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Alterations of gray matter asymmetry in internet gaming disorder

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Structural asymmetry is a subtle but pervasive property of the human brain, which has been found altered in various psychiatric and neurocognitive disorders. However, little is known regarding potential alterations of structural asymmetry underlying internet gaming disorder (IGD). Therefore, this study aimed to investigate the structural features of gray matter asymmetry in IGD. High-resolution structural magnetic resonance imaging data were collected from 104 individuals with IGD and 104 recreational game users (RGUs). We applied a whole-brain voxel-based asymmetry (VBA) approach to determine the asymmetrical aberrations of gray matter in relation to IGD. Furthermore, the local abnormalities of structural asymmetry were employed as features to examine the effect of classification using a support vector machine (SVM). The results indicated that individuals with IGD as compared to RGUs showed asymmetrical alterations of gray matter in the medial prefrontal cortex (mPFC), orbitofrontal cortex, precuneus, middle temporal gyrus, superior parietal lobule and inferior temporal gyrus, regions implicated in hedonic motivation, self-reflection, information integration and visuospatial attention processing. Moreover, these atypical asymmetrical features can distinguish IGD subjects from RGUs with high accuracy. These results suggested that disrupted structural asymmetry of motivational reward, visuospatial and default mode circuits might be potential biomarkers for identifying pathological gaming dependence. These findings extended our understanding of structural underpinnings of IGD and provided new insights for developing effective interventions to alleviate compulsive gaming usage.

Internet gaming disorder (IGD) has received increased attention among scientists and policy makers owing to its speedy expansion over the last two decades. According to the Global Games Market Report from NewZoo in 2022, there are more than 3.2 billion active gamers in the world (https://newzoo.com/resources?type=trendreports%26tag=all). A recent meta-analysis revealed that the prevalence of internet gaming disorder (IGD) is incredibly high (9.9%) among adolescents and young adults, which has become a significant public problem, such as occupational, social and academic impairments[1]. IGD have been included in the Section 3 of the 5th edition of the Diagnostic and Statistical Manual (DSM-5, as a disorder that warrants further study)[2]. As a behavioral addiction, IGD shares comparable behavioral symptoms and neurobiological underpinnings with substance misuse[3–5].

Advances regarding neurobiological features of behavioral addiction can help to identify the theoretical mechanism of pathological gaming usage and develop interventions for preventing or treating such addiction. Even though the majority of previous studies on behavioral addiction have focused on functional abnormalities[6,7], meta-analysis of structural imaging studies on behavioral addiction have demonstrated gray matter alterations in multiple brain regions, including the dorsolateral prefrontal cortex, medial superior frontal gyrus, orbitofrontal gyrus, anterior cingulate cortex, striatum, motor cortex and precuneus[5,8]. Dovetailing with these observations, recent studies have showed that individuals with IGD exhibited the abnormalities of gray matter volume in the default mode circuits[9,10]. However, studies on the relationship between morphological alterations and IGD are also scarce and inconsistent.

Left–right asymmetry is fundamentally a neurobiological characteristic of human brain organization[11,12], which has been found altered in various psychiatric and neurocognitive disorders[13], including attention-deficit/hyperactivity disorder (ADHD)[14], obsessive–compulsive disorder[13], autism spectrum disorder[15], mood

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disorders[15]. One meta-analysis has demonstrated that rightward asymmetry (i.e., a shift toward the right hemisphere) of gray matter in frontal, temporal, parietal and limbic lobes were found in major depression disorder[16]. In the context of addiction, atypical structural asymmetry has been observed in prior studies of substance dependence[17]. In an exploratory study, patients with alcohol dependence exhibited an increased rightward asymmetry of gray matter in the cerebellum and lingual gyrus[18]. Recently, one mega-analysis study from the Addiction Working Group of the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) consortium has reported that participants with substance dependent were associated with less rightward asymmetry of the nucleus accumbens[19]. Although the literature indicates that IGD may share comparable psychological and neurobiological mechanisms of substance use disorder[3,20], no study has explored the relationship between atypical structural asymmetry and online gaming dependence.

