyang Huichuang Medical Equipment Co., Ltd., Beijing, China) using two infrared wavelengths of 760 and 850 nm was used to monitor cortical hemodynamic changes in response to the drug cue reactivity tasks. The sampling frequency was 10 Hz. 42 channels were configured by using 19 transmitting and 16 receiving probes at an inter-probe distance of 3 cm. Fig. 2 shows the configuration of the optical probes covering the prefrontal and motor cortex.

fNIRS data were processed based on the modified Beer–Lambert law [29]. Since the Oxy-Hb signal shows a higher signal-to-noise ratio [30], only the oxy-Hb was analysed in the present study. The fNIRS data was registered within the Montreal Neurological Institute (MNI) standard brain space by using the ICBM152 brain template [31]. 8 regions of interest corresponding to the 42 channels were represented by combining 1 to 4 neighboring channels (Fig. 2).

2.4. fNIRS signal processing

2.4.1. Brain activation analysis

During the drug-cue paradigm, the SPM-fNIRS toolbox was used to analyse the changes of oxy-Hb concentration over time [32,33]. The moving standard deviation method and spline interpolation was used to remove the movement artefacts. Physical noises, such as respiration and cardiac pulsation, were reduced by a band-stop filter with stop band frequencies of 0.12–0.35 Hz and 0.7–2.0 Hz, respectively. In the first level, the general linear model (GLM) analysis was used to estimate the cue-induced effects for each participant from the channel-specific fNIRS response. In the second-level analysis, the group effects were estimated using the summary-statistics approach (SPM 12; https://www.fil.ion.ucl.ac.uk/spm) [34].

2.4.2. Analysis of functional connectivity

For each drug-cue and neutral-cue block pre- and post-exercise, the individual block time-courses were concatenated and the Pearson

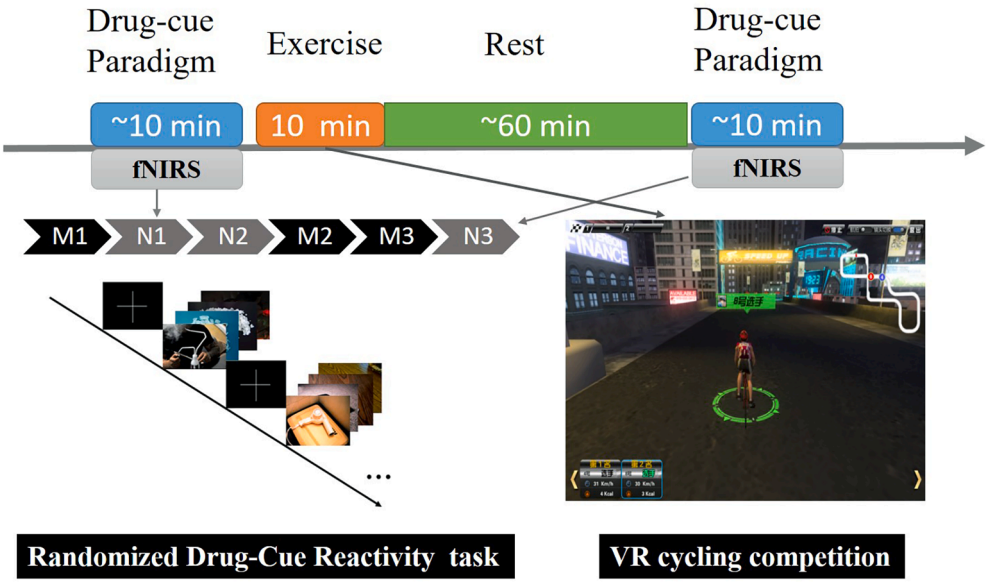

Fig. 1. Study design. Each participant underwent two sessions of the drug-cue reactivity task during fNIRS measurement with VR cycling competition and rest between these two sessions.

