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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, Poultais, & 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



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

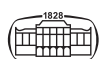
In order to identify individuals with ED, we used flyers and posters to raise awareness of the study. We specified that potential participants must: a) be between the ages of 18 and 70; b) exercise for ten hours or more per week; c) exercise despite illness or injury. Individuals who fulfilled these pre-screening 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	$\chi^2 = 0.01, p = 0.91$
Exercise hours per week, mean (SD)	NA	14.83 (5.11)	NA
MDD diagnosis, yes/no	0/28	14/15	$\chi^2 = 15.41, p < 0.001$
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.



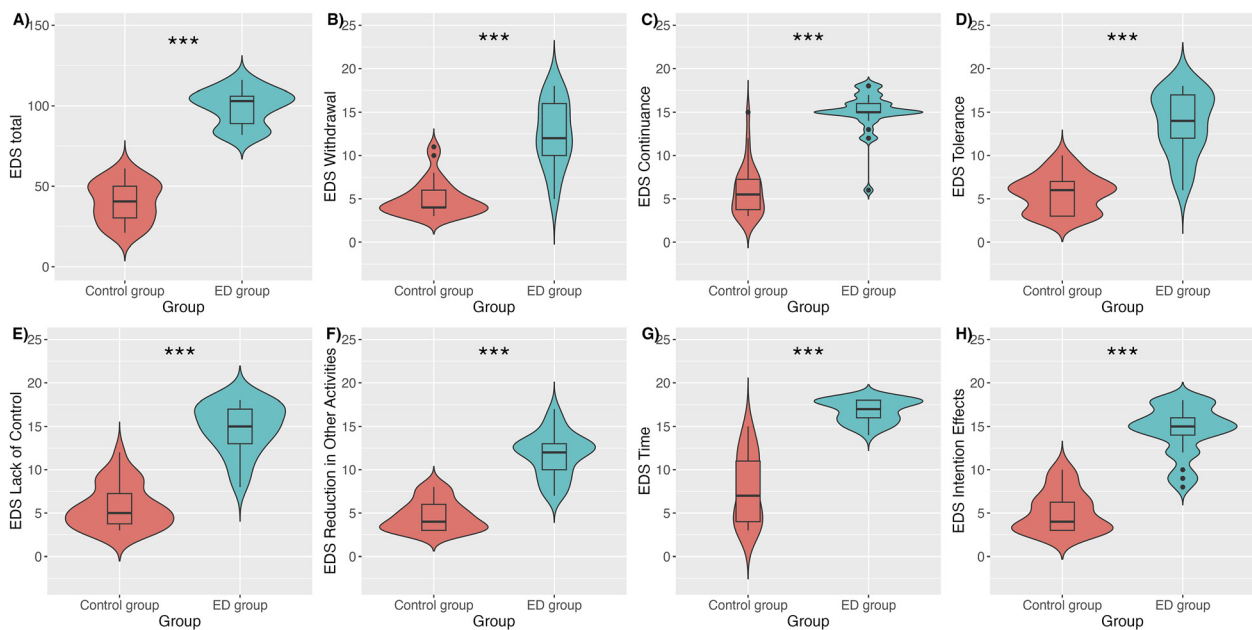


Fig. 1. Scores on the Exercise Dependence Scale (EDS) for both study groups including A) the total score and the subscales B) Withdrawal, C) Continuance, D) Tolerance, E) Lack of Control, F) Reduction in Other Activities, G) Time, and H) Intention Effects