Against this background, the current study aimed to investigate the structural brain asymmetry associated with pathological gaming usage. Of note, a majority of gaming users do not develop gaming addiction and exhibit recreational game users (RGUs) without adverse impact[21]. Thus, we aimed to identify whether existed any alterations of gray matter asymmetry in online gaming addiction by comparing IGD subjects to RGUs. Specifically, we applied a voxel-based asymmetry (VBA) analysis to determine asymmetry of homologous left–right hemispheric voxels over the whole brain with no a priori region of interest[22]. Due to the fact that IGD subjects experience repeated hedonic incentive and cognitive exercises, previous neuroimaging research has shown that excessive online gaming produces extensive abnormalities in reward, craving, and visuospatial attention circuits[5,8,23]. In addition, recent studies have suggested that individuals with IGD showed negative self-concept and avatar identification[24,25], which have been accompanied by decreased functional interaction within default mode network (DMN)[26,27]. Therefore, we hypothesized that individuals with IGD, as compared with RGUs, might show disruption of structural asymmetry in motivational reward, attention, sensorimotor, and DMN circuits.

Furthermore, we used a machine learning approach, called support vector machine (SVM), to identify the association between the anomalous structural asymmetry and IGD in the present study. The classification analysis of SVM can achieve reliable performance in uncovering the relationships between variables by training classifiers[28], which has as recently attracted more and more attention in the investigation of the neurobiological characteristics of addicts[29–31]. Thus, the structural asymmetrical abnormalities were employed as features to examine the effect of classification among IGD and RGUs subjects using the SVM approach.

Methods
Participants
The present study was approved by the Ethics Committee of Hangzhou Normal University (No. 2016E2KS031) and conducted from May 2016 to December 2021. All participants provided written informed consent in accordance with the Declaration of Helsinki. Two hundred eight participants (104 IGD and 104 RGUs) were recruited through posters and Internet advertisements. All participants were right-handed. Additionally, the two groups were matched on age and years of education (Table 1). All participants we selected were familiar with a multiplayer online battle arena (MOBA; e.g., League of Legends) game. Before formal scanning, each participant completed a written informed consent form and underwent a structured psychiatric interview (Mini International Neuropsychiatric Interview)[32]. All participants were also free of psychiatric and neurologic disorders (e.g., major depression, anxiety disorders, schizophrenia, and substance dependence disorders). All participants were medication-free and were instructed not to use any substances, including coffee, on the day of scanning.

Similar to previous studies[23,33], the IGD participants in the current study were defined as gamers who scored greater than 50 on Young's online Internet addiction test (IAT)[34] and met at least 5 of the 9 criteria for IGD per the DSM-5 definition[35]. In addition, the IGD participants need to respond positively to the following statement: "You expend most of your online time playing online games (> 80%) (Yes, No)." We selected RGUs using the following criteria: met fewer than five (of nine) of the proposed DSM-5 criteria and score lower than 50 on the Young's modified IAT. All participants needed to fill out a 10-item (1–10 Likert rating) questionnaire modified from an established scale of tobacco craving to measure their game craving before scanning[36]. Specifically, the cigarette was replaced by online game in the questionnaire.

Characteristic	IGD	RGU	*p*
Education (years)	14.66 ± 1.40	14.91 ± 1.66	0.24
Age (years)	20.93 ± 2.17	21.52 ± 2.55	0.092
IAT	66.14 ± 9.18	36.27 ± 7.14	0.001
DSM	5.94 ± 1.04	2.09 ± 1.25	0.001
Craving	52.17 ± 17.16	32.42 ± 15.43	0.001
Years playing games	1.86 ± 0.37	1.85 ± 0.38	0.86
Gaming time per week (h)	13.70 ± 9.65	8.33 ± 6.48	0.001

Table 1. Demographic data of different groups. *IGD* internet gaming disorder, *RGU* recreational game use, *IAT* internet addiction test, *DSM* The Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition).

Magnetic resonance imaging data acquisition

The magnetic resonance imaging data were acquired using a Siemens Trio 3T scanner (Siemens, Erlangen, Germany). Whole-brain T1- weighted MR images were collected via a three-dimensional spoiled gradient-recalled sequence in 486 s (192 slices, repetition time = 2530 ms, echo time = 2.34 ms, slice thickness = 1 mm × 1 mm × 1 mm, flip angle = 7º, inversion time = 1100 ms, field of view = 256 × 256 mm^2). Head motions were minimized by filling the empty space around the subjects' heads with sponge and fixing their lower jaws with tape.

