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ORIGINAL RESEARCH

Sex differences in resting-state cerebral activity alterations in internet gaming disorder

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Abstract

Although evidence has shown that the prevalence rates of Internet gaming disorder (IGD) differ between males and females, few studies have examined whether such sex differences extend to brain function. This study aimed to explore the sex differences in resting-state cerebral activity alterations in IGD. Thirty male participants with IGD (IGDm), 23 female participants with IGD (IGDf), and 30 male and 22 female age-matched healthy controls (HC) underwent resting-state functional MRI. Maps of the amplitude of low-frequency fluctuation (ALFF) and functional connectivity (FC) were constructed. A two-factor ANCOVA model was performed, with sex and diagnosis as the between-subject factors. Then, post hoc pair-wise comparisons were performed using two-sample t-tests within the interaction masks. The Barratt Impulsiveness Scale-11 (BIS-11) was used to assess the behavioral inhibition function. We found that the ALFF values in the orbital part of the left superior frontal gyrus (SFG) were lower in IGDm than in HCm, which were negatively correlated with BIS-11 scores. IGDm also demonstrated lower connectivity between the orbital part of the left SFG and the posterior cingulate cortex (PCC), the right angular gyrus, and the right dorsolateral prefrontal cortex than HCm. Furthermore, IGDm had lower seed connectivity between the orbital part of the left SFG and the PCC than ICDf. Our findings suggest that (1) the altered ALFF values in the orbital part of the left SFG represent a clinically relevant biomarker for the behavioral inhibition function of IGDm; (2) IGD may interact with sex-specific patterns of FC in male and female subjects.

Keywords Resting-state functional magnetic resonance imaging · Internet gaming disorder · Sex differences · Amplitude of low-frequency fluctuation · Functional connectivity

Introduction

Internet use is an integral part of the daily lives of many young adults, and a loss of control over Internet use could lead to various negative effects. Internet gaming disorder (IGD) has become a major public health concern worldwide among both adolescents and young adults. Gaming disorder, both online and offline, has been defined for the first time in the 11th Revision of the International Classification of Diseases (ICD-11). Males are hypothesized to be more prone to gaming disorder than females (Rehbein et al. 2010). An epidemiological study found that the overall prevalence of IGD was 4.4% in Europe and was higher among males than females (5.2% versus 3.8%) (Durkee et al. 2012). Among Hong Kong adolescents, the prevalence rates of IGD were found to range from 17 to 26.8%. Furthermore, a higher prevalence of IGD and more Internet addictive behaviors have been found in males than in females (Shek and Yu 2016). Additionally, male sex may be a risk factor for IGD (Munno et al. 2017). These studies have indicated that there are sex variances in the severity of Internet dependency. Factors such as high urgency and the motivation to play for immersion might predispose

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males to have a higher tendency for IGD (Billieux et al. 2011). In addition, males with IGD were found to be more affected by genetic influences than females with IGD. It has been suggested that males present more severe IGD symptoms, which could be partly due to a genetic vulnerability to poor effortful control (Li et al. 2014a). Moreover, high levels of testosterone in male adolescents may contribute to characteristics related to IGD, such as taking greater risks, being less responsive to punishment, and exhibiting more aggressive behaviors (Mehta and Beer 2010; Goudriaan et al. 2010). This male preponderance has led to questions concerning how sex effects are related to causes of IGD.

Previous studies have discussed the importance of sex differences in behavioral addictions (Fattore et al. 2014). However, the exact mechanisms underlying these sex differences remain unknown. Sex differences in the clinical features of substance addiction have also been highlighted (Becker et al. 2016). Researchers have suggested that sex differences in neural functioning and organization may influence many disorders, including substance addiction (Cahill 2006). Currently, differences in brain function and morphometry are being considered as possible explanations for such sex-related variability in substance addition (Ide et al. 2017; Franklin et al. 2014), which also suggests possible sex differences in the mechanism of brain alterations in IGD. IGD differs from substance addiction because no chemical or substance intake is involved. However, excessive Internet use may also lead to physical dependence similar to that observed in substance addiction (Meng et al. 2015). Evidence has revealed that many behavioral symptoms, even the neural mechanisms underlying IGD, resemble substance addiction (Weinstein et al. 2017). Clearly, defining these between-sex differences would be a critical step towards a better understanding of IGD. However, to date, few neuroimaging studies have been conducted to tackle this important issue.

Recent neuroimaging studies have provided evidence of structural and functional changes in several brain regions in IGD, particularly in the frontal lobe structures implicated in cognitive processes. Impaired function of the prefrontal cortex (PFC) may relate to high impulsivity, which, in turn, may contribute to the impaired inhibitory control associated with IGD (Weinstein et al. 2017). A functional study reported that male participants with IGD had lower functional connectivity (FC) of the left amygdala with the left dorsolateral prefrontal cortex (DLPFC), which was negatively correlated with impulsivity (Ko et al. 2015). A previous structural imaging study observed decreased grey matter volume (GMV) in the left DLPFC and bilateral anterior cingulate cortex (ACC) in IGD, including both male and female participants, and the GMV of the ACC was negatively correlated with a performance change in cognitive control, such as in inhibitory control (H. Wang et al. 2015). In an arterial spin-labeling perfusion study that recruited both male and female adolescents, the IGD group showed significantly increased resting cerebral blood flow in the PFC, a brain region that is important for executive function and inhibition (Feng et al. 2013). These imaging studies characterized how both frontal lobe structures and functions are altered in association with impaired inhibitory control in IGD. The PFC, as a core cognitive brain region, is also rich in sex hormone receptors and might develop at different rates in males and females (Cahill 2006); this brain region also plays a core role in the sex differences associated with substance addiction (Hu et al. 2015). In a previous study with a large sample of healthy males and females, researchers found evidence of effects of an interaction between behavioral inhibition and sex on structural brain characteristics, which were reflected in the PFC (Li et al. 2014b). However, whether between-sex differences can influence the neural processes in IGD remains unknown. A recent task fMRI study demonstrated that significant sex-related differences were observed in connectivity patterns during specific conditions of gaming in IGD (Dong et al. 2018). To our knowledge, no study has examined the sex-related differences using resting-state fMRI. The above studies aroused our interest in exploring the resting-state neural mechanisms underlying sex-related differences in IGD in the PFC region and the relationship of these differences with behavioral inhibition function.