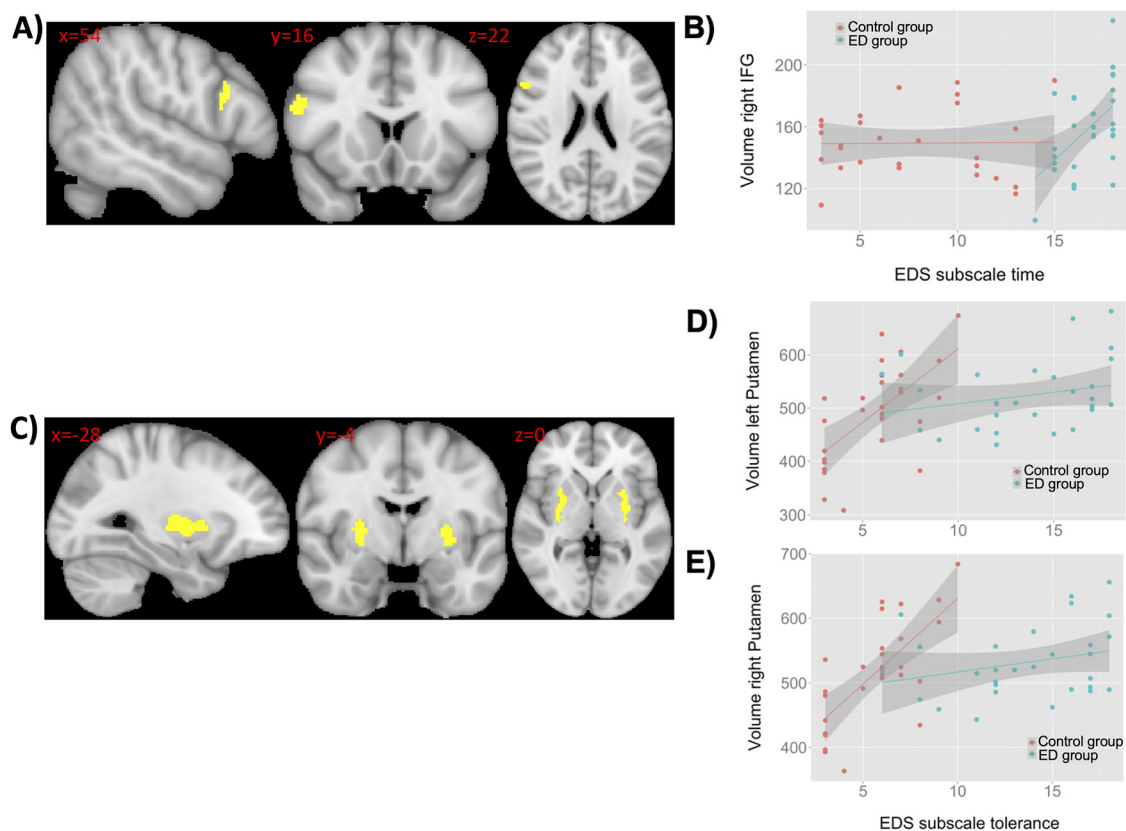


Fig. 2. A) Significant differences between study groups in the relationship between the EDS subscale time and volume of the right inferior frontal gyrus ($p_{FWE} = 0.02$, voxel number = 45, centre of mass: $x = 54$, $y = 16$, $z = 22$). B) Scatterplot depicting the associations between volume of the 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: $x = -28$, $y = -4$, $z = -2$) and right putamen ($p_{FWE} = 0.011$, voxel number = 221, centre of mass: $x = 26$, $y = 0$, $z = -4$), 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

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 $p < 0.007$).

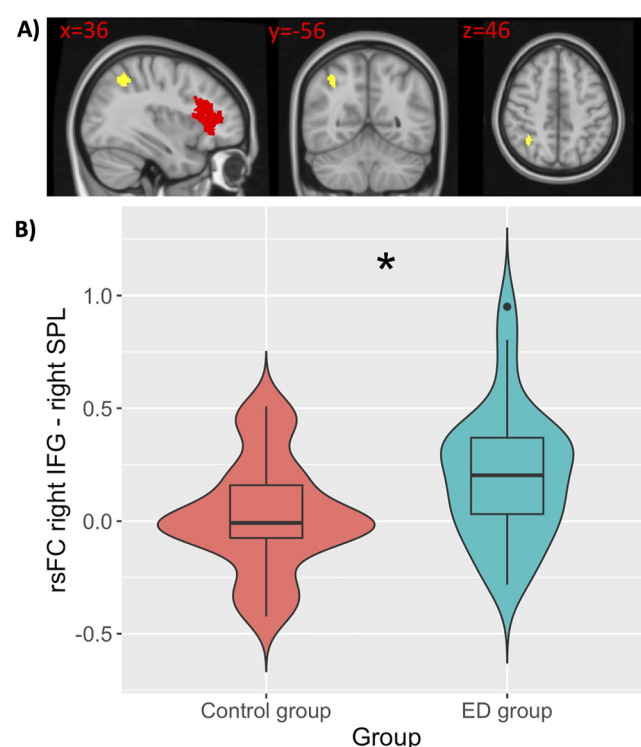


Fig. 3. A) Significant group difference in resting-state functional connectivity (rsFC) from the right inferior frontal gyrus (IFG, depicted in red) to a cluster in the left superior parietal lobule (SPL, depicted in yellow) ($p_{FDR} = 0.017$, voxel number = 82, $x = 36$ $y = -56$ $z = 46$). B) Distribution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

