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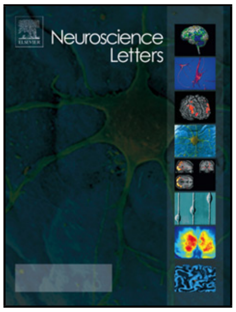

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Sex difference in the effect of Internet gaming disorder on the brain functions: Evidence from resting-state fMRI

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Highlights

- First study trying to explore sex difference in IGD by ReHo..
- Selecting RGU as control group overcome the limitations of low frequency game.
- the number of subjects is sizeable to make the results more scientific.

Abstract:

Objective: Studies have shown that males are more prevalence than females in Internet gaming disorder (IGD). This study was set to explore the sex difference on the effect of IGD in resting states of the brain.

Methods: Resting-state fMRI data were collected from 58 recreational Internet game users (RGU, male=29) and 46 IGD subjects (male=23). Regional homogeneity (ReHo) was used to calculate group difference between the subjects. A two-way ANOVA was used to explore the IGD-by-sex interactions. Correlations between addiction severity and the ReHo values were also calculated.

Results: Significant sex-by-group interactions were found associated with the brain features in the right posterior cingulate (rPCC), left middle occipital gyrus (lMOG), right middle temporal gyrus (rMTG), and right postcentral gyrus (rPG). Post-hoc analysis revealed that comparing with same-sex RGUs, male IGD showed decreased ReHo in the rPCC, and the ReHo in the rPCC was also negatively associated with Internet addiction test (IAT) scores for male subjects. Moreover, male IGDs showed increased ReHo, but female ones showed decreased ReHo, in both lMOG and rMTG, when comparing with same-sex RGUs.

Conclusions: Sex differences were observed in brain regions that are responsible for executive control, visual and auditory perception. These sex differences should be taken into consideration in future studies and the treatment of IGD.

Key words: Internet gaming disorder, sex differences, regional homogeneity, recreational Internet game users, functional magnetic resonance imaging.

Introduction

More and more adolescents and adults become addicted to internet games that making this the fastest growing addiction in the world [1]. Internet gaming disorder

(IGD) has also drawn increasing attention amongst scientists as a mental disorder [2, 3]. As a subtype of Internet Addiction, IGD has some of the following clinical features that are similar to substance use disorder (SUD): withdrawal symptoms, excessive behavior and cravings. This indicates that IGD and SUD may share some neurobiological mechanisms.

Recent research used functional magnetic resonance imaging (fMRI) to depict IGD from a neurological perspective to explain the underlying neural mechanisms [5]. FMRI evidences have shown that IGD was associated with changes to brain regions responsible for attention and control, decision-making, and sensory-motor coordination [6]. It has been suggested that IGD may impair individual's risk evaluation [7]. In a study comparing the reward/loss processing between IGD and the recreational Internet game users (RGU), the RGU showed greater activations in cortico-striatal and prefrontal cortex (PFC), compared to IGD [8]. Another study found higher fractional anisotropy in the thalamus and posterior cingulate (PCC) [9]. Higher FA in the thalamus was associated with greater severity of IGD [9]. In addition, individuals with IGD showed higher activations in inferior parietal lobule, middle occipital gyrus [10] and the dorsolateral prefrontal cortex (DLPFC) that were involved in visual processing and cognitive controlwhile dealing with gaming cue [11]. In structural study, IGD also showed decreased gray matter volume in inferior temporal gyri, MOG, and inferior occipital gyrus [12]. However, these studies have one common limitation: most of these used male-only subjects, because the prevalent of IGD in males than females [13-17]. Researches focused on female IGD are scarce.

