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Regional gray matter volume associated with exercise dependence: A voxel-based morphometry study

Feifei Zhang[1] | Song Wang[1,2,3] | Yang Feng[1] | Kun Qin[1] | Huiru Li[1] | Baolin Wu[1] | Zhiyun Jia[1,4] | Qiyong Gong[1,2,4]

[1]Huaxi MR Research Center (HMRRC), Department of Radiology, West China Hospital of Sichuan University, Chengdu, China

[2]Department of Psychoradiology, Chengdu Mental Health Center, Chengdu, China

[3]Research Unit of Psychoradiology, Chinese Academy of Medical Sciences, Chengdu, China

[4]Department of Nuclear Medicine, West China Hospital of Sichuan University, Chengdu, China

Correspondence
Zhiyun Jia, Department of Nuclear Medicine, West China Hospital of Sichuan University, No. 37 Guo Xue Xiang, Chengdu, Sichuan 610041, China.
Email: zhiyunjia@hotmail.com

Qiyong Gong, Huaxi MR Research Center (HMRRC), Department of Radiology, West China Hospital of Sichuan University, Chengdu 610041, China.
Email: qiyonggong@hmrrc.org.cn

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Abstract

Although regular physical exercise has multiple positive benefits for the general population, excessive exercise may lead to exercise dependence (EXD), which is harmful to one's physical and mental health. Increasing evidence suggests that stress is a potential risk factor for the onset and development of EXD. However, little is known about the neural substrates of EXD and the underlying neuropsychological mechanism by which stress affects EXD. Herein, we investigate these issues in 86 individuals who exercise regularly by estimating their cortical gray matter volume (GMV) utilizing a voxel-based morphometry method based on structural magnetic resonance imaging. Whole-brain correlation analyses and prediction analyses showed negative relationships between EXD and GMV of the right orbitofrontal cortex (OFC), left subgenual cingulate gyrus (sgCG), and left inferior parietal lobe (IPL). Furthermore, mediation analyses found that the GMV of the right OFC was an important mediator between stress and EXD. Importantly, these results remained significant even when adjusting for sex, age, body mass index, family socioeconomic status, general intelligence and total intracranial volume, as well as depression and anxiety. Collectively, the results of the present study provide crucial evidence of the neuroanatomical basis of EXD and reveal a potential neuropsychological pathway in predicting EXD in which GMV mediates the relationship between stress and EXD.

KEYWORDS
exercise dependence, mental health, stress, structural magnetic resonance imaging, voxel-based morphometry

1 | INTRODUCTION

Regular physical exercise has multiple positive benefits in both mental and physical aspects (Biddle, 2016; Morgan, 1985). However, excessive physical exercise can lead to other problems known as exercise dependence (EXD) or exercise addiction (Landolfi, 2013). EXD is a desire for physical activity in leisure time, which leads to uncontrollable excessive exercise behavior and is manifested by physical and/or psychological symptoms (de Coverley Veale, 1987; Hausenblas & Symons Downs, 2002). Similar to other addicts, dependent exercisers experience withdrawal symptoms, including increased anxiety, depression, and impaired sleep (Lichtenstein, Christiansen, Bilenberg, &

Feifei Zhang and Song Wang contributed equally to this work.

Støving, 2014; Lichtenstein, Nielsen, Gudex, Hinze, & Jørgensen, 2018). In addition, there is great evidence that EXD leads to bodily pain, such as muscle injury, and worsening relationships with family and colleagues (Landolfi, 2013; Lichtenstein et al., 2014). Although EXD is not currently listed as an addiction disorder in the Diagnostic and Statistical Manual of Mental Diseases (DSM)-5 and there are no specific criteria for diagnosis (American Psychiatric Association, 2013), a large number of behavioral studies have classified EXD as a kind of behavioral addiction (Hausenblas & Symons Downs, 2002; Landolfi, 2013). The most commonly used measurement of EXD is the Exercise Dependence Scale-Revised (EDS-R), which is used to evaluate the symptoms and risk of EXD in subjects who participated in routine exercise (Downs, Hausenblas, & Nigg, 2004). It has been reported that the prevalence of risk for EXD is 3–7% in regular exercisers and university students and 6–9% in athletes (Marques et al., 2019). EDS-R is based on the diagnostic criteria of substance addiction in the DSM and has good recognition ability for this abnormal behavior pattern (Hausenblas & Symons Downs, 2002), yet it is worth noting that the EDS-R has no diagnostic effect (Griffiths, Szabo, & Terry, 2005). Due to the high prevalence and physical and psychological harmfulness of EXD, the main purpose of the present study was to explore the relationship between symptoms of EXD and the brain structure using the EDS-R.

Although behavioral studies on EXD have gained considerable attention in recent years (Hausenblas, Schreiber, & Smoliga, 2017; Landolfi, 2013), to the best of our knowledge, no study has directly investigated the neural substrates of EXD. However, a battery of previous studies has examined the relationship between the brain and EXD-related constructs. Many studies have indicated that the effects of exercise are largely related to the neurobiology of the reward-related system, which includes learning, motivation, emotion, and decision-making (Sutherland, McHugh, Pariyadath, & Stein, 2012), and different functions are closely related to different brain regions. The orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) are mainly involved in reward-related executive control, motivation, and decision-making (Boecker et al., 2008; Goldstein & Volkow, 2002) and the striatum is related to learning in the rewarding process (O'Doherty et al., 2004). In addition, the amygdala, thalamus, and other brain regions are the key components in regulating the rewarding process (Haber & Knutson, 2010). Amygdala is mainly involved in negative emotion processing and can promote reward behavior by eliminating fear memory (Zhang, Kim, & Tonegawa, 2020). Thalamus is an important component of arousal, which is related to reward expectation (Anders, Lotze, Erb, Grodd, & Birbaumer, 2004; Le, Zhang, Zhornitsky, Wang, & Li, 2020). On the one hand, these regions have been reported in exercise studies. During cycling exercise, compared with the rest, the activation of cognitive-related areas, including the ACC and OFC, showed reduced activation during the entire exercise state (Fontes et al., 2020). In addition, another running study found that the excitability of subjects increased significantly after running, but the availability of opioid receptors in the prefrontal cortex (PFC) decreased, indicating that the increase in pleasure level correlated negatively with opioid binding in the PFC/OFC and ACC (Boecker et al., 2008). A population-based study also reported that increased gray matter volume (GMV) of the ACC and hippocampus is associated with exercise (Jochem et al., 2017). However, the effect was different in the elderly and young (Hamer, Sharma, & Batty, 2018). Exercise has protective effects on the PFC in elderly individuals (Northey et al., 2020) and negative effects on the ACC and the PFC in young adults (Ruotsalainen et al., 2019; Tarkka et al., 2019). In conclusion, a large number of studies have shown that exercise may cause structural changes in the PFC, leading to the weakening of prefrontal top-down executive control (Miller & Cohen, 2001) in which inhibitory control is suspended and stimulus-driven behavior is emphasized. On the other hand, evidence from studies on addiction suggests that the structure and function of reward-related regions (e.g., the ACC, OFC, thalamus, and amygdala) are crucial for the onset and development of addiction behavior (Hammond, Allick, Rahman, & Nanavati, 2019; Qin et al., 2020; Tuulari et al., 2018; Zhou et al., 2019). Specifically, a recent meta-analysis of behavior addiction reported GMV atrophy in reward-related regions such as the ACC and OFC (Qin et al., 2020). Meanwhile, a systematic review reported that brain activation of the ACC and inferior frontal gyrus is related to addictive disorders (Hammond et al., 2019). Based on the above findings, EXD may be linked with reward-related regions, such as the OFC, ACC, amygdala, thalamus, and striatum. Given that no studies have examined the structural brain correlates of EXD, the first goal of the present study was to explore the association of EXD symptoms with gray matter structures among a sample of regularly exercised healthy adults based on structural magnetic resonance imaging (sMRI).