The purpose of this study was to explore the sex-specific neuroimaging differences involved in IGD in resting-state. We used the Barratt Impulsiveness Scale-11 (BIS-11) to assess behavioral inhibition function in subjects with IGD. Based on previous studies, we hypothesized that male participants with IGD may show decreased brain activity in the PFC regions and that sex-specific changes in the brain may be associated with the subjects' clinical characteristics.

Materials and methods

Participants

The current study was approved by the Research Ethics Committee of Ren Ji Hospital and School of Medicine, Shanghai Jiao Tong University, China {No.[2016]079 k(2)}. All participants were informed of the aims of the study before their MRI examinations. Each participant provided written informed consent.

Between October 2016 and July 2017, 105 native Chinese-speaking, right-handed young participants, including 53 participants with IGD (30 males, 23 females) and 52 healthy controls (HC) (30 males, 22 females) were recruited for this study. The IGD participants were recruited from the psychological outpatient clinic at the Shanghai Mental Health Center and were interviewed by two experienced psychiatrists. The criteria were assessed according to the modified diagnostic questionnaire for Internet Addiction [i.e., (Young's

Diagnostic Questionnaire for Internet Addiction, YDQ)] test modified by Beard (Beard and Wolf 2001). It consists of eight "yes" or "no" questions, which were translated into Chinese. It includes the following questions: (1) Do you feel absorbed in the Internet (remember previous online activity or the desired next online session)? (2) Do you feel satisfied with Internet use if you increase your amount of online time? (3) Have you failed to control, reduce, or quit Internet use repeatedly? (4) Do you feel nervous, temperamental, depressed, or sensitive when trying to reduce or quit Internet use repeatedly? (5) Do you stay online longer than originally intended? (6) Have you taken the risk of losing a significant job, relationship, educational or career opportunity because of the Internet? (7) Have you lied to your family members or others to hide the truth of your involvement with Internet? (8) Do you use the Internet as a way of escaping from problems or of relieving an anxious mood? Respondents who answered "yes" to questions 1 through 5 and at least any one of the remaining three questions were classified as suffering from Internet addiction. To create a more controlled and homogenous IGD sample, only those who reported playing massive multiplayer online role-playing games, such as World of Warcraft, as their main use of the Internet were selected as participants for the study. They also needed to report their gaming history and game playing hours per weeks. We confirmed the reliability of the self-reports by talking with their parents. In addition, we evaluated the severity of IGD using the Chen Internet Addiction Scale (CIAS), which is a self-reported measure with good reliability and validity and has been used to measure the severity of Internet addiction. The questionnaire contains 26 items answered on a four-point scale, and the diagnostic cutoff point (63/64) exhibited the best diagnostic accuracy (Ko et al. 2005). The HC participants were recruited through advertisements in the community. They were similar in age and the number of educational years to the IGD participants. The HC participants were also tested with the YDQ criteria modified by Beard and Wolf and none of them met the diagnostic criteria for IGD.

None of the participants had the following: (1) previous hospitalization for psychiatric disorders or a history of psychiatric disorders, such as anxiety, depression or attention-deficit hyperactivity disorder; (2) substance use disorders; (3) mental retardation; (4) neurological illness or injury; and (5) intolerance to MRI. All participants were evaluated by brain MRI.

We used the BIS-11 to assess behavioral inhibition function. The BIS-11 is a questionnaire consisting of 30 items that is designed to assess the personality/ behavioral construct of impulsiveness. Participants rate their frequency of several common impulsive or non-impulsive behaviors/ traits on a scale from 1 (rarely/never) to 4 (almost always/always) and higher scores signify higher impulsivity (Patton et al. 1995). All questionnaires were initially written in English and then translated into Chinese.

MRI acquisition

Images were obtained using a 3.0 T MRI scanner (GE Signa HDxt 3 T, USA) with a standard 8-channel head coil. Restraining foam pads were used to reduce head motion, and earplugs were used to reduce scanner noise. Resting-state functional MRI (rs-fMRI) data were acquired using a gradient-echo echo-planar sequence (TR = 2000 ms, TE = 30 ms, FOV = 230 × 230 mm^2, matrix = 64 × 64, thickness = 4 mm, gap = 0, and slices = 34). For each participant, the rs-fMRI scan lasted 7 min and 20 s and a total of 220 volumes were acquired. During imaging, the participants were instructed to relax with their eyes closed while refraining from falling asleep and without engaging in any directed, systematic thought. The physiological state in the scanner was confirmed by a self-report completed by each participant immediately after the scan.

In addition, the following sequences were also performed to confirm the absence of structural lesions: (1) axial T1-weighted fast field echo sequences (TR = 331 ms, TE = 4.6 ms, FOV = 256 × 256 mm^2, matrix = 512 × 512, thickness = 4 mm, gap = 0, slices = 34); (2) axial T2-weighted turbo spin-echo sequences (TR = 3013 ms, TE = 80 ms, FOV = 256 × 256 mm^2, matrix = 512 × 512, thickness = 4 mm, gap = 0, slices = 34). All images were evaluated by two experienced neuroradiologists and no participants were excluded on this basis.