MRI data analysis

The processing of high spatial-resolution structural images was performed using Computational Anatomy Toolbox (CAT12; http://www.neuro.uni-jena.de/cat/) in statistical parametric mapping software (SPM12; http://www.fil.ion.ucl.ac.uk/spm/software/spm12). To map structural asymmetries over the whole brain, the voxel-based asymmetry (VBA) approach as described by Kurth et al. (2015) was applied. Initially, all T1 images were segmented to generate optimally spatially normalized gray and white matter compartments. Then, the gray and white matter segments were flipped to create a symmetric DARTEL template. Finally, the modulation was applied by multiplying the normalized gray matter segments with the Jacobian determinant from the deformation matrix to correct the confounding effect of variance induced by individual whole-brain size. All asymmetry images (AI) were generated using an asymmetry formula for each homologous voxel using the original and flipped gray matter segments constrained to the right hemisphere: (Original − Flipped) / 0.5 × (Original + Flipped). Positive values reflect rightward asymmetry, negative values reflect leftward asymmetry. All asymmetry images were smoothed with an isotropic smoothing kernel of 8 mm. The analysis flow of the current study can be shown in Fig. 1.

Statistical analysis

To explore differences in the structural asymmetry between groups, a voxel-wise two-sample t-test was performed using the spatially normalized and smoothed AI maps and gender, age and educational level were regressed as covariates in all analyses. Whole-brain statistical significance was defined at $p < 0.05$ after FDR correction. To