Actually, sex plays an important role in addictive behaviors. Studies on cocaine and gambling addiction suggested that females are more likely to develop dependence, anxiety and depression [18]. The neuroimaging studies of cocaine dependence revealed that females showed more craving and had a higher activation in PFC than males [19]. In addition, higher activation has been found in tobacco dependent female superior frontal gyrus (SFG) and PCC [20]. Structurally, females with methamphetamine (METH) addiction showed a smaller rSFG and a larger nucleus accumbens than METH addicted males [21]. Another study showed that substance dependence individuals and controls differed in insula morphology, and those differences were modulated by gender [22]. Evidence from tasks and structure has reported sex differences in behavioral addiction. IGD have some similarly neural mechanism with SUD [4], and whether sex differences are also significant in IGD, it will be the focus of this study. In our previous work, the differences between groups of male IGD and female IGD in the two stages of game activity and forced mandatory break have been reported [23]. In the current study, we focus on exploring sex differences in IGD under resting-state.

Comparing with other resting-state analytical method, Regional homogeneity (ReHo) explores the regional synchronization of whole brain level without a priori knowledge of the structure or function of the brain [24]. Moreover, it is more sensitive to between-group differences [25]. To date, this approach has been widely used to reveal the potential neural mechanisms underlying dysfunctions in behavioral addiction [4, 26]. Current study measured ReHo in both male and female IGD and RGU groups. We hypothesized that 1) key ReHo differences between male and female groups would be reflected the brain regions that involved in underlying general cognitive functions. In addition, IGD was associated with excessive games, which required individuals to keep their eyes on the screen for a long time [26]. Therefore, we also hypothesized that 2) gender differences might be reflected in audiovisual perception.

Materials and methods

Participants:

The study was approved by Human Investigations Committee of Zhejiang Normal University. The written informed consent was obtained from all subjects. The whole process of experiment was conformed to the Declaration of Helsinki. Through advertisements, fifty-eight RGU (male=29， female=29) and forty-six IGD (male=23， female=23) were recruited. The RGU group plays online games but do not transition from non-addiction to addiction [8, 27]. RGU had more gaming experience and longer game duration than the general control group. All participants underwent assessment about structured psychiatric interviews (MINI) [28], excluded other psychiatric disorders (e.g., depression, anxiety, schizophrenia and SUD). In addition, participants were asked not to take drugs and substances (e.g., coffee, tea) on the day of the experiment.

Addiction screening criteria is based on Young’s online Internet addiction test (IAT) and the nine-item diagnostic criteria of IGD proposed by the DSM-5 committee [29]. The inclusion criteria of IGD are following: 1) IAT score more than 50 points [7, 30, 31]; 2) DSM-5 score more than 5 points; 3) Online games are main Internet activity; 4) Online game time more than 2 hours per day, and total game duration more than 2 years. The inclusion criteria for the RGU as follows: 1) IAT score less than 50 points and DSM-5 score more than 5 points; 2) The duration of the game refers to the IGD. 3) No feeling of guilt about playing online game and do not affect the individual life (e.g., school, family, work, social obligations). Table 1 shows the demographic information of the two groups.

Insert Table 1

Image acquisition

The fMRI resting data were acquired using 3T MRI system (Siemens Trio). During resting-state fMRI, the subjects were instructed to keep their eyes closed, remain motionless and awake. In addition, participants need minimize head movement. Specific parameters are as follows: repetition time (TR) = 2000ms, interleaved 33 slices, echo time (TE) = 30ms, thickness = 3.0 mm, flip angle = 90°, field of view (FOV) = 220mm × 220mm, matrix = 64 × 64. Each fMRI scan lasted

420s, and included 210 imaging volumes.

Preprocessing of image data

Preprocessing and ReHo process were conducted with DPABI_v2.3 (a toolbox for Data Processing & Analysis for Brain Imaging. http://rfmri.org/dpabi), based on MATLAB toolbox [32]. The first 10 volumes of each participant were discarded to minimize the instability of the initial signal and adapt participants to the scaning environment, leaving 200 volumes. The rest of the process included slice timing to correct for time differences, head-motion correction and spatial normalization using the standard EPI template. Data with head-motion exceeding 2.5 mm of maximum translation and 2.5° of maximum rotation during the scanning process were excluded from the further analysis. As nuisance signals, six motion vectors (e.g., cerebral spinal fluid, white matter) were regressed out. Following this, data were detrended to remove linear trends and temporally filtered (0.01–0.08 Hz) to remove low-frequency drift and high-frequency noise.

