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FULL-LENGTH REPORT

Brain alterations in individuals with exercise dependence: A multimodal neuroimaging investigation

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ABSTRACT

Background: Exercise dependence (ED) is characterised by behavioural and psychological symptoms that resemble those of substance use disorders. However, it remains inconclusive whether ED is accompanied by similar brain alterations as seen in substance use disorders. Therefore, we investigated brain alterations in individuals with ED and inactive control participants. *Methods:* In this cross-sectional neuroimaging investigation, 29 individuals with ED as assessed with the Exercise Dependence Scale (EDS) and 28 inactive control participants (max one hour exercising per week) underwent structural and functional resting-state magnetic resonance imaging (MRI). Group differences were explored using voxel-based morphometry and functional connectivity analyses. Analyses were restricted to the striatum, amygdala, and inferior frontal gyrus (IFG). Exploratory analyses tested whether relationships between brain structure and function were differently related to EDS subscales among groups. *Results:* No structural differences were found between the two groups. However, right IFG and bilateral putamen volumes were differently related to the EDS subscales "time" and "tolerance", respectively, between the two groups. Resting-state functional connectivity was increased from right IFG to right superior parietal lobule in individuals with ED compared to inactive control participants. Furthermore, functional connectivity of the angular gyrus to the left IFG and bilateral caudate showed divergent relationships to the EDS subscale "tolerance" among groups. *Discussion:* The findings suggest that ED may be accompanied by alterations in cognition-related brain structures, but also functional changes that may drive compulsive habitual behaviour. Further prospective studies are needed to disentangle beneficial and detrimental brain effects of ED.

KEYWORDS

exercise dependence, multimodal neuroimaging, inferior frontal gyrus, fronto-parietal connectivity, dorsal striatum, compulsion

INTRODUCTION

In the past three decades, there has been an increasing number of investigations into the potentially addictive nature of several behaviours. While addiction to substances has been robustly documented and relies on well-established diagnostic criteria, behavioural addictions are less well understood, with gambling and gaming disorder being the only form of non-substance related disorder currently included in the ICD-11 (World Health Organization, 2019). The inclusion of potential behavioural addictions such as internet or

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smartphone use, sex, and shopping, is currently the subject of discussion (Brand et al., 2022; Grant, Potenza, Weinstein, & Gorelick, 2010). Among these behaviours, exercise has emerged as a form of activity with potentially addictive characteristics (Colledge et al., 2020). Although regular exercise generally evokes beneficial mental and physical effects (Biddle, 2016), over-exercising, defined as the tendency to exercise beyond what is required for health or athletic achievement has also been associated with harmful consequences (Baekeland, 1970; Colledge & Meyer, 2022; Lichtenstein, Nielsen, Gudex, Hinze, & Jørgensen, 2018). This phenomenon is not currently a diagnosable condition and several terminologies have been used for describing exercise addiction, including exercise dependence (ED), compulsive exercise, and exercise abuse (Szabo, Griffiths, Marcos, Mervó, & Demetrovics, 2015). However, although the terms exercise addiction and ED are often (erroneously) used as synonyms, exercise addiction incorporates a synthesis of dependence and compulsion, whereas ED does not necessarily imply addiction and as such pathology (Goodman, 1990). In this study, participants were assessed with the Exercise Dependence Scale (EDS) (Downs, Hausenblas, & Nigg, 2004), which is based on the DSM-IV criteria for substance dependence. We therefore use ED and findings should be read with the discrepancy to exercise addiction in mind. In accordance with the diagnostic criteria of substance use disorders (Weinstein & Weinstein, 2014), exercise addiction is characterised as rigid adherence to exercise, continuance despite negative consequences, withdrawal symptoms when planned exercise cannot be carried out, escalation of exercise time to still experience hedonic rewards, and neglecting other activities. The prevalence of ED risk among regular exercisers is around 3% (Szabo et al., 2015), although heterogeneous estimates exist, which may be explained by differences in disciplines (Di Lodovico, Poulnais, & Gorwood, 2019). ED as operationalized with the EDS (Downs et al., 2004) comprises the following components: tolerance, withdrawal symptoms, intention effects, lack of control, time (spent in activities necessary to obtain exercise), reduction in other activities, and continuance (Hausenblas & Downs, 2002). Consistent with other addictive disorders, we have previously shown in the same individuals as in the current neuroimaging investigation that ED is accompanied by psychiatric comorbidities, such as eating disorders, depression, anxiety, personality, and obsessive-compulsive disorders (Meyer et al., 2021) as well as increased levels of ADHD symptoms and childhood traumas (Colledge et al., 2022). However, ED also appears to differ from substance use disorders, as obsessive-compulsive (Cluster C) rather than impulsive (Cluster B) personality traits were most commonly identified (Meyer et al., 2021). This suggests that the qualitative and compulsive dimension of unhealthy exercise, which is characterised by rigid exercise schedules, prioritisation of exercise over other activities and feeling guilt and anxiety when exercise is missed (Adkins & Keel, 2005), appears to be more relevant in the identification of ED (Meyer et al., 2021).