Considering the harmful influence of EXD on a person's physical and mental health (de Coverley Veale, 1987; Hausenblas & Symons Downs, 2002; Lichtenstein et al., 2014; Lichtenstein et al., 2018), it is important to determine reliable psychosocial predictors of EXD to formulate corresponding prevention strategies and intervention measures to reduce EXD. Evidence from extensive studies suggests that stress may be one of the psychosocial factors affecting the onset and development of EXD (Lichtenstein et al., 2018). According to previous reports, individuals experiencing EXD often see exercise as a positive way to relieve stress (Schuch et al., 2019; Szabo, 1995); as this is effective, they rely on exercise to release stress every time and will constantly increase their exercise to obtain greater pleasure (Landolfi, 2013), which may lead to uncontrolled exercise addiction (de Coverley Veale, 1987; Ruisoto & Contador, 2019). This process may in some way support the idea that stress plays a role in developing addictions (Ruisoto & Contador, 2019) and in addiction relapse (Sharp, 2017; Sinha & Jastreboff, 2013). There is evidence of significantly higher emotional stress in high-risk exercise addiction participants compared with low-risk participants (Lichtenstein et al., 2018). On the other hand, numerous studies have suggested that stress affects brain regions in the reward pathway to promote addictive behaviors (Sinha & Jastreboff, 2013). The stress response is initiated through the amygdala and regulated through negative feedback from glucocorticoids to the hippocampus, OFC, and medial PFC, (McEwen, 2007) and these regions regulate reward processes (Dias-Ferreira et al., 2009). Given these findings, the second goal of the

present study was to elucidate the potential neuropsychological mechanism of how stress affects EXD through gray matter structures.

To achieve these goals, each participant underwent sMRI scanning and completed standard measurements of EXD and stress. In this study, the voxel-based morphometry (VBM) approach was employed to estimate cortical GMV (Ashburner & Friston, 2000). As a well-validated method, the VBM approach has been widely used to examine the structural neural markers of individual differences in cognition, personality, and social behaviors (Pan et al., 2021; Wang et al., 2017; Wang, Zhao, et al., 2018). First, whole-brain correlation analyses and prediction analyses were performed to identify the brain regions linked with EXD. In light of previous findings on the neural bases of EXD-related constructs (Boecker et al., 2008; Esch & Stefano, 2010; Fontes et al., 2020; Hammond et al., 2019; Qin et al., 2020; Tuulari et al., 2018; Zhou et al., 2019), we hypothesized that the GMV in reward-related regions (e.g., OFC, ACC, amygdala, thalamus, and striatum) is related to EXD. Second, correlation analyses and mediation analyses were conducted to probe the relations among stress, EXD, and GMV. Given the effects of stress on the brain (Boecker et al., 2008; Dias-Ferreira et al., 2009; McEwen, 2007; Sinha & Jastreboff, 2013) and EXD (Lichtenstein et al., 2018; Ruisoto & Contador, 2019; Schuch et al., 2019; Szabo, 1995), we further speculated that some brain regions related to EXD are linked to stress and that there is a mediation mechanism in which stress affects EXD through GMV. Finally, supplemental analyses with depression and anxiety as additional covariates were performed to assess the specificity of the findings.

2 | METHODS

2.1 | Participants and procedures

This study was approved by the Ethics Committee of the West China Hospital of Sichuan University. All participants were recruited through electronic advertising in universities and gymnasiums. Each subject provided written informed consent. The inclusion criteria were as follows: participating in regular exercise (exercise at least twice a week for at least 30 min each time for a minimum of 3 months; Nomura, Ishiguro, Ohira, & Ikeda, 2018; O'Donovan, Lee, Hamer, & Stamatakis, 2017) considered to have the symptoms of EXD according to the EDS-R score; (Downs et al., 2004; Hausenblas & Downs, 2002) being right-handed; being a native Mandarin Chinese speaker; and being between 18 and 50 years of age. The exclusion criteria were as follows: eating disorders, such as anorexia nervosa or bulimia nervosa; a history of physical or psychiatric disorders; a history of current or ongoing serious medical problems; claustrophobia; and any contraindications for MRI scan. Power analysis using G-Power software (Faul, Erdfelder, Lang, & Buchner, 2007) showed that at least 84 participants were needed to detect medium-sized effects ($r = .3$, $\alpha = .05$, $1 - \beta = .80$) for correlation-based analysis (King, 2019; Kong, Zhao, You, & Xiang, 2019). Thus, a total of 86 adult participants were finally recruited in the present study (46 males, mean age = 22.3 ± 3.6 years, range 18–41 years). First, behavioral assessment for the risk of EXD and the levels of stress, depression, and anxiety, and demographic information such as family socioeconomic status (SES), general intelligence, handedness, age, sex, height, and weight were evaluated by self-reported measurements. Body mass index (BMI) was calculated from self-reported height and weight according to the Adolphe Quetelet formula: body weight (kg)/height (m^2). Then, each subject underwent MRI scanning, which was completed by a professional radiologist.

2.2 | Behavioral measures

2.2.1 | EDS-R

We adopted the EDS-R (Downs et al., 2004) to measure an individual's risk of being addicted to exercise. The EDS-R is a multidimensional measurement with 21 items across 7 aspects, including tolerance, withdrawal, intention, lack of control, exercise time, reduction in other activities, and continuance (Downs et al., 2004; Hausenblas & Downs, 2002). The participants were asked to indicate how each item reflected their current sports beliefs and behaviors in the past 3 months, with a 6-point Likert scale ranging from 1 (never) to 6 (always). The total score of all items represents the EDS-R score, and a higher score indicates a stronger prevalence of EXD symptoms. Previous studies have revealed that the EDS-R shows acceptable internal reliability (Cronbach's α ranged from .78 to .92) and test–retest reliability ($R = .95$, 7 days; Downs et al., 2004; Weik & Hale, 2009). The Chinese version of the EDS has shown adequate reliability and validity among regularly exercised Chinese residents (Lu et al., 2012). In the present sample, the Cronbach's α for the EDS-R was .83, indicating adequate internal reliability.

2.2.2 | Depression, anxiety, and stress scale (DASS)

The DASS is a widely used instrument for assessing the severity of three negative emotional syndromes in clinical and nonclinical samples and shows a high distinction among depression, anxiety, and stress (Lovibond & Lovibond, 1995; Norton, 2007). We used the stress subscale of the DASS (Lovibond & Lovibond, 1995) to evaluate the stress symptoms of the participants. According to previous studies, anxiety and depression are not only associated with EXD (Lichtenstein et al., 2014; Lichtenstein et al., 2018), but also have a significant effect on gray matter structure (Chen et al., 2020; Prange et al., 2019). To test the specificity of the association between stress, EXD, and GMV, we used the other two subscales of the DASS to evaluate the levels of depression and anxiety. The DASS is a 4-point Likert-type self-report questionnaire with response options ranging from 0 (not at all) to 3 (applied very much). The scores of each subscale were obtained by calculating the responses to the corresponding items, and higher scores indicate more negative experiences in the past week. The

Chinese version of the DASS has been proven to have satisfactory psychometric properties among different populations (Chan et al., 2012; Jiang et al., 2020). In the present study, the internal reliability of the DASS was adequate, with a Cronbach's $\alpha = .84$.

2.2.3 | Family SES scale

Considering the potential effects of SES on gray matter structures (Brito & Noble, 2014; Yaple & Yu, 2020), we adopted the subjective SES scale to eliminate the possible impact of family SES on the association between EXD and GMV. Family SES evaluates the SES of participants' parents in terms of education, occupational prestige, and income (Adler, Epel, Castellazzo, & Ickovics, 2000). The scale includes a 10-step ladder chart, and the subjects are asked to indicate the overall level of SES of their parents in the local society, ranging from 1 (bottom) to 10 (top) (Adler et al., 2000). There is increasing evidence showing that the SES scale is a better predictor of health-related outcomes than objective measures (Cundiff & Matthews, 2017). The scale has also been widely used in the Chinese population (Hu, Adler, Goldman, Weinstein, & Seeman, 2005; Kong, Wang, Hu, & Liu, 2015).

2.2.4 | Brief Raven's advanced progressive matrix (RAPM)

Numerous studies have proven that general intelligence is associated with gray matter structures (Basten, Hilger, & Fiebach, 2015). To exclude the possible influence of general intelligence on the relation between GMV and EXD, we used a brief-RAPM (Bors & Stokes, 1998) with 12 nonverbal items to evaluate general intelligence. Participants were shown a matrix of pictures with missing parts, asked to select the missing parts from eight options and to complete all tests within 15 min (Bors & Stokes, 1998). The total number of correct answers was used as the general intelligence score for each participant. In the present sample, the Cronbach's α of the RAPM was .78, indicating adequate internal reliability.

2.3 | MRI data acquisition and preprocessing

2.3.1 | Data acquisition

The MRI scan was performed using a Siemens 3.0 Tesla system (Tim Trio, Siemens Healthineers, Erlangen, Germany) with an eight-channel head coil at West China Hospital of Sichuan University, Chengdu, China. High-resolution T1-weighted anatomical images were obtained using a rapid gradient-echo planar imaging sequence with acquisition parameters of repetition time = 1.96 s, echo time = 2.26 ms, flip angle = 90°, contiguous slices = 176 with a thickness of 1 mm each, matrix = 256 × 256, and field of view = 240 mm × 240 mm.

