Effects of acute aerobic exercise on sweet taste preference and its brain mechanisms in tobacco addicts

Hongen Liu
Guangxi normal university
Yanbai Han
Guangxi normal university
Wei Liang
Shenzhen University
Lin Zhou
Hebei Normal University
Yingying Zhang
Shandong Sports University
Pinghan Sun
Shandong Sports University
Hainan Fan
Shandong Sports University
Zhao Xu
xuzhao@sdpei.edu.cn

Shandong Sports University

Article

Keywords: Aerobic exercise, Tobacco dependence, Sweetness sensitivity, Sweetness preference, fNIRS

Posted Date: April 12th, 2024

DOI: https://doi.org/10.21203/rs.3.rs-4195409/v1

Additional Declarations: No competing interests reported.

Abstract

Aerobic exercise can improve cravings for smoking and inhibition control in tobacco-dependent individuals; however, its effect on their sweet taste preferences remains unclear. This study aims to examine the effects of acute aerobic exercise on sweet taste preferences and nerve sensitivity in brain regions associated with the prefrontal cortex in tobacco-dependent subjects. Participants were asked to perform 35 minutes of exercise or rest. They took the sweet taste preference test and the Visual Food Cues Paradigm Task immediately before and immediately after the experiment. After the intervention with acute high-intensity exercise, participants' preference for low-sweetness foods increased significantly (F = 14.220, P < 0.001). Following the moderate-intensity exercise intervention, when participants were shown pictures of low-sweetness food, the average concentration of oxyhemoglobin in the right orbitofrontal cortex increased significantly (F = 14.215, P < 0.001). Additionally, the change in functional connection strength between the right dorsolateral prefrontal cortex and the left ventrolateral prefrontal cortex was significantly enhanced (F = 4.113, P = 0.046). These results suggest that acute aerobic exercise can alter the sweet taste preferences of tobacco-dependent subjects, as well as the level of PFC activation and functional connectivity, thereby temporarily restoring the nerve sensitivity related to sweet taste that has been impaired by nicotine.

Introduction

People who use tobacco products are at a high risk of developing nicotine dependence (formerly known as nicotine addiction), characterized by a lack of control over the need for nicotine. In recent decades, the health crisis stemming from nicotine dependence has emerged as a public health issue of international concern. Nicotine dependence not only harms the respiratory and cardiovascular systems but also adversely affects the central nervous system, thereby impacting cognitive function [1,2]. According to the latest survey by the World Health Organization (WHO), there are 1.337 billion smokers worldwide, with one out of every three smokers dying from smoking-related diseases. Notably, 22.9%, or about 310 million of these smokers, are from China. Consequently, taking appropriate measures to control nicotine dependence is of great significance for smokers.

Exercise has been shown to be an effective substitute for nicotine [3-5], with an increasing number of studies confirming the positive effects of exercise on nicotine dependence. A functional brain imaging study demonstrated that smokers' desire for tobacco products decreased post-exercise, accompanied by changes in the activation of brain regions related to reward, motivation, and visuospatial attention [6]. Moreover, moderate to high-intensity aerobic exercise can stimulate the release of neurotransmitters like dopamine (DA), which replace nicotine in activating the brain's reward system, thus inducing relaxation and pleasure [7]. The cognitive hypothesis suggests that exercise can enhance cognitive function in smokers, inhibit impulsive smoking thoughts, reduce tobacco-dependent individuals' attention bias towards smoking stimuli, and decrease smoking behavior [8]. This is attributed to the susceptibility of tobacco-dependent individuals' brains to the long-term cognitive effects of nicotine exposure, where

moderate-intensity exercise can influence signal transduction mediated by nicotinic acetylcholine receptors in the prefrontal cortex, effectively improving nicotine-induced cognitive behavior [9]. Additionally, the emotional hypothesis posits that during smoking cessation, exercise (especially at high intensities) can alleviate anxiety and negative emotions, adjust emotional responses, improve self-efficacy and confidence, and enhance adherence to smoking cessation efforts, thereby aiding in quitting smoking [10,11]. Therefore, moderate-to-high intensity exercise interventions may represent a promising strategy for nicotine addiction withdrawal, offering advantages over health education alone [12-14].

In addition, recent research has found that the repeated use of addictive drugs impairs the brain's reward system [15], consisting of neural structures that induce compulsive behaviors and sustain substance addiction [16,17]. Drug addiction leads individuals to prioritize drug-related rewards over natural and non-drug-related rewards, showing decreased responsiveness [18-20]. Evidence suggests that tobacco-dependent individuals exhibit reduced sensitivity to natural rewards due to nicotine, with certain brain regions showing less activation when smokers view pictures of tasty foods compared to non-smokers [21]. Research on the effects of opioids on sweet taste sensitivity indicates that opioid-dependent individuals exhibit decreased sensitivity to low sweetness [22]. Thus, nicotine in tobacco diminishes sweet taste sensitivity and alters the sweet taste preference of tobacco-dependent individuals, consequently affecting the intake of sweet foods [23,24].

Therefore, enhancing the sweet taste preferences of tobacco-dependent individuals, restoring their compromised sweet taste sensitivity, and promoting appetite to better their eating patterns represent potential methods to alleviate nicotine withdrawal symptoms. Although previous studies on the relationship between taste and brain imaging exist, they predominantly focused on the cortical activation within specific brain regions rather than on networks. These studies revealed that the central nervous system adapts to varying task demands in two primary ways: altering neural activation in particular brain regions and modulating the intensity of interactions among these regions through functional connections [25-27]. Despite evidence suggesting the critical role of intermodulation between brain areas in altering taste preferences, and the potential for exercise to modify the strength of functional connections related to taste, research on the impact of exercise on functional brain connectivity remains scarce [28,29]. Consequently, there is a need to further investigate how movement changes during a Functional near-infrared spectroscopy (fNIRS) task can modulate the strength of functional connections within the left and right prefrontal cortex (PFC) regions.

Considering the factors mentioned above, this study aimed to investigate the effects of acute aerobic exercise on sweet taste preference and PFC-related brain sensitivity in individuals addicted to tobacco. It further sought to elucidate the correlation of network connections between regions of interest (ROIs) under various sweet stimuli, both before and after exercise, in subjects dependent on tobacco. This investigation, conducted by analyzing brain functional connectivity, provides insights and experimental evidence for the role of exercise intervention in tobacco withdrawal.

Methods

Study design and procedure. Participants were randomly divided into moderate- and high-intensity exercise groups, and a control group, with 20 participants in each group. At baseline, demographic information and questionnaire data were collected. Subsequently, participants in the exercise groups were asked to perform 35 minutes of exercise, while those in the control group rested in a quiet room for the same duration. Before starting the experiment and immediately after completing the exercise intervention or control session, each group un-derwent visual analogue scales (VAS) for sweet taste preference and visual food cue paradigm task tests (VFCP). fNIRS was utilized to measure oxyhemoglobin (HbO) concentration in the ROIs and the strength of functional connectivity between them. Participants were instructed to refrain from strenuous exercise or alcohol consumption for 24 hours prior to the experiment, to cease eating 2 hours before, and to avoid smoking and consuming caffeinated beverages. (Figure 1)

Participants. An a priori, two-tailed power calculation with an alpha of 0.05 and a power of 80%, based on an effect size of 0.27 [30], suggested that a total minimum of 39 participants, 13 for each group, were required for this study. Sixty eligible male participants (age range, 18~25 years) were recruited from a university for this study, meeting the following inclusion criteria: (1) normal body mass index (BMI $\geq$ 18.5 and < 23 kg/m^2); (2) Fagerstrom Test for Nicotine Dependence (FTND) score $\geq$ 6 or smoking more than 10 cigarettes per day; (3) no history of eating disorder, psychiatric diagnoses, or neurologic illnesses; (4) no history of other substance-type abuse (e.g., methamphetamine, alcohol, etc.); and (5) right-handedness. This study adhered to the Declaration of Helsinki guidelines and received approval from the Ethics Committee of Shandong Sport University (No. 2019023). All subjects consented to participate and signed an informed consent form. The study was registered at www.chictr.org.cn (ChiCTR2300067314).