Whereas the clinical characterisation of compulsive exercising has gained considerable attention (Hausenblas, Schreiber, & Smoliga, 2017; Landolfi, 2013; Weinstein & Szabo, 2023), its neural correlates are poorly understood. Discrete brain regions have been linked to different stages in the addiction cycle (Koob & Volkow, 2010, 2016): the ventral (euphoria, reward) and dorsal striatum (habits, perseveration) as focal points for the binge/intoxication stage, a key role for the extended amygdala in the withdrawal/negative affect stage, and orbital (craving) and inferior frontal cortices (inhibitory control) as hubs for the preoccupation/anticipation stage. It has been proposed that drug addiction involves a shift from an initial voluntary (and more impulsive) use to a habitual and ultimately compulsive behaviour that is also reflected by a transition from ventral to dorsal striatal regions and impaired prefrontal inhibitory control mechanisms (Everitt & Robbins, 2013). Meta-analytic research confirmed these alterations in primary dorsal striatal, and frontal circuits engaged in reward processing, habit formation, and executive control across different substances (Klugah-Brown et al., 2020). In light of the current debate about the validity of ED, the question arises whether its symptoms map more onto impulsivity- or compulsivity-related brain regions. To date, only a few neuroimaging studies in individuals with ED have been conducted. A voxel-based morphometry (VBM) study showed negative relationships between EDS scores and grey matter volume (GMV) in the right orbitofrontal cortex (OFC), left subgenual cingulate, and left inferior parietal lobe (IPL), with GMV also purportedly mediating the impact of stress on EDS symptoms (Zhang, Gao, et al., 2021). In a follow-up analysis, Zhang and colleagues showed a positive relationship between OFC GMV and OFC function (amplitudes of low-frequency fluctuation, ALFF), whereas GMV in the OFC mediated the relationship between OFC function and EDS symptoms (Zhang et al., 2023). It has been argued that these neural abnormalities in the right OFC may reflect a decrease in executive control function that underlies ED. A recent resting-state functional MRI (fMRI) study further revealed positive associations between functional connectivity in the default mode network (DMN), negative perfectionism and EDS scores in participants with ED (Xie et al., 2022). The DMN is considered to be related to self-directed thought, introspection and decision-making (Raichle, 2015), whereas negative perfectionism has been positively associated with the degree of compulsiveness and obsessiveness in excessive exercisers (Gulker, Laskis, & Kuba, 2001). Some studies have assessed the effects of other behavioural addictions on the brain. A recent meta-analysis investigated alterations in resting-state functional connectivity (rsFC) and brain volume in behavioural addictions compared to healthy individuals (Zeng, Han, Gao, Sun, & Yuan, 2023). GMV was reduced in the anterior cingulate cortex, extending to the middle cingulate cortex and the superior frontal gyrus. Results on rsFC revealed that behavioural addictions exhibit abnormalities in various networks associated with inhibition, salience attribution, self-referential mental processes, and reward-driven

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behaviours. In line with the hypothesis that distinct brain regions are related to different stages of addiction (Koob & Volkow, 2016), an fMRI study showed increased functional connectivity of the dorsal striatum (caudate and putamen) during gaming in subjects with internet gaming disorder compared to healthy control individuals (Kim et al., 2022). Internet addiction disorder has also been associated with reduced amygdala GMV and lower amygdala-orbitofrontal connectivity that was negatively correlated with impulsivity (Ko et al., 2015). Another study in problematic smartphone users found reduced resting-state functional connectivity (rsFC) between the right inferior frontal gyrus (IFG) and limbic areas including the left amygdala, which was associated with the severity of problematic smartphone use, the degree of self-control, and the amount of smartphone use (Pyeon et al., 2021).

This study is part of recent efforts to characterise ED and contains neuroimaging data from a sample whose clinical characteristics have previously been published (Colledge et al., 2022; Meyer et al., 2021). Here, we aim to investigate structural and functional brain alterations in individuals with ED (as defined with a score >15 in at least three EDS subscales) compared to inactive healthy control participants using structural and fMRI. VBM and rsFC analyses were restricted to brain regions affected in drug addictions and consisted of key regions in the binge/intoxication, withdrawal/negative affect, and craving/preoccupation stage, namely the ventral and dorsal striatum, amygdala, and IFG. Given that a shift from impulsivity to compulsivity may take place in ED and behavioural addictions (Adkins & Keel, 2005; Cox & Orford, 2004; Demetrovics, van den Brink, Paksi, Horvath, & Maraz, 2022), similar to drug addictions (Everitt & Robbins, 2013), we predicted structural and functional alterations in individuals with ED particularly in regions related to compulsion (including habit formation) and inhibitory control, i.e. the dorsal striatum and IFG. Furthermore, complementary exploratory analyses were performed to test whether dimensional relationships between brain structure/function and scores on the EDS subscales were differently expressed among the two groups. Although this second analysis was exploratory, we expected to see relationships between striatal abnormalities and EDS tolerance and time, amygdala abnormalities and EDS withdrawal symptoms, and IFG abnormalities and EDS lack of control and continuance in the ED but not the control group.