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

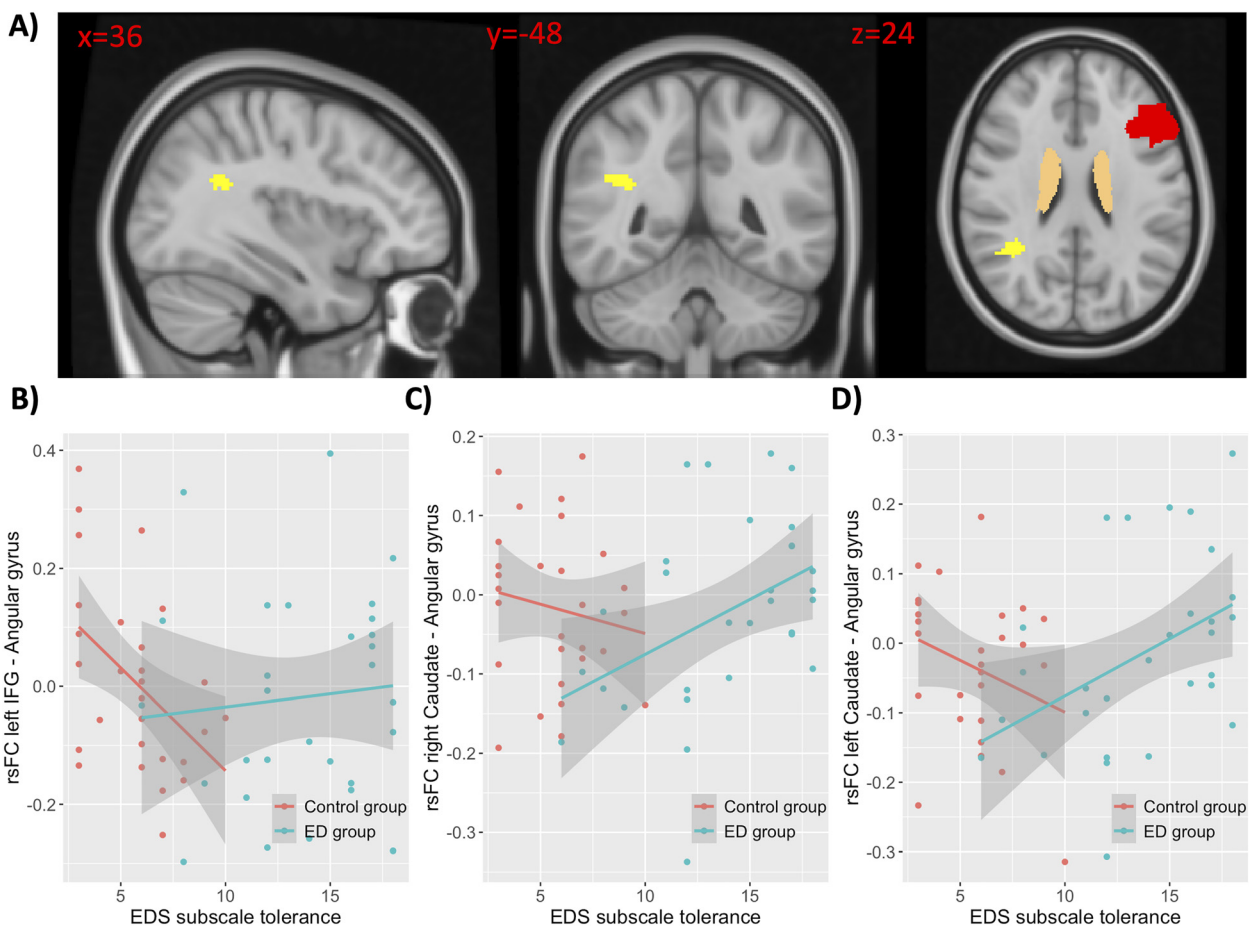


Fig. 4. A) Significant differences in the relationship between the EDS subscale tolerance and resting-state functional connectivity (rsFC) from selected seeds to a cluster in the angular gyrus between study groups ($p_{FDR} = 0.019$, voxel number = 88, $x = 36$ $y = -48$ $z = 24$). Scatterplots depict 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)