Intervention content. Participants were instructed to complete 35 minutes of aerobic exercise on a power bike (Monark 928E, Sweden), adhering to the guidelines set by the American College of Sports Medicine (ACSM). The exercise routine consisted of a 5-minute warm-up, followed by a 25-minute main exercise period, and concluded with a 5-minute cool-down, throughout which a consistent speed of 50 rpm was maintained. During the main exercise phase, participants were required to cycle with their heart rate maintained within one of two predefined intensity ranges: 65-75% or 75%-85% of their estimated maximum heart rate (HR_{max}). The formula for estimating HR_{max} is 206.9 - 0.67×age [31].

Procedure and measures. A mixed experimental design of 3 (groups: moderate-intensity exercise group, high-intensity exercise group, quiet control group) ×2 (test times: pre-test, post-test) was used, where “groups” was a between-subjects factor and “test time” was a within-subjects factor. The independent variable was exercise intensity, and the dependent variables were the explicit preference scores of tobacco-dependent subjects for different sweet foods and pictures of different sweet foods, changes in HbO concentration in various ROIs of the PFC, and changes in functional connection strength between ROIs.

Subjective sweetness preference test. Participants were randomly presented with an image of sweet food as a stimulus. They rated the food's sweetness in the image using a 100-mm visual analog scale (VAS), with the ends labeled 'not at all sweet' and 'extremely sweet.' They were then asked the question: 'How pleasant would it be to experience a mouthful of this food right now?' For each food image, the VAS scale was displayed on the screen, and participants selected a point along the scale to indicate their degree of liking (see Figure 2). After the score was recorded, the next image was automatically presented in a random order.

Visual food cue paradigm. The visual food cue paradigm was adapted from Killgore's research [32]. Participants were shown color pictures against a white background on a computer screen placed 30 cm away. These pictures featured high-sweetness foods (such as cotton candy, doughnuts, lollipops), low-sweetness food (including tomatoes, whole wheat bread, milk), and non-food contrast pictures similar to food in color and texture (such as flowers, tableware, condiments). Participants were instructed to carefully observe each picture and imagine the taste of the food depicted. fNIRS technology monitored the activation of the ROIs while participants completed the visual food cue paradigm task. The entire task was divided into seven blocks, with each block consisting of 12 pictures from the same sweetness category or non-food category. Pictures were presented randomly and remained visible for 3 seconds each, with a 10-second fixation period (+) separating each block. (Figure 3).

fNIRS data acquisition. An fNIRS imager (Shimadzu, Japan) was used to acquire changes in hemodynamic signals in the PFC during the visual food cue paradigm task. The system operated with three wavelengths (780, 805, and 830 nm) and had a sampling rate of 13.33 Hz. The PFC was targeted as the area of interest, and participants wore an optode cap, using the international 10-20 system for positioning reference. An 8×8 multichannel layout was used, consisting of eight emitter and eight detector optodes, creating a total of 22 channels. Optode probes were placed at 3 cm intervals to ensure optimal coverage (Figure 4).

Furthermore, the coordinates of each channel were determined using a 3D localizer (Polhemus, USA). The 3D information of the brain structure corresponding to each channel was calculated through SPM simulation, and brain areas were identified based on the Brodmann area system (Table 1).

Table 1. Channels corresponding to PFC brain regions.

Brodmann area	Right area channels	Left area channels
Dorsolateral prefrontal cortex	1	7
Ventrolateral prefrontal cortex	8, 16	15, 22
Frontal polar cortex	2, 3, 4, 9, 10, 11	4, 5, 6, 12, 13, 14
Orbitofrontal cortex	17, 18, 19	19, 20, 21

fNIRS data processing. The fNIRS data were processed using Homer2 software based on MATLAB (R2013b). Motion artefacts, defined as a signal change exceeding 10% standard deviation within 0.5 seconds, were detected. A low-pass filter with a frequency of 0.1 Hz was applied to correct signal distortion caused by respiration, heartbeat, vascular motion, and machine thermal noise. Additionally, a high-pass filter with a frequency of 0.01 Hz was utilized to remove baseline drift. The changes in optical density data at the three wavelengths were transformed into changes in the concentrations of HbO, deoxyhemoglobin (HbR), and total hemoglobin (HbT) in the detection area of the cerebral cortex according to the modified Beer–Lambert law (MBLL). Given that HbO exhibits a superior signal-to-noise ratio in accordance with the MBLL [33], only HbO concentration data were used during the analysis.

After extracting the HbO data for each subject at each time point, the concentrations of HbO across all channels within each ROI were averaged for each condition, yielding the average HbO concentration for each ROI. The correlation coefficient (r) of the HbO concentrations between all ROIs in the time series was then analyzed using Pearson correlation analysis. The r values were subsequently converted to z values through Fisher-z transformation, with these converted z-values representing the strength of functional connectivity between the ROIs.

Statistical analysis. All statistical analyses were performed using IBM SPSS26.0. Descriptive statistics for all continuous variables are expressed as mean±standard deviation (M±SD). The Shapir-Wilk test was used to analyze the normality of the data, and Levene's test was used to measure the homogeneity of variance. If normal distributions were detected, a mixed design analysis of variance (ANOVA) was employed with group as a between-subject variable and test time as a within-subject variable, including sweet taste preference score, PFC region activity, and functional connection strength between ROIs as dependent variables. Post-hoc analysis was conducted to identify any interaction effects. The significance level was set at 0.05. The Bonferroni method was utilized for multiple comparison corrections. Effect sizes were expressed using partial Eta squared (Partial η^2), with Partial $\eta^2 < 0.06$ indicating a small effect, $0.06 <$ Partial $\eta^2 < 0.14$ indicating a medium effect, and Partial $\eta^2 > 0.14$ indicating a strong effect [34]. The strength of functional connectivity between ROIs was interpreted according to the Pearson correlation coefficient r. $0.05 \leq r < 0.07$ was defined as moderate correlation between ROIs, and $0.07 \leq r < 1$ was defined as strong correlation between ROIs; if $r < 0.05$, the correlation was considered weak or lacking.

Results

Baseline Characteristics of Participants. Sample characteristics and tests of baseline differences in demographic and smoking background are presented in Table 2. There were no significant differences for baseline characteristics between the moderate (n = 20), high (n = 20), and control (n = 20) groups.

Table 2
Demographic and Smoke data characteristics of all participants

Variables	Moderate (n = 20)	High (n = 20)	Rest (n = 20)
Demographic, M(SD)			
Age(year)	21.0(1.5)	20.4(1.5)	21.1(2.4)
Height(cm)	177.8(6.6)	178.2 (5.2)	181.7(5.9)
Weight(kg)	69.7(7.4)	72.4(11.2)	73.2(8.2)
BMI(kg/m^2)	22.1(2.4)	22.7(2.5)	22.16(2.1)
Quality of life (scores)	3.1(0.6)	3.3(0.6)	3.2(0.5)
Health status, n (%)			
Poor	0	0	0
Medium	13(65.0)	12(60.0)	15(75.0)
Good	7(35.0)	8(40.0)	5(25.0)
VAS and VFCP, M(SD)			
VAS (scores)	51.1(13.3)	51.7(13.6)	51.4(14.9)
VFCP($HbO\times10^{-7}mmol$)	35.2(14.9)	46.6(16.0)	34.81(18.6)
Smoke data, M(SD)			
Length as a smoker(years)	3.7(1.6)	3.4 (2.0)	3.5(1.9)
Smoking volume(cigarettes/day)	6.4(4.0)	6.7(4.2)	6.4(4.7)
FTND (scores)	4.5(1.1)	4.4(1.0)	4.5(1.1)

Note: BMI, body mass index; VAS, visual analog scale; VFCP, visual food cue paradigm; HbO, oxyhemoglobin concentration; FTND, fagerstrom test for nicotine dependence.