METHODS

Participants

In order to identify individuals with ED, we used flyers and posters to raise awareness of the study. We specified that potential participants must: a) be between the ages of 18 and 70; b) exercise for ten hours or more per week; c) exercise despite illness or injury. Individuals who fulfilled these prescreening criteria were invited to complete a German version of the EDS (Müller et al., 2013). The EDS has seven subscales to describe multidimensional maladaptive pattern of exercise as described above. Scores of 15 or more out of a possible 18 points on three or more of the subscales are classified as indicating risk for ED; lower scores indicate symptoms without addiction, while the lowest scoring is classed as "nondependent-asymptomatic" (Hausenblas & Downs, 2002). Internal consistency of the EDS total score and its subscales was good (EDS_{total} alpha = 0.98, components range 0.82–0.96). In our study, only individuals scoring at or above the at-risk (>15) threshold on at least three of the seven subscales were included.

To recruit a control group, we used forum posts on a university website to identify individuals who exercise only one hour per week or less. Specific ages and genders were being sought, to match the control population to the ED group. Healthy control participants had no psychiatric or neurological diagnoses, as confirmed by individual screening via email. No formal power analysis for the secondary neuroimaging analysis was conducted. However, the

Table 1. Sociodemographic and behavioural characteristics of the study sample

-	Healthy control group (N = 28)	Exercise dependence group (N = 29)	Group comparison
Age, mean (SD)	29.82 (13.59)	27.59 (12.21)	$W = 456$, $p = 0.43$
Gender, f/m	13/15	12/17	$\chi2 = 0.01$, $p = 0.91$
Exercise hours per week, mean (SD)	NA	14.83 (5.11)	NA
MDD diagnosis, yes/no	0/28	14/15	$\chi2 = 15.41$, $p < 0.001$
BDI, mean (SD)	NA	13.38 (10.01)	NA
EDS total score, mean (SD)	40.18 (12.46)	99.1 (10.94)	$W = 0$, $p < 0.001$
EDS withdrawal effects, mean (SD)	5 (2.05)	12.48 (3.8)	$W = 37$, $p < 0.001$
EDS continuance, mean (SD)	5.93 (2.94)	15.03 (2.31)	$W = 24$, $p < 0.001$
EDS tolerance, mean (SD)	5.64 (2.11)	13.66 (3.63)	$W = 30$, $p < 0.001$
EDS lack of control, mean (SD)	5.71 (2.52)	14.83 (2.87)	$W = 14$, $p < 0.001$
EDS reduction in other activities, mean (SD)	4.68 (1.72)	11.79 (2.55)	$W = 11$, $p < 0.001$
EDS time, mean (SD)	7.89 (4.01)	16.79 (1.29)	$W = 7$, $p < 0.001$
EDS intention effects, mean (SD)	5.18 (2.37)	14.52 (2.85)	$W = 11.5$, $p < 0.001$

Notes. MDD = major depressive disorder, EDS = exercise dependence scale, SD = standard deviation.

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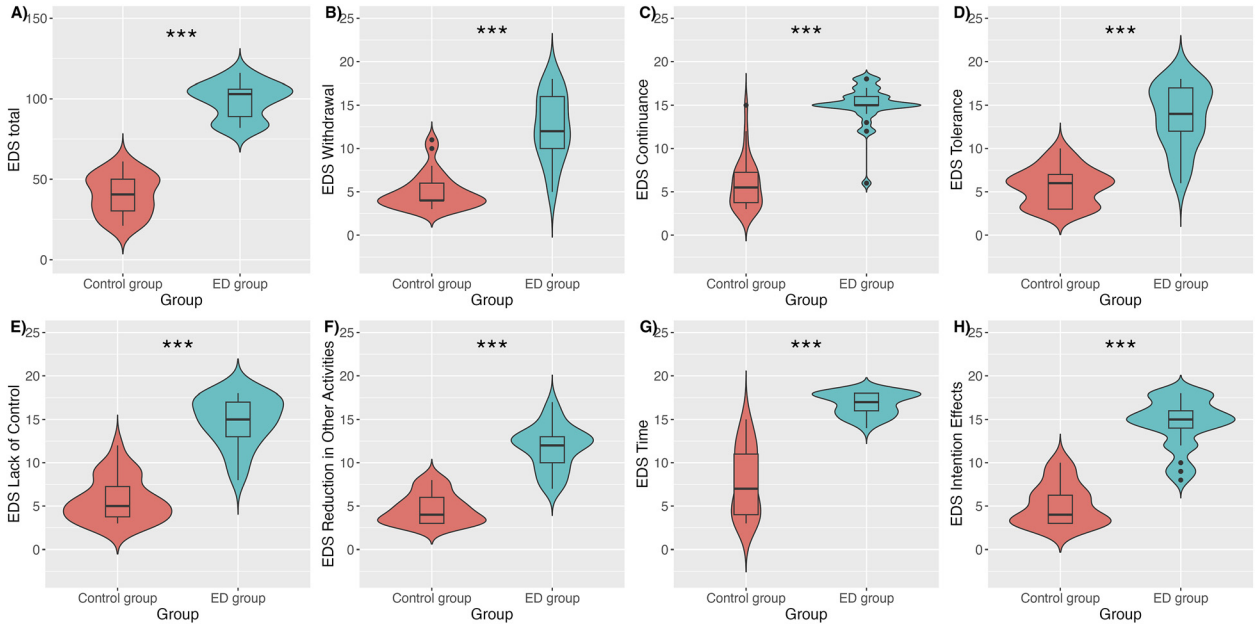