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



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 (Striener, 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

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REFERENCES

- Adkins, E. C., & Keel, P. K. (2005). Does “excessive” or “compulsive” best describe exercise as a symptom of bulimia nervosa? *International Journal of Eating Disorders*, 38(1), 24–29. <https://doi.org/10.1002/eat.20140>.
- Asscheman, S. J., Thakkar, K. N., & Neggers, S. F. W. (2015). Changes in effective connectivity of the superior parietal lobe during inhibition and redirection of eye movements: Supplementary issue: Behavioral neuroscience. *Journal of Experimental Neuroscience*, 9 JEN-S32736. <https://doi.org/10.4137/JEN.S32736>.
- Baekeland, F. (1970). Exercise deprivation - sleep and psychological reactions. *Archives of General Psychiatry*, 22(4), 365. <https://doi.org/10.1001/archpsyc.1970.01740280077014>.
- Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Beck depression inventory (BDI-II)* (10). Pearson. <https://psycnet.apa.org/doi/10.1037/t00742-000>.
- Bell, R. P., Garavan, H., & Foxe, J. J. (2014). Neural correlates of craving and impulsivity in abstinent former cocaine users: Towards biomarkers of relapse risk. *Neuropharmacology*, 85, 461–470. <https://doi.org/10.1016/j.neuropharm.2014.05.011>.
- Berryhill, M. E., Phuong, L., Picasso, L., Cabeza, R., & Olson, I. R. (2007). Parietal lobe and episodic memory: Bilateral damage causes impaired free recall of autobiographical memory. *Journal of Neuroscience*, 27(52), 14415–14423. <https://doi.org/10.1523/jneurosci.4163-07.2007>.
- Biddle, S. (2016). Physical activity and mental health: Evidence is growing. *World Psychiatry*, 15(2), 176–177. <https://doi.org/10.1002/wps.20331>.
- Brand, M., Rumpf, H. J., Demetrovics, Z., Muller, A., Stark, R., King, D. L., ... Potenza, M. N. (2022). Which conditions should be considered as disorders in the International Classification of Diseases (ICD-11) designation of “other specified disorders due to addictive behaviors”? *Journal of Behavioral Addictions*, 11(2), 150–159. <https://doi.org/10.1556/2006.2020.00035>.
- Choi, J., Cho, H., Kim, J. Y., Jung, D. J., Ahn, K. J., Kang, H. B., ... Kim, D. J. (2017). Structural alterations in the prefrontal cortex mediate the relationship between Internet gaming disorder and depressed mood. *Scientific Reports*, 7. <https://doi.org/10.1038/s41598-017-01275-5>.
- Colledge, F., Buchner, U., Schmidt, A., Wiesbeck, G., Lang, U. D. E., Puhse, U., ... Walter, M. (2022). Individuals at risk of exercise addiction have higher scores for depression, ADHD, and childhood trauma. *Frontiers in Sports and Active Living*, 3. <https://doi.org/10.3389/fspor.2021.761844>.
- Colledge, F., Cody, R., Buchner, U. G., Schmidt, A., Puhse, U., Gerber, M., ... Walter, M. (2020). Excessive exercise-A meta-review. *Frontiers in Psychiatry*, 11. <https://doi.org/10.3389/fpsyt.2020.521572>.
- Colledge, F., & Meyer, M. (2022). Exercise addiction—status, identification and treatment. *Praxis*, <https://doi.org/10.1024/1661-8157/a003875>.