Data processing

Rs-fMRI preprocessing was performed using the Data Processing & Analysis for Brain Imaging (DPABI) (version 2.3) toolkit (http://rfmri.org/dpabi), which is based on Statistical Parametric Mapping (SPM) (http://www.fil.ion.ucl.ac.uk/spm) and Resting-State fMRI Data Analysis Toolkit (REST) (http://www.restfmri.net). After discarding the first 10 volumes of each functional time series, the remaining 210 images were corrected for slice timing and realigned to the first volume for head motion. Nuisance covariates, including the Friston-24 head motion parameters (six head motion parameters, six head motion parameters from the previous time point, and the 12 corresponding squared items) and the global, white matter and cerebrospinal fluid signals, were regressed out to minimize physiological noise. Afterward, the functional images were normalized to the standard Montreal Neurological Institute (MNI) space. The normalized volumes were resampled to a voxel size of 3 mm × 3 mm × 3 mm and spatially smoothed with an isotropic Gaussian filter of 6 mm full width at half maximum.

No participant exhibited head movement greater than 1.5 mm with a maximum translation in the *x*, *y*, or *z*-axes or a maximum rotation of 1.5° in any of the three axes. To further control the effect of head motion on the group results, mean framewise displacement (FD) for each participant, which was derived with the Jenkinson relative root mean square algorithm and considered the voxel-wise differences in motion in its derivation (Jenkinson et al. 2002; Yan et al. 2013), was included as a covariate in the following voxel-wised group analyses. In addition, two-sample t-tests were also performed to compare the group differences in head motion using the means of the FD Jenkinson measurements. No significant differences were found among any of the groups in terms of the mean FD.

Data analysis

The first step of the analysis was to identify brain regions with sex (Male, Female) and diagnosis (IGD, HC) interactions in the regional amplitude of low-frequency fluctuation (ALFF). Next, we proceeded in a hypothesis-driven manner to test for altered FC with broader brain circuitry specifically involving the brain regions (seed regions) in which a significant sex-diagnosis interaction in the ALFF was observed.

For the voxel-wise analysis, we set the threshold to uncorrected $p < 0.001$ and cluster size >32 voxels, corresponding to a corrected cluster $p < 0.05$ (AlphaSim-corrected), as was determined using the newest Analysis of Functional Neuroimages (AFNI) Program: 3dClustSim (https://afni.nimh.nih.gov/afni/), in which the z statistical image was used to estimate smoothness.

Calculation of ALFF

The ALFF measurement represents the sum of the signal powers across a low-frequency range that is derived from a Fourier decomposition of the rs-fMRI time series (Zang et al. 2007). After the abovementioned preprocessing, the time series for each voxel was bandpass filtered (0.01–0.08 Hz). The averaged square root was termed the ALFF. The individual ALFF map was normalized by the individual's global mean ALFF. The mean across the voxels for ALFF map was calculated, and the value at each voxel was divided by the mean individually.

Statistical analysis of ALFF

To test the sex-diagnosis interaction on ALFF, the statistical analyses were performed using two-factor analysis of covariance (ANCOVA) using SPM8, with sex (Male, Female) and diagnosis (IGD, HC) as between-subject factors. When interaction effects occurred, post hoc pair-wise comparisons were performed using two-sample t-tests within the interaction masks. Each model included age, years of education, and mean FD as covariates.

Calculation of seed-based FC

Brain regions in which a sex-diagnosis interaction in the regional ALFF was observed were considered seed regions; for each seed region, the blood-oxygen-level-dependent time series of the voxels within the seed region was averaged to generate the reference time series for the seed region. A correlation map for each participant was produced by computing the correlation coefficients between the reference time series and the time series from the other brain voxels. The correlation coefficients were then converted to z values using Fisher's z-transform to improve the normality of the distribution.

Statistical analysis of seed-based FC

To test the sex-diagnosis interaction on FC, a two-factor ANCOVA model was also specified using SPM8, with sex (Male, Female) and diagnosis (IGD, HC) as between-subject factors. Then, post hoc pair-wise comparisons were performed using two-sample t-tests within the interaction masks. Each model included age, years of education, and mean FD as covariates.

Correlation analysis

For the region showing sex-specific brain alterations, the ALFF values were extracted from both IGDm and IGDf. We hope to identify the relationships between the function of the PFC and the inhibition function. The correlations of ALFF values with the BIS-11 scores were assessed using partial correlation analyse, with age, years of education, the mean FD, CIAS scores, gaming history and game playing hours per weeks as covariates. For the correlation analyses, a two-tailed p value of 0.025 (0.05/2) with the Bonferroni correction was considered statistically significant.

Behavioral and clinical data

The demographic and clinical measures of the groups were compared using the Statistical Package for the Social Sciences (SPSS) software version 19.0 (Chicago, IL). A two-tailed p value of 0.05 was considered statistically significant.