Fig. 1. Scores on the Exercise Dependence Scale (EDS) for both study groups including **A)** the total score and the subscales **B)** Withdrawal, **C)** Continuance, **D)** Tolerance, **E)** Lack of Control, **F)** Reduction in Other Activities, **G)** Time, and **H)** Intention Effects

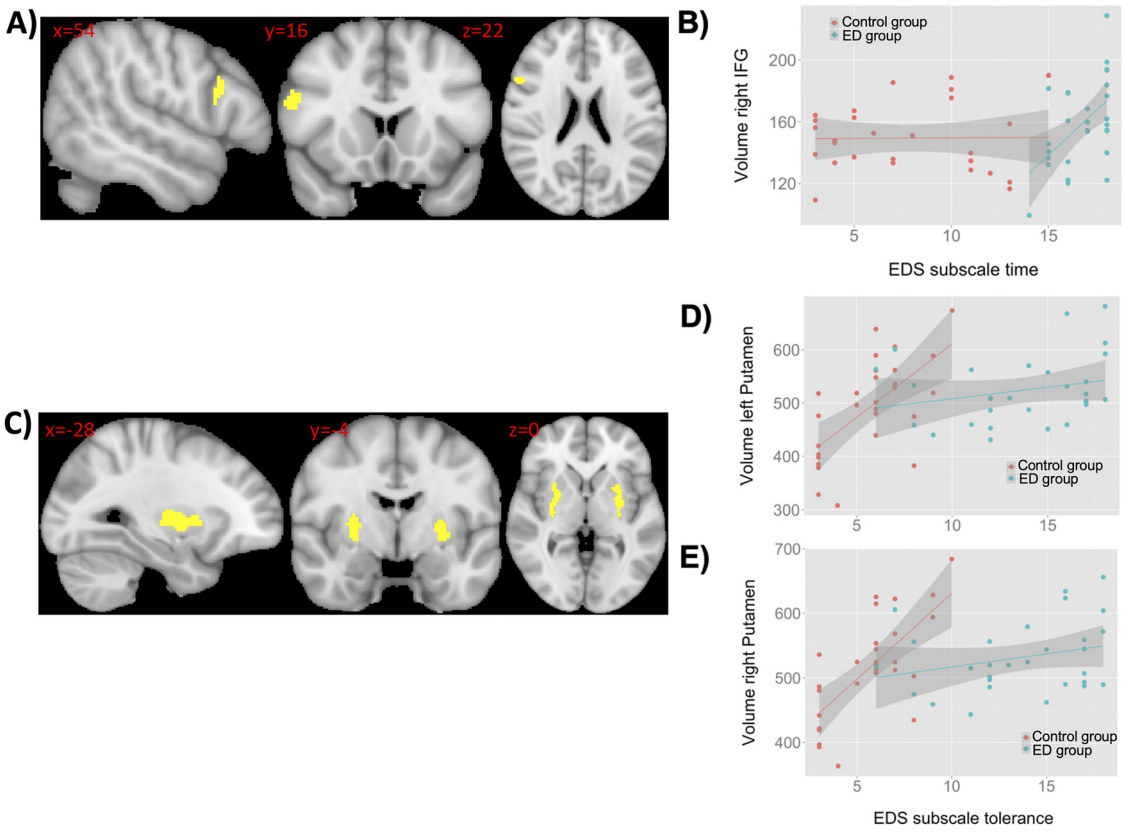

Fig. 2. **A)** Significant differences between study groups in the relationship between the EDS subscale time and volume of the right inferior frontal gyrus ($p_{FWE} = 0.02$, voxel number = 45, centre of mass: x = 54, y = 16, y = 22). **B)** Scatterplot depicting the associations between volume of the right inferior frontal gyrus and EDS time factor in the sample with exercise dependence (ED) ($r = 0.62$, $p < 0.001$) and the inactive control group ($r = -0.045$, $p = 0.821$). **C)** Significant group differences in the relationships between left ($p_{FWE} = 0.01$, voxel number = 228, centre of mass: x = −28, y = −4, y = −2) and right putamen ($p_{FWE} = 0.011$, voxel number = 221, centre of mass: x = 26, y = 0, y = −4), and the EDS subscale tolerance. **D)** Associations between EDS tolerance scores and left putamen volume in the ED sample ($r = 0.26$, $p = 0.18$) and inactive control group ($r = 0.64$, $p < 0.001$). **E)** Scatterplot depicting the relations between right putamen volume and the EDS tolerance factor in the ED sample ($r = 0.28$, $p = 0.141$) and the inactive control group ($r = 0.70$, $p < 0.001$). Left hemisphere is displayed on the right

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obtained sample size for this MRI analysis of 57 individuals was comparable to previous studies using MRI in subjects with behavioural addictions and control individuals (Choi et al., 2017; Ding et al., 2019; Kim et al., 2022; Ko et al., 2009; Lee, Park, Namkoong, Kim, & Jung, 2018).

Measures

In the study group with ED, individuals also completed a Beck Depression Inventory (BDI-II) (Beck, Steer, & Brown, 1996) to assess depressive symptoms and underwent a Structured Clinical Interview for DSM-5 (SCID-5) (First, Williams, Karg, & Spitzer, 2016) to determine the co-occurrence of psychiatric diagnoses.