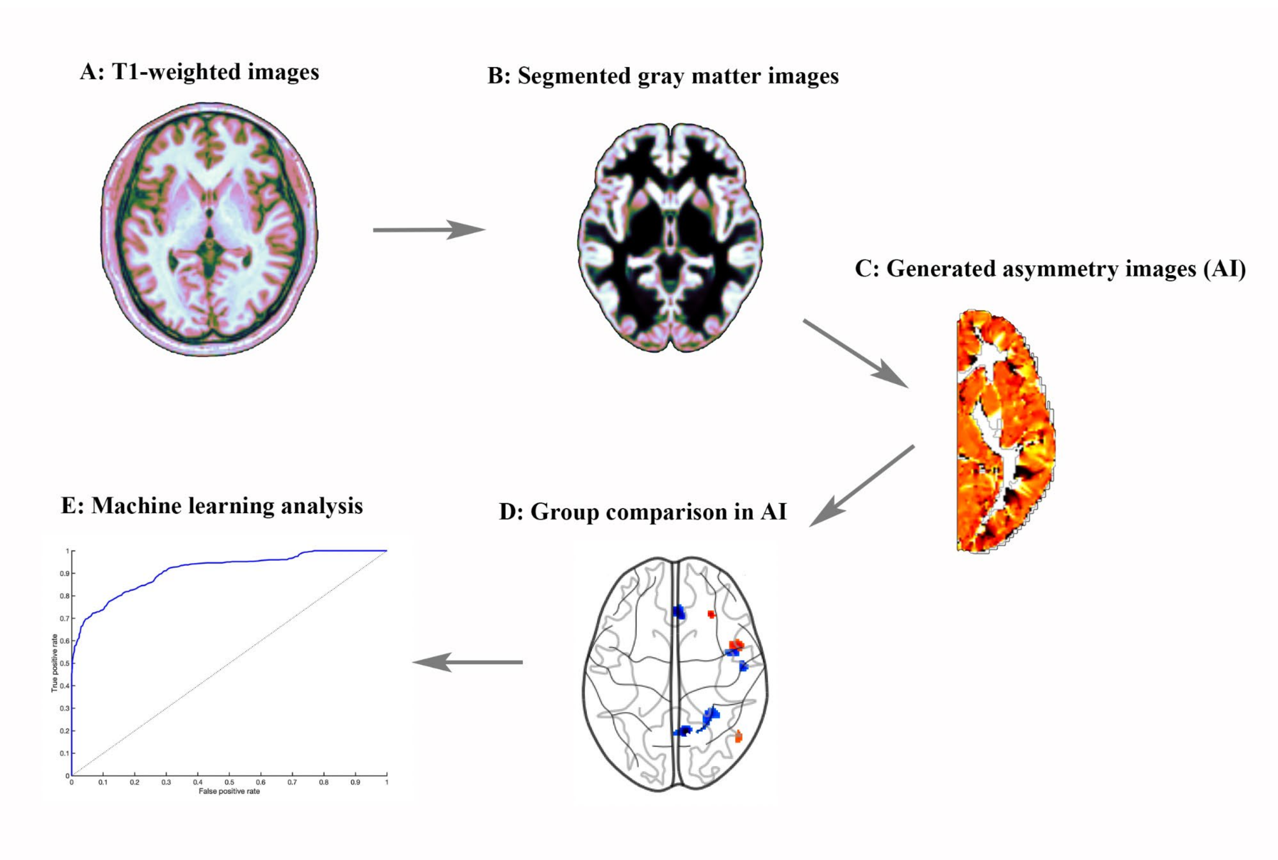

Fig. 1. The summary of the data analyses in the current study. From acquired T1-weighted images (**A**), the gray matter images (**B**) were segmented to generate asymmetry images (**C**). Then, two-sample t-test (**D**) and machine learning (**E**) analyses were performed to investigate the group differences in the asymmetrical metrics and their relationships with participants' craving.

delineate the altered asymmetrical patterns, the asymmetrical values extracted at the peak voxels were plotted between the IGD and RGUs groups.

Machine learning analysis

To evaluate whether the structural asymmetrical alterations could serve as potential classifying indices for IGD, machine learning analyses were performed using the support vector machine (SVM) algorithm with metrics of structural asymmetry that showed significant group differences. A linear SVM classifier was performed on the LibSVM library toolbox 3.23 in the MATLAB environment[37]. To estimate the overall accuracy of the classifier, a 10-fold cross-validation procedure was performed to divide the sample set into two complementary data sets randomly, of which one was the training data and the other was the test data. In brief, the SVM generated a maximal-margin hyperplane in the feature space and divided each training data into two groups. For each training data, 10-fold cross-validation procedure was also applied to determine the penalty coefficient of SVM for the best accuracy ((i.e., grid search method). The accuracy and area under the curve (AUC) were subsequently calculated by the test data to quantify the performance of classifiers. To avoid possible bias, this procedure was repeated 10 times and the average accuracy and AUC were obtained as the final result.

To estimate the statistical significance of classification accuracy and AUC, a permutation test was applied 1000 times. In permutation testing, the data label was randomly permuted before training. That is, the same cross-validation procedure mentioned above was performed on the permuted dataset. The P-value was determined by calculating the proportion of the 1,000 permutations for which the accuracy of the permuted data was equal to or larger than the accuracy of the original data. A smaller p value suggested that the classifier was well performing.

Results

Demographic characteristics

There were no significant differences between the IGD subjects and RGUs in age, education, and gaming history (all with $p > 0.05$). Consistent with the inclusion criteria, IGD participants had significantly higher scores on IAT scores, DSM scores, craving scores, and gaming time per week (Table 1).

Results of structural asymmetry

Whole-brain group comparison between IGD subjects and RGUs subjects was performed using VBA. The results showed that IGD subjects had significant rightward asymmetry of gray matter in the orbitofrontal cortex (OFC) and middle temporal gyrus (MTG) (Fig. 2; Table 2). In addition, significant leftward asymmetry of gray matter was found in the medial prefrontal cortex (mPFC), precuneus, superior parietal lobule (SPL), anterior and posterior inferior temporal gyrus (ITG) among IGD participants (Fig. 3).