- Cox, R., & Orford, J. (2004). A qualitative study of the meaning of exercise for people who could be labelled as ‘addicted’ to exercise—Can ‘addiction’ be applied to high frequency exercising? *Addiction Research & Theory*, 12(2), 167–188. <https://doi.org/10.1080/1606635310001634537>.
- Dafny, N., Brown, M., Burks, T. F., & Rigor, B. M. (1979). Morphine tolerance and dependence: Sensitivity of caudate nucleus neurons. *Brain Research*, 162(2), 363–368. [https://doi.org/10.1016/0006-8993\(79\)90299-3](https://doi.org/10.1016/0006-8993(79)90299-3).
- Damoiseaux, J. S., Beckmann, C. F., Arigita, E. J. S., Barkhof, F., Scheltens, P., Stam, C. J., ... Rombouts, S. (2008). Reduced resting-state brain activity in the “default network” in normal aging. *Cerebral Cortex*, 18(8), 1856–1864. <https://doi.org/10.1093/cercor/bhm207>.
- Demetrovics, Z., van den Brink, W., Paksi, B., Horvath, Z., & Maraz, A. (2022). Relating compulsivity and impulsivity with severity of behavioral addictions: A dynamic interpretation of large-scale cross-sectional findings. *Frontiers in Psychiatry*, 13. <https://doi.org/10.3389/fpsyt.2022.831992>.
- Di Lodovico, L., Poulmais, S., & Gorwood, P. (2019). Which sports are more at risk of physical exercise addiction: A systematic review. *Addictive Behaviors*, 93, 257–262. <https://doi.org/10.1016/j.addbeh.2018.12.030>.
- Ding, Q. G., Huang, L. N., Li, Q., Dong, Q., Qian, Z., Yin, X. W., & Liang, P. (2019). A functional magnetic resonance imaging study of exercise addiction. *Zhonghua yi xue za zhi*, 99(35), 2773–2776. <https://doi.org/10.3760/cma.j.issn.0376-2491.2019.35.011>.
- Doganci, N., Iannotti, G. R., & Ptak, R. (2023). Task-based functional connectivity identifies two segregated networks underlying intentional action. *Neuroimage*, 268. <https://doi.org/10.1016/j.neuroimage.2023.119866>.
- Dosenbach, N. U. F., Fair, D. A., Cohen, A. L., Schlaggar, B. L., & Petersen, S. E. (2008). A dual-networks architecture of top-down control. *Trends in Cognitive Sciences*, 12(3), 99–105. <https://doi.org/10.1016/j.tics.2008.01.001>.
- Douaud, G., Smith, S., Jenkinson, M., Behrens, T., Johansen-Berg, H., Vickers, J., ... James, A. (2007). Anatomically related grey and white matter abnormalities in adolescent-onset schizophrenia. *Brain*, 130, 2375–2386. <https://doi.org/10.1093/brain/awm184>.
- 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.
- Dupuy, O., Gauthier, C. J., Fraser, S. A., Desjardins-Creepeau, L., Desjardins, M., Mekary, S., ... Bherer, L. (2015). Higher levels of cardiovascular fitness are associated with better executive function and prefrontal oxygenation in younger and older women. *Frontiers in Human Neuroscience*, 9. <https://doi.org/10.3389/fnhum.2015.00066>.
- Everitt, B. J., & Robbins, T. W. (2013). From the ventral to the dorsal striatum: Devolving views of their roles in drug addiction. *Neuroscience and Biobehavioral Reviews*, 37(9), 1946–1954. <https://doi.org/10.1016/j.neubiorev.2013.02.010>.
- First, M. B., Williams, J. B. W., Karg, R. S., & Spitzer, R. L. (2016). *Structured clinical interview for DSM-5, clinician version (SCID-5-CV)*. Arlington, VA: American Psychiatric Association.
- Fornaro, S., & Vallesi, A. (2023). Functional connectivity abnormalities of brain networks in obsessive-compulsive disorder: A systematic review. *Current Psychology*. <https://doi.org/10.1007/s12144-023-04312-x>.