Sweetness preference score. A 3×2 ANOVA was conducted to compare the sweetness preference scores of the moderate-intensity exercise group, high-intensity exercise group, and resting control group before and after the experiment, focusing on participants' dominant sweetness preference for two sweet foods. The results revealed a significant interactive effect ($F_{(2, 57)} = 5.345$, $P = 0.025$) and a time main effect ($F_{(1, 57)} = 7.662$, $P = 0.008$) for participants' preference scores for low-sweetness foods, with no significant effect for high-sweetness foods. Further simple effect analysis showed a significant increase in participants' preference for low-sweetness foods after a high-intensity exercise intervention ($F = 14.220$, $P = 0.000$), without significant changes induced by the other intervention modalities (Fig. 5).

Activation of the prefrontal cortex. We calculated the average HbO concentration response amplitude in the participants' brain regions, including all channels from task initiation (0 to 36 seconds), in relevant brain regions. The mean HbO amplitude in each brain region of the participants' prefrontal lobes served as the dependent variable for a 3×2 repeated-measures ANOVA across three conditions. The results showed that viewing low-fat food pictures significantly affected the right orbitofrontal cortex (rOFC) with significant interactive ($F_{(2, 57)}$ = 4.220, P = 0.020) and time main effects ($F_{(1, 57)}$ = 8.134, P = 0.006), while other brain regions exhibited no significant interactions. Further analysis of simple effects indicated a significant increase in mean HbO concentration in the rOFC when participants were presented with a low-sweetness food picture after moderate-intensity exercise (F = 14.215, P = 0.000), with no significant changes observed in the control group before and after the intervention (Fig. 6).

PFC Functional connections. We calculated the strength of functional connectivity between the eight ROIs. A 3×2 repeated-measures ANOVA was conducted for the moderate-intensity exercise group, high-intensity exercise group, and resting control group, focusing on the change in functional connectivity strength among participants' prefrontal brain regions as the dependent variable. The results showed that when participants viewed low-sweetness food pictures, there was a significant main effect for “group” ($F_{(1, 57)}$ = 4.964, P = 0.001) and an interactive effect ($F_{(2, 57)}$ = 4.243, P = 0.019) on the change in functional connectivity strength between the right dorsolateral prefrontal cortex (rDLPFC) and the left ventrolateral prefrontal cortex (lVLPFC), with no significant interactive effects in other brain regions. Further analysis of simple effects revealed that the strength of rDLPFC-lVLPFC functional connectivity significantly increased following the moderate-intensity exercise intervention when participants were exposed to low-sweetness food picture stimuli (F = 4.113, P = 0.046), whereas no significant changes were observed in the control group before and after the intervention (Fig. 7).

Discussion

This study investigated the effects of acute aerobic exercise on sweet taste preference and neural responses in the PFC's sweet taste-related regions among tobacco-dependent individuals. Additionally, we explored the network correlations between ROIs through brain functional connectivity, assessing neurophysiological activities in response to different sweet stimuli before and after exercise. The findings corroborate our hypothesis: compared to controls, tobacco-dependent individuals exhibit heightened OFC activation in response to low-sweetness food pictures after engaging in moderate-intensity aerobic exercise. Furthermore, increased functional connectivity between the rDLPFC and lVLPFC following moderate-intensity exercise, coupled with changes in sweet taste preference, particularly after high-intensity exercise, indicates that acute aerobic exercise may enhance the sweet taste sensitivity altered by tobacco dependence. This enhancement likely results from increased nerve activation sensitivity and intensified interbrain interactions within sweet taste-associated regions.

The taste system plays an important role in the regulation of normal life processes. In particular, sweetness as a taste indicator in food can elicit pleasant feelings and thus increase the desire to eat. Studies have found that tobacco burning produces a large number of toxic substances, damaging the

taste system to varying degrees when exposed. However, this damage is reversible, with the extent of damage closely related to exposure time and tobacco concentration [35]. Tobacco-dependent individuals have reduced sensitivity to sweet tastes after smoking [36], which is mainly manifested by a higher sucrose detection threshold; the higher the nicotine intake, the higher the sucrose detection threshold and the lower the sucrose sensitivity [24,37]. Numerous studies have demonstrated that physical activity can promote the recovery of energy homeostasis and physiological reward mechanisms [13,38], influencing the intake of sweet food through changes in body energy homeostasis and food reward pathways [39]. Physical activity has also been confirmed to modify appetite and food preferences, with exercise intensity positively correlating with taste sensitivity [39]. This study's findings corroborate that tobacco-dependent individuals exhibit altered sweet food perception after high-intensity aerobic exercise, suggesting that physical activities can improve taste perception impaired by tobacco components [40]. Exercise influences individual eating behaviors by modulating the interaction between peripheral appetite hormones and the central food reward system, directly affecting sweet food preference [41].

Further analysis with fNIRS revealed that, after exercise interventions, the activation level of the OFC in tobacco-dependent individuals significantly increased during the selection of sweet tastes. This aligns with primate research, indicating the amygdala, VLPFC, and particularly the OFC, play crucial roles in the visual evaluation of food stimuli [32,42]. Serving as part of the food evaluation system, the OFC not only responds to visual food presentations but also assesses their subjective reward value. Studies have highlighted the OFC's pivotal role in processing visual, olfactory, and gustatory information, evaluating the reward value of food stimuli [43–45]. Moreover, the OFC is essential for mediating the hedonic aspects of food consumption, where it sends hedonic signals to the DLPFC, thereby initiating specific eating behaviors [46]. fMRI studies have further shown that OFC and VLPFC activation is associated with the memory of food reward effects [47], and the ventral cortex, including the OFC, contributes to food reward and reinforcement processes [48]. These elements collectively contribute to varying levels of PFC activation in response to the sight of sweet foods.

Furthermore, we assessed the strength of the functional connections between the bilateral PFC brain regions using Pearson’s correlation coefficients, discovering a significant increase in the connection strength between the rDLPFC and lVLPFC following acute aerobic exercise. This indicates that acute aerobic exercise enhances the functional connectivity of the brain’s hemispheres in tobacco-dependent individuals. The PFC plays a very important role in the cognitive assessment of sweet taste, among which the DLPFC is considered to be a key brain region involved in the regulation of eating behavior and is responsible for the top-down cognitive control of food intake [49,50]. The DLPFC is also key in inhibitory control [51,52], integrating reward signals, and orchestrating goal-oriented behaviors [53], including self-control in eating [54,55]. When making food choices, the DLPFC regulates activity in reward evaluation areas and factors in high-level considerations such as health implications on self-control. Meanwhile, the VLPFC is involved in reward assessment and targeting during eating. A cross-sectional study found that VLPFC activity varied with sweet food intake and that visual food cues in the VLPFC significantly

heightened neural response activity to aid in impulse control over anticipated food intake [56]. Hence, the DLPFC and VLPFC are integral to the brain's response to sweet tastes, with their enhanced functional connection playing a significant role in modifying sweet taste preferences.