Results of machine learning

To appraise the classification effects for IGD, a linear SVM analysis using disrupted asymmetrical values was used in the classification model. The performance of classifier achieved an accuracy of 82.46%. The area under

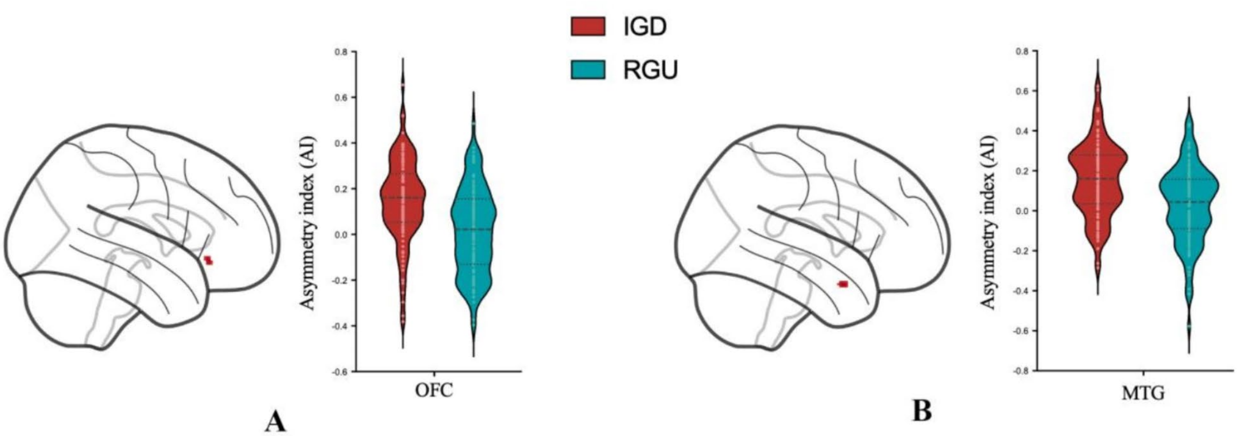

Fig. 2. Brain regions showing significant rightward asymmetry of gray matter in the orbitofrontal cortex (OFC) and middle temporal gyrus (MTG) among IGD participants. The clusters showing significant differences is shown on the left. To delineate the altered asymmetrical patterns, the violin diagram of group differences using the asymmetrical values extracted at the peak voxels is presented on the right.

Cluster number	x	y	z	Region	Peak intensity	Brodmann's area
Rightward asymmetry						
1	29	32	− 11	OFC	5.16	47
2	51	6	− 26	MTG	4.78	21
Leftward asymmetry						
1	4	32	50	mPFC	− 5.72	8
2	9	− 60	54	Precuneus	− 7.16	7
3	29	− 48	68	SPL	− 4.49	5
4	47	2	− 45	Anterior ITG	− 4.56	20
5	54	− 9	− 42	Posterior ITG	− 4.36	20

Table 2. Regions showing group differences on abnormal structural asymmetry. *OFC* orbitofrontal cortex, *MTG* middle temporal gyrus, *mPFC* medial prefrontal cortex, *SPL* superior parietal lobule, *ITG* inferior temporal gyrus.