- Good, C. D., Johnsrude, I. S., Ashburner, J., Henson, R. N. A., Friston, K. J., & Frackowiak, R. S. J. (2001). A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage*, 14(1), 21–36. <https://doi.org/10.1006/nimg.2001.0786>.
- Goodman, A. (1990). Addiction - definition and implications. *British Journal of Addiction*, 85(11), 1403–1408. <https://doi.org/10.1111/j.1360-0443.1990.tb01620.x>.
- Grant, J. E., Potenza, M. N., Weinstein, A., & Gorelick, D. A. (2010). Introduction to behavioral addictions. *American Journal of Drug and Alcohol Abuse*, 36(5), 233–241. <https://doi.org/10.3109/00952990.2010.491884>.
- Gulker, M. G., Laskis, T. A., & Kuba, S. A. (2001). Do excessive exercisers have a higher rate of obsessive-compulsive symptomatology? *Psychology, Health & Medicine*, 6(4), 387–398. <https://doi.org/10.1080/13548500126535>.
- Hartwigsen, G., Neef, N. E., Camilleri, J. A., Margulies, D. S., & Eickhoff, S. B. (2019). Functional segregation of the right inferior frontal gyrus: Evidence from coactivation-based parcellation. *Cerebral Cortex*, 29(4), 1532–1546. <https://doi.org/10.1093/cercor/bhy049>.
- 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-British Medical Journal*, 357. <https://doi.org/10.1136/bmj.j1745>.
- Kim, S. J., Eom, H., Jung, Y. H., Kim, M. K., Kim, E., & Kim, J. J. (2022). Brain functional connectivity during and after imagery of gaming and alternative leisure activities in patients with internet gaming disorder. *Neuroscience Letters*, 772. <https://doi.org/10.1016/j.neulet.2022.136451>.
- Klugh-Brown, B., Di, X., Zweerings, J., Mathiak, K., Becker, B., & Biswal, B. (2020). Common and separable neural alterations in substance use disorders: A coordinate-based meta-analysis of functional neuroimaging studies in humans. *Human Brain Mapping*, 41(16), 4459–4477. <https://doi.org/10.1002/hbm.25085>.
- Ko, C. H., Hsieh, T. J., Wang, P. W., Lin, W. C., Yen, C. F., Chen, C. S., & Yen, J. Y. (2015). Altered gray matter density and disrupted functional connectivity of the amygdala in adults with Internet gaming disorder. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 57, 185–192. <https://doi.org/10.1016/j.pnpbp.2014.11.003>.
- Ko, C. H., Liu, G. C., Hsiao, S. M., Yen, J. Y., Yang, M. J., Lin, W. C., ... Chen, C. S. (2009). Brain activities associated with gaming urge of online gaming addiction. *Journal of Psychiatric Research*, 43(7), 739–747. <https://doi.org/10.1016/j.jpsychires.2008.09.012>.
- Koob, G. F., & Volkow, N. D. (2010). Neurocircuitry of addiction. *Neuropsychopharmacology*, 35(1), 217–238. <https://doi.org/10.1038/npp.2009.110>.
- Koob, G. F., & Volkow, N. D. (2016). Neurobiology of addiction: A neurocircuitry analysis. *Lancet Psychiatry*, 3(8), 760–773. [https://doi.org/10.1016/S2215-0366\(16\)00104-8](https://doi.org/10.1016/S2215-0366(16)00104-8).
- Landolfi, E. (2013). Exercise addiction. *Sports Medicine*, 43(2), 111–119. <https://doi.org/10.1007/s40279-012-0013-x>.
- 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>.
- 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>.
- Löffler, A., Haggard, P., & Bode, S. (2020). Decoding changes of mind in voluntary action-dynamics of intentional choice representations. *Cerebral Cortex*, 30(3), 1199–1212. <https://doi.org/10.1093/cercor/bhz160>.
- Mackey, S., Allgaier, N., Chaarani, B., Spechler, P., Orr, C., Bunn, J., ... Grp, E. A. W. (2019). Mega-analysis of gray matter volume in substance dependence: General and substance-specific regional effects. *American Journal of Psychiatry*, 176(2), 119–128. <https://doi.org/10.1176/appi.ajp.2018.17040415>.
- Meyer, M., Sattler, I., Schilling, H., Lang, U. E., Schmidt, A., Colledge, F., & Walter, M. (2021). Mental disorders in individuals with exercise addiction-A cross-sectional study. *Frontiers in Psychiatry*, 12. <https://doi.org/10.3389/fpsy.2021.751550>.
- Müller, A., Claes, L., Smits, D., Gefeller, O., Hilbert, A., Herberg, A., ... de Zwaan, M. (2013). Validation of the German version of the exercise dependence scale. *European Journal of Psychological Assessment*, 29(3), 213–219. <https://doi.org/10.1027/1015-5759/a000144>.
- Müller, A., Cook, B., Zander, H., Herberg, A., Müller, V., & de Zwaan, M. (2014). Does the German version of the Exercise Dependence Scale measure exercise dependence? *Psychology of Sport and Exercise*, 15(3), 288–292. <https://doi.org/10.1016/j.psychsport.2013.12.003>.
- Pando-Naude, V., Toxto, S., Fernandez-Lozano, S., Parsons, C. E., Alcauter, S., & Garza-Villarreal, E. A. (2021). Gray and white matter morphology in substance use disorders: A neuroimaging systematic review and meta-analysis. *Translational Psychiatry*, 11(1). <https://doi.org/10.1038/s41398-020-01128-2>.
- Park, J., Kim, T., Kim, M., Lee, T. Y., & Kwon, J. S. (2020). Functional connectivity of the striatum as a neural correlate of symptom severity in patient with obsessive-compulsive disorder. *Psychiatry Investigation*, 17(2), 87. <https://doi.org/10.30773/pi.2019.0206>.
- Putra, H. A., Park, K., Yamashita, F., Mizuno, K., & Watanabe, Y. (2022). Regional gray matter volume correlates to physical and mental fatigue in healthy middle-aged adults. *Neuroimage: Reports*, 2(4), 100128. <https://doi.org/10.1016/j.ynirp.2022.100128>.
- Pyeon, A., Choi, J., Cho, H., Kim, J. Y., Choi, I. Y., Ahn, K. J., ... Kim, D. J. (2021). Altered connectivity in the right inferior frontal gyrus associated with self-control in adolescents exhibiting problematic smartphone use: A fMRI study. *Journal of Behavioral Addictions*, 10(4), 1048–1060. <https://doi.org/10.1556/2006.2021.00085>.
- Qin, K., Zhang, F. F., Chen, T. L., Li, L., Li, W. B., Suo, X. L., ... Gong, Q. Y. (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>.