Next, we performed ReHo analysis on the pre-processed data. It need to say that ReHo is a voxel-wise based data-driven approach [33], calculating Kendall's coefficient concordance of the time series of a given voxel with its nearest neighbors (26 voxels) to measures the functional coherence of adjacent regions [34]. To get the standardized ReHo map, divided the raw ReHo map by the global mean ReHo, and Spatial smoothed with a Gaussian kernel of 4 * 4* 4 mm^3 full-width at half-maximum [35].

Statistical analyses

ReHo analysis

The between-group comparisons were conducted with analyses of variance (ANOVA). The ANOVAs were defined by two between-subjects factors (IGD vs. RGU; males vs. females). To examine interaction in ReHo, we performed two-way ANOVA among pairs of the four groups: 1.male with IGD (mIGD); 2.female with

IGD (fIGD); 3.male with RGU (mRGU); 4.female with RGU (fRGU). The resultant statistical map was set at a combined threshold of $p < 0.01$ (3dClustSim Correction) and a minimum cluster size was 150 voxels.

Correlation analysis

To examine brain–behavior relationships, the association between the ReHo strength and the severity of the disorder was calculated by extracting ReHo value in the brain area with significant interactions. Pearson correlation analysis tested relations between the ReHo and IAT. Statistical analyses were conducted using SPSS 18.0 Statistics, with $p < 0.0125$.

Results

Significant IGD-by-sex interactions were found associated with the rPCC, the lMOG, the right middle temporal gyrus (rMTG) and the right postcentral gyrus (rPG). (*Table 2, Figure 1*).

Insert Table 2 and Figure 1

In rPCC ($F_{interation} = 20.473$, $p = 0.000$, uncorrected for multiple comparisons), the mIGD showed lower ReHo compared to mRGU ($p = 0.000$), but not significant between fIGD and fRGU. IAT scores was significant negatively associated with ReHo in the males ($r = -0.540$, $p = 0.000$). (*Figure 2*).

Insert Figure 2

The results of lMOG ($F_{interation} = 21.910$, $p = 0.000$, uncorrected) and rMTG ($F_{interation} = 28.081$, $p = 0.000$, uncorrected) were similar, the mIGD showed higher ReHo compared to mRGU (*lMOG:* $p = 0.000$; *rMTG:* $p = 0.004$), but the fIGD had lower ReHo compared to fRGU (*lMOG:* $p = 0.012$; *rMTG:* $p = 0.000$). According to correlation analysis, IAT scores were negatively associated with ReHo in rMTG in female subjects (*r = -0.543, p = 0.000*). (*Figure 3, Figure 4*).

Insert Figure 3, Figure 4

In rPG ($F_{interation}$ = *22.456, p = 0.000*, uncorrected), the mIGD showed lower ReHo (*p = 0.000*), but the female IGD had higher ReHo (*p = 0.002*), compared to sex-matched controls. IAT scores were negatively associated with ReHo in the male (*r = -0.348, p = 0.011*), but positively correlated with it in the female (*r = 0.416, p = 0.002*) (*Figure 5*).

Insert Figure 5

Discussion

In this study, we collected an rs-fMRI data to investigate the sex differences of IGD. IGD-by-sex interaction in the following brain areas was observed: rPCC, lMOG, rMTG and rPG. We concluded that these differences may reflect how IGD affecting males and females differently in function of risk assessment and audiovisual information processing.

IGD impaired the cognitive function of male subjects but not female

In the rPCC, the mIGD showed lower ReHo compared to mRGU, but no differences were found between fIGD and fRGU. The decreased ReHo of mIGD indicates the decline of regional synchronization in the PCC during the resting-state, compared with mRGU. In addition, this change was further examined in the correlation analysis revealed a negative correlation between the ReHo and the IAT scores in the male group. Previous studies have reported that healthy males show stronger activation and functional connectivity in the limbic system during playing games, compared to healthy females [36]. This result is consistent with the findings.