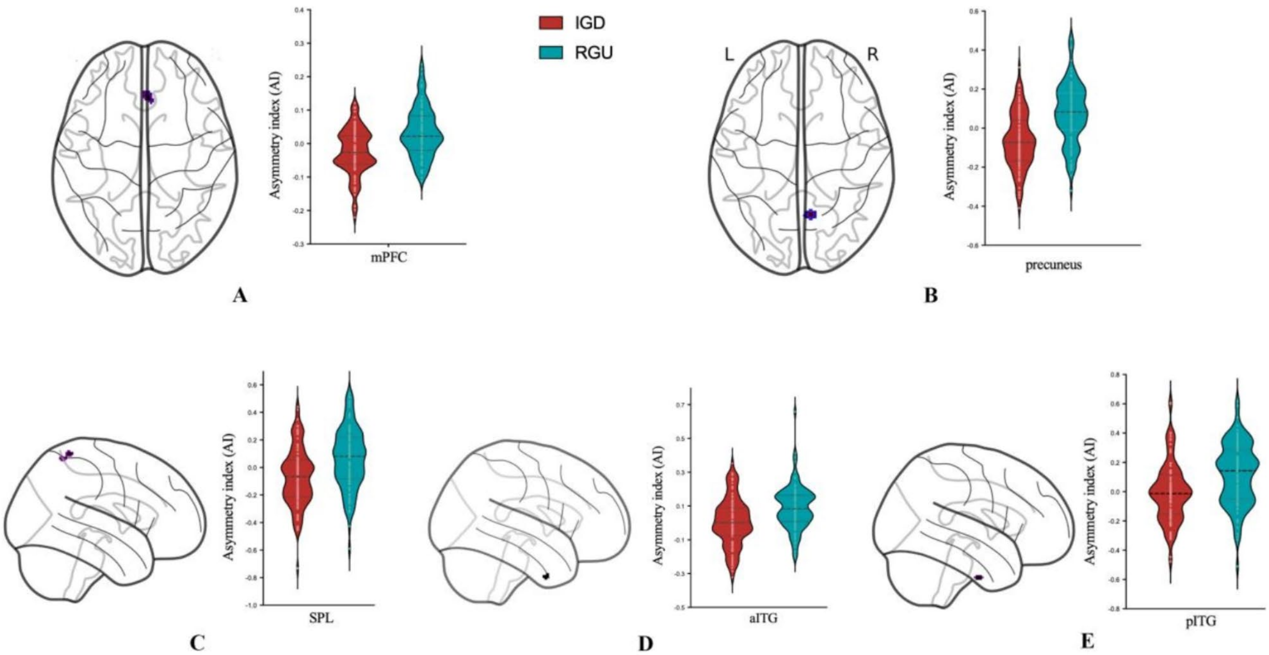

Fig. 3. Brain regions showing significant leftward asymmetry of gray matter in the the medial prefrontal cortex (mPFC), precuneus, superior parietal lobule (SPL) and inferior temporal gyrus (ITG) among IGD participants. The clusters showing significant differences is shown on the left. To delineate the altered asymmetrical patterns, the violin diagram of group differences using the asymmetrical values extracted at the peak voxels is presented on the right.

the receiver operating characteristic (ROC) curve (AUC) was 0.91 for the classification distinguishing IGD subject and RGUs. The p of the permutation test for accuracy and AUC were 0.001. The performance of the classifier is shown in Fig. 4.

Discussion

This preliminary study is, to our knowledge, the first to apply the voxel-based asymmetry (VBA) approach to investigate the neuroanatomical characteristics of gray matter asymmetry in IGD. First, we found that individuals with IGD as compared with RGUs had significant rightward asymmetry of gray matter in the OFC and MTG. Second, we revealed a greater leftward asymmetry of the mPFC, precuneus, SPL and ITG in IGD