2.3.2 | Data preprocessing

Image analysis was performed in MATLAB (r2013b) using an automated Computational Anatomy Toolbox (CAT12, http://dbm.neuro.uni-jena.de/cat12/) based on Statistical Parametric Mapping (SPM12, Welcome Department of Imaging Neuroscience, London, UK). First, for better registration, we manually reoriented the image to the anterior commissure in SPM12. Second, the high-resolution structure images were segmented into gray matter, white matter, cerebrospinal fluid, bone, nonbrain soft tissue, and background using ICBM Tissue Probabilistic Atlases provided by SPM12. Third, we used Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) in SPM12 to perform morphological and anatomical registration, normalization, and modulation analysis (Ashburner, 2007). All gray matter images were aligned and resampled to 1.5 × 1.5 × 1.5 mm^3 and then normalized to Montreal Neurological Institute (MNI152) space. The inverse Jacobian matrix of local transformation was used to modulate the segmented gray matter to retain the volume measurement. Fourth, the normalized and modulated data were smoothed with a 6-mm full width at half maximum Gaussian kernel. The resulting images representing the GMV were used in the subsequent analyses.

2.4 | Statistical analyses

2.4.1 | GMV-behavior correlation analyses

A whole-brain correlation analysis was performed to explore the brain areas in which GMV was associated with EXD, using age, sex, BMI, general intelligence, family SES and total intracranial volume (TIV) (including gray matter, white matter, and cerebrospinal fluid volumes) as the controlling variables. A mask with an absolute threshold of 0.2 was used to eliminate the edge effect near the gray matter and white matter boundaries (Wang, Dai, et al., 2018). The Gaussian random field approach, which was successfully used in the VBM study (Andrea, Cathy, Karl, & John, 2005; Wang et al., 2020), was used to determine the regions of significance (Worsley, Evans, Marrett, & Neelin, 1992), with a threshold of p <.001 at the voxel level and p <.05 at the cluster level. This approach provided significant clusters of voxels at the family-wise error rate of p <.05 (for a p-voxel threshold <.001). The above analyses were carried out in SPM12.

2.4.2 | Prediction analyses

To examine the robustness of the association between EXD and the identified meaningful GMV, we performed prediction analyses using a balanced fourfold cross-validation procedure that was carried out using a machine learning method (Kong et al., 2015; Supekar et al., 2013; Wang, Dai, et al., 2018; Wang

et al., 2019). To conduct the prediction analysis, we extract the GMV of the significant regions obtained from the whole brain correlation analysis first. We used these regions as masks and extracted the value of the total volume of all voxels in the mask in SPM12 software. Then, we randomly divided the data into four subsets to ensure that there was no significant difference in the distribution of these variables between subsets. Next, we used the data of the three subsets to establish a linear regression model and used the model to predict the unused data subset. The parameter $r_{(predicted,observation)}$ referred to the correlation between the actual observation data and the prediction data and was obtained after all data subsets had been predicted. Finally, the nonparametric testing method with 5,000 iterations was conducted to examine the significance of $r_{(predicted,observation)}$ (Kong et al., 2015; Supekar et al., 2013). This analysis was performed while controlling for age, sex, BMI, general intelligence, family SES, and TIV.

2.4.3 | Mediation analyses

To explore the indirect effect of GMV on the relationship between stress and EXD, SPSS macro PROCESS (including bootstrapping method) was used for mediating analyses (Hayes, 2013). In the present analysis, the stress score was an independent variable (X), the identified GMV of the brain region was considered the mediator variable (M), the EDS-R score was a dependent variable (Y); and age, sex, BMI, general intelligence, family SES, and TIV were considered the controlling variables. There are four paths, including path *a* (representing the relationship between X and Y), path *b* (representing the relationship between M and Y after controlling X), path *c* (representing the relationship between X and Y) and path c' (representing the relationship between X and Y after adjusting M), and the indirect effect is $c - c'$ (or $a \times b$). When zero is not included in the bootstrapped 95% confidence intervals (CIs) (5,000 iterations), the estimation of indirect effects is considered significant.

3 | RESULTS

3.1 | Neurostructural basis of EXD

Table 1 shows the averages, standard deviations, and correlations of all the behavioral measures included in the present study. No significant association of EXD and age ($r = .12$, $p = .274$), sex ($t[84] = 0.25$, $p = .792$), BMI ($r = .11$, $p = .289$), general intelligence ($r = -.12$, $p = .266$), family SES ($r = .12$, $p = .245$), or TIV ($r = -0.11$, $p = 0.287$) was identified in the current study. On average, 86 subjects exercised 5.2 ± 2.3 times a week for 1.5 ± 0.6 hr each time and persisted in exercising for 4.52 ± 2.1 months. In addition, the EDS-R scores showed that all the participants in the present study had symptoms of EXD.

To examine the relationship between GMV and EXD, a whole-brain correlation analysis was performed with sex, age, BMI, family SES, general intelligence, and TIV as covariates. EXD was found to correlate negatively with the GMV of the right OFC ($r = -.49$, p <.001), left subgenual cingulate gyrus (sgCG, $r = -.43$, p <.001), and left inferior parietal lobe (IPL, $r = -.49$, p <.001; see Table 2 and Figure 1) after correcting for multiple comparisons with the Gaussian random field approach. No significant positive association between EXD and GMV was found in this analysis.

Then, through predictive analysis, the stability of the relationship between the identified gray matter regions from the whole-brain correlation analyses and EXD was verified. EXD was found to be significantly predicted by the GMV of the right OFC ($r_{final\ (predicted,observation)} = .45$, p <.001), left sgCG ($r_{final(predicted,observation)} = .38$, p <.001) and left IPL ($r_{final(predicted,observation)} = .44$, p <.001) after adjusting for sex, age, BMI, family SES, general intelligence, and TIV.

3.2 | Brain structures linking stress and EXD

To investigate the hypothesis that stress affects EXD through GMV, the stress subscale of the DASS was administered. Behaviorally, we

TABLE 1 Means, *SD*s, and correlations of behavioral measures

Variable	Mean	*SD*	1	2	3	4	5	6	7	8
1. Age	22.33	3.65	—							
2. BMI	22.36	3.84	0.43***	—						
3. EXD	59.98	9.80	0.12	0.11	—					
4. Stress	4.89	2.78	0.07	0.04	0.33**	—				
5. Depression	3.02	2.27	0.11	0.04	0.14	0.62***	—			
6. Anxiety	2.38	2.29	0.03	−0.01	0.13	0.66***	0.62***	—		
7. General intelligence	6.21	2.67	−0.84	−0.11	−0.12	−0.10	−0.15	−0.14	—	
8. Family SES	4.52	1.73	0.17	0.03	0.12	0.06	−0.18	−0.10	−0.02	—

Abbreviations: BMI, body mass index; EXD, exercise dependence; SD, standard deviation; SES, socioeconomic status.
**p <.01.
***p <.001.

TABLE 2 Brain regions where gray matter volume was significantly associated with exercise dependence

Region	Peak MNI coordinate			Peak *T* score	Cluster size (voxels)
	x	*y*	*z*		
Right orbitofrontal cortex	26	53	−16	−4.31	207
Left subgenual cingulate gyrus	−8	8	−16	−4.41	283
Left inferior parietal lobe	−45	−39	56	−5.03	270

Note: The threshold for significant regions was set as follows: p <.001 at voxel level and p <.05 at the cluster level, Gaussian random field approach.
Abbreviation: MNI, Montreal Neurological Institute.