- Raichle, M. E. (2015). The brain's default mode network. *Annual Review of Neuroscience*, 38(38), 433–447. <https://doi.org/10.1146/annurev-neuro-071013-014030>.
- Schacter, D. L., Addis, D. R., Hassabis, D., Martin, V. C., Spreng, R. N., & Szpunar, K. K. (2012). The future of memory: Remembering, imagining, and the brain. *Neuron*, 76(4), 677–694. <https://doi.org/10.1016/j.neuron.2012.11.001>.
- Si, R. G., Rowe, J. B., & Zhang, J. X. (2021). Functional localization and categorization of intentional decisions in humans: A meta-analysis of brain imaging studies. *Neuroimage*, 242. <https://doi.org/10.1016/j.neuroimage.2021.118468>.
- Singer, H. S. (2013). Motor control, habits, complex motor stereotypies, and Tourette syndrome. *Annals of the new york academy of sciences*, 1304(1), 22–31. <https://doi.org/10.1111/nyas.12281>.
- Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-Berg, H., ... Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage*, 23, S208–S219. <https://doi.org/10.1016/j.neuroimage.2004.07.051>.
- Smith, S. M., & Nichols, T. E. (2009). Threshold-free cluster enhancement: Addressing problems of smoothing, threshold dependence and localisation in cluster inference. *Neuroimage*, 44(1), 83–98. <https://doi.org/10.1016/j.neuroimage.2008.03.061>.
- Striemer, C. L., Chouinard, P. A., & Goodale, M. A. (2011). Programs for action in superior parietal cortex: A triple-pulse TMS investigation. *Neuropsychologia*, 49(9), 2391–2399. <https://doi.org/10.1016/j.neuropsychologia.2011.04.015>.
- Szabo, A., & Demetrovics, Z. (2022). *Passion and addiction in sports and exercise*. Routledge.
- Szabo, A., Griffiths, M., Marcos, R., Mervó, B., & Demetrovics, Z. (2015). Focus: Addiction: Methodological and conceptual limitations in exercise addiction research. *The Yale Journal of Biology and Medicine*, 88(3), 303.
- Tiffany, S. T. (1990). A cognitive model of drug urges and drug-use behavior: Role of automatic and nonautomatic processes. *Psychological review*, 97(2), 147. <https://doi.org/10.1037/0033-295X.97.2.147>.
- Volkow, N. D., Wang, G. J., Telang, F., Fowler, J. S., Logan, J., Childress, A. R., ... Wong, C. (2006). Cocaine cues and dopamine in dorsal striatum: Mechanism of craving in cocaine addiction. *Journal of Neuroscience*, 26(24), 6583–6588. <https://doi.org/10.1523/jneurosci.1544-06.2006>.
- Wagner, A. D., Shannon, B. J., Kahn, I., & Buckner, R. L. (2005). Parietal lobe contributions to episodic memory retrieval. *Trends in Cognitive Sciences*, 9(9), 445–453. <https://doi.org/10.1016/j.tics.2005.07.001>.
- Weinstein, A., & Szabo, A. (2023). Exercise addiction: A narrative overview of research issues. *Dialogues in Clinical Neuroscience*, 25(1), 1–13. <https://doi.org/10.1080/19585969.2023.2164841>.
- Weinstein, A. M., Voss, M. W., Prakash, R. S., Chaddock, L., Szabo, A., White, S. M., ... Erickson, K. I. (2012). The association between aerobic fitness and executive function is mediated by prefrontal cortex volume. *Brain Behavior and Immunity*, 26(5), 811–819. <https://doi.org/10.1016/j.bbi.2011.11.008>.