The PCC is an integral part of default mode network (DMN) and playing an important role in attention and self-monitoring. Furthermore, the PCC involves the related cognitive functions and executive control, coupling between DMN and executive control network (ECN) [37]. Previous studies found abnormal resting state indicators in the PCC, including abnormal ReHo value and amplitude of low fluctuation in IGD [4, 38, 39]. Another studies revealed compromised functional connectivity between PCC and cerebellar regions of the alcohol addiction group, comparing to the healthy controls [40]. It has been suggested that the desynchronization of fMRI signal in the PCC in the alcohol addiction group purposed a compensatory mechanism for task processing [40, 41]. In addition, PCC was associated with the estimation of game information and the reward system [42, 43]. Therefore in the current study, the abnormal decreased ReHo in male group in the PCC may be associated with weakened function of risk assessment of Internet gaming, or a compensatory mechanism of the weakened risk assessment function.

Another study showed that the PCC was associated with the mental simulation of routes [44]. Kim' research [4] suggested that abnormal ReHo in the PCC may be involved immersion of the internet gaming. Therefore, the decreased ReHo may also indicate that mIGD are more likely to be immersed in Internet games, compared to mRGU, while fIGD do not show this trend in our study. We speculate that this difference could be related to gaming motivation. In the questionnaire on motivation, mIGD showed strong participation motivation, while females showed more entertainment motivation (lower participation motivation). In addition, it has been showed that greater activation was found in male mesocorticolimbic system during computer game playing, which was also attributable to higher motivational states [36]. Therefore, motivation may be a factor that needs to be considered in the future study of sex-specific differences in IGD.

IGD affect the audiovisual function of both men and women

Both lMOG and rMTG showed a similar negative multiplicative interaction: mIGD showed higher ReHo compared to mRGU, and the fIGD had lower ReHo compared to fRGU. Moreover, there were significant ReHo differences between men and women in RGUs, as well as between men and women who are suffering from IGD. The lMOG (Brodmann area 18) is located on the occipital lobe which is the visual processing center of the mammalian brain [45]. The occipital lobe' primary function was to deal with different visual information, such as visuospatial processing, color resolution, and motion perception [46-48]. The rMTG is found in the the lateral of the temporal lobe, the key area for auditory processing [26]. Current ReHo differences show interesting sex-by-group interactions in the audiovisual area.

On the one hand, the ReHo differences between men and women in RGUs indicate that inherent gender difference in brain function. Many studies have demonstrated gender differences in brain response characteristics in the audiovisual area [49]. Multivariate pattern analysis indicated that local BOLD signal patterns in several temporal-lobe regions from females reflect a sex difference in the strategies for the processing of auditory information [50]. Another study using ReHo compared sex differences of spontaneous brain activity, and suggested that men and women had regional specific differences in primary visual network [51]. Current sex differences in RGUs seem to be consistent with previous researches. On the other hand, when considering the men and women in IGDs, changes in ReHo showed interesting reversals (see Fig.3 and Fig.4). The individuals with IGD often present compulsive gaming behaviors, showing an excessive audiovisual response during gaming process. Previous study indicated that IGD showed abnormally decreased ReHo in the occipital lobe compared to the control group [26]. This result is consistent with the ReHo change in the female group, while increased ReHo in mIGD currently lacks strong evidence to explain, which may require further exploration in the future.

Finally, IGD-by-sex interaction is also found in the rPG. As the primary somatosensory cortex, the postcentral gyrus involved the input and processing of haptic information. So far, the postcentral gyrus was mentioned in few studies about addiction [52], but its function was still not clear in the development of addiction for individual. We speculate that during gaming, players respond to game information with keystrokes, which may be related to changes in rPG [8], and it may be potential regions of interest for further researches of gender difference in IGD.