Procedures

MRI data acquisition. All participants underwent an MRI session including structural and resting-state functional MRI sequences using a 3T Magnetom Prisma scanner (SIEMENS, Erlangen, Germany) with a 20-channel phased-array radiofrequency head coil. Foam pads across the forehead were used to minimize head movement.

A whole brain 3-dimensional T1-weighted magnetisation prepared rapid acquisition gradient (MPRAGE) sequence was applied. For the resting-state sequence, participants were instructed to keep the eyes open, to think of nothing in particular, and not to fall asleep. We used a gradient echo planar imaging (EPI) sequence and the MPRAGE sequence described above was used for anatomical reference. Further specifications are presented in the Supplementary Material.

Structural and functional brain analysis. A VBM analysis was performed to investigate group differences in brain GMV. MRI data was analysed with the standard automated processing stream of FSL-VBM (Douaud et al., 2007) (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM), an optimised VBM protocol (Good et al., 2001) performed with FSL tools (Smith et al., 2004) (further information in the Supplementary Material). Resting-state data was processed and analysed using CONN toolbox (21.a, http://www.nitrc.org/projects/conn) (Whitfield-Gabrieli & Nieto-Castanon, 2012), an open-source Matlab/SPM-based software. Data preparation included a default pre-processing pipeline for volume-based analysis and denoising (see Supplementary Material for detailed information).

Statistical analysis

Group and slope comparisons. Two different types of region-of-interest (ROI) analyses were conducted with the structural and functional data. ROIs related to addictive behaviours and compulsion as described above were selected: bilateral caudate, putamen, nucleus accumbens, amygdala and bilateral IFG. One mask with all ROIs (Supplementary Fig. 1) was created based on the Harvard-Oxford cortical and subcortical structural atlas implemented in FSL and conn. First, a general linear model was applied to investigate if specific grey matter volumes and rsFC differ between both study groups (ANCOVA). Age, gender, and diagnosis of depression were demeaned across all participants and included as covariates. The diagnosis of depression was included to avoid confounding effects related to this diagnosis, as depression was the most common diagnosis in our sample (14 diagnoses, Table 1).

In a second exploratory analysis, EDS slope comparisons between the study groups were conducted including the same covariates. Here, we tested whether the relationships between GMV/functional connectivity and EDS scores were differently expressed between the two groups. Beside the total score, slope comparisons were conducted for all EDS subscales. Statistical maps of the VBM analysis were thresholded at $p < 0.05$, family-wise error (FWE) corrected for multiple comparisons using the threshold-free cluster enhancement (TFCE) technique (Smith & Nichols, 2009). For rsFC analyses, all selected ROIs were jointly included as sources; targets were voxels covering the whole brain. To define clusters of interest, an uncorrected threshold of $p < 0.001$ was applied and results were considered significant with an FDR-corrected $p < 0.05$ cluster-level threshold (see further details in the Supplementary Material). Due to the exploratory approach of this analysis, we report results with and without correction for multiple comparisons (Bonferroni-corrected p-value p <0.007).

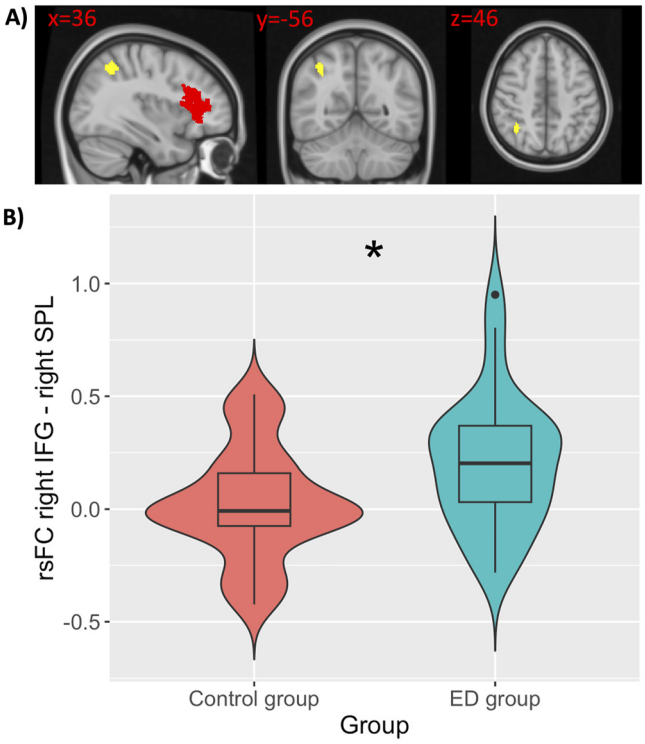

Fig. 3. **A)** Significant group difference in resting-state functional connectivity (rsFC) from the right inferior frontal gyrus (IFG, depicted in red) to a cluster in the left superior parietal lobule (SPL, depicted in yellow) (p_{FDR} = 0.017, voxel number = 82, x = 36 y = −56 z = 46). **B)** Distribution per group in right IFG-left SPL rsFC

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Behavioural and exploratory analysis. Demographics and behavioural measures were compared between groups using Wilcoxon tests and chi-squared tests for nominal data. When significant group differences in structural and functional analyses were detected, values were exported and correlated with behavioural measures (age, BDI-II, EDS total, and subscales). Correlations of significant differences in slope comparisons were conducted using Spearman rank correlation. Statistical analyses outside MRI-specific software were carried out using R.