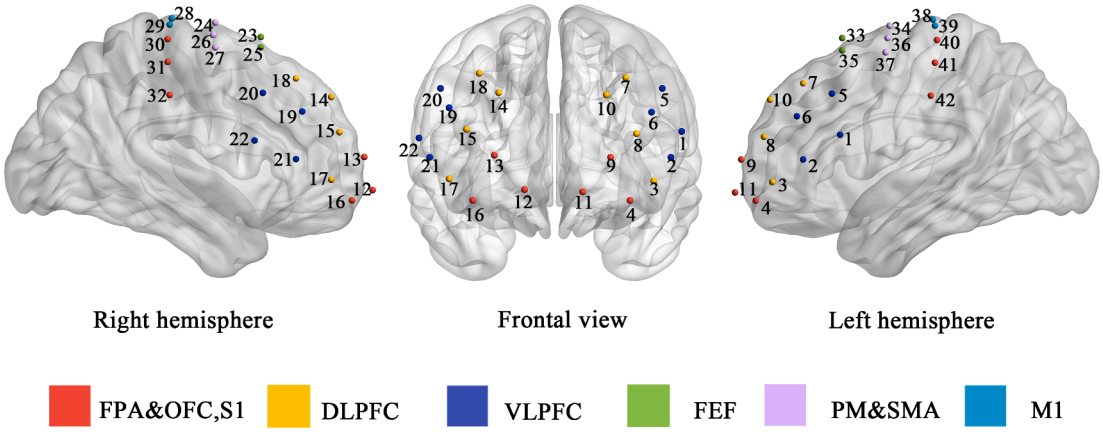

Fig. 2. The spatial configurations of fNIRS channels used in the present study. 19 transmitting and 16 receiving probes arranged alternately at an inter-probe distance of 3 cm, resulting in 42 channels per set. Estimated fNIRS channel locations only used for data analysis are exhibited in MNI space. Six sub-regions of the prefrontal cortex and motor cortex are indicated with colours. FPA: frontopolar area; OFC: orbitofrontal cortex; S1: primary somatosensory cortex; DLPFC: dorsolateral prefrontal cortex;VLPFC: ventrolateral prefrontal cortex; FEF:frontal eye field ; PM:pre-motor cortex ; SMA:supplementary motor cortex ; M1: primary motor cortex.

correlation coefficient was computed between the 42 pairs of channels. A Fisher's Z-transformation was applied. For each channel-pair, a paired *t*-test (drug cues > neutral cues) was computed across participants. Then the 42 channels were grouped into 8 regions of interest. For each region-pair, a one-sample *t*-test was performed on the channel-wise t-statistic. A FDR correction was applied to the region-wise *p*-values to control for multiple comparisons. The *p*-value threshold was set at $p < 0.05$.

3. Results

3.1. Cue induced activations in MA dependent individuals

The SPM12 results showed that different brain regions were activated depending on the type of cue (drug-related or neutral) shown to the participants (Fig. 3). The bilateral OFC and DLPFC were activated under drug-cue exposure, with the right OFC and DLPFC showing increased activation.

3.2. The effect of exercise on cue-induced activations in MA dependent individuals

Fig. 4 shows the influence of exercise on cue-induced activations in MA- dependent individuals. Before the exercise intervention, MA dependent individuals show activations in the bilateral DLPFC and OFC in response to drug-related and neutral cues ($p < 0.05$) (Fig. 4A). However, bilateral DLPFC and left OFC activations were not elicited by drug-related cues after 10 min VR enhanced cycling exercise (Fig. 4B). Acute exercise decreased cue-induced craving associated with brain activation in the DLPFC and OFC.

3.3. The effect of exercise on functional connectivity in MA dependent individuals

Fig. 5 shows significant changes in functional connectivity in response to drug cues relative to neutral cues before and after exercise intervention ($p < 0.05$, FDR corrected). There were more significant