Another relevant aspect of research in this field involves two perspectives on the central mechanism by which exercise can alter addiction. One hypothesis suggests that exercise itself may lead to a form of addiction, potentially substituting for drug addiction. Proponents of this theory argue that exercise stimulates the secretion of pleasure-related substances, such as dopamine (DA) and endorphins [57], which can repair long-term damage to pleasure-associated brain areas caused by addictive substances [30]. However, irrespective of this theory's future validation, DA plays a pivotal role in how exercise ameliorates addiction symptoms. Research has shown [58] that aerobic exercise not only enhances the release, synthesis, and secretion of DA but also accelerates its metabolism and catabolism, increases DA receptor density, and improves drug-induced neural adaptability. Moreover, aerobic exercise is known to foster brain plasticity, thereby enhancing the structure of brain regions involved in inhibitory control [59]. This improvement is primarily linked to synaptic plasticity, with exercise enhancing synaptic transmission efficiency[60,61]. Additionally, in individuals without drug addiction, aerobic exercise has been shown to reduce brain tissue loss in critical areas such as the left temporal lobe, dorsal anterior cingulate cortex, and PFC, thereby improving brain structure and plasticity in regions essential for inhibition and control. Aerobic exercise also selectively bolsters cognitive control by activating the DLPFC and OFC [62], aiding in modifying food choices [30]. Furthermore, aerobic exercise increases arousal levels through activation of the reticular activation system (RAS), a neural network in the brainstem that regulates projections to the PFC, crucial for cognitive control and emotional regulation.

A primary strength of this study is its pioneering use of fNIRS to investigate the impact of acute exercise at varying intensities on the neural sensitivity within the reward regions of male nicotine addicts, addressing a notable research gap. However, the study's limitations include its exclusive focus on male subjects, restricting the direct applicability of findings to female nicotine addicts. Additionally, we confined our observations to changes in blood oxygen concentration and the correlation between functional connections within the prefrontal brain regions. Expanding our analysis to include other brain areas, like the striatum and motor area, could provide a more comprehensive understanding. Furthermore, while acute exercise showed promising short-term effects on sweet taste preference and the desire to smoke in tobacco-dependent individuals, the effects of chronic exercise remain unexplored. Future research will delve into the chronic exercise effects on these mechanisms, aiming to elucidate the specific cognitive processes through which long-term exercise may aid tobacco cessation among smokers.

Conclusions

This study confirmed that acute aerobic exercise alters sweet taste preferences in tobacco addicts, notably enhancing their liking for foods with low sweetness. Additionally, such exercise significantly improves the responsiveness of neurons within the PFC that are involved in taste processing in tobacco

addicts. It also regulates the transmission and integration of sweet taste information in the central nervous system. Notably, these effects include increased activation of the rOFC in response to low-sweetness stimuli and enhanced functional connectivity between the rDLPFC and lVLPFC following acute moderate-intensity aerobic exercise. These findings suggest that acute aerobic exercise can temporarily restore the drug-diminished neural sensitivity to sweet tastes in tobacco addicts. This is instrumental in advancing our understanding of the neural mechanisms underlying sweet taste control in this population and offers a theoretical foundation for using aerobic exercise to repair brain damage caused by tobacco dependence.

Declarations

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contribution

H.L.: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Roles/Writing - original draft. Y.H.: Conceptualization, Formal analysis, Supervision. W.L., L.Z., Y.Z.: Writing - review & editing. P.S.: Collected data. H.F.: Visualization. Z.X.: Funding acquisition, Project administration, Resources, Supervision. All authors have read and agreed to the published version of the manuscript.

Acknowledgments

We would like to thank all participating research staff who agreed to contribute to the data collection.

Data Availability

All data generated or analyzed during this study are presented in the manuscript. Please contact the corresponding author for access to data presented in this study.

References

1. Bruijnzeel, A. W. *et al.* Effects in rats of adolescent exposure to cannabis smoke or THC on emotional behavior and cognitive function in adulthood. Psychopharmacology 236, 2773–2784, doi:10.1007/s00213-019-05255-7 (2019).

2. Le Foll, B. *et al.* Tobacco and nicotine use. Nature reviews. Disease primers 8, 19, doi:10.1038/s41572-022-00346-w (2022).
3. Cheung, Y. T. *et al.* Brief handgrip and isometric exercise intervention for smoking cessation: A pilot randomized trial. Addictive behaviors 100, 106119, doi:10.1016/j.addbeh.2019.106119 (2020).
4. Sanchez, V. *et al.* Exercise during abstinence normalizes ultrastructural synaptic plasticity associated with nicotine-seeking following extended access self-administration. The European journal of neuroscience 50, 2707–2721, doi:10.1111/ejn.14408 (2019).
5. Taylor, A. H., Ussher, M. H. & Faulkner, G. The acute effects of exercise on cigarette cravings, withdrawal symptoms, affect and smoking behaviour: a systematic review. Addiction (Abingdon, England) 102, 534–543, doi:10.1111/j.1360-0443.2006.01739.x (2007).
6. Janse Van Rensburg, K., Taylor, A., Hodgson, T. & Benattayallah, A. Acute exercise modulates cigarette cravings and brain activation in response to smoking-related images: an fMRI study. Psychopharmacology 203, 589–598, doi:10.1007/s00213-008-1405-3 (2009).
7. Sutoo, D. & Akiyama, K. Regulation of brain function by exercise. Neurobiol Dis 13, 1–14, doi:10.1016/s0969-9961(03)00030-5 (2003).
8. Janse Van Rensburg, K. & Taylor, A. H. The effects of acute exercise on cognitive functioning and cigarette cravings during temporary abstinence from smoking. Hum Psychopharmacol 23, 193–199, doi:10.1002/hup.925 (2008).
9. Zhou, Y., Li, C., Li, R. & Zhou, C. Exercise improves nicotine reward-associated cognitive behaviors and related α7 nAChR-mediated signal transduction in adolescent rats. Journal of cellular physiology 233, 5756–5767, doi:10.1002/jcp.26295 (2018).
10. De Jesus, S. & Prapavessis, H. Smoking behaviour and sensations during the pre-quit period of an exercise-aided smoking cessation intervention. Addictive behaviors 81, 143–149, doi:10.1016/j.addbeh.2018.01.035 (2018).
11. Everson-Hock, E. S., Taylor, A. H. & Ussher, M. Readiness to use physical activity as a smoking cessation aid: a multiple behaviour change application of the Transtheoretical Model among quitters attending Stop Smoking Clinics. Patient education and counseling 79, 156–159, doi:10.1016/j.pec.2009.09.016 (2010).
12. Linke, S. E. & Ussher, M. Exercise-based treatments for substance use disorders: evidence, theory, and practicality. The American journal of drug and alcohol abuse 41, 7–15, doi:10.3109/00952990.2014.976708 (2015).
13. Liu, H., Zhang, Y., Zhang, S. & Xu, Z. Effects of acute aerobic exercise on food-reward mechanisms in smoking-addicted individuals: An fNIRS study. Physiology & behavior 254, 113889, doi:10.1016/j.physbeh.2022.113889 (2022).
14. Ussher, M. H., Faulkner, G. E. J., Angus, K., Hartmann-Boyce, J. & Taylor, A. H. Exercise interventions for smoking cessation. The Cochrane database of systematic reviews 2019, CD002295, doi:10.1002/14651858.CD002295.pub6 (2019).