Limitations

There are several limitations in this study to be noted. First, for the interactions found in these brain regions, it is difficult to verify the causal relationship with sex/group. It will be an interesting work to explore and confirm this relationship in future studies. Second, the sample size for this experiment was adequate and gender matched, but our control group chose RGU instead of normal subjects without game experience, which limits the generalizability of the results. In the future study, we may compare the three groups (IGD/RGU/HC) of subjects to observe the differences. Third, for some demographic factors, we find it hard to match perfectly, such as IQ, economic status, self-efficiency etc. All these potential variables will have an impact on our results and future studies should take into account the matching of these variables. Finally, as diagnostic criteria of IGD remain controversial, our findings based on this criterion may be affected. So we look forward to the specific and perfect diagnostic criteria.

Conclusions

This study found that wide ReHo differences between male and female groups during the resting state. Significant interaction areas were in rPCC, lMOG, rMTG and rPG, which involved in executive control network, visual and auditory processing. Among them, mIGD showed decreased regional synchronization in rPCC, but not in fIGD. In addition, both men and women showed abnormal ReHo in lMOG and rMTG. It is interesting that women exhibited poor synchronization while men showed brain compensation effects. Therefore, the gender differences need to be taken into consideration for future studies about IGD, and current results provide evidence to support the idea that sex differences in IGD

Acknowledgments

MW analyzed the data and wrote the first draft of the manuscript. ZW contributed to experimental programming and data collection. XD contributed to fMRI data collection. GD & YH designed this research, and improved the manuscript. All authors contributed to and had approved the final manuscript.

Competing interests

The authors declared that no competing interests exist.

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Figure Legends

Figure 1: The regions of significantly interaction between gender and group.

After controlling for the age and education level, significantly interaction was observed (AlphaSim corrected, $p<0.01$) in several regions, including the right posterior cingulate, left middle occipital gyrus, right middle temporal gyrus and right postcentral gyrus.

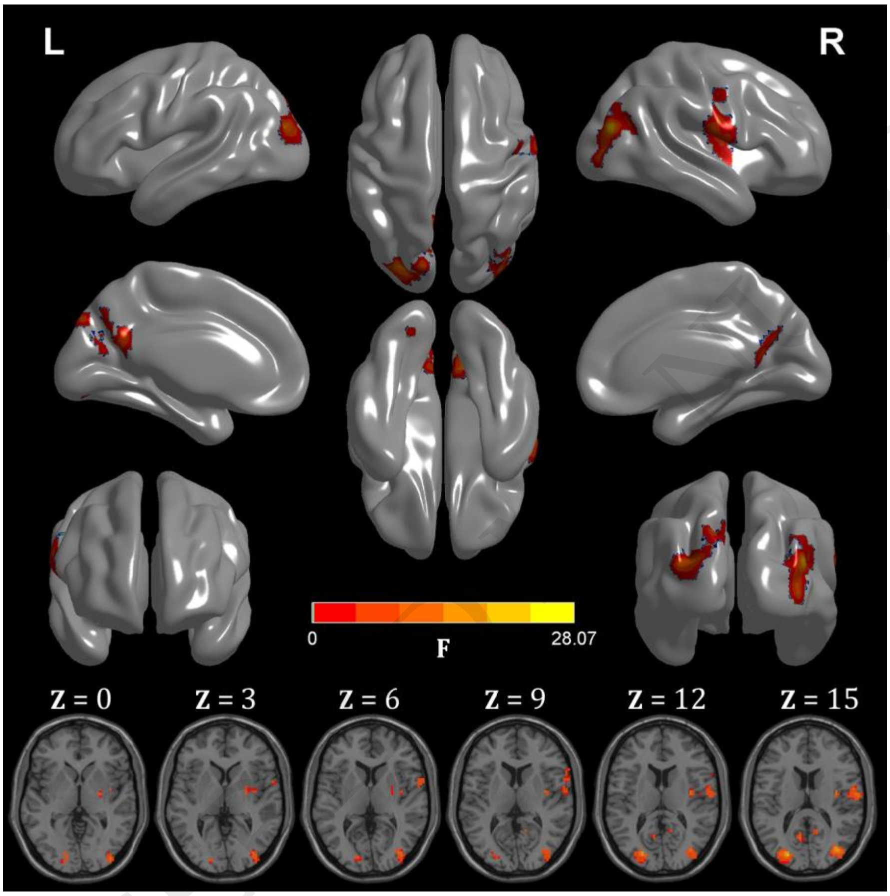

Figure 2: The IGD-by-sex interaction and the relevance of ReHo and IAT scores in right posterior cingulate.