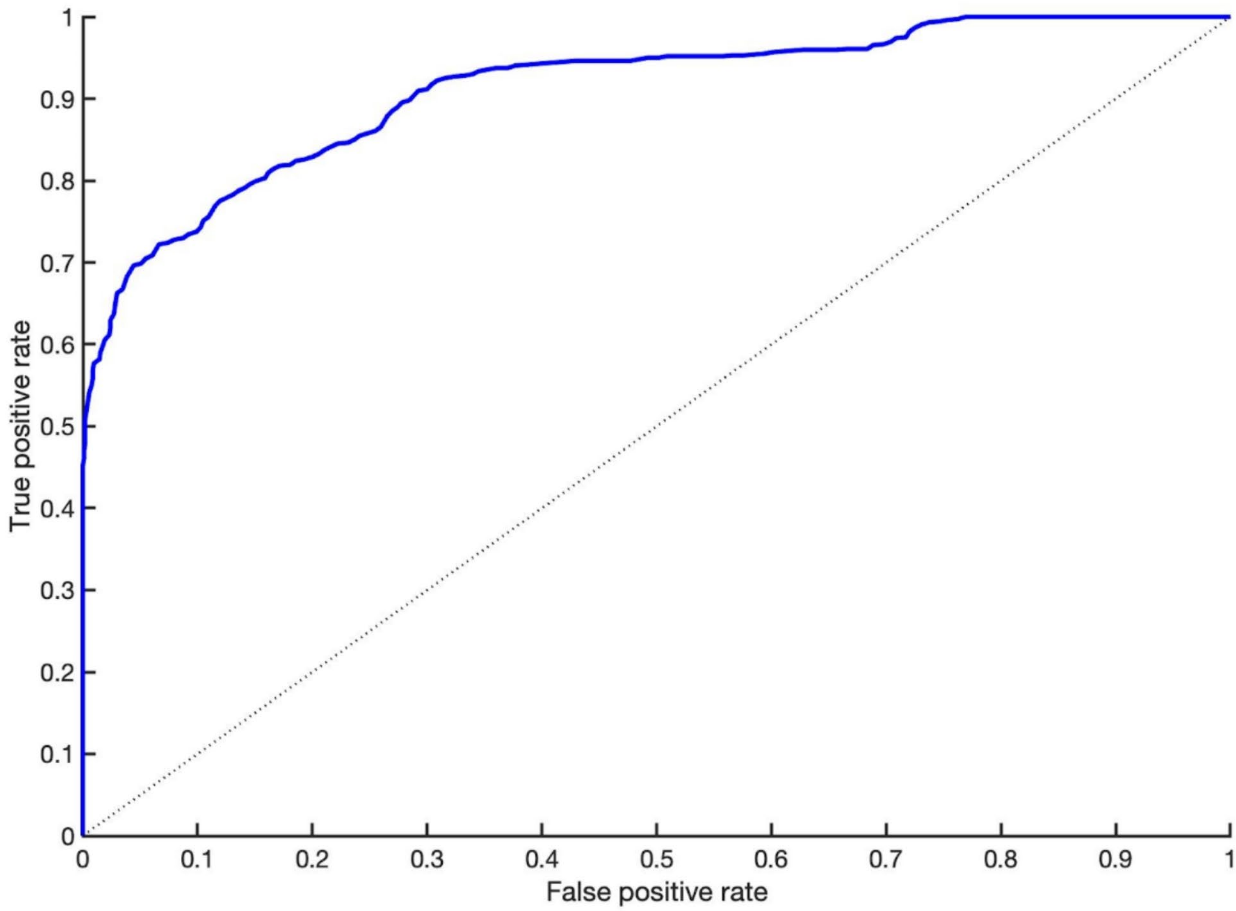

Fig. 4. Receiver operating characteristic curves of classification results using asymmetrical features of gray matter for differentiating the IGD subjects from the RGU subjects.

subjects. Furthermore, the machine learning analysis confirmed that the values in the aforementioned regions could be used to classify individuals with IGD from the RGUs with high accuracy and area under curve (AUC).

Brain lateralization is a quantified neurobiological feature that varies as a function of mental disorders and cognitive capacities[16]. Conforming to our expectation, we observed that IGD participants demonstrated rightward asymmetry of gray matter in reward-related regions (i.e., OFC and MTG). The OFC, a part of the mesocorticolimbic circuits, has been engaged in the reward-value computations and outcome anticipation of incentive stimuli, which may contribute to the problematic compulsive use in substance misuse[38,39]. Previous studies have suggested that both drug and behavioral addiction showed structural and functional brain abnormalities in OFC[40,41].Meanwhile, previous studies have noted that the MTG is not only related to face perception, audio-visual recognition and memory retrieval[42,43], but has also been implicated in the preferences for instant reward and incentive anticipation in substance dependence[44–46]. Recent studies have also reported that enhanced activation of OFC and MTG was associated with game urge/craving, risky decision-making, and reward prediction error in individuals with IGD[33,47,48]. Furthermore, supporting our findings, former studies have demonstrated that individuals with IGD showed decreased cortical thickness and volumes in these regions[49,50]. Altogether, the disturbance of structural asymmetry in reward-related regions observed in IGD may reflect enhanced reinforcement motivation and hedonic desire for gaming-cues in everyday life.

In addition, we identified that the IGD subjects, compared to RGUs, showed abnormalities of structural asymmetry in the visuospatial attention regions. The SPL, pertaining to the dorsal attention network, has a crucial role in visual perception, spatial cognition and attention[51,52], which has shown the distortion of activation and functional coupling during the processing of cue-induced craving and risky decision-making in substance use disorders[52,53]. Accordingly, prior studies have found that individuals with IGD showed morphological alteration of gray matter and increased activation in response to game-related cues in SPL[54,55]. The ITG is involved in the visual object recognition, face perception, and attentional selection, which has been found greater cortical thickness and hyperactivation in individuals with IGD as compared to RGUs[50,55]. In fact, to become an expert of online gaming, the IGD subjects need to attend to each tiny change in the screen and manipulate their avatars deftly to achieve the intended movement, such as dodging attacks of enemies and switching weapons, which reshapes players' visuospatial attention capacities[56,57]. Hence, the aberrations of structural asymmetry in the

SPL and ITG may suggest that extensive gaming usage causes the expansion of visual attention processing in response to gaming cues, which would activate the spatial, visual, and attention centers located in the parietal and temporal lobes.