Results

Demographic and clinical characteristics of participants

Table 1 lists the demographic and clinical measures for the male and female participants with IGD (IGDm, IGDf), together with the male and female healthy controls (HCm, HCf). No significant differences were found among any of the groups in

Table 1 Demographic and clinical characteristics of the participants

	Internet gaming disorder		Healthy controls				
	Males	Females	Males	Females	Main effect of diagnosis	Main effect of sex	Sex-diagnosis
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	F/*p* values	F/*p* values	F/*p* values
Number	30	23	30	22	–	–	–
Age (year)	21.87 ± 3.08	21.91 ± 2.92	20.73 ± 2.16	21.09 ± 3.85	3.037/0.084	0.071/0.790	0.035/0.852
Education (year)	11.03 ± 2.24	12.13 ± 2.80	12.07 ± 2.23	12.36 ± 3.70	1.391/0.241	1.685/0.197	0.555/0.458
BIS-11	61.57 ± 7.03	60.22 ± 8.11	52.27 ± 6.90	54.32 ± 7.08	**28.230/<0.001**	0.060/0.807	1.412/0.237
CIAS	74.43 ± 9.19	74.35 ± 9.21	41.97 ± 11.31	46.14 ± 9.97	**236.338/<0.001**	1.071/0.303	1.162/0.284
Game playing per week (Hours)	35.40 ± 14.47	33.09 ± 14.13	4.97 ± 2.24	3.77 ± 2.16	**216.397/<0.001**	0.746/0.390	0.076/0.783
Gaming history (Months)	26.60 ± 8.02	25.65 ± 7.78	11.00 ± 6.96	10.41 ± 4.92	**120.845/<0.001**	0.301/0.585	0.016/0.899

Abbreviations: SD = standard deviation; BIS-11 = Barratt Impulsiveness Scale-11; CIAS = Chen Internet Addiction Scale

p value <0.05 was considered statistically significant (highlighted in bold)

terms of age or years of education. In this study, the IGD group was composed of participants who scored over 64 on the CIAS. The participants with IGD had been playing games for at least 1 year and spent least 12 h on games per week (See Table 1 for details). According to the main effect of diagnosis, the participants with IGD had higher BIS-11 scores [$p < 0.001$; F (1,101) = 28.230] than the HC. According to the main effect of sex, no significant differences were observed between males and females in BIS-11 scores [$p = 0.807$; F (1,101) = 0.060]. According to the sex-diagnosis interaction effects, no significant differences were observed in BIS-11 scores [$p = 0.237$; F (1,101) = 1.412]. In addition, no significant differences were found in the BIS-11 scores between sexes in the IGD group (IGDm versus IGDf: $p = 0.520$; $t = 0.648$) or in the HC group (HCm versus HCf: $p = 0.300$; $t = -1.048$).

Regional neural functional changes

Main effect of diagnosis

A significant main effect of diagnosis was found in the ALFF values of the orbital part of the right middle frontal gyrus (MFG) and the orbital part of the left superior frontal gyrus (SFG) (Table 2).

Main effect of sex

Regarding the main effect of sex, no significant brain region differences were found between males and females.

Interaction of sex and diagnosis

A sex-diagnosis interaction effect on the ALFF values was identified in the orbital part of the left SFG (Table 2, Fig. 1a). Post hoc analyses revealed that the ALFF values in the orbital part of the left SFG were lower in IGDm than in HCm (Table 2, Fig. 1b), but no difference was observed between IGDf and HCf. The ALFF values in the orbital part of the left SFG did not significantly differ between IGDm and IGDf or between HCm and HCf.

Neural network functional changes

Main effect of diagnosis

With regard to the main effect of diagnosis, the IGD participants had lower connectivity between the orbital part of the left SFG and the posterior cingulate cortex (PCC), the left angular gyrus (AG), the right AG, and the left SFG compared with the HC participants (Table 2).

Main effect of sex

Regarding the main effect of sex, no significant brain region differences were found between males and females.

Interaction of sex and diagnosis

The seed was located in the orbital part of the left SFG. A sex-diagnosis interaction effect on FC was evident by the positive FC that was observed in the PCC, the right AG, and the right DLPFC (Table 2, Fig. 2a). Post hoc pair-wise comparisons showed that IGDm exhibited lower seed connectivity of the orbital part of the left SFG with the PCC, the right AG, and the right DLPFC than HCm (Table 2, Fig. 2b), but no significant group difference was observed between IGDf and HCf. In the IGD group, IGDm had lower seed connectivity of the orbital part of the left SFG with the PCC than ICDf (Table 2, Fig. 2b).

Table 2 Sex-diagnosis interaction and the main effect of diagnosis on ALFF/ FC

	Comparisons	Peak MNI coordinate region	BA	Peak MNI coordinates			Number of cluster voxels	Peak t value
				x	y	z		
ALFF	Main effect of diagnosis							
	IGD < HC	Orbit part of right middle frontal gyrus	11	33	57	-9	57	−5.035
		Orbit part of left superior frontal gyrus	11	−30	57	−6	35	−4.638
	Sex-diagnosis interaction							
	IGDm < HCm	Orbit part of left superior frontal gyrus	11	−30	60	−3	39	−5.332
FC	Main effect of diagnosis							
	IGD < HC	Posterior cingulate cortex	23	−6	−36	27	183	−5.3405
		Left angular gyrus	19	−39	−72	42	292	−6.2097
		Right angular gyrus	39	42	−57	21	145	−5.5485
		Left Superior Frontal Gyrus	8	−30	15	48	57	−5.8328
	Sex-diagnosis interaction							
	IGDm < HCm	Posterior cingulate cortex	23	−3	−63	21	138	−7.2092
		Right angular gyrus	39	45	−63	36	44	−7.5651
		Right dorsolateral prefrontal cortex	9	24	24	48	38	−6.0634
	IGDm < IGDf	Posterior cingulate cortex	23	0	−66	21	61	−5.1393

The threshold was set to voxel $p < 0.001$ and cluster size >32 voxels, corresponding to a corrected cluster $p < 0.05$ (AlphaSim-corrected)

Abbreviations: ALFF = amplitude of low-frequency fluctuation; FC = functional connectivity; MNI = Montreal Neurological Institute; BA = Brodmann's area; IGDm = male participants with Internet Gaming Disorder; HCm = male healthy controls; IGD = Internet Gaming Disorder; HC = healthy controls

In the HC group, no significant difference was observed between HCm and HCf.