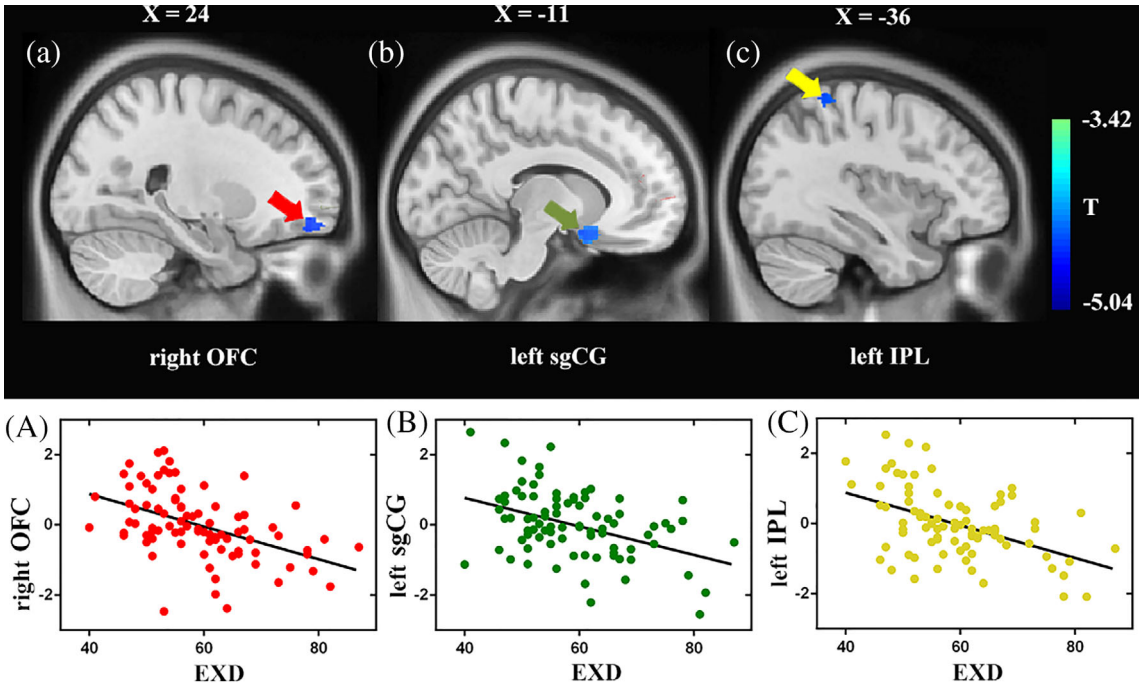

FIGURE 1 Brain regions associated with EXD. Brain images showed that the GMVs in the right OFC (a), left sgCG (b), and left IPL (c) were negatively correlated with EXD. Scatter plots depicting the correlation between EXD and the GMV in the right OFC (a), left sgCG (b), and left IPL (c). The scores on the *x*-axis represent the raw EXD scores. The scores on the *y*-axis represent the standardized residuals of the GMV after sex, age, BMI, general intelligence, family SES, and TIV were regressed out. EXD, exercise dependence; GMV, gray matter volume; IPL, inferior parietal lobe; OFC, orbitofrontal cortex; sgCG, subgenual cingulate cortex

confirmed that EXD was positively associated with stress (r = .33, p = .002). After controlling for sex, age, BMI, family SES, general intelligence, and TIV, the association between EXD and stress was still significant (r = .31, p = .005). Then, we explored whether the gray matter regions related to EXD were also linked with stress. The results revealed a negative correlation between stress and GMV in the right OFC (r = −.26, p = .014) and left sgCG (r = −.25, p = .021). However, no correlation was found between IPL volume and stress (r = −.08, p = .431). After adjusting for sex, age, BMI, family SES, general intelligence and TIV, stress was still associated with GMV in the right OFC (r = −.26, p = .021) and left sgCG (r = −.22, p = .049) but not with GMV in the IPL (r = −.03, p = .774).

Next, mediation analyses were performed to explore the mediating role of the right OFC and left sgCG in the relationship between stress and EXD, with sex, age, BMI, family SES, general intelligence, and TIV as covariates. Interestingly, only the right OFC was found to play a mediating role in the relationship between stress and EXD (indirect effect = 0.399; 95% CI = [0.02, 0.89], p <.05; Figure 2). However, no significant mediating effect was found in the left sgCG (indirect effect = 0.290; 95% CI = [−0.02, 0.70], p >.05). To confirm the specificity of the above findings, we performed another two mediation analyses with depression and anxiety as additional covariates. The same results were found: the right OFC (indirect effect = 0.660; 95% CI = [0.18, 1.31], p <.05) but not the left sgCG (indirect effect = 0.310; 95% CI = [−0.13, 0.74], p >.05) could mediate the relation between stress and EXD. In summary, the right OFC may play a mediating role in the relationship between stress and EXD.

To assess the directionality of the relationship between stress, the OFC, and EXD, another mediation analysis was performed with the GMV of the OFC as X, stress as M and EXD as Y. The results showed that stress did not mediate the effect of the GMV of the OFC on EXD (indirect effect = −10.25; 95% CI = [−33.51, 3.69], p >.05)

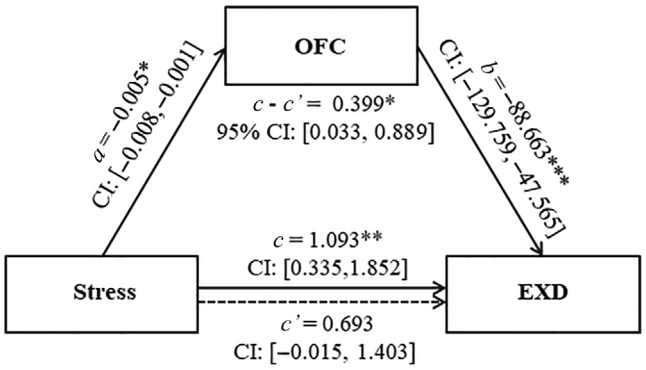

FIGURE 2 The GMV of the right OFC mediates the association between stress and EXD. The illustration demonstrates that stress affects the EXD through the GMV of the right OFC. Sex, age, BMI, general intelligence, family SES, and TIV were controlled in the model. EXD, exercise dependence; GMV, gray matter volume; OFC, orbitofrontal cortex. *p <.05; **p <.01; ***p <.001

after adjusting for sex, age, BMI, family SES, general intelligence, and TIV. These findings indicated that there may be only one effective neuropsychological pathway for predicting EXD in which stress affects EXD through the GMV of the OFC.

4 | DISCUSSION

The current study aimed to investigate the structural neural correlates of EXD and the underlying neuropsychological mechanism of how stress affects EXD in the brain among a sample of regular exercisers with EXD symptoms. There are two main results of our study. First, whole-brain correlation analyses and prediction analyses revealed that EXD was negatively linked with GMV in the right OFC, left sgCG, and left IPL. Second, mediation analyses found that the GMV of the right OFC mediated the impact of stress on EXD. Importantly, these results remained significant even when adjusting for sex, age, BMI, family SES, general intelligence, and TIV, as well as depression and anxiety, suggesting the specificity of the findings. In brief, the current research provides crucial evidence for the neuroanatomical basis of EXD and reveals a potential neuropsychological pathway for the prediction of EXD in which stress affects EXD via the GMV.

First, we found that the GMV of the right OFC correlated negatively with EXD. The OFC is one of the important parts of the reward-related system (Haber & Knutson, 2010) and is involved in executive functions, motivation, and compulsive aspects of addiction (Goldstein & Volkow, 2002). GMV loss in the OFC has been identified in addiction disorders and correlates with addictive severity (Mackey et al., 2019; Qin et al., 2020). In addition, others found that atrophy in the OFC structure may indicate vulnerability to addictive development (Becker et al., 2015). According to previous findings, in the reward system, the OFC plays a crucial role in the top-down inhibition process (Miller & Cohen, 2001), which includes the inhibition and control of reward-related impulses (O'Doherty, Dayan, Friston, Critchley, & Dolan, 2003). Impairment of the OFC may lead to excessive input of reward information, resulting in a loss of control of the limbic system aspect of the reward system (Miller & Cohen, 2001). As a result, expectations and cravings in addiction are enhanced (Goldstein & Volkow, 2002), leading to self-directed/willed behaviors becoming automatic sensory-driven addiction behaviors (Rosenkranz & Grace, 2001). Moreover, animal and human studies have shown that OFC structural damage is related to defects in value-based decision-making and flexible inhibitory control (Solbakk & Løvstad, 2014; Zhou et al., 2019). The disrupted GMV of the OFC might contribute to the main symptoms of EXD; that is, addicts may continue addictive behavior when they know that adverse decisions will lead to adverse consequences (Bechara, Tranel, & Damasio, 2000). In other words, GMV reduction in the OFC may lead to impaired executive function and value-based decision-making in the reward system, which will lead to an addictive disorder and increase the motivation and compulsion of EXD (Zhou et al., 2019).