Ethics

The study was approved by the local ethics committee (Ethikkommission Nordwest- und Zentralschweiz) and conducted according to the Declaration of Helsinki. All participants gave written informed consent before inclusion in the study.

RESULTS

Sample characteristics

The two study groups were equal in age and gender distribution (Table 1). Current or remitted depressive episodes were more frequent in the ED group. The most common comorbid psychiatric diagnoses were depressive, personality, and obsessive-compulsive disorders in the ED sample. Eating disorders were diagnosed in four participants. For the EDS total score and all subscales, mean values per group were significantly lower in the control group compared to the group with ED (Fig. 1, Table 1).

Structural brain alterations

Group comparisons did not show any significant GMV differences between individuals with ED and inactive control participants after controlling for age, gender, and depression

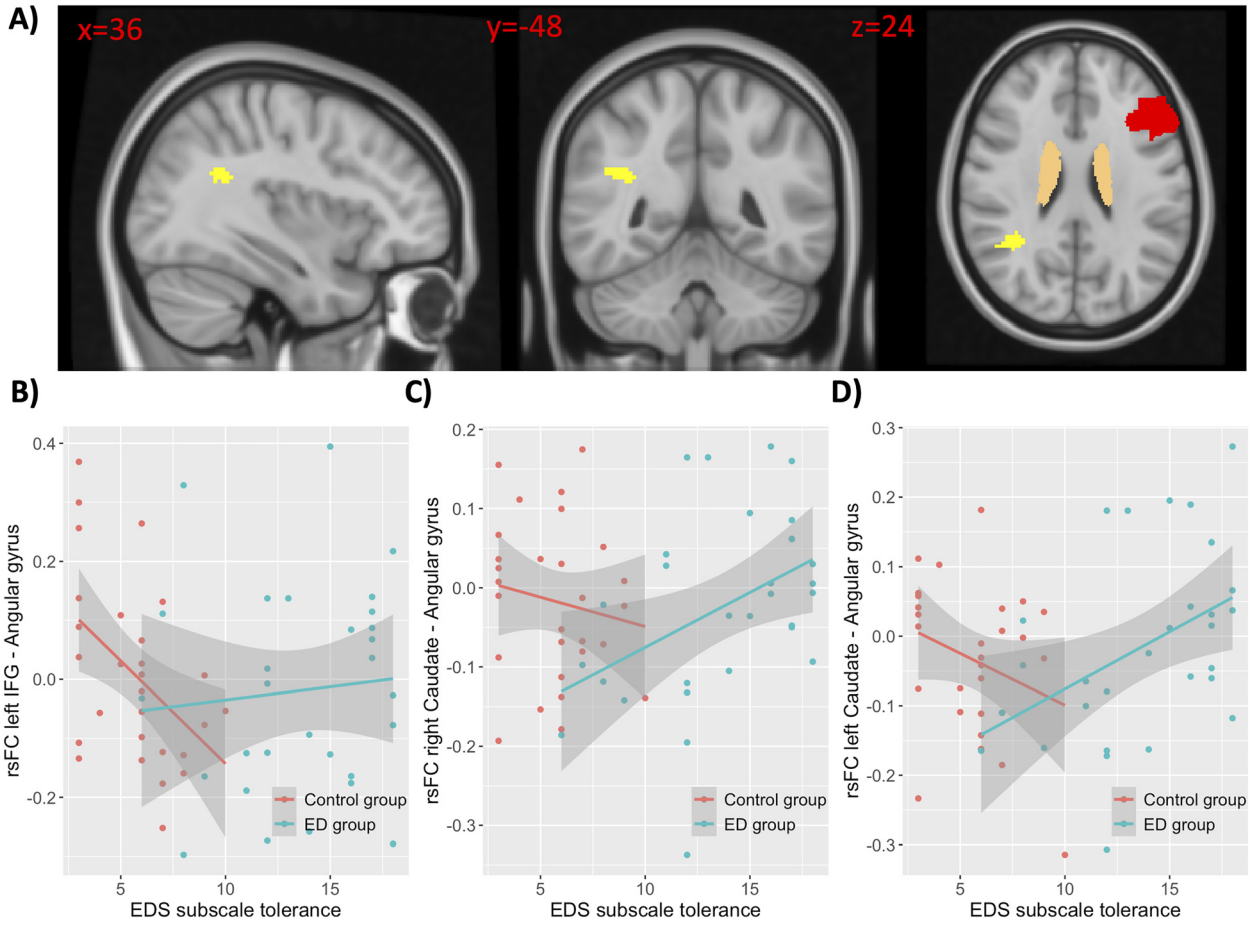

Fig. 4. **A)** Significant differences in the relationship between the EDS subscale tolerance and resting-state functional connectivity (rsFC) from selected seeds to a cluster in the angular gyrus between study groups ($p_{FDR} = 0.019$, voxel number = 88, x = 36 y = −48 z = 24). Scatterplots depict the relation between the EDS subscale tolerance and rsFC from **B)** left inferior frontal gyrus (IFG) in the group with exercise dependence (ED) ($r = 0.17$, $p = 0.39$) and inactive control group ($r = -0.49$, $p < 0.01$), **C)** the right caudate in the group with ED ($r = 0.41$, $p < 0.05$) and inactive control group ($r = -0.14$, $p = 0.48$) and **D)** the left caudate in the group with ED ($r = 0.49$, $p < 0.01$) and inactive control group ($r = -0.25$, $p = 0.2$). Cluster in angular gyrus depicted in yellow, seed regions in red (left IFG) and beige (bilateral caudate)