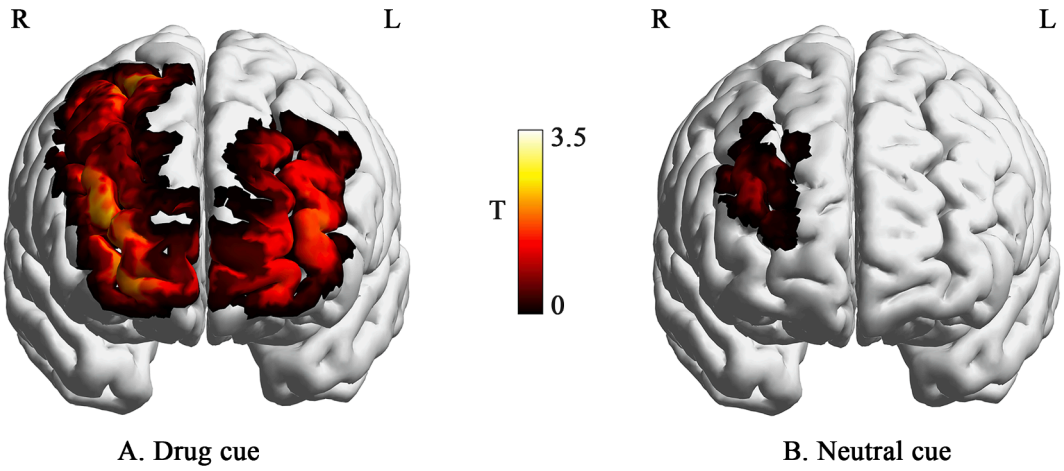

Fig. 3. Drug and neutral cues induced brain activations in the dorsolateral prefrontal cortex (DLPFC) and orbitofrontal cortex (OFC) regions in MA dependent individuals ($p < 0.05$). (A) Enhanced hemodynamic responses in bilateral OFC and DLPFC to drug-related cues relative to baseline (drug cue - baseline contrast). (B) Enhanced hemodynamic responses in right OFC to neutral cues relative to baseline (neutral cue -baseline contrast).

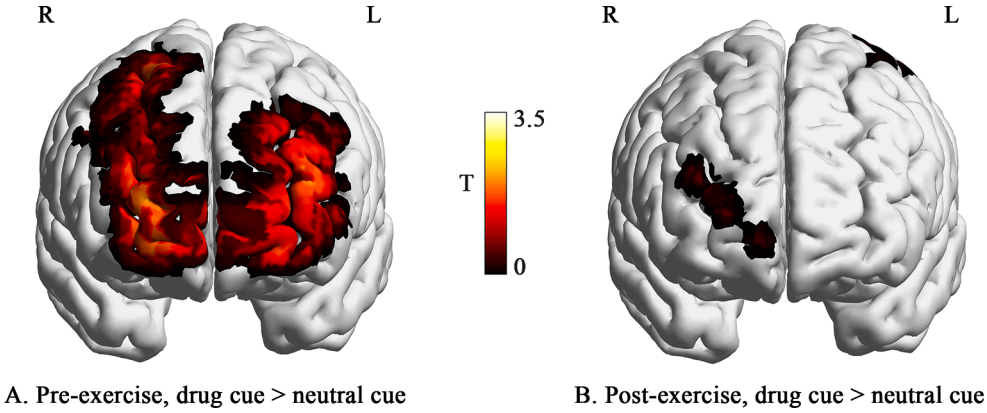

Fig. 4. The influence of exercise on cue-induced activations in MA dependent individuals. (A) Brain activations in the bilateral dorsolateral prefrontal cortex (DLPFC) and orbitofrontal cortex (OFC) regions triggered by drug cues versus neutral cues, before VR-enhanced cycling exercise (drug cue - neutral cue contrast). (B) Brain activations in left primary motor cortex and right OFC triggered by drug cues versus neutral cues, after VR enhanced cycling exercise (drug cue - neutral cue contrast).