The present study observed a negative correlation between EXD and GMV in the left sgCG, which is consistent with other previous studies on addiction (Daumann et al., 2011; Montag et al., 2018; Wang et al., 2015) and exercise (Ruotsalainen et al., 2019). The sgCG is the effective part of the ACC and is mainly involved in executive control and the regulation of emotional responses (Bush, Luu, & Posner, 2000). A previous study demonstrated that the GMV of the sgCG correlated negatively with impulsiveness (Lee, Park, Namkoong, Kim, & Jung, 2018; Wang et al., 2015) and inhibitory control (Lee, Namkoong, Lee, & Jung, 2018). The negative correlation between the GMV of the sgCG and EDS score may reflect that increased EXD symptom levels are accompanied by a loss of regulatory control, such as decreased inhibitory control and an increased risk of EXD development. Additionally, it is worth noting that the smaller GMV of the sgCG may be one of the reasons for the loss of behavioral and emotional control in addiction patients (Montag et al., 2018). A previous review reported that the sgCG may be associated with emotional changes in withdrawal symptoms in EXD (Bush et al., 2000). Therefore, the changes in the sgCG in subjects experiencing EXD may play a key role in the dysfunctional interaction between executive control ability and emotional regulation.

We also found that EXD was negatively related to the GMV of the left IPL. A GMV decrease in the IPL has been reported in patients suffering from the substance (e.g., alcohol and drug; Mackey et al., 2019) and nonsubstance dependence (e.g., internet games; Lee, Namkoong et al., 2018; Pan et al., 2018). The IPL plays an important role in guiding attention by integrating behavioral and cognitive information into the external world (Gottlieb, 2007). The GMV reduction of the IPL may indicate an impaired behavioral adjustment to external stimuli (Lee, Namkoong, Lee, & Jung, 2018) and may cause a person to direct attention toward reward-indicating stimuli (Li et al., 2014) in EXD. The present finding of GMV atrophy in the IPL may indicate that impairments in executive function when responding to external stimuli among individuals experiencing EXD and exercisers may lead these individuals to pay more attention to reward stimuli even if they are injured or their life or work habits have been affected. In other words,

impairment of the IPL in individuals experiencing EXD may contribute to a maladaptive interaction among executive control, attention, and reward-seeking (Lee, Namkoong, Lee, & Jung, 2018).

Interestingly, we found that the GMV of the OFC served as a mediator in the link between stress and EXD. Previous studies have shown that stress is one of the risk factors for addictive disorders and relapse regarding addictive behaviors (Sinha & Jastreboff, 2013). Additionally, stress correlates positively with the degree of drug dependence (Jasinska, Stein, Kaiser, Naumer, & Yalachkov, 2014). Evidence has shown that exercisers regard physical activity as a strategy to cope with stress, (Schuch et al., 2019; Szabo, 1995) and they also feel depressed and stressed after being forced to stop exercising (Aidman & Woollard, 2003; Appaneal, Levine, Perna, & Roh, 2009). Previous research reported significantly more emotional stress in those at high risk for EXD than in low-risk EXD individuals (Lichtenstein et al., 2018). The association of stress and EXD was confirmed in the current study in which a higher risk of EXD was positively related to higher stress ($r = .33$, $p = .002$). Furthermore, hierarchical regression analysis showed that stress had an incremental predictive ability for EXD ($\triangle R^2 = 12.8\%$, $\beta = 0.46$, $p = .003$) even after controlling for age, sex, BMI, family SES, general intelligence, and TIV. Thus, our research presents new evidence for the predictive role of stress in EXD. At the neural level, we also observed a significant negative correlation between the GMV of the OFC and stress. Numerous studies have demonstrated that stress is associated with the OFC and can impair the structure and function of the OFC (Arnsten, 2009). Previous studies have shown that stress can specifically enhance the inhibition of OFC activity (Page & Coutellier, 2019) by reducing the density of GABAergic neurons (Varga, Csabai, Miseta, Wiborg, & Czéh, 2017) and by increasing stress hormones (McEwen & Gianaros, 2011). In prior drug addiction studies, both stress and drug abuse impaired executive function including self-regulation of negative emotional states and decision-making, and functional connectivity of the OFC (Ruisoto & Contador, 2019). The present finding of a negative relationship between stress and the GMV of the OFC is in some way consistent with the previously proposed damage that stress inflicts on the PFC (McEwen, 2007; Sinha & Jastreboff, 2013). Collectively, stress may be one of the risk factors that affect the balance between executive control and reward-seeking and increases the risk of addiction (Koob & Schulkin, 2019; Ruisoto & Contador, 2019).

Some limitations of this study should be acknowledged. First, it is worth noting that all participants in this study are healthy people with regular exercise (moderate exercise), and there is still a lack of clear diagnostic criteria for exercise addiction. Therefore, the subjects in our study are healthy people with exercise addiction symptoms, and they cannot be classified as addicts only according to the results of the questionnaire survey. Future studies need to further use clinical methods to identify exercise addicts. Second, the present study identified only three cortical areas, while other hypothetical cortical and subcortical areas were not identified, which may be related to the single index of the GMV as the measure of brain structure in the present study. In the future, researchers may consider using other brain structures (e.g., cortical surface area and cortical thickness) and function (e.g., resting-state functional activity and connectivity; Bullmore & Sporns, 2012) measurements to study the neural basis of EXD. Third, this study is a cross-sectional study, which cannot obtain the causal directionality relationship among stress, brain structures, and EXD. It is worth noting that the mediation analysis conducted in the current research is statistical and does not imply causality. Future studies using a more sophisticated approach (e.g., longitudinal designs) are needed to determine the causal direction of the relationship between these variables. Besides, although the Gaussian random field approach is successfully used in the VBM study to determine the regions of significance (Andrea et al., 2005; Ashburner & Friston, 2000; Worsley et al., 1992), it is much less reliable and reproducible than the method using voxel high correlation threshold (Turner, Paul, Miller, & Barbey, 2018). Future studies need to adopt more rigorous correction to further verify the stability of the results. Forth, although the behavioral evaluation of the EXD in the present study is based on a self-evaluation questionnaire with good psychometric properties (Hausenblas & Downs, 2002; Lu et al., 2012; Weik & Hale, 2009), the reliability and validity of the questionnaire may be affected by social expectation bias. In the future, using behavioral experiments or behavioral evaluations in a natural setting should be considered to reduce the response deviation and improve measurement accuracy. Finally, it has been found that the neural changes of exercise in different age groups are not consistent (Eyme et al., 2019; Hamer et al., 2018; Northey et al., 2020). In the current study, because all the subjects were young people with similar age, the mechanism of age in EXD was not found. In future research, we need to further expand the age range of the subjects with EXD symptoms, and further explore the neural mechanism of EXD symptoms.

5 | CONCLUSION

The present study provides initial evidence indicating that a higher risk of EXD is linked to a smaller GMV in the right OFC, left sgCG, and left IPL in a sample of regular exercisers, which sheds light on the neuroanatomical basis of EXD. Furthermore, our study found that the right OFC mediates the relationship between stress and EXD, revealing a potential neuropsychological mechanism for how stress affects EXD. Our findings might facilitate the diagnosis of EXD and target selection for corresponding interventions (e.g., the behavioral intervention (Lichtenstein et al., 2018), brain intervention, or training programs (Boecker et al., 2008; Esch & Stefano, 2010; Fontes et al., 2020; Tuulari et al., 2018)) to help individuals reduce EXD and improve their quality of life.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data supporting the results of this study can be obtained from the corresponding authors upon reasonable request. Code availability

statement: All the code for this study is available through the corresponding authors.

ORCID

Song Wang https://orcid.org/0000-0002-0776-2505
Baolin Wu https://orcid.org/0000-0003-4574-9747
Zhiyun Jia https://orcid.org/0000-0003-1886-5654
Qiyong Gong https://orcid.org/0000-0002-5912-4871

REFERENCES

Adler, N. E., Epel, E. S., Castellazzo, G., & Ickovics, J. R. (2000). Relationship of subjective and objective social status with psychological and physiological functioning: Preliminary data in healthy white women. *Health Psychology*, *19*(6), 586–592. https://doi.org/10.1037//0278-6133.19.6.586

Aidman, E. V., & Woollard, S. (2003). The influence of self-reported exercise addiction on acute emotional and physiological responses to brief exercise deprivation. *Psychology of Sport and Exercise*, *4*(3), 225–236. https://doi.org/10.1016/S1469-0292(02)00003-1

Anders, S., Lotze, M., Erb, M., Grodd, W., & Birbaumer, N. (2004). Brain activity underlying emotional valence and arousal: A response-related fMRI study. *Human Brain Mapping*, *23*(4), 200–209. https://doi.org/10.1002/hbm.20048

Andrea, M., Cathy, J. P., Karl, J. F., & John, A. (2005). Voxel-based morphometry of the human brain: Methods and applications. *Current Medical Imaging*, *1*(2), 105–113. https://doi.org/10.2174/1573405054038726

Appaneal, R. N., Levine, B. R., Perna, F. M., & Roh, J. L. (2009). Measuring postinjury depression among male and female competitive athletes. *Journal of Sport & Exercise Psychology*, *31*(1), 60–76. https://doi.org/10.1123/jsep.31.1.60

Arnsten, A. F. (2009). Stress signalling pathways that impair prefrontal cortex structure and function. *Nature Reviews. Neuroscience*, *10*(6), 410–422. https://doi.org/10.1038/nrn2648

Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *NeuroImage*, *38*(1), 95–113. https://doi.org/10.1016/j.neuroimage.2007.07.007

Ashburner, J., & Friston, K. J. (2000). Voxel-based morphometry—The methods. *NeuroImage*, *11*(6 Pt 1, 805–821. https://doi.org/10.1006/nimg.2000.0582

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5)*. Arlington: American Psychiatric Association.