Correlations between ALFF and clinical symptoms

The mean ALFF values of the orbital part of the left SFG were extracted from both IGDm and IGDf. In the IGDm group, we found that the participants with lower ALFF values in the orbital part of the left SFG exhibited higher BIS-11 scores ($p = 0.022$, $r = -0.439$, corrected). In the IGDf group, we found that there was no correlation between the ALFF values and the BIS-11 scores ($p = 0.487$, $r = 0.165$). The ALFF values in the orbital part of the left SFG were more strongly correlated with BIS-11 in IGDm than in IGDf (r = −0.439 vs. r = 0.165; $p = 0.0307$). (Fig. 3).

Discussion

In this study, we explored the sex-specific differences involved in IGD in cerebral activity. First, we observed ALFF values in the orbital part of the left SFG were lower in IGDm than in HCm. However, no difference was observed between IGDf and HCf or between IGDm and IGDf ($p < 0.05$, AlphaSim-corrected). The lower ALFF values in the orbital part of the left SFG were associated with higher impulsivity in IGDm, but this relationship was not observed in IGDf. These findings suggest a functional role of the SFG in mediating the clinical characteristics of IGDm. Second, when the orbital part of the left SFG was set as the seed region, IGDm had lower seed connectivity with the right DLPFC, the right AG, and the PCC than HCm. In addition, IGDm showed lower connectivity between the orbital part of the left SFG and the PCC than IGDf. These findings suggest that IGD may interact with sex-specific patterns of FC in male and female subjects.

Regional neural functional changes

In the present study, a sex-diagnosis interaction effect on the ALFF values was identified in the SFG. Our findings are partly consistent with previous ALFF studies comparing IGD and HC, which reported significant alternations in the PFC regions (Yuan et al. 2013; Park et al. 2016). These studies, including both male and female participants, suggest that the PFC may be the key area in IGD by using ALFF methods. Anatomically, the SFG is located at the superior part of the PFC and is involved in a range of processes reliant on cognitive control. However, further comparisons only showed that IGDm exhibit decreased ALFF in SFG as compared to HCm. The lack of group differences between IGDf and IGDm or between IGDf and HCf was unexpected. We speculate that the alteration in the SFG may be associated with the neural processes in IGDm.

Then, we expanded on the functional results with brain-behavioral correlations. We found the ALFF values in the orbital part of the left SFG were more strongly correlated with