(Ⅰ) Two-way ANOVA showing significant interaction effect ($p = 0.000$, uncorrected for multiple comparisons), with the male IGD showing lower ReHo compared to male RGU ($p = 0.000$). (Ⅱ) line chart showing change tendency of male and female. (Ⅲ) IAT scores was significant negatively associated with ReHo in the male ($r = -0.540, p = 0.000$). *：$p<0.05$; **：$p<0.01$; ***：$p<0.001$. *b*: Bonferroni

Correction.

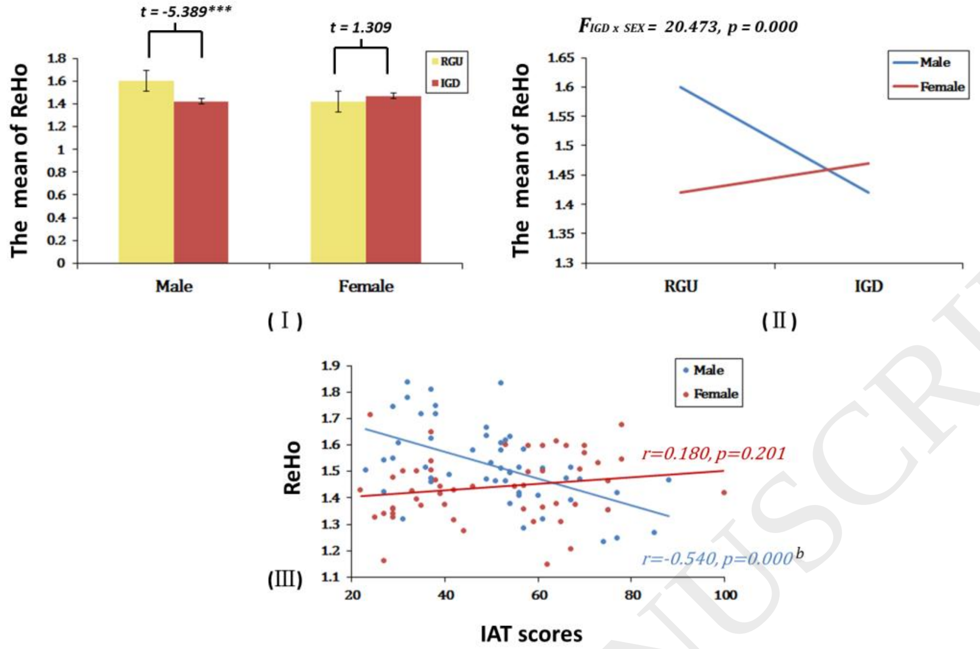

Figure 3: The IGD-by-sex interaction and the relevance of ReHo and IAT scores in left middle occipital gyrus.

(Ⅰ) Two-way ANOVA showing significant interaction effect (*p = 0.000*, uncorrected for multiple comparisons), with the male IGD showing higher ReHo compared to male RGU (*p = 0.000*), and the female IGD had lower ReHo compared to female RGU (*p = 0.012*). (Ⅱ) line chart showing change tendency of male and female. (Ⅲ) IAT scores were positively associated with ReHo values in the male, but negatively correlated with them in the female. However, both correlations did not reach statistical significance. *：*p<0.05*; **：*p<0.01*; ***：*p<0.001*.