Basten, U., Hilger, K., & Fiebach, C. J. (2015). Where smart brains are different: A quantitative meta-analysis of functional and structural brain imaging studies on intelligence. *Intelligence*, *51*, 10–27. https://doi.org/10.1016/j.intell.2015.04.009

Bechara, A., Tranel, D., & Damasio, H. (2000). Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. *Brain*, *123* (Pt 11, 2189–2202. https://doi.org/10.1093/brain/123.11.2189

Becker, B., Wagner, D., Koester, P., Tittgemeyer, M., Mercer-Chalmers-Bender, K., Hurlemann, R., … Daumann, J. (2015). Smaller amygdala and medial prefrontal cortex predict escalating stimulant use. *Brain*, *138*(Pt 7, 2074–2086. https://doi.org/10.1093/brain/awv113

Biddle, S. (2016). Physical activity and mental health: Evidence is growing. *World Psychiatry*, *15*(2), 176–177. https://doi.org/10.1002/wps.20331

Boecker, H., Sprenger, T., Spilker, M. E., Henriksen, G., Koppenhoefer, M., Wagner, K. J., … Tolle, T. R. (2008). The runner's high: Opioidergic mechanisms in the human brain. *Cerebral Cortex*, *18*(11), 2523–2531. https://doi.org/10.1093/cercor/bhn013

Bors, D. A., & Stokes, T. L. (1998). Raven's advanced progressive matrices: Norms for first-year university students and the development of a short form. *Educational and Psychological Measurement*, *58*(3), 382–398. https://doi.org/10.1177/0013164498058003002

Brito, N. H., & Noble, K. G. (2014). Socioeconomic status and structural brain development. *Frontiers in Neuroscience*, *8*, 276. https://doi.org/10.3389/fnins.2014.00276

Bullmore, E. T., & Sporns, O. (2012). The economy of brain network organization. *Nature Reviews Neuroscience*, *13*(5), 336–349. https://doi.org/10.1038/nrn3214

Bush, G., Luu, P., & Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Sciences*, *4*(6), 215–222. https://doi.org/10.1016/s1364-6613(00)01483-2

Chan, R. C. K., Xu, T., Huang, J., Wang, Y., Zhao, Q., Shum, D. H. K., … Potangaroa, R. (2012). Extending the utility of the depression anxiety stress scale by examining its psychometric properties in Chinese settings. *Psychiatry Res*, *200*(2), 879–883. https://doi.org/10.1016/j.psychres.2012.06.041

Chen, Y., Cui, Q., Fan, Y. S., Guo, X., Tang, Q., Sheng, W., … Chen, H. (2020). Progressive brain structural alterations assessed via causal analysis in patients with generalized anxiety disorder. *Neuropsychopharmacology*, *45*, 1689–1697. https://doi.org/10.1038/s41386-020-0704-1

Cundiff, J. M., & Matthews, K. A. (2017). Is subjective social status a unique correlate of physical health? A meta-analysis. *Health Psychology*, *36*(12), 1109–1125. https://doi.org/10.1037/hea0000534

Daumann, J., Koester, P., Becker, B., Wagner, D., Imperati, D., Gouzoulis-Mayfrank, E., & Tittgemeyer, M. (2011). Medial prefrontal gray matter volume reductions in users of amphetamine-type stimulants revealed by combined tract-based spatial statistics and voxel-based morphometry. *NeuroImage*, *54*(2), 794–801. https://doi.org/10.1016/j.neuroimage.2010.08.065

de Coverley Veale, D. M. (1987). Exercise dependence. *British Journal of Addiction*, *82*(7), 735–740. https://doi.org/10.1111/j.1360-0443.1987.tb01539.x

Dias-Ferreira, E., Sousa, J. C., Melo, I., Morgado, P., Mesquita, A. R., Cerqueira, J. J., … Sousa, N. (2009). Chronic stress causes frontostriatal reorganization and affects decision-making. *Science*, *325*(5940), 621–625. https://doi.org/10.1126/science.1171203

Downs, D. S., Hausenblas, H. A., & Nigg, C. R. (2004). Factorial validity and psychometric examination of the exercise dependence scale-revised. *Measurement in Physical Education and Exercise Science*, *8*(4), 183–201. https://doi.org/10.1207/s15327841mpee0804_1

Esch, T., & Stefano, G. B. (2010). Endogenous reward mechanisms and their importance in stress reduction, exercise and the brain. *Archives of Medical Science*, *6*(3), 447–455. https://doi.org/10.5114/aoms.2010.14269

Eyme, K. M., Domin, M., Gerlach, F. H., Hosten, N., Schmidt, C. O., Gaser, C., … Lotze, M. (2019). Physically active life style is associated with increased grey matter brain volume in a medial parieto-frontal network. *Behavioural Brain Research*, *359*, 215–222. https://doi.org/10.1016/j.bbr.2018.10.042

Faul, F., Erdfelder, E., Lang, A. G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, *39*(2), 175–191. https://doi.org/10.3758/bf03193146

Fontes, E. B., Bortolotti, H., Grandjean da Costa, K., Machado de Campos, B., Castanho, G. K., Hohl, R., … Min, L. L. (2020). Modulation of cortical and subcortical brain areas at low and high exercise intensities. *British Journal of Sports Medicine*, *54*(2), 110–115. https://doi.org/10.1136/bjsports-2018-100295

Goldstein, R. Z., & Volkow, N. D. (2002). Drug addiction and its underlying neurobiological basis: Neuroimaging evidence for the involvement of the frontal cortex. *The American Journal of Psychiatry*, *159*(10), 1642–1652. https://doi.org/10.1176/appi.ajp.159.10.1642

Gottlieb, J. (2007). From thought to action: The parietal cortex as a bridge between perception, action, and cognition. *Neuron*, *53*(1), 9–16. https://doi.org/10.1016/j.neuron.2006.12.009

Griffiths, M. D., Szabo, A., & Terry, A. (2005). The exercise addiction inventory: A quick and easy screening tool for health practitioners. *British Journal of Sports Medicine*, *39*(6), e30. https://doi.org/10.1136/bjsm.2004.017020

Haber, S. N., & Knutson, B. (2010). The reward circuit: Linking primate anatomy and human imaging. *Neuropsychopharmacology*, *35*(1), 4–26. https://doi.org/10.1038/npp.2009.129

Hamer, M., Sharma, N., & Batty, G. D. (2018). Association of objectively measured physical activity with brain structure: UKbiobank study. *Journal of Internal Medicine*, *284*(4), 439–443. https://doi.org/10.1111/joim.12772

Hammond, C. J., Allick, A., Rahman, N., & Nanavati, J. (2019). Structural and functional neural targets of addiction treatment in adolescents and young adults: A systematic review and meta-analysis. *Journal of Child and Adolescent Psychopharmacology*, *29*(7), 498–507. https://doi.org/10.1089/cap.2019.0007

Hausenblas, H. A., & Downs, D. S. (2002). How much is too much? The development and validation of the exercise dependence scale. *Psychology & Health*, *17*(4), 387–404. https://doi.org/10.1080/0887044022000004894

Hausenblas, H. A., Schreiber, K., & Smoliga, J. M. (2017). Addiction to exercise. *BMJ*, *357*, j1745. https://doi.org/10.1136/bmj.j1745

Hausenblas, H. A., & Symons Downs, D. (2002). Exercise dependence: A systematic review. *Psychology of Sport and Exercise*, *3*(2), 89–123. https://doi.org/10.1016/S1469-0292(00)00015-7

Hayes, A. (2013). *Introduction to mediation, moderation, and conditional process analysis: A regression-based approach*. New York, NY: Te Guilford Press.