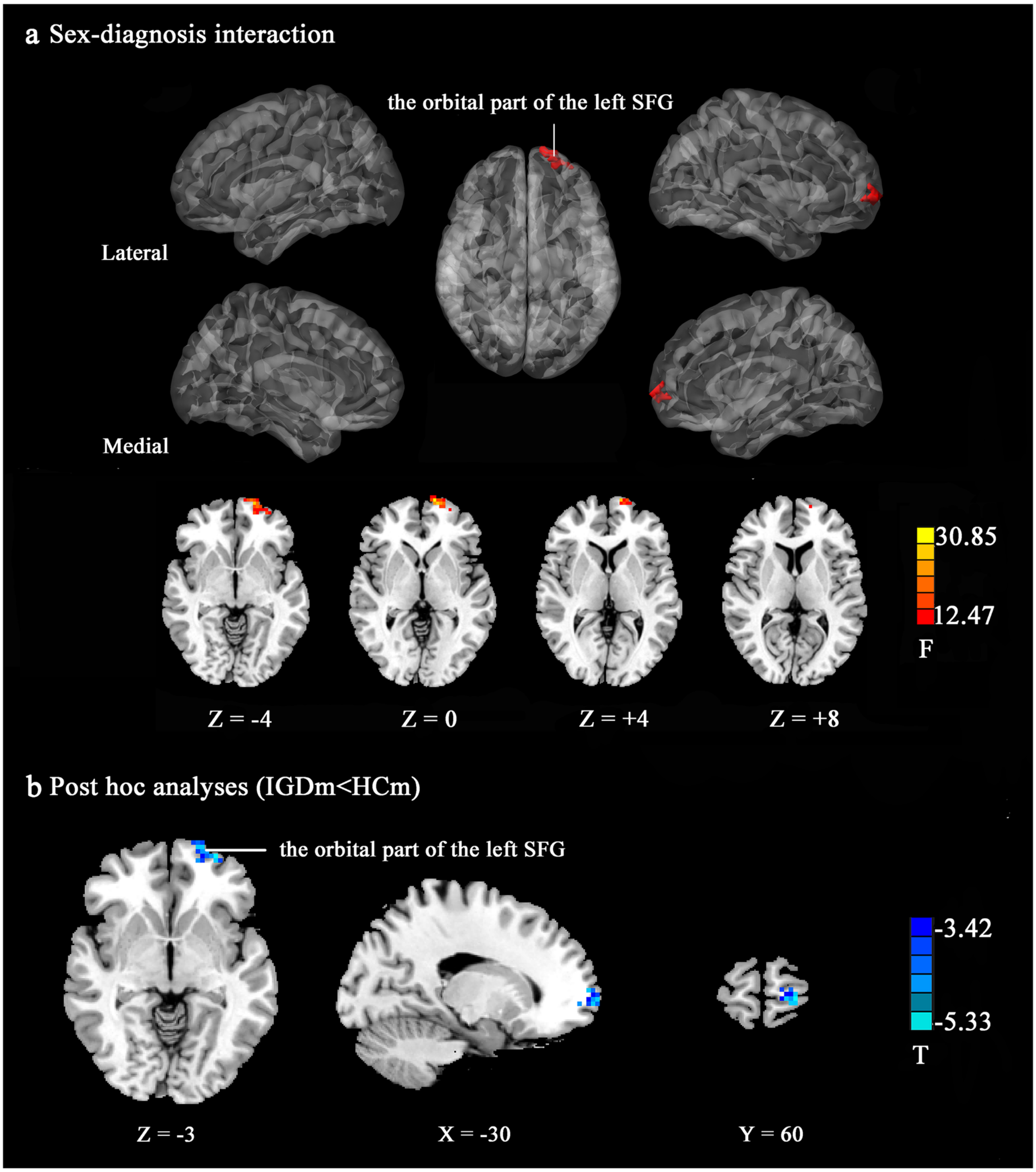

Fig. 1 ALFF results: A: Sex-diagnosis interaction effect on the ALFF maps: A significant sex-diagnosis interaction was identified in the orbital part of the left SFG. B: Post hoc analyses on the ALFF map: IGDm showed lower ALFF values in the orbital part of the left SFG than HCm. Abbreviations: ALFF = amplitude of low-frequency fluctuation; SFG = superior frontal gyrus; IGDm = male participants with Internet Gaming Disorder; HCm = male healthy controls; R = right hemisphere; L = left hemisphere

BIS-11 in IGDm than in IGDf. One of the core behaviors of IGD is impulse control deficits with a lack of control over Internet game playing. A preponderance of evidence suggests that impulsivity likely predisposes individuals to IGD (Argyriou et al. 2017). Previous neuroimaging studies reported that functional impairment in the PFC regions was associated with high impulsivity in IGD (Dieter et al. 2017; Dong et al. 2012). However, few studies have reported the relationship of sex-related differences with impulsivity characteristics in IGD. Numerous studies have found that IGD and substance addiction share similar neural mechanisms (Ko et al. 2009; Chen et al. 2014; de Ruiter et al. 2012). Alcohol use is correlated with impulsivity in both males and females, and this correlation is stronger in males (Stoltenberg et al. 2008). Additionally, a previous neuroimaging study revealed sex differences in impulsivity characteristics in persons with positive family histories (FHP) for alcoholism, and FHP participants showed greater activation in the inferior frontal gyrus during inhibitory responses. This effect was more pronounced in FHP males than females (DeVito et al. 2013). Another study