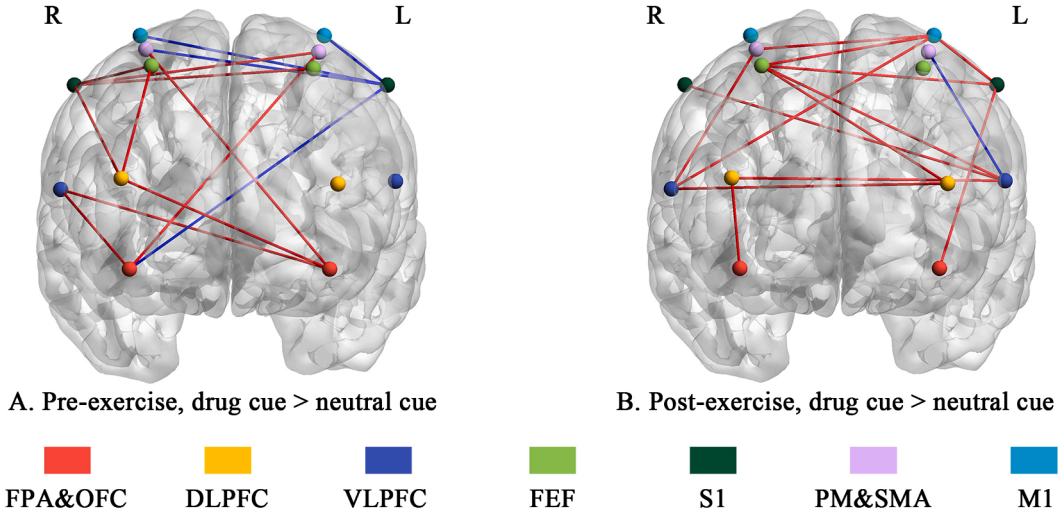

Fig. 5. The influence of exercise on cue-induced functional connectivity in MA dependent individuals. Red lines show increased connectivity, and blue lines show decreased connectivity ($p < 0.05$, FDR corrected). (A) Significant changes in functional connectivity in response to drug cues relative to neutral cues before exercise (drug cue > neutral cue). (B) Significant changes in functional connectivity in response to drug cues relative to neutral cues after VR enhanced cycling exercise (drug cue > neutral cue). FPA: frontopolar area; OFC: orbitofrontal cortex; S1: primary somatosensory cortex; DLPFC: dorsolateral prefrontal cortex;VLPFC: ventrolateral prefrontal cortex; FEF:frontal eye field ; PM:pre-motor cortex ; SMA:supplementary motor cortex ; M1: primary motor cortex.

increases in functional connectivity between prefrontal and motor cortex under drug-cue exposure after VR-enhanced cycling exercise (paired *t*-test, $p < 0.05$) (Fig. 5B). Specifically, left ventrolateral prefrontal cortex (VLPFC, a key region in processing a "stop" signal under drug cue exposure) showed significantly increased connectivity to the right DLPFC, right S1, and right FEF, and the right VLPFC showed significantly increased connectivity to the left DLPFC, right M1, and left premotor cortex during the post-exercise drug-cue reactivity task compared to the pre-exercise drug-cue reactivity task.

4. Discussion

In the present study, we used a within-subject design to compared PFC and motor cortex activation and connectivity in response to drug-related cues following acute exercise intervention in the same subject. The main findings of the present studies supported our hypothesis. The drug-cue induced brain activations are located in the PFC, including bilateral OFC and DLPFC in the MA-dependent individuals. Acute exercise decreases brain activation in the DLPFC and OFC under the drug cue exposure. Acute exercise also affected the functional connectivity between PFC and motor cortex in response to drug-related cues relative to neural cues.

4.1. Cue induced activations in MA dependent individuals

The sight of drug cues can trigger craving. Visual drug cues are widely employed in experiments, since they are easy to use, relatively cheap, and can be used repeatedly [35]. Previous studies have suggested neuroimaging recordings are more sensitive in detecting group differences in conditioned responses to the drug-related cues, since no differences in arousal ratings and skin conductance responses to the drug-related cues were found between addicted and non-addicted individuals [21]. Therefore, self-reported rate of craving was not reported in the present study. Our study is based on recent models of neural representation of cue-induced craving, and we particularly focus on the DLPFC and OFC regions, which are closely associated with the cue reactivity among addictive individuals [16,18]. We observed enhanced hemodynamic responses in bilateral DLPFC and OFC to drug related cues relative to neutral cues in the MA dependent individuals, which is in line with previous studies reporting cue-related activations in the DLPFC and OFC in cocaine [36], cigarette [22 37,19], and alcohol dependent individuals [20,21].

Activation of the prefrontal cortex (PFC) in response to relevant cues has been frequently reported in behavioral addictions, because PFC roles are most pertinent to addiction [18]. Drug-addicted individuals show hypoactivity in PFC when they are tested in in the stage of withdrawal [38]. However, drug-related cues that elicit cravings may reactivate the PFC. The activation of PFC regions have been also reported to contribute to the craving in online gaming addiction and gambling, similar to that of the cue-induced craving in substance dependence. Participants with online gaming addiction viewing pictures of the games showed BOLD activations in OFC and DLPFC [39]. Pathological gambling participants watching gambling videos showed significantly greater activity in DLPFC compared with healthy control [40]. These patterns are consistent with the OFC's role in processing relative reward [41], and with the DLPFC's role in reward, motivation and decision-making [22].

4.2. The effect of exercise on cue-induced activations in MA dependent individuals

Exercise has been proposed as a novel treatment for individuals with substance use disorder undergoing treatment at different stages of addiction rehabilitation [10,42]. Previous research has shown that both acute and long-term exercise can reduce self-reported cravings in response to drug-related cues in MA-dependent individuals [8,9]. Our study provides further neurobiological evidence supporting exercise therapy to control craving in MA-dependent individuals. We observed that acute VR-enhanced competitive cycling exercise attenuated the hemodynamic response in PFC, including bilateral DLPFC and OFC, during drug-related cue exposure. Previous fMRI studies on smokers show that acute exercise reduced self-reported craving, which correlated with reduced BOLD responses in DLPFC [43,44]. Since increased craving is associated with recruitment of the DLPFC [45], the post-exercise decrease of cue-related activation in the DLPFC may suggest a protective effect of acute exercise against cue-induced cravings. Indeed, by using transcranial magnetic stimulation (TMS), Hayashi and coworkers found that in smokers, the inactivation of DLPFC prevents the increase of craving during exposure to the cues [22]. Furthermore, the OFC has been considered as a target for drug abuse [46]. Previous studies on smokers have suggested that exercise can reduce the motivational drive (via OFC) toward smoking, that OFC become hypoactive following exercise under the exposure of the same cues in smokers [44].