- Weinstein, A., & Weinstein, Y. (2014). Exercise addiction- diagnosis, bio-psychological mechanisms and treatment issues. *Current Pharmaceutical Design*, 20(25), 4062–4069. <https://doi.org/10.2174/13816128113199990614>.
- Whitfield-Gabrieli, S., & Nieto-Castanon, A. (2012). Conn: A functional connectivity toolbox for correlated and anti-correlated brain networks. *Brain connectivity*, 2(3), 125–141. <https://doi.org/10.1089/brain.2012.0073>.
- Wong, D. F., Kuwabara, H., Schretlen, D. J., Bonson, K. R., Zhou, Y., Nandi, A., ... London, E. D. (2006). Increased occupancy of dopamine receptors in human striatum during cue-elicited cocaine craving. *Neuropsychopharmacology*, 31(12), 2716–2727. <https://doi.org/10.1038/sj.npp.1301194>.
- World Health Organization (2019). *ICD-11: International classification of diseases* (11th revision). World Health Organization.
- Xie, H. S., Zhang, F. F., Cao, Y., Long, X. P., Wu, B. L., Gong, Q. Y., & Jia, Z. Y. (2022). Brain default mode network mediates the association between negative perfectionism and exercise dependence. *Journal of Behavioral Addictions*, 11(3), 928–940. <https://doi.org/10.1556/2006.2022.00067>.
- Yin, H. H., Knowlton, B. J., & Balleine, B. W. (2004). Lesions of dorsolateral striatum preserve outcome expectancy but disrupt habit formation in instrumental learning. *European Journal of Neuroscience*, 19(1), 181–189. <https://doi.org/10.1111/j.1460-9568.2004.03095.x>.
- Zeng, X., Han, X., Gao, F., Sun, Y., & Yuan, Z. (2023). Abnormal structural alterations and disrupted functional connectivity in behavioral addiction: A meta-analysis of VBM and fMRI studies. *Journal of Behavioral Addictions*, 12(3), 599–612. <https://doi.org/10.1556/2006.2023.00025>.
- Zhang, M. Z., Gao, X. Y., Yang, Z. G., Wen, M. M., Huang, H. Y., Zheng, R. P., ... Zhang, Y. (2021). Shared gray matter alterations in subtypes of addiction: A voxel-wise meta-analysis. *Psychopharmacology*, 238(9), 2365–2379. <https://doi.org/10.1007/s00213-021-05920-w>.
- Zhang, F. F., Wang, S., Feng, Y., Qin, K., Li, H. R., Wu, B. L., ... Gong, Q. Y. (2021). Regional gray matter volume associated with exercise dependence: A voxel-based morphometry study. *Human Brain Mapping*, 42(15), 4857–4868. <https://doi.org/10.1002/hbm.25585>.
- Zhang, F. F., Xie, H. S., Wang, S., Li, F., Gong, Q. Y., & Jia, Z. Y. (2023). The role of the orbitofrontal cortex in exercise addiction and exercise motivation: A brain imaging study based on multi-modal magnetic resonance imaging. *Journal of Affective Disorders*, 325, 240–247. <https://doi.org/10.1016/j.jad.2023.01.030>.
- Zuo, X. N., Xu, T., & Milham, M. P. (2019). Harnessing reliability for neuroscience research. *Nature Human Behaviour*, 3(8), 768–771. <https://doi.org/10.1038/s41562-019-0655-x>.