Moreover, we found that individuals with IGD showed increased leftward asymmetry in the mPFC and precuneus, which has been repeatedly reported in the substance misuse[17]. The mPFC and precuneus, also known as midline regions of the DMN[58], has been implicated in self-reference, information integration, decision-making, and episodic memory retrieval for self-tagged addiction stimuli[27,59]. Furthermore, prior study has demonstrated that IGD subjects exhibited increased volumes in the mPFC and precuneus[10,60]. Previous research has proposed that maladaptive self-reflection processing plays a pivotal role in the development and maintenance of IGD, which is accompanied by impaired self-concept and large discrepancies between actual-self and virtual-avatar[61,62]. Supporting these assumptions, previous fMRI research has revealed that IGD subjects exhibited hyperactivations in the DMN midline regions during virtual-avatar relative to actual-self processing[24,63]. Our observed pattern of disturbed volumetric asymmetry in the mPFC and precuneus might reflect that individuals with IGD have deficits in the self-relevant cognitive processes that was accompanied by excessive gaming usage.

In the light of the dual-systems and exteroception model of addiction[59,64], the augmented exteroceptive processing and repeated hedonic experiences to external gaming cues may contribute to the disturbance of information integration and self-relevant evaluation, which produces the impaired insight and an intense desire for instant gratification. Consequently, the alterations of gray matter asymmetry in the motivation reward, visuospatial and default mode regions might reflect exaggerated gaming-related hedonic processing and greater predisposition to tag gaming cues as relevant to self, which promotes the indulgence of game playing and problematic avatar-identification in IGD[62]. In support of these findings, cortical asymmetry of brain oscillations in the two hemispheres via the resting electrophysiology have been found among individuals with substance use disorder and behavioral addiction, which was associated with reward bias and approach-related motivations[65,66]. It needed to note that there were different directions in the asymmetry of mPFC and OFC. The dissociation effect might imply that these two key hubs play different roles in the development and maintenance of pathological gaming usage, which warrants more research determine these differences.

Certain limitations of the present study warrant consideration. First, for a clear definition of research sample, this study excluded cases of comorbidity with mental health disorders, such as attention deficit and hyperactivity disorder (ADHD), depression and anxiety disorder. Recent studies have revealed that these variables had a bidirectional and complicated interplay with online gaming addiction[67,68]. Therefore, future studies are warranted to take these factors into account and might introduce them as covariates in the analysis. Second, given the nature of asymmetry index, the interpretation of altered asymmetry is not as clear cut as the functional alteration, which is not possible to deem one of the hemispheres as responsible for a given asymmetry[13,22]. we need to be cautious when interpreting these findings. Furthermore, cognitive measures such as reward-related tasks are needed to interpret the imaging findings further. Finally, due to the cross-sectional design, the present study has difficulty in determining whether the altered structural asymmetry was a predisposition to IGD or the corresponding consequences of extensive gaming usage. As such, future longitudinal studies are needed.

Conclusions

In sum, using VBA analysis, the present study highlighted neuroanatomical correlates between structural asymmetry and online gaming dependence. This study demonstrated that individuals with IGD showed asymmetrical abnormalities of gray matter in the regions that are responsible for motivational reward and visuospatial attention processing. Moreover, IGD subjects had alterations of structural asymmetry in the midline regions of the DMN (i.e., mPFC and precuneus). The machine learning results further support that the atypical features of the aforementioned regions might be potential neural markers for identifying the IGD subjects from the RGUs subjects. The findings may provide clues that extend our understanding the neurobiological characteristics of IGD.

Data availability

The datasets used and analyzed during the current study, and the corresponding code, available from the corresponding author on reasonable request.

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Author contributions

Shuaiyu Chen wrote the first draft of the manuscript. Shuaiyu Chen, Qian Zhuang, Jin Yan, Lixia Yuan and Tongtong Wang analyzed the data. Min Wang, Matthew Lock and Lingxiao Wang contributed to fMRI data collection. Qian Zhuang and Guang-heng Dong designed this research and edited the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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