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diagnosis. However, in the exploratory slope comparison analyses, we found a significant difference in the relationship between the EDS subscale time and GMV in the right IFG among the two groups (Fig. 2A). This difference was driven by a significant positive relationship in the ED group ($r = 0.62$, $p < 0.001$), whereas the inactive control group showed no such relationship ($r = -0.05$, $p = 0.821$) (Fig. 2B). There was neither a positive ($p = 0.352$) nor a negative ($p = 0.509$) relationship between right IFG volume and the actual time exercising per week in the study group with ED (controlled for depression diagnosis). There were also significant group differences in the relationships between the EDS factor tolerance and left and right putamen volume (Fig. 2C). These dissociable associations were due to significant positive correlations between left ($r = 0.64$, $p < 0.001$)/right putamen ($r = 0.70$, $p < 0.001$) and EDS tolerance in the control group, while neither the left ($r = 0.26$, $p = 0.18$) nor right putamen ($r = 0.28$, $p = 0.141$) showed significant correlation with tolerance scores in the ED sample (Fig. 2D and E). With the Bonferroni-corrected p-threshold (p <0.007), the uncorrected significant results remained significant.

Functional brain alterations

A significant group difference was detected in the right superior parietal lobule (SPL) ($p_{FDR} = 0.017$, voxel number = 82, x = 36 y = −56 z = 46, Fig. 3A). Post-hoc comparisons indicated that the ED group exhibited increased right IFG-right SPL rsFC compared to the inactive control group (Fig. 3B). After excluding an outlier in the ED group, the group difference was still significant (t (53.87) = -2.26, $p = 0.03$). Correlation analyses revealed no associations between this rsFC group effect and age, BDI-II, and EDS scores.

Exploratory slope comparisons between the groups further showed significant differences in the relationship between the EDS subscale tolerance and rsFC of the angular gyrus ($p_{FDR} = 0.019$, voxel number = 88, x = 36 y = −48 z = 24, Fig. 4A). While the relationship between left IFG-angular gyrus rsFC and EDS tolerance was significantly negative in the control group ($r = -0.49$, $p < 0.01$), there was no relationship in the ED group ($r = 0.17$, $p = 0.39$) (Fig. 4B). In contrast, whereas the relationships between angular gyrus-left/right caudate rsFC and EDS tolerance were significant and positive in the ED group ($r = 0.49$, $p < 0.01$ and $r = 0.41$, $p < 0.05$, respectively), these relationships did not reach significance in the control group ($r = -0.25$, $p = 0.2$ and $r = -0.14$, $p = 0.48$, respectively) (Fig. 4C and D). After applying correction for multiple testing, the relationship between the EDS subscale tolerance and rsFC of the angular gyrus did not remain significant.

DISCUSSION AND CONCLUSIONS

In this cross-sectional MRI study, we compared differences in brain structure and function between individuals with ED and inactive control participants. We did not find any structural brain differences between the two study groups. Additional exploratory analyses revealed that right IFG and bilateral putamen volumes were differently related to the EDS factors time and tolerance in individuals with ED compared to control individuals. Group comparisons in rsFC indicated increased right IFG-right SPL connectivity in individuals with ED compared to inactive control participants. Finally, in an exploratory rsFC analysis, angular gyrus connectivity to the left IFG and bilateral caudate were differently related to the EDS factor tolerance in both study groups which did not remain significant after multiple comparison correction.

The time spent in activities linked to exercise as assessed with the EDS was positively related to the right IFG volume in the sample with ED. The right IFG is a key hub for various cognitive functions including attention, motor inhibition and imagery (Hartwigsen, Neef, Camilleri, Margulies, & Eickhoff, 2019). Notably, higher cardiorespiratory fitness (VO_{2max}) has also been associated with improved cognitive functioning, mediated by right IFG volume (Weinstein et al., 2012). The beneficial effect of cardiorespiratory fitness on right IFG-mediated cognitive functions may particularly take place in individuals with high fitness levels (Dupuy et al., 2015). Thus, our finding of a positive relationship between right IFG volume and the EDS factor time may rather reflect a beneficial effect of exercising on cognitive functioning. In other words, the fitness level may be reflected in brain structure, though a causal relationship cannot be determined in this study. In contrast, the hours spent exercising per week were not related to right IFG volume in the ED group, which indicates that right IFG volume may be more related to the time spent in activities necessary to obtain exercise than the actual hours of exercising per se.