4.3. The effect of exercise on cue-induced brain networks in MA dependent individuals

Exercise positively impacts brain function. The motor cortex is one of the brain regions to be influenced by the beneficial effects of exercise [47]. We observed an increased hemodynamic response in the premotor cortex under drug-cue exposure after 10 min VR-enhanced cycling exercise. In addition, we found an increased functional connectivity between PFC and motor cortex following exercise under the drug-cue exposure. The PFC is a core region in cognitive control, decision making, and linking cognition to action [48]. The cortico-cortical connection between PFC and motor cortex transfers crucial executive information to motor control [49]. Clinical and neuroimaging studies have suggested that the anatomical and functional connectivity between these two cortices plays an importance role in inhibitory stimulus control [50]. The exercise-induced increases in functional connectivity between the PFC and motor cortex under drug-cue exposure may suggest a promising role of physical exercise in promoting greater executive control of MA-dependent individuals' compulsive behavior.

From a brain functional network perspective, the VLPFC is a key region of inhibitory control and emotion regulation. It has been proposed that VLPFC plays a key role in processing a "stop" signal against addiction, by which excessive or inappropriate drug-taking behavior is stopped [16,18]. DLPFC, on the hand, might be responsible for processing a "go" signal in addiction. We observed an increased functional connectivity between VLPFC and DLPFC following exercise under drug-cue exposure (Fig. 5B), whereas no functional connectivity between DLPFC and VLPFC was observed before exercise under the same drug-cue exposure (Fig. 5A). We also observed an increased functional connectivity between right DLPFC and right OFC following exercise during the drug-cue reactivity task. Signals occurring in moments of craving are mainly processed by OFC and respond to input from DLPFC [22]. Previous studies that applied transcranial direct current stimulation (tDCS) to the DLPFC in smokers found an increased functional connectivity between DLPFC and OFC [51]. The DLPFC is a core region of the executive control network (ECN) and top-down regulation of emotion of craving. Previous high-frequency TMS over DLPFC studies have also shown that targeted modulation of DLPFC activation and related functional networks correlated with craving reduction [52]. Exercise may facilitate cognitive effort and inhibitory control through the interaction between DLPFC and VLPFC under the drug-cue exposure in MA-dependent individuals.

4.4. Study limitations

Some limitations of the present study should be mentioned. Firstly, fNIRS can be measured only on the cortical surface to a depth of 2–3 cm. Therefore, we selected the PFC and motor cortex to assess the effects of acute exercise on drug-cue induced craving in MA-dependent

individuals. However, other regions, such as the superior parietal cortex, insula, and thalamus are also involved in processing cue-induced craving, which cannot be reliably measured by the fNIRS technique. Secondly, a healthy control group could further explore the impact of MA-addiction on cue-related brain functional responses. Thirdly, we investigated the acute effects of the competitive cycling exercise on addiction among MA-dependent individuals. However, the beneficial effects of exercise on addiction depend on the level/type/timing of exercise exposure. Long-term exercise effects on the drug-cue induced craving should also be investigated to validate exercise therapy for the MA-dependent individuals.

5. Conclusion

In the present study, we provide further evidence that acute VR-enhanced competitive cycling exercise could attenuate drug-related craving during a drug-cue reactivity task. We observed enhanced hemodynamic responses in bilateral DLPFC and OFC to drug related cues versus neutral cues in MA-dependent individuals. In contrast, the hemodynamic responses in DLPFC and OFC were significantly reduced following exercise under the same drug-cue exposure. Moreover, following exercise, increased functional connectivity between PFC and motor cortex, in particular, increased functional connectivity of DLPFC/ OFC and DLPFC/ VLPFC was observed. Physical exercise, by reducing PFC activity and by strengthening the functional connectivity between the PFC and the motor cortex, thus appears to facilitate inhibitory and executive control over MA-craving.

6. Role of Funding Source

Nothing declared.