15. Zhou, Y. *et al.* Effects of moderate- and high-intensity acute aerobic exercise on food reward and appetite in individuals with methamphetamine dependence. Physiol Behav 211, 112649, doi:10.1016/j.physbeh.2019.112649 (2019).
16. Audiffren, M., Tomporowski, P. D. & Zagrodnik, J. Acute aerobic exercise and information processing: energizing motor processes during a choice reaction time task. Acta psychologica 129, 410–419, doi:10.1016/j.actpsy.2008.09.006 (2008).
17. Schultz, W. Neuronal Reward and Decision Signals: From Theories to Data. Physiological reviews 95, 853–951, doi:10.1152/physrev.00023.2014 (2015).
18. Feltenstein, M. W. & See, R. E. The neurocircuitry of addiction: an overview. British journal of pharmacology 154, 261–274, doi:10.1038/bjp.2008.51 (2008).
19. Green, A. *et al.* Opiate agonists and antagonists modulate taste perception in opiate-maintained and recently detoxified subjects. Journal of psychopharmacology (Oxford, England) 27, 265–275, doi:10.1177/0269881112472567 (2013).
20. Negus, S. S. & Banks, M. L. Medications development for opioid abuse. *Cold Spring Harbor perspectives in medicine* 3, a012104, doi:10.1101/cshperspect.a012104 (2013).
21. Rubinstein, M. L., Luks, T. L., Dryden, W. Y., Rait, M. A. & Simpson, G. V. Adolescent smokers show decreased brain responses to pleasurable food images compared with nonsmokers. Nicotine & tobacco research: official journal of the Society for Research on Nicotine and Tobacco 13, 751–755, doi:10.1093/ntr/ntr046 (2011).
22. Garfield, J. B. B. & Lubman, D. I. Associations between opioid dependence and sweet taste preference. Psychopharmacology (Berl) 238, 1473–1484, doi:10.1007/s00213-021-05774-2 (2021).
23. Mason, T. B., Dolgon-Krutolow, A., Smith, K. E. & Leventhal, A. M. Body Dissatisfaction and Binge Eating: The Moderating Roles of Sweet Taste Reward Sensitivity and Dietary Restraint among Tobacco Product Users. International journal of environmental research and public health 19, 15523, doi:10.3390/ijerph192315523 (2022).
24. Pepino, M. Y. & Mennella, J. A. Effects of cigarette smoking and family history of alcoholism on sweet taste perception and food cravings in women. Alcohol Clin Exp Res 31, 1891–1899, doi:10.1111/j.1530-0277.2007.00519.x (2007).
25. Mouillot, T. *et al.* Taste Perception and Cerebral Activity in the Human Gustatory Cortex Induced by Glucose, Fructose, and Sucrose Solutions. Chemical senses 44, 435–447, doi:10.1093/chemse/bjz034 (2019).
26. Nakajima, K. I. Neural insights into sweet taste transduction and hunger-induced taste modification in mice. Bioscience, biotechnology, and biochemistry 86, 1485–1489, doi:10.1093/bbb/zbac142 (2022).
27. Yeung, A. W. K., Goto, T. K. & Leung, W. K. Basic taste processing recruits bilateral anteroventral and middle dorsal insulae: An activation likelihood estimation meta-analysis of fMRI studies. Brain and behavior 7, e00655, doi:10.1002/brb3.655 (2017).

28. Van Opstal, A. M. *et al.* Brain activity and connectivity changes in response to nutritive natural sugars, non-nutritive natural sugar replacements and artificial sweeteners. Nutritional neuroscience 24, 395–405, doi:10.1080/1028415x.2019.1639306 (2021).
29. Uematsu, A., Kitamura, A., Iwatsuki, K., Uneyama, H. & Tsurugizawa, T. Correlation Between Activation of the Prelimbic Cortex, Basolateral Amygdala, and Agranular Insular Cortex During Taste Memory Formation. *Cerebral cortex (New York, N.Y.*: 1991) 25, 2719–2728, doi:10.1093/cercor/bhu069 (2015).
30. Zhou, Y. *et al.* Effects of Acute Dance and Aerobic Exercise on Drug Craving and Food Reward in Women with Methamphetamine Dependence. Medicine and science in sports and exercise 53, 2245–2253, doi:10.1249/mss.0000000000002723 (2021).
31. Gellish, R. L. *et al.* Longitudinal modeling of the relationship between age and maximal heart rate. Medicine and science in sports and exercise 39, 822–829, doi:10.1097/mss.0b013e31803349c6 (2007).
32. Killgore, W. D. *et al.* Cortical and limbic activation during viewing of high- versus low-calorie foods. NeuroImage 19, 1381–1394, doi:10.1016/s1053-8119(03)00191-5 (2003).
33. Strangman, G., Culver, J. P., Thompson, J. H. & Boas, D. A. A quantitative comparison of simultaneous BOLD fMRI and NIRS recordings during functional brain activation. NeuroImage 17, 719–731 (2002).
34. Cohen, J. Statistical power analysis for the behavioral sciences. Computers, Environment and Urban Systems 14, 71, doi:10.1016/0198-9715(90)90050-4 (1990).
35. Kroemer, N. B. *et al.* Sweet taste potentiates the reinforcing effects of e-cigarettes. European neuropsychopharmacology: the journal of the European College of Neuropsychopharmacology 28, 1089–1102, doi:10.1016/j.euroneuro.2018.07.102 (2018).
36. Da Ré, A. F. *et al.* Tobacco Influence on Taste and Smell: Systematic Review of the Literature. International archives of otorhinolaryngology 22, 81–87, doi:10.1055/s-0036-1597921 (2018).
37. Trius-Soler, M., Santillán-Alarcón, D. A., Martínez-Huélamo, M., Lamuela-Raventós, R. M. & Moreno, J. J. Effect of physiological factors, pathologies, and acquired habits on the sweet taste threshold: A systematic review and meta-analysis. Comprehensive reviews in food science and food safety 19, 3755–3773, doi:10.1111/1541-4337.12643 (2020).
38. Church, T. Exercise in obesity, metabolic syndrome, and diabetes. Progress in cardiovascular diseases 53, 412–418, doi:10.1016/j.pcad.2011.03.013 (2011).
39. Lutter, M. & Nestler, E. J. Homeostatic and hedonic signals interact in the regulation of food intake. The Journal of nutrition 139, 629–632, doi:10.3945/jn.108.097618 (2009).
40. Mathieu, M. E., Reid, R. E. R. & King, N. A. Sensory Profile of Adults with Reduced Food Intake and the Potential Roles of Nutrition and Physical Activity Interventions. Advances in nutrition (Bethesda, Md.) 10, 1120–1125, doi:10.1093/advances/nmz044 (2019).
41. Malik, S., McGlone, F., Bedrossian, D. & Dagher, A. Ghrelin modulates brain activity in areas that control appetitive behavior. Cell metabolism 7, 400–409, doi:10.1016/j.cmet.2008.03.007 (2008).