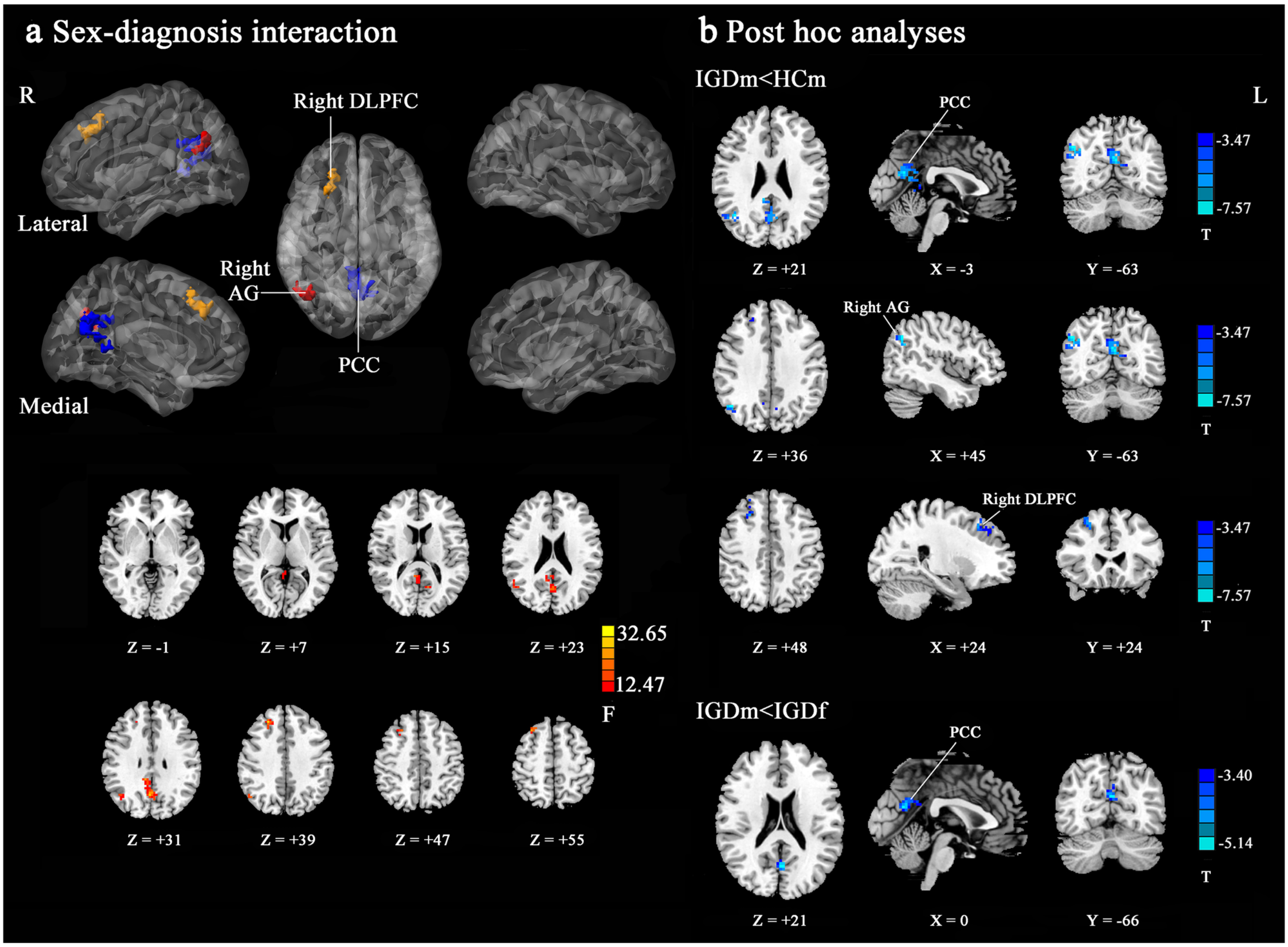

Fig. 2 FC results: A: Sex-diagnosis interaction effect on the FC maps: A significant sex-diagnosis interaction was identified within the FC changes between the orbital part of the left SFG and the PCC, the right AG, and the right DLPFC. Colours represent areas of the brain: blue = PCC; red = AG; orange = DLPFC. B: Post hoc analyses on the FC maps: IGDm showed lower FC values between the orbital part of the left SFG and the PCC, the right AG and the right DLPFC than HCm. IGDm exhibited lower FC values between the orbital part of the left SFG and the PCC than ICDf. Abbreviations: FC = functional connectivity; SFG = superior frontal gyrus; PCC = posterior cingulate cortex; AG = angular gyrus; DLPFC = dorsolateral prefrontal cortex; IGDm = male participants with Internet Gaming Disorder; HCm = male healthy controls; IGDf = female participants with Internet Gaming Disorder; R = right hemisphere; L = left hemisphere

demonstrated that a larger right SFG was found in male methamphetamine users, along with greater impulsivity (Kogachi et al. 2017). We found the dysfunctional PFC in IGDm may be associated with high impulsivity, and this finding is partly consistent with those of previous studies of substance addiction. As this relationship was not observed in IGDf, the findings suggest that different neural mechanisms may underlie behavioral in IGDf in comparison with IGDm.

However, the definite neural mechanisms underlying the brain-behavioral differences between sexes remain unclear. Some studies have demonstrated that the brain changes vary differentially by sex in substance addiction, suggesting either differential neurotoxic sensitivities for males and females or sexually dimorphic endophenotypic risk factors (Kvamme et al. 2016). However, no chemical or substance intake is involved in IGD. We speculate that males are more susceptible to the effects of long-term online-game playing in comparison with females. It has been proposed that greater PFC input into the dorsal striatum reflects enhanced top-down cognitive control and less impulsive responding. Compared to female rats, male rats displayed less efficient inhibitory control because myelin-associated protein levels in the PFC are lower in male rats than in females (Bayless and Daniel 2015). From studies in humans, the PFC is the last of the cortical structures to mature (Giedd 2004). In fact, the cortex matures later in males and does not catch up to females in the PFC regions by adulthood (Raznahan et al. 2010; Giedd 2004). The PFC and striatum are developmentally "off-balance," and this contributes to less top–down inhibitory control of motivated behavior (Ernst et al. 2006). In addition, males have shown lower levels of impulse control in comparison with females, and their impulse control also increased more gradually (Shulman et al. 2015). Given the putative role of inhibitory control in the initiation of IGD, young males may tend to experiment with