CRediT authorship contribution statement

Liping Qi: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Software, Writing – original draft, Writing - reviewing & editing. **Zhi-Hao Tian:** Conceptualization, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing - reviewing & editing. **Yin Yue:** Data curation, Formal analysis, Investigation, Visualization, Writing – original draft. **Shuo Guan:** Data curation, Investigation, Validation. **Lei Tang:** Supervision, Project administration, Resources. **Guijun Dong:** Conceptualization, Project administration, Resources, Software.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was supported by the National Natural Science Foundation of China, China (grant numbers: 31600797), National Natural Science Foundation of Liaoning, China (grant number: 2021-MS-115).

References

[1] K.C. Morley, J.L. Cornish, A. Faingold, K. Wood, P.S. Haber, Pharmacotherapeutic agents in the treatment of methamphetamine dependence, Expert Opin. Invest. Drugs 26 (5) (2017) 563–578.
[2] A.C. May, R.L. Aupperle, J.L. Stewart, Dark Times: The Role of Negative Reinforcement in Methamphetamine Addiction, Front. Psychiatry 11 (Mar 17 2020).
[3] S. Kuhn, J. Gallinat, Common biology of craving across legal and illegal drugs - a quantitative meta-analysis of cue-reactivity brain response, Eur. J. Neurosci. 33 (Apr 2011) 1318–1326.
[4] C.A. Hanlon, L.T. Dowdle, T. Naselaris, M. Canterberry, B.M. Cortese, Visual cortex activation to drug cues: A meta-analysis of functional neuroimaging papers in addiction and substance abuse literature, Drug Alcohol Depend. 143 (2014) 206–212.
[5] M.M. Ellingsen, T. Clausen, S.L. Johannesen, E.W. Martinsen, M. Hallgren, Effects of acute exercise on drug craving in adults with poly-substance use disorder. A randomized controlled trial, Mental Health Physical Activity 21 (2021) 100423.
[6] M.P. Paulus, J.L. Stewart, Neurobiology, Clinical Presentation, and Treatment of Methamphetamine Use Disorder A Review, Jama Psychiatry 77 (Sep 2020) 959–966.
[7] F. Colledge, M. Gerber, U. Puhse, S. Ludyga, Anaerobic Exercise Training in the Therapy of Substance Use Disorders: A Systematic Review, Front. Psychiatry, 9(Dec 4 2018).
[8] D.S. Wang, C.L. Zhou, M. Zhao, X.P. Wu, Y.K. Chang, Dose-response relationships between exercise intensity, cravings, and inhibitory control in methamphetamine dependence: An ERPs study, Drug Alcohol Depend. 161 (2016) 331–339.
[9] D.S. Wang, C.L. Zhou, Y.K. Chang, Acute exercise ameliorates craving and inhibitory deficits in methamphetamine: An ERP study, Physiol. Behav. 147 (2015) 38–46.
[10] W.J. Lynch, A.B. Peterson, V. Sanchez, J. Abel, M.A. Smith, Exercise as a novel treatment for drug addiction: A neurobiological and stage-dependent hypothesis, Neurosci. Biobehav. Rev. 37 (Sep 2013) 1622–1644.
[11] K.G. Costa, D.A. Cabral, R. Hohl, E.B. Fontes, Rewiring the Addicted Brain Through a Psychobiological Model of Physical Exercise, Front. Psychiatry, 10 (Aug 27 2019).
[12] D.R. Mestre, C. Maiano, V. Dagonneau, C.S. Mercier, Does Virtual Reality Enhance Exercise Performance, Enjoyment, and Dissociation? An Exploratory Study on a Stationary Bike Apparatus, Presence-Virtual Augmented Reality 20 (Feb 2011) 1–14.
[13] J. Qian, D.J. McDonough, Z. Gao, The Effectiveness of Virtual Reality Exercise on Individual's Physiological, Psychological and Rehabilitative Outcomes: A Systematic Review, Int. J. Environ. Res. Public Health 17 (Jun 10 2020).