42. Avery, J. A., Liu, A. G., Ingeholm, J. E., Gotts, S. J. & Martin, A. Viewing images of foods evokes taste quality-specific activity in gustatory insular cortex. Proceedings of the National Academy of Sciences of the United States of America 118, e2010932118, doi:10.1073/pnas.2010932118 (2021).
43. Rolls, E. T. The orbitofrontal cortex and reward. *Cerebral cortex (New York, N.Y.*: 1991) 10, 284–294, doi:10.1093/cercor/10.3.284 (2000).
44. Critchley, H. D. & Rolls, E. T. Hunger and satiety modify the responses of olfactory and visual neurons in the primate orbitofrontal cortex. Journal of neurophysiology 75, 1673–1686, doi:10.1152/jn.1996.75.4.1673 (1996).
45. Rolls, E. T. The neural control of feeding in primates. Neurophysiology of Ingestion 6, 137–169, doi:10.1016/B978-0-08-041988-6.50013-4 (1993).
46. Camus, M. *et al.* Repetitive transcranial magnetic stimulation over the right dorsolateral prefrontal cortex decreases valuations during food choices. The European journal of neuroscience 30, 1980–1988, doi:10.1111/j.1460-9568.2009.06991.x (2009).
47. Pelchat, M. L., Johnson, A., Chan, R., Valdez, J. & Ragland, J. D. Images of desire: food-craving activation during fMRI. *NeuroImage* 23, 1486–1493, doi:10.1016/j.neuroimage.2004.08.023 (2004).
48. Volkow, N. D. & Baler, R. D. NOW vs LATER brain circuits: implications for obesity and addiction. Trends in neurosciences 38, 345–352, doi:10.1016/j.tins.2015.04.002 (2015).
49. Tangney, J. P., Baumeister, R. F. & Boone, A. L. High self-control predicts good adjustment, less pathology, better grades, and interpersonal success. Journal of personality 72, 271–324, doi:10.1111/j.0022-3506.2004.00263.x (2004).
50. Telzer, E. H., Masten, C. L., Berkman, E. T., Lieberman, M. D. & Fuligni, A. J. Neural regions associated with self control and mentalizing are recruited during prosocial behaviors towards the family. NeuroImage 58, 242–249, doi:10.1016/j.neuroimage.2011.06.013 (2011).
51. Lapenta, O. M., Sierve, K. D., de Macedo, E. C., Fregni, F. & Boggio, P. S. Transcranial direct current stimulation modulates ERP-indexed inhibitory control and reduces food consumption. Appetite 83, 42–48, doi:10.1016/j.appet.2014.08.005 (2014).
52. Gluck, M. E., Viswanath, P. & Stinson, E. J. Obesity, Appetite, and the Prefrontal Cortex. Current obesity reports 6, 380–388, doi:10.1007/s13679-017-0289-0 (2017).
53. Volkow, N. D., Wang, G. J., Tomasi, D. & Baler, R. D. Obesity and addiction: neurobiological overlaps. Obesity reviews: an official journal of the International Association for the Study of Obesity 14, 2–18, doi:10.1111/j.1467-789X.2012.01031.x (2013).
54. Steinbeis, N., Haushofer, J., Fehr, E. & Singer, T. Development of Behavioral Control and Associated vmPFC-DLPFC Connectivity Explains Children's Increased Resistance to Temptation in Intertemporal Choice. *Cerebral cortex (New York, N.Y.*: 1991) 26, 32–42, doi:10.1093/cercor/bhu167 (2016).
55. Peters, J. & D'Esposito, M. Effects of Medial Orbitofrontal Cortex Lesions on Self-Control in Intertemporal Choice. Current biology: CB 26, 2625–2628, doi:10.1016/j.cub.2016.07.035 (2016).
56. Crézé, C. *et al.* The Impact of Caloric and Non-Caloric Sweeteners on Food Intake and Brain Responses to Food: A Randomized Crossover Controlled Trial in Healthy Humans. *Nutrients* 10,

doi:10.3390/nu10050615 (2018).

57. Boecker, H. *et al.* The runner's high: opioidergic mechanisms in the human brain. *Cerebral cortex (New York, N.Y.*: 1991) 18, 2523–2531, doi:10.1093/cercor/bhn013 (2008).
58. Robison, L. S., Swenson, S., Hamilton, J. & Thanos, P. K. Exercise Reduces Dopamine D1R and Increases D2R in Rats: Implications for Addiction. Medicine and science in sports and exercise 50, 1596–1602, doi:10.1249/mss.0000000000001627 (2018).
59. Rhodes, J. S. *et al.* Exercise increases hippocampal neurogenesis to high levels but does not improve spatial learning in mice bred for increased voluntary wheel running. Behavioral neuroscience 117, 1006–1016, doi:10.1037/0735-7044.117.5.1006 (2003).
60. Albaladejo-García, C., García-Aguilar, F. & Moreno, F. J. The role of inhibitory control in sport performance: Systematic review and meta-analysis in stop-signal paradigm. Neuroscience and biobehavioral reviews 147, 105108, doi:10.1016/j.neubiorev.2023.105108 (2023).
61. Thackray, A. E. & Stensel, D. J. The impact of acute exercise on appetite control: Current insights and future perspectives. Appetite 186, 106557, doi:https://doi.org/10.1016/j.appet.2023.106557 (2023).
62. Talukdar, T. *et al.* Aerobic Fitness Explains Individual Differences in the Functional Brain Connectome of Healthy Young Adults. *Cerebral cortex (New York, N.Y.*: 1991) 28, 3600–3609, doi:10.1093/cercor/bhx232 (2018).

Figures

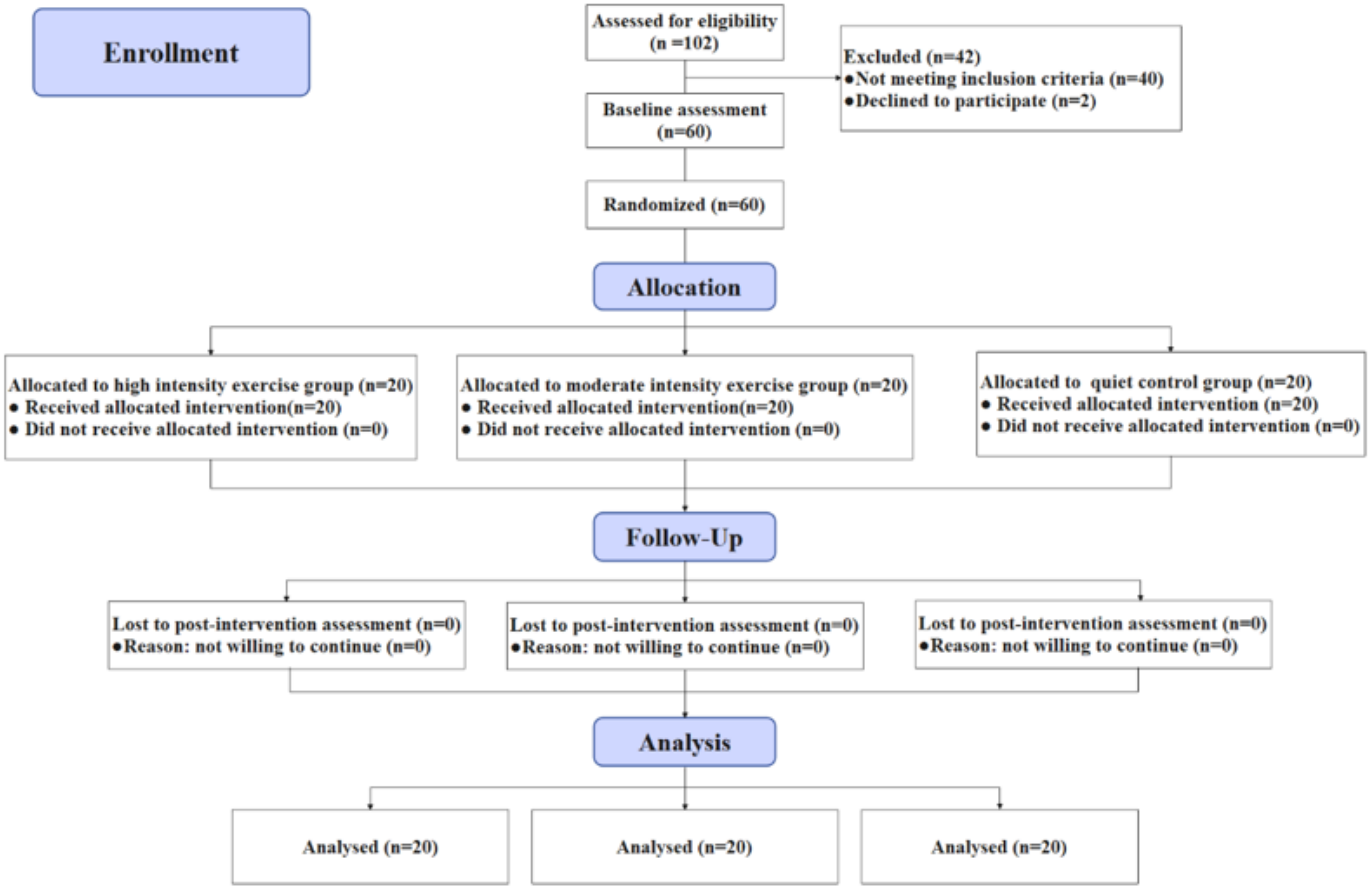

Figure 1

Schematic diagram of study design.