Hu, P., Adler, N. E., Goldman, N., Weinstein, M., & Seeman, T. E. (2005). Relationship between subjective social status and measures of health in older Taiwanese persons. *Journal of the American Geriatrics Society*, *53*(3), 483–488. https://doi.org/10.1111/j.1532-5415.2005.53169.x

Jasinska, A. J., Stein, E. A., Kaiser, J., Naumer, M. J., & Yalachkov, Y. (2014). Factors modulating neural reactivity to drug cues in addiction: A survey of human neuroimaging studies. *Neuroscience and Biobehavioral Reviews*, *38*, 1–16. https://doi.org/10.1016/j.neubiorev.2013.10.013

Jiang, L. C., Yan, Y. J., Jin, Z. S., Hu, M. L., Wang, L., Song, Y., … Xiao, T. (2020). The depression anxiety stress scale-21 in Chinese hospital workers: Reliability, latent structure, and measurement invariance across genders. *Frontiers in Psychology*, *11*, 247. https://doi.org/10.3389/fpsyg.2020.00247

Jochem, C., Baumeister, S. E., Wittfeld, K., Leitzmann, M. F., Bahls, M., Schminke, U., … Jörgen Grabe, H. (2017). Domains of physical activity and brain volumes: A population-based study. *NeuroImage*, *156*, 101–108. https://doi.org/10.1016/j.neuroimage.2017.05.020

King, M. L. (2019). The neural correlates of well-being: A systematic review of the human neuroimaging and neuropsychological literature. *Cognitive, Affective, & Behavioral Neuroscience*, *19*(4), 779–796. https://doi.org/10.3758/s13415-019-00720-4

Kong, F., Wang, X., Hu, S., & Liu, J. (2015). Neural correlates of psychological resilience and their relation to life satisfaction in a sample of healthy young adults. *NeuroImage*, *123*, 165–172. https://doi.org/10.1016/j.neuroimage.2015.08.020

Kong, F., Zhao, J., You, X., & Xiang, Y. (2019). Gratitude and the brain: Trait gratitude mediates the association between structural variations in the medial prefrontal cortex and life satisfaction. *Emotion*, *20*, 917–926. https://doi.org/10.1037/emo0000617

Koob, G. F., & Schulkin, J. (2019). Addiction and stress: An allostatic view. *Neuroscience and Biobehavioral Reviews*, *106*, 245–262. https://doi.org/10.1016/j.neubiorev.2018.09.008

Landolfi, E. (2013). Exercise addiction. *Sports Medicine*, *43*(2), 111–119. https://doi.org/10.1007/s40279-012-0013-x

Le, T. M., Zhang, S., Zhornitsky, S., Wang, W., & Li, C. R. (2020). Neural correlates of reward-directed action and inhibition of action. *Cortex*, *123*, 42–56. https://doi.org/10.1016/j.cortex.2019.10.007

Lee, D., Namkoong, K., Lee, J., & Jung, Y. C. (2018). Abnormal gray matter volume and impulsivity in young adults with Internet gaming disorder. *Addiction Biology*, *23*(5), 1160–1167. https://doi.org/10.1111/adb.12552

Lee, D., Park, J., Namkoong, K., Kim, I. Y., & Jung, Y. C. (2018). Gray matter differences in the anterior cingulate and orbitofrontal cortex of young adults with internet gaming disorder: Surface-based morphometry. *Journal of Behavioral Addictions*, *7*(1), 21–30. https://doi.org/10.1556/2006.7.2018.20

Li, Y., Qiao, L., Sun, J., Wei, D., Li, W., Qiu, J., … Shi, H. (2014). Gender-specific neuroanatomical basis of behavioral inhibition/approach systems (BIS/BAS) in a large sample of young adults: A voxel-based morphometric investigation. *Behavioural Brain Research*, *274*, 400–408. https://doi.org/10.1016/j.bbr.2014.08.041

Lichtenstein, M. B., Christiansen, E., Bilenberg, N., & Støving, R. K. (2014). Validation of the exercise addiction inventory in a Danish sport context. *Scandinavian Journal of Medicine & Science in Sports*, *24*(2), 447–453. https://doi.org/10.1111/j.1600-0838.2012.01515.x

Lichtenstein, M. B., Nielsen, R. O., Gudex, C., Hinze, C. J., & Jørgensen, U. (2018). Exercise addiction is associated with emotional distress in injured and non-injured regular exercisers. *Addictive Behaviors Reports*, *8*, 33–39. https://doi.org/10.1016/j.abrep.2018.06.001

Lovibond, P. F., & Lovibond, S. H. (1995). The structure of negative emotional states: Comparison of the depression anxiety stress scales (DASS) with the Beck depression and anxiety inventories. *Behaviour Research and Therapy*, *33*(3), 335–343. https://doi.org/10.1016/0005-7967(94)00075-u

Lu, F. J., Hsu, E. Y., Wang, J. M., Huang, M. Y., Chang, J. N., & Wang, C. H. (2012). Exercisers' identities and exercise dependence: The mediating effect of exercise commitment. *Perceptual and Motor Skills*, *115*(2), 618–631. https://doi.org/10.2466/06.13.21.pms.115.5.618-631

Mackey, S., Allgaier, N., Chaarani, B., Spechler, P., Orr, C., Bunn, J., … Garavan, H. (2019). Mega-analysis of gray matter volume in substance dependence: General and substance-specific regional effects. *The American Journal of Psychiatry*, *176*(2), 119–128. https://doi.org/10.1176/appi.ajp.2018.17040415

Marques, A., Peralta, M., Sarmento, H., Loureiro, V., Gouveia, É. R., & Gaspar de Matos, M. (2019). Prevalence of risk for exercise dependence: A systematic review. *Sports Medicine*, *49*(2), 319–330. https://doi.org/10.1007/s40279-018-1011-4

McEwen, B. S. (2007). Physiology and neurobiology of stress and adaptation: Central role of the brain. *Physiological Reviews*, *87*(3), 873–904. https://doi.org/10.1152/physrev.00041.2006

McEwen, B. S., & Gianaros, P. J. (2011). Stress- and allostasis-induced brain plasticity. *Annual Review of Medicine*, *62*, 431–445. https://doi.org/10.1146/annurev-med-052209-100430

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience*, *24*, 167–202. https://doi.org/10.1146/annurev.neuro.24.1.167

Montag, C., Zhao, Z., Sindermann, C., Xu, L., Fu, M., Li, J., … Becker, B. (2018). Internet communication disorder and the structure of the human brain: Initial insights on WeChat addiction. *Scientific Reports*, *8*(1), 2155. https://doi.org/10.1038/s41598-018-19904-y

Morgan, W. P. (1985). Affective beneficence of vigorous physical activity. *Medicine and Science in Sports and Exercise*, *17*(1), 94–100.

Nomura, T., Ishiguro, T., Ohira, M., & Ikeda, Y. (2018). Regular exercise behavior is related to lower extremity muscle strength in patients with type 2 diabetes: Data from the multicenter survey of the isometric lower extremity strength in type 2 diabetes study. *Journal of Diabetes Investigation*, *9*(2), 426–429. https://doi.org/10.1111/jdi.12703

Northey, J. M., Rattray, B., Pumpa, K. L., Pryor, D. J., Fraser, M. A., Shaw, M. E., … Cherbuin, N. (2020). Objectively measured physical activity is associated with dorsolateral prefrontal cortex volume in older adults. *NeuroImage*, *221*, 117150. https://doi.org/10.1016/j.neuroimage.2020.117150

Norton, P. J. (2007). Depression anxiety and stress scales (DASS-21): Psychometric analysis across four racial groups. *Anxiety, Stress, and Coping*, *20*(3), 253–265. https://doi.org/10.1080/10615800701309279

O'Doherty, J., Dayan, P., Schultz, J., Deichmann, R., Friston, K., & Dolan, R. J. (2004). Dissociable roles of ventral and dorsal striatum in instrumental conditioning. *Science*, *304*(5669), 452–454. https://doi.org/10.1126/science.1094285

O'Doherty, J. P., Dayan, P., Friston, K., Critchley, H., & Dolan, R. J. (2003). Temporal difference models and reward-related learning in the human brain. *Neuron*, *38*(2), 329–337. https://doi.org/10.1016/s0896-6273(03)00169-7

O'Donovan, G., Lee, I. M., Hamer, M., & Stamatakis, E. (2017). Association of "weekend warrior" and other leisure time physical activity patterns with risks for all-cause, cardiovascular disease, and cancer mortality. *JAMA Internal Medicine*, *177*(3), 335–342. https://doi.org/10.1001/jamainternmed.2016.8014

Page, C. E., & Coutellier, L. (2019). Prefrontal excitatory/inhibitory balance in stress and emotional disorders: Evidence for over-inhibition. *Neuroscience and Biobehavioral Reviews*, *105*, 39–51. https://doi.org/10.1016/j.neubiorev.2019.07.024