Furthermore, there were positive relationships between bilateral putamen volume and the tolerance EDS subfactor in the control group. Given the prominent role of the putamen in habit formation (Singer, 2013; Yin, Knowlton, & Balleine, 2004), it was surprising that this relationship was not found in the sample with ED. However, a recent study showed a positive correlation between physical fatigue and left putamen volume in healthy middle-aged adults (Putra, Park, Yamashita, Mizuno, & Watanabe, 2022). The increase in putamen volume has been interpreted as compensation to counteract the development of fatigue. The positive putamen-tolerance relationship identified in inactive control participants may thus reflect the motivation to increase physical activity.

In contrast with other studies in patients with substance use disorders and behavioural addictions (Mackey et al., 2019; Pando-Naude et al., 2021; Qin et al., 2020; Zhang, Wang, et al., 2021), the present study found no GMV reductions in the striatum, amygdala and IFG in individuals with ED compared to control participants. Potential reasons may be the modest sample sizes or that ED has no detrimental impact on brain volume. Large-scale studies at different stages of ED are warranted.

The rsFC analysis revealed that individuals with ED showed increased right IFG-right SPL connectivity

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compared to the inactive control individuals. It has previously been shown that increased right IFG activity when inhibiting a response was related to reduced attentional impulsiveness and increased motor impulsiveness in abstinent cocaine users (Bell, Garavan, & Foxe, 2014). As part of the fronto-parietal control (attention) network, the right IFG is involved in initiating and adjusting context-dependent control to enable flexible goal-directed behaviour (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008). The right SPL is also responsible for top-down attentional control to attend to salient stimuli and ignore distractors (Asscheman, Thakkar, & Neggers, 2015). It can particularly be linked to the specification of spatial parameters for motor attention and execution (Striemer, Chouinard, & Goodale, 2011) and its interaction with the IFG subserves the generation of intentional actions (Doganci, Iannotti, & Ptak, 2023). Based on this evidence, our finding of increased right IFG-SPL coupling in individuals with ED may reflect the generation of motor representations, as well as the preparation of subsequent motor actions and their monitoring (Loffler, Haggard, & Bode, 2020; Si, Rowe, & Zhang, 2021). Notably, increased fronto-parietal resting-state connectivity has repeatedly been observed in obsessive-compulsive disorder (Fornaro & Vallesi, 2023). IFG-SPL hyperconnectivity may thus underlie a lack of cognitive control over compulsive behaviours, in this case, exercise.

Exploratory analyses further showed positive relationships between bilateral caudate-angular gyrus rsFC and the EDS factor tolerance in the ED group, although these results must be interpreted with caution, as they did not remain significant after correcting for multiple comparisons. Increased connectivity between the right dorsal striatum and angular gyrus has also been reported in obsessive-compulsive disorder (Park, Kim, Kim, Lee, & Kwon, 2020). The caudate plays an important role in drug tolerance (Dafny, Brown, Burks, & Rigor, 1979) and previous studies in cocaine addiction showed associations between cue-induced dopamine increases in the caudate and craving (Volkow et al., 2006; Wong et al., 2006), suggesting a neural mechanism for habit-based (automatised) craving (Tiffany, 1990). The angular gyrus is part of the DMN, in particular the posterior DMN (Damoiseaux et al., 2008), and is activated in episodic/contextual retrieval (Wagner, Shannon, Kahn, & Buckner, 2005) and simulating one's future (Schacter et al., 2012). For instance, it has been shown that angular gyrus damage contributed to deficits in recollective aspects of episodic memory (Berryhill, Phuong, Picasso, Cabeza, & Olson, 2007). Increases in caudate-angular gyrus connectivity may thus further drive the craving for exercise by activating autobiographical memory and future thinking.

The results of our study should be acknowledged with some limitations. First, healthy control participants were not active (exercise only one hour/week or less), which means that it was not possible to disentangle the effect of healthy, non-problematic exercise from ED. Future studies are warranted to compare brain alterations between non-dependent active control individuals and individuals along the continuum of ED. Also, prospective studies will help to explore causal relationships between brain alterations and ED. The reliability of the EDS to assess ED is suboptimal, as athletes and leisure exercisers may interpret the questions differently (Szabo et al., 2015) and it has been postulated that the prevalence of ED may be overestimated when using the EDS (Müller et al., 2014). To address this methodological inaccuracy, future studies should include thorough clinical assessments such as in-depth interviews (Szabo & Demetrovics, 2022). Another methodological issue of the study is that it was not preregistered. Our sample size was modest in regard to a neuroimaging study with 57 individuals in total. As the reliability of MRI results has been questioned (Zuo, Xu, & Milham, 2019), larger study samples and improved data sampling methods are needed and may reproduce our results. Finally, we focused our analysis on brain regions related to substance use disorders and compulsion according to our hypotheses, no whole-brain analyses were conducted. Interpretations should be made with this caveat in mind.

To conclude, this multimodal neuroimaging study provides evidence for subtle structural and functional brain alterations in individuals with ED. While ED may also be accompanied by effects on cognition-related prefrontal brain structures, changes in fronto-parietal and dorsal striatal-DMN connectivity might point towards a habitual and compulsive behaviour. Further large-scale and longitudinal studies are needed to improve the neurobiological understanding of ED to be able to disentangle the effects of exercise itself and its addiction-related symptoms.

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SUPPLEMENTARY MATERIAL

Supplementary data to this article can be found online at https://doi.org/10.1556/2006.2024.00028.

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