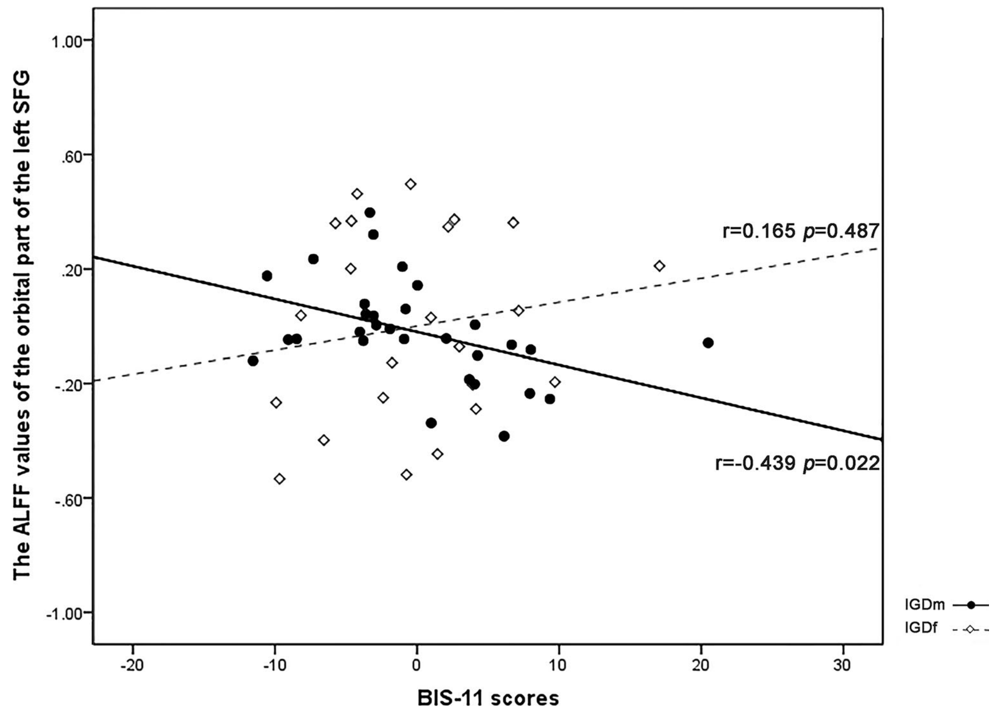

Fig. 3 Correlations between ALFF and clinical symptoms: Scatterplot showing the relationship between ALFF values of the orbital part of the left SFG and BIS-11 scores. The dots represent the adjusted values after controlling age, years of education, and the mean FD. In the IGDm group, the ALFF values in the orbital part of the left SFG were negatively correlated with the BIS-11 scores ($p = 0.022$, $r = -0.439$, corrected). In the IGDf group, we found that there was no correlation between the ALFF values and the BIS-11 scores ($p = 0.487$, $r = 0.165$). Abbreviations: ALFF = amplitude of low-frequency fluctuation; SFG = superior frontal gyrus; BIS-11 = Barratt Impulsiveness Scale-11; FD = framewise displacement; IGDm = male participants with Internet Gaming Disorder; IGDf = female participants with Internet Gaming Disorder

pathological Internet use to a greater degree than young females do. While this interpretation is speculative, future research will explore this hypothesis.

Neural network functional changes

The sex-diagnosis interaction effect on FC was evident, and these brain regions overlapped substantially with the executive control network (ECN) and the default mode network (DMN).

IGDm had lower SFG seed connectivity with the DLPFC in comparison with HCm. The DLPFC, an important brain region for governing cognitive-behavioral control, has been shown to play a core role in the ECN (Seeley et al. 2007). DLPFC function has been linked to cognitive processes that are necessary for the executive control of behavior: selecting and successfully monitoring behaviors that facilitate the attainment of chosen goals (Everitt et al. 2007; R. Z. Goldstein and Volkow 2011). The implication of the DLPFC function and structure with cognitive control deficits has been detected in IGD, and it could be an important feature in indexing impaired executive control within IGD (Yuan et al. 2017; Yuan et al. 2011; Yuan et al. 2016). Few previous studies have been focused on the investigation of sexual dimorphism in FC in IGD; in fact, Dong et al. explored the sex differences in IGD using task-fMRI. The observed FC differences in resting-state of our study partly resonated with this task-fMRI study, which suggested that the impaired executive control (DLPFC) was largely observed in IGDm during gaming. However, they also reported decreased FC in both IGDm and IGDf during the mandatory break (Dong et al. 2018). Our resting-state data only suggested that executive control was more impaired in IGDm in comparison with HCm. Both of these findings raise the possibility that different patterns of connectivity in DLPFC might be related to different levels of susceptibility to IGD between males and females.

IGDm also exhibited lower seed connectivity of the SFG with the AC and the PCC than HCm, with IGDm demonstrating weaker FC between the SFG and the PCC than ICDf. The PCC and the AG are core nodes within the DMN. Previous studies found sex differences among regions of the DMN in healthy controls. A meta-analysis demonstrated that males exhibit lower intranetwork connectivity in the DMN than females (Mak et al. 2017). In addition, regions involved in the DMN, such as the PCC, are smaller in males than in females (J. M. Goldstein et al. 2001). Some studies described a lower degree of FC between the PCC and PFC in males than in females (Tomasi and Volkow 2012). However, whether sex differences in DMN can influence the neural processes in IGD remains unknown. Interestingly, in this study, we observed a lower FC between the SFG and the PCC in IGDm in comparison with IGDf. It may reflect a sex-specific pattern of the DMN in IGD. Recent studies have shown that IGD is accompanied by altered activity patterns in the DMN (Dong et al. 2017; Li et al. 2015). Addicts' decreased FC in the DMN suggested deficits in cognitive control, including attention and self-monitoring (Ma et al. 2011). The altered modulation in DMN might also impair IGD subjects' ability to activate the decision-relevant brain regions effectively to choose advantageous options (L. Wang et al. 2016). The existing evidence indicates that the IGDm exhibits an imbalance in the DMN, and we speculate that this skewed balance may be linked to cognition processing.

Limitations

This study is characterized by some limitations. First, while our primary aim was to investigate the interaction of sex on cerebral activity differences, the current study failed to match the sex of IGD completely, such that only 23 IGDf and 30 IGDm were recruited. Second, given the small sample size, only tentative conclusions can be drawn. Third, the ALFF values did not significantly differ between IGDm and IGDf in the current study. This study needs to be replicated with a larger sample of subjects. Fourth, the origins of how these brain differences developed remain unknown. The cross-sectional design prevented us from determining whether the sex effects on the brain are vulnerability factors for IGD. A longitudinal study would help to clarify the roles of this variable in the development of IGD. In addition, most of the participants were young adults, and therefore, we could not demonstrate whether PFC development may contribute to IGD vulnerability. Hence, younger samples are needed in future studies.

Conclusion

Deficits in impulse inhibition are related to IGD, which is more prevalent in males than in females. Understanding the sex differences in brain activity and the relationship with impulse inhibition may help elucidate the neurobiological basis of IGD. In current study, we only found lower ALFF values in IGDm in comparison with HCm. The regional neural functional alterations were associated with higher impulsivity in IGDm, but this relationship was not observed in IGDf. These changes represent a clinically relevant biomarker for the behavioral inhibition function of IGDm. IGDm also demonstrated lower FC between the brain regions overlapped substantially with the ECN and DMN in comparison with HCm. In particular, IGDm demonstrated weaker FC between the SFG and the PCC than ICDf. We hypothesize that this skewed balance may highlight the importance of considering sex in IGD research.

Author contributions YZ, YD FL and JX were responsible for the study concept and design. YW, WJ, WD, MC contributed to the acquisition of data. YS, XH, and YW assisted with data analysis and interpretation of findings. YS drafted the manuscript. All authors critically reviewed content and approved final version for publication.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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