Pan, N., Wang, S., Zhao, Y., Lai, H., Qin, K., Li, J., … Gong, Q. (2021). Brain gray matter structures associated with trait impulsivity: A systematic review and voxel-based meta-analysis. *Human Brain Mapping*, *42*(7), 2214–2235. https://doi.org/10.1002/hbm.25361

Pan, N., Yang, Y., Du, X., Qi, X., Du, G., Zhang, Y., … Zhang, Q. (2018). Brain structures associated with internet addiction tendency in adolescent online game players. *Frontiers in Psychiatry*, *9*, 67. https://doi.org/10.3389/fpsyt.2018.00067

Prange, S., Metereau, E., Maillet, A., Lhommée, E., Klinger, H., Pelissier, P., … Thobois, S. (2019). Early limbic microstructural alterations in apathy and depression in de novo Parkinson's disease. *Movement Disorders*, *34*(11), 1644–1654. https://doi.org/10.1002/mds.27793

Qin, K., Zhang, F., Chen, T., Li, L., Li, W., Suo, X., … Gong, Q. (2020). Shared gray matter alterations in individuals with diverse behavioral addictions: A voxel-wise meta-analysis. *Journal of Behavioral Addictions*, *9*(1), 44–57. https://doi.org/10.1556/2006.2020.00006

Rosenkranz, J. A., & Grace, A. A. (2001). Dopamine attenuates prefrontal cortical suppression of sensory inputs to the basolateral amygdala of rats. *The Journal of Neuroscience*, *21*(11), 4090–4103. https://doi.org/10.1523/jneurosci.21-11-04090.2001

Ruisoto, P., & Contador, I. (2019). The role of stress in drug addiction. An integrative review. *Physiology & Behavior*, *202*, 62–68. https://doi.org/10.1016/j.physbeh.2019.01.022

Ruotsalainen, I., Renvall, V., Gorbach, T., Syväoja, H. J., Tammelin, T. H., Karvanen, J., & Parviainen, T. (2019). Aerobic fitness, but not physical activity, is associated with grey matter volume in adolescents. *Behavioural Brain Research*, *362*, 122–130. https://doi.org/10.1016/j.bbr.2018.12.041

Schuch, F. B., Stubbs, B., Meyer, J., Heissel, A., Zech, P., Vancampfort, D., … Hiles, S. A. (2019). Physical activity protects from incident anxiety: A meta-analysis of prospective cohort studies. *Depression and Anxiety*, *36*(9), 846–858. https://doi.org/10.1002/da.22915

Sharp, B. M. (2017). Basolateral amygdala and stress-induced hyperexcitability affect motivated behaviors and addiction. *Translational Psychiatry*, *7*(8), e1194. https://doi.org/10.1038/tp.2017.161

Sinha, R., & Jastreboff, A. M. (2013). Stress as a common risk factor for obesity and addiction. *Biological Psychiatry*, *73*(9), 827–835. https://doi.org/10.1016/j.biopsych.2013.01.032

Solbakk, A. K., & Løvstad, M. (2014). Effects of focal prefrontal cortex lesions on electrophysiological indices of executive attention and action control. *Scandinavian Journal of Psychology*, *55*(3), 233–243. https://doi.org/10.1111/sjop.12106

Supekar, K., Swigart, A. G., Tenison, C., Jolles, D. D., Rosenberg-Lee, M., Fuchs, L., & Menon, V. (2013). Neural predictors of individual differences in response to math tutoring in primary-grade school children. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(20), 8230–8235. https://doi.org/10.1073/pnas.1222154110

Sutherland, M. T., McHugh, M. J., Pariyadath, V., & Stein, E. A. (2012). Resting state functional connectivity in addiction: Lessons learned and a road ahead. *NeuroImage*, *62*(4), 2281–2295. https://doi.org/10.1016/j.neuroimage.2012.01.117

Szabo, A. (1995). The impact of exercise deprivation on well-being of habitual exercises. *Australian Journal of Science and Medicine in Sport*, *27*(3), 68–75.

Tarkka, I. M., Hautasaari, P., Pesonen, H., Niskanen, E., Rottensteiner, M., Kaprio, J., … Kujala, U. M. (2019). Long-term physical activity may modify brain structure and function: Studies in young healthy twins. *Journal of Physical Activity & Health*, *16*(8), 637–643. https://doi.org/10.1123/jpah.2018-0416

Turner, B. O., Paul, E. J., Miller, M. B., & Barbey, A. K. (2018). Small sample sizes reduce the replicability of task-based fMRI studies. *Communications Biology*, *1*, 62. https://doi.org/10.1038/s42003-018-0073-z

Tuulari, J. J., Tuominen, L., Arponen, E., Kalliokoski, K. K., Hirvonen, J., Saanijoki, T., & Nummenmaa, L. (2018). Aerobic exercise modulates anticipatory reward processing via the μ-opioid receptor system. *Human Brain Mapping*, *39*(10), 3972–3983. https://doi.org/10.1002/hbm.24224

Varga, Z., Csabai, D., Miseta, A., Wiborg, O., & Czéh, B. (2017). Chronic stress affects the number of GABAergic neurons in the orbitofrontal cortex of rats. *Behavioural Brain Research*, *316*, 104–114. https://doi.org/10.1016/j.bbr.2016.08.030

Wang, H., Jin, C., Yuan, K., Shakir, T. M., Mao, C., Niu, X., … Zhang, M. (2015). The alteration of gray matter volume and cognitive control in adolescents with internet gaming disorder. *Frontiers in Behavioral Neuroscience*, *9*, 64. https://doi.org/10.3389/fnbeh.2015.00064

Wang, S., Dai, J., Li, J., Wang, X., Chen, T., Yang, X., … Gong, Q. (2018). Neuroanatomical correlates of grit: Growth mindset mediates the association between gray matter structure and trait grit in late adolescence. *Human Brain Mapping*, *39*(4), 1688–1699. https://doi.org/10.1002/hbm.23944

Wang, S., Kong, F., Zhou, M., Chen, T., Yang, X., Chen, G., & Gong, Q. (2017). Brain structure linking delay discounting and academic performance. *Human Brain Mapping*, *38*(8), 3917–3926. https://doi.org/10.1002/hbm.23638

Wang, S., Zhao, Y., Cheng, B., Wang, X., Yang, X., Chen, T., … Gong, Q. (2018). The optimistic brain: Trait optimism mediates the influence of resting-state brain activity and connectivity on anxiety in late adolescence. *Human Brain Mapping*, *39*(10), 3943–3955. https://doi.org/10.1002/hbm.24222

Wang, S., Zhao, Y., Li, J., Lai, H., Qiu, C., Pan, N., & Gong, Q. (2020). Neurostructural correlates of hope: Dispositional hope mediates the impact of the SMA gray matter volume on subjective well-being in late adolescence. *Social Cognitive and Affective Neuroscience*, *15*(4), 395–404. https://doi.org/10.1093/scan/nsaa046

Wang, S., Zhao, Y., Zhang, L., Wang, X., Wang, X., Cheng, B., … Gong, Q. (2019). Stress and the brain: Perceived stress mediates the impact of the superior frontal gyrus spontaneous activity on depressive symptoms in late adolescence. *Human Brain Mapping*, *40*(17), 4982–4993. https://doi.org/10.1002/hbm.24752

Weik, M., & Hale, B. D. (2009). Contrasting gender differences on two measures of exercise dependence. *British Journal of Sports Medicine*, *43*(3), 204–207. https://doi.org/10.1136/bjsm.2007.045138

Worsley, K. J., Evans, A. C., Marrett, S., & Neelin, P. (1992). A three-dimensional statistical analysis for CBF activation studies in human

brain. *Journal of Cerebral Blood Flow and Metabolism*, *12*(6), 900–918. https://doi.org/10.1038/jcbfm.1992.127

Yaple, Z. A., & Yu, R. (2020). Functional and structural brain correlates of socioeconomic status. *Cerebral Cortex*, *30*(1), 181–196. https://doi.org/10.1093/cercor/bhz080

Zhang, X., Kim, J., & Tonegawa, S. (2020). Amygdala reward neurons form and store fear extinction memory. *Neuron*, *105*(6), 1077–1093. https://doi.org/10.1016/j.neuron.2019.12.025

Zhou, F., Montag, C., Trautner, P., Kendrick, K. M., Markett, S., & Becker, B. (2019). Orbitofrontal gray matter deficits as marker of Internet gaming disorder: Converging evidence from a cross-sectional and prospective longitudinal design. *Addiction Biology*, *24*(1), 100–109. https://doi.org/10.1111/adb.12552

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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