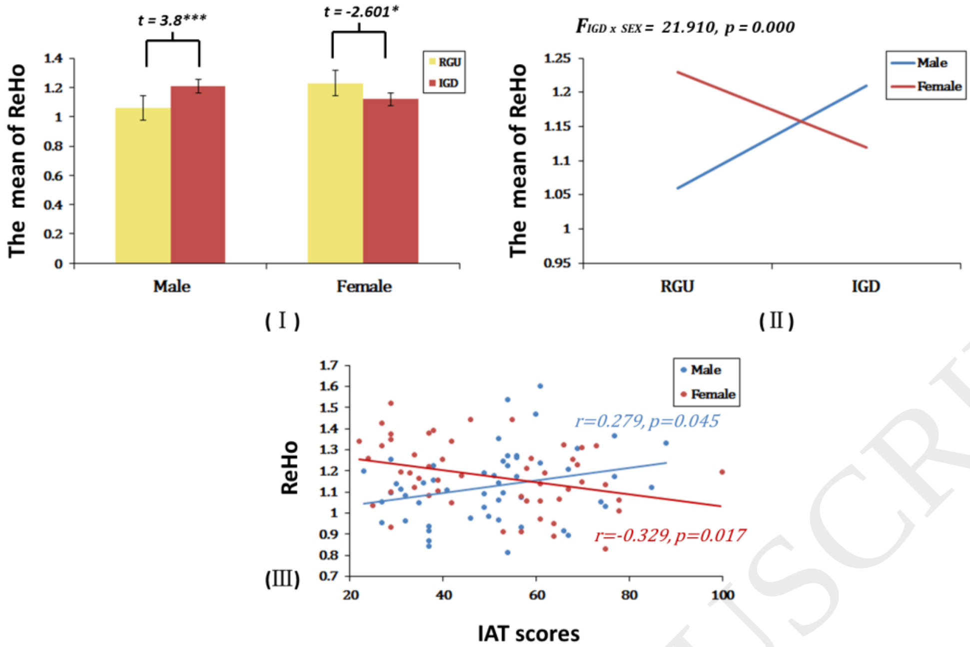

Figure 4: The IGD-by-sex interaction and the relevance of ReHo and IAT scores in right middle temporal gyrus.

(Ⅰ) Two-way ANOVA showing significant interaction effect (p = *0.000*, uncorrected for multiple comparisons), with the male IGD showing higher ReHo compared to male RGU (p = *0.004*), and the female IGD had lower ReHo compared to female RGU (p = *0.000*). (Ⅱ) line chart showing change tendency of male and female. (Ⅲ) IAT scores was positive associated with ReHo in the male (r = *0.197*, p = *0.161*), and significant negative correlation in the female (r = *-0.543*, p = *0.000*). *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$. *b*: Bonferroni Correction.