[14] N. Zeng, Z. Pope, J.E. Lee, Z. Gao, Virtual Reality Exercise for Anxiety and Depression: A Preliminary Review of Current Research in an Emerging Field, J. Clin. Med. 7 (Mar 4 2018).
[15] M.E. Walton, J.T. Devlin, M.F.S. Rushworth, Interactions between decision making and performance monitoring within prefrontal cortex, Nat. Neurosci. 7 (Nov 2004) 1259–1265.
[16] O. George, G.F. Koob, Control of craving by the prefrontal cortex, PNAS 110 (2013) 4165–4166.
[17] X.M. Li, et al., The top-down regulation from the prefrontal cortex to insula via hypnotic aversion suggestions reduces smoking craving, Hum. Brain Mapp. 40 (2019) 1718–1728.
[18] R.Z. Goldstein, N.D. Volkow, Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications, Nat. Rev. Neurosci. 12 (11) (2011) 652–669.
[19] Y. Yalachkov, J. Kaiser, M.J. Naumer, Brain Regions Related to Tool Use and Action Knowledge Reflect Nicotine Dependence, J. Neurosci. 29 (2009) 4922–4929.
[20] A. Heinz, et al., Brain activation elicited by affectively positive stimuli is associated with a lower risk of relapse in detoxified alcoholic subjects, Alcoholism-Clin. Experimental Res. 31 (Jul 2007) 1138–1147.
[21] S.M. Grusser et al., Cue-induced activation of the striatum and medial prefrontal cortex is associated with subsequent relapse in abstinent alcoholics, Psychopharmacology 175 (Sep 2004), 296-302.
[22] T. Hayashi, J.H. Ko, A.P. Strafella, A. Dagher, Dorsolateral prefrontal and orbitofrontal cortex interactions during self-control of cigarette craving, PNAS 110 (2013) 4422–4427.
[23] X. Gu, B. Yang, S. Gao, L.F. Yan, D. Xu, W. Wang, Prefrontal fNIRS-based clinical data analysis of brain functions in individuals abusing different types of drugs, J. Biomed. Semant. 12 (1) (2021).
[24] K. Yamamuro, M. Makinodan, S. Kimoto, N. Kishimoto, T. Morimoto, M. Toritsuka, K. Matsuoka, Y. Takebayashi, T. Takata, M. Takahashi, Y. Tanimura, Y. Nishihata, Y. Matsuda, T. Ota, H. Yoshino, J. Iida, T. Kishimoto, Differential patterns of blood oxygenation in the prefrontal cortex between patients with methamphetamine-induced psychosis and schizophrenia, Sci. Rep. 5 (1) (2015).
[25] F. Herold, P. Wiegel, F. Scholkmann, N.G. Muller, Applications of Functional Near-Infrared Spectroscopy (fNIRS) Neuroimaging in Exercise-Cognition Science: A Systematic, Methodology-Focused Review, J. Clin. Med. 7 (Dec 2018).
[26] L. Qi, Y. Yin, L. Bu, Z. Tang, L. Tang, G. Dong, Acute VR competitive cycling exercise enhanced cortical activations and brain functional network efficiency in MA-dependent individuals, Neurosci. Lett. 757 (2021) 135969.
[27] L. Bu, L. Qi, W.u. Yan, Q. Yan, Z. Tang, F. Li, X. Liu, C. Diao, K. Li, G. Dong, Acute kick-boxing exercise alters effective connectivity in the brain of females with methamphetamine dependencies, Neurosci. Lett. 720 (2020) 134780.
[28] L. Bu, Y. Wu, Q. Yan, L. Tang, X. Liu, C. Diao, K. Li, G. Dong, Effects of physical training on brain functional connectivity of methamphetamine dependencies as assessed using functional near-infrared spectroscopy, Neurosci. Lett. 715 (2020) 134605.
[29] D.T. Delpy, M. Cope, P. Vanderzee, S. Arridge, S. Wray, J. Wyatt, Estimation of Optical Pathlength through Tissue from Direct Time of Flight Measurement, Phys. Med. Biol. 33 (Dec 1988) 1433–1442.
[30] T.J. Huppert, R.D. Hoge, S.G. Diamond, M.A. Franceschini, D.A. Boas, A temporal comparison of BOLD, ASL, and NIRS hemodynamic responses to motor stimuli in adult humans, Neuroimage 29 (2) (2006) 368–382.