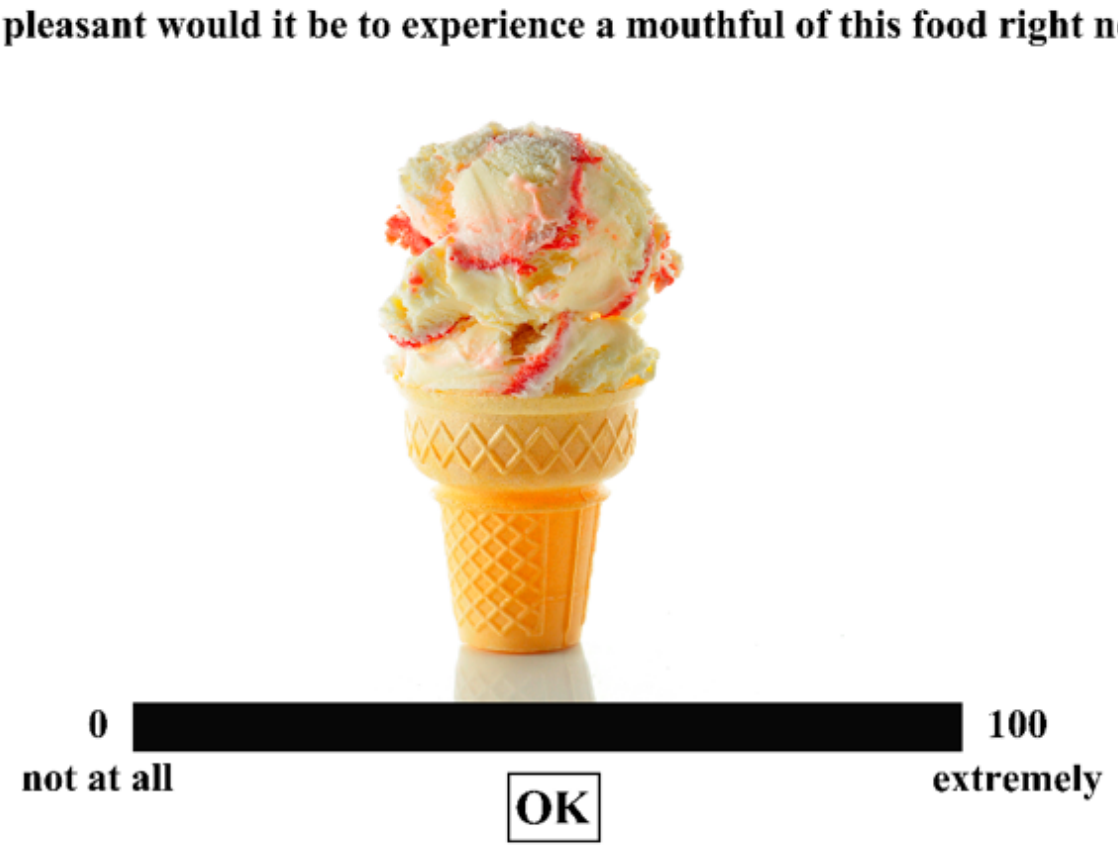

Figure 2

VAS sweet taste preference test

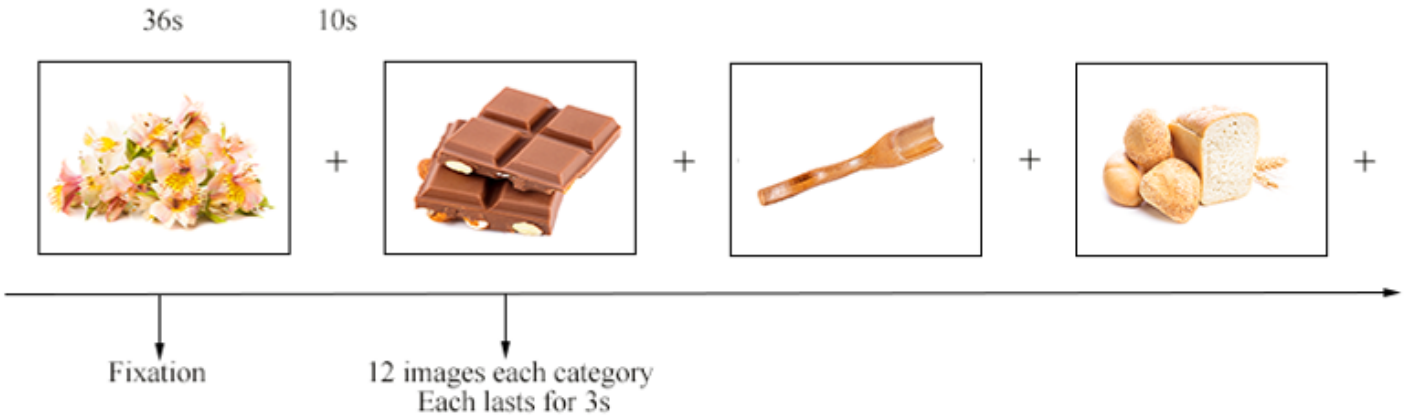

Figure 3

Food pictures fNIRS task

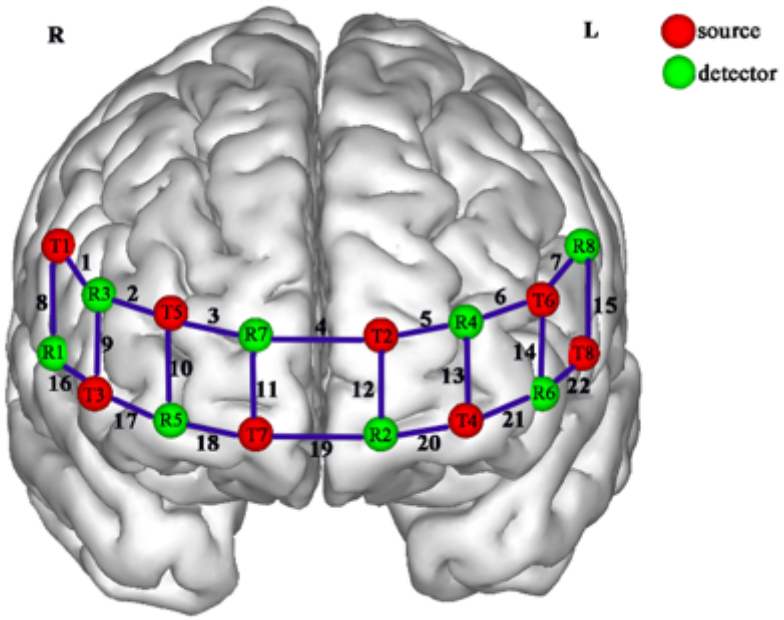

Figure 4

PFC channel layout (front view)

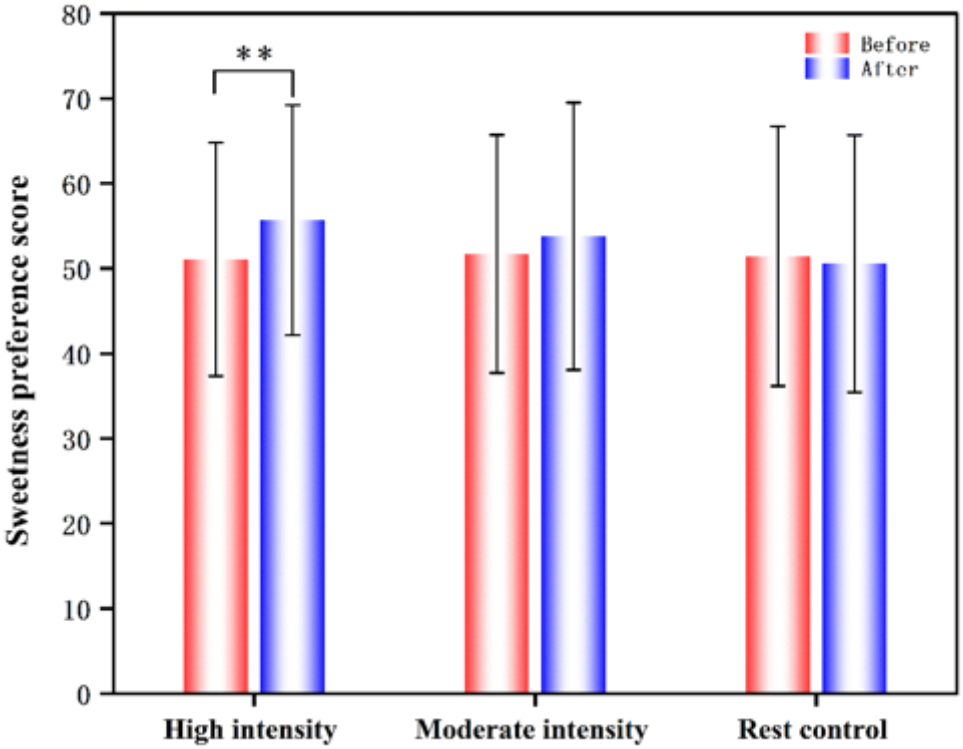

Figure 5

Low sweetness preference score before and after the test (**$P < 0.01$)

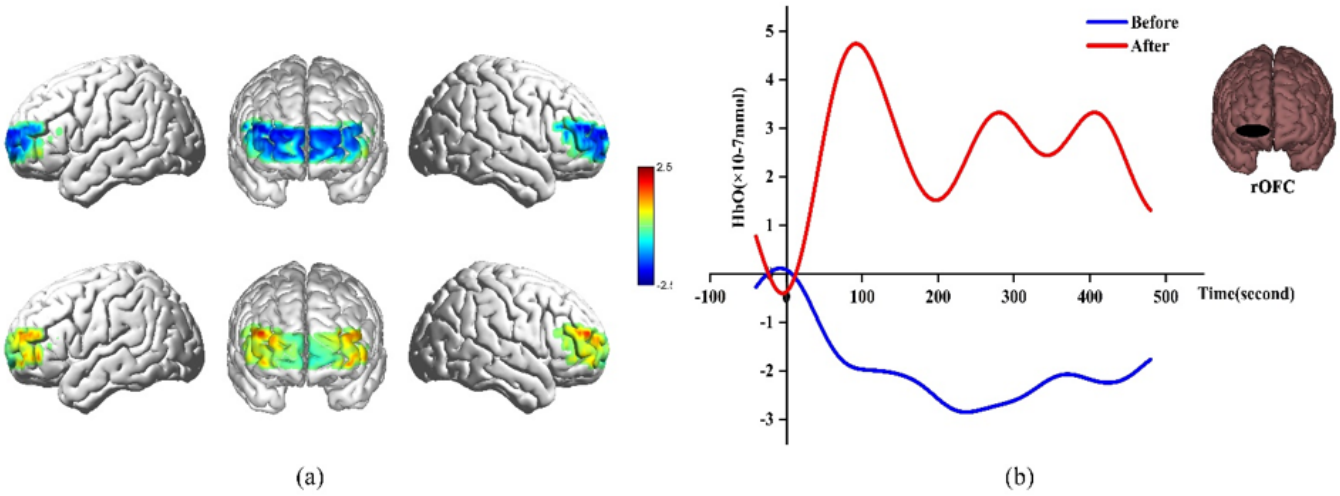

Figure 6

The changes in HbO concentration in each brain region of the prefrontal lobe before and after the intervention in the moderate-intensity exercise group when observing low sweet food pictures (a) and the trend of HbO concentration in rOFC before and after exercise (b)

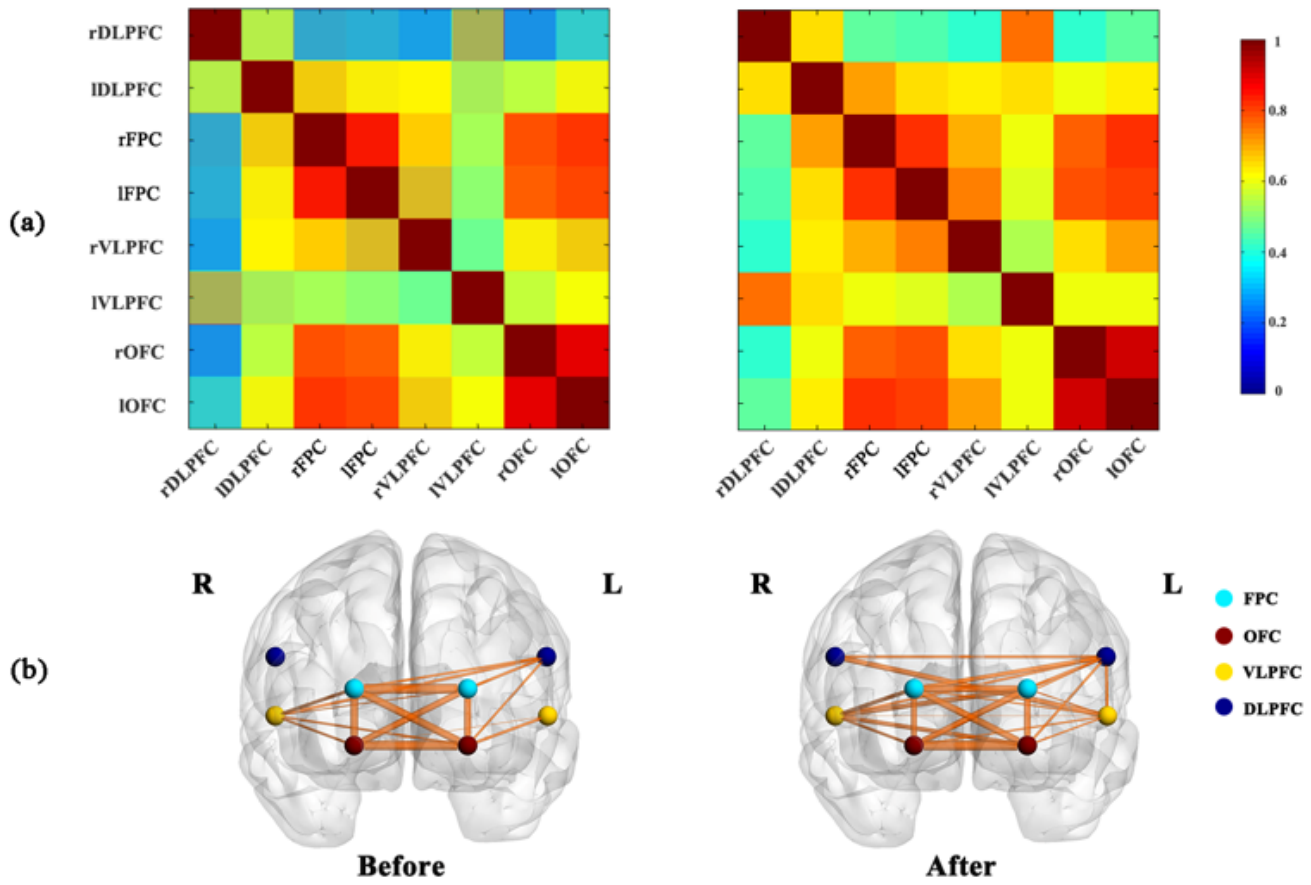

Figure 7

The changes in the functional connectivity matrix of ROIs (a) and the functional connectivity intensity between ROIs (b) before and after the intervention in the moderate-intensity exercise group when observing low sweet food pictures. The line represents correlations between brain regions, and the thicker the line, the stronger the correlation.