[31] S. Cutini, P. Scatturin, M. Zorzi, A new method based on ICBM152 head surface for probe placement in multichannel fNIRS, Neuroimage 54 (2) (2011) 919–927.
[32] J. Ye, S. Tak, K. Jang, J. Jung, J. Jang, NIRS-SPM: Statistical parametric mapping for near-infrared spectroscopy, Neuroimage 44 (2) (2009) 428–447.
[33] S. Tak, M. Uga, G. Flandin, I. Dan, W.D. Penny, Sensor space group analysis for fNIRS data, J. Neurosci. Methods 264 (2016) 103–112.
[34] W. Penny, A. Holmes, *Random effects analysis.* (Statistical Parametric Mapping: The Analysis of Functional Brain Images.), Elsevier, London, 2006.
[35] M.A. Sayette, S. Shiffman, S.T. Tiffany, R.S. Niaura, C.S. Martin, W.G. Shadel, The measurement of drug craving, Addiction 95 (Aug 2000) S189–S210.
[36] N.D. Volkow, et al., Cognitive control of drug craving inhibits brain reward regions in cocaine abusers, Neuroimage 49 (2010) 2536–2543.
[37] H. Kober, et al., Prefrontal-striatal pathway underlies cognitive regulation of craving, PNAS 107 (2010) 14811–14816.
[38] N.D. Volkow, J.S. Fowler, G.J. Wang, The addicted human brain: insights from imaging studies, J. Clin. Invest. 111 (May 2003) 1444–1451.
[39] C.-H. Ko, G.-C. Liu, S. Hsiao, J.-Y. Yen, M.-J. Yang, W.-C. Lin, C.-F. Yen, C.-S. Chen, Brain activities associated with gaming urge of online gaming addiction, J. Psychiatr. Res. 43 (7) (2009) 739–747.
[40] D.N. Crockford, B. Goodyear, J. Edwards, J. Quickfall, N. el-Guebaly, Cue-induced brain activity in pathological gamblers, Biol. Psychiatry 58 (Nov 15 2005) 787-795.
[41] J. O'Doherty, M.L. Kringelbach, E.T. Rolls, J. Hornak, C. Andrews, Abstract reward and punishment representations in the human orbitofrontal cortex, Nat. Neurosci. 4 (1) (2001) 95–102.
[42] L.J. Mooney, C. Cooper, E.D. London, J. Chudzynski, B. Dolezal, D. Dickerson, M.-L. Brecht, J. Peñate, R.A. Rawson, Exercise for methamphetamine dependence: Rationale, design, and methodology, Contemporary Clin. Trials 37 (1) (2014) 139–147.
[43] K.J. Van Rensburg, A. Taylor, T. Hodgson, The effects of acute exercise on attentional bias towards smoking-related stimuli during temporary abstinence from smoking, Addiction 104 (Nov 2009) 1910–1917.
[44] K. Janse Van Rensburg, A. Taylor, T. Hodgson, A. Benattayallah, Acute exercise modulates cigarette cravings and brain activation in response to smoking-related images: an fMRI study, Psychopharmacology 203 (3) (2009) 589–598.
[45] D. McBride, S.P. Barrett, J.T. Kelly, A. Aw, A. Dagher, Effects of expectancy and abstinence on the neural response to smoking cues in cigarette smokers: An fMRI study, Neuropsychopharmacology 31 (Dec 2006) 2728–2738.
[46] N.D. Volkow, J.S. Fowler, Addiction, a disease of compulsion and drive: Involvement of the orbitofrontal cortex, Cereb. Cortex 10 (Mar 2000) 318–325.
[47] C.S. Mang, N.J. Snow, K.L. Campbell, C.J.D. Ross, L.A. Boyd, A single bout of high-intensity aerobic exercise facilitates response to paired associative stimulation and promotes sequence-specific implicit motor learning, J. Appl. Physiol. 117 (2014) 1325–1336.
[48] K. Yarrow, P. Brown, J.W. Krakauer, Inside the brain of an elite athlete: the neural processes that support high achievement in sports, Nat. Rev. Neurosci. 10 (8) (2009) 585–596.
[49] O. Cohen, E. Sherman, N. Zinger, S. Perlmutter, Y. Prut, Getting ready to move: transmitted information in the corticospinal pathway during preparation for movement, Curr. Opin. Neurobiol. 20 (6) (2010) 696–703.
[50] V. Oldrati, J. Patricelli, B. Colombo, A. Antonietti, The role of dorsolateral prefrontal cortex in inhibition mechanism: A study on cognitive reflection test and similar tasks through neuromodulation, Neuropsychologia 91 (Oct 2016) 499–508.
[51] A.M. Kroczek, et al., Effects of transcranial direct current stimulation on craving, heart-rate variability and prefrontal hemodynamics during smoking cue exposure, Drug Alcohol Depend. 168 (2016) 123–127.
[52] H. Su, et al., High frequency repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex for methamphetamine use disorders: A randomised clinical trial, Drug Alcohol Depend. 175 (2017) 84–91.