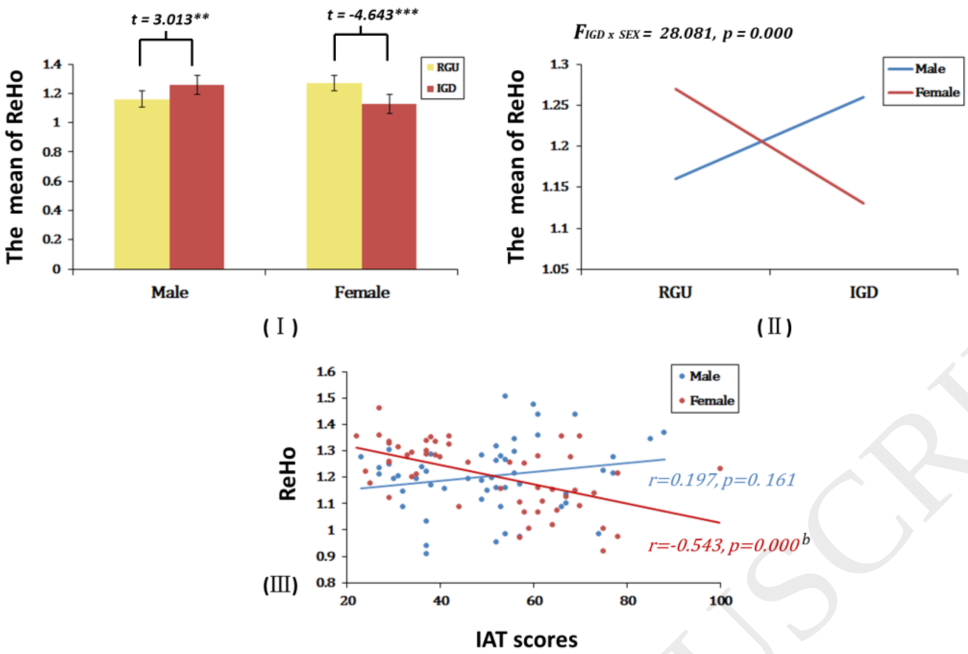

Figure 5: The IGD-by-sex interaction and the relevance of ReHo and IAT scores in right postcentral gyrus.

(Ⅰ) Two-way ANOVA showing significant interaction effect (*p = 0.000*, uncorrected for multiple comparisons), with the male IGD showing lower ReHo compared to male RGU (*p = 0.000*), and the female IGD had higher ReHo compared to female RGU (*p = 0.002*). (Ⅱ) line chart showing change tendency of male and female. (Ⅲ) IAT scores was negatively associated with ReHo in the male (*r = -0.348*, *p = 0.011*), and significant positive correlation in the female (*r = 0.416*, *p = 0.002*). *: *p<0.05*; **: *p<0.01*; ***: *p<0.001*. *b*: Bonferroni Correction.

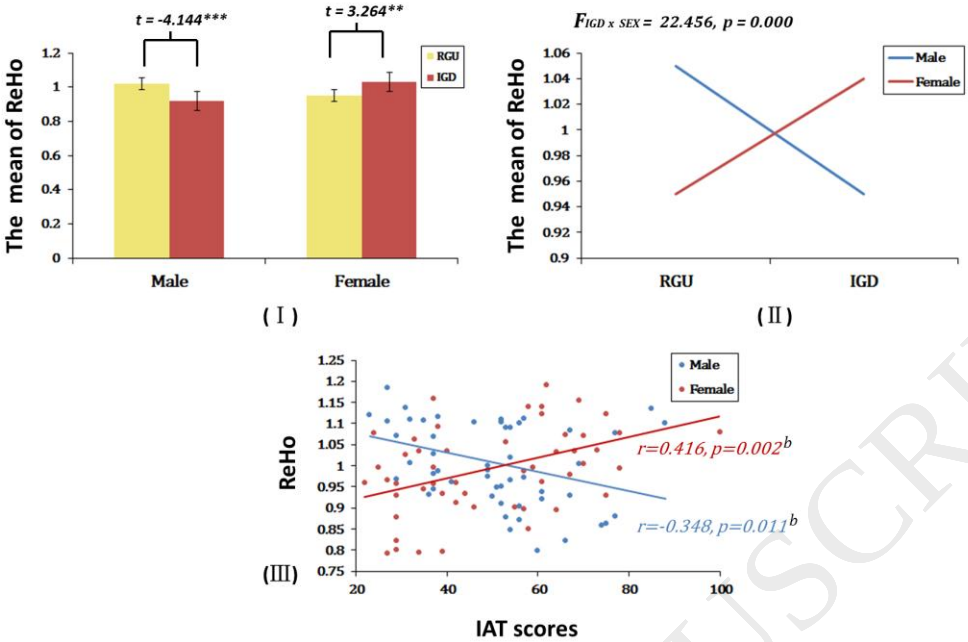
t = -4.144***
t = 3.264**
RGU
IGD
The mean of ReHo
Male
Female
(Ⅰ)
F IGD x SEX = 22.456, p = 0.000
Male
Female
RGU
IGD
(Ⅱ)
Male
Female
r=0.416, p=0.002b
r=-0.348, p=0.011b
ReHo
(Ⅲ)
IAT scores

Table 1. Demographic information and group differences

	IGD (n=46)		RGU (n=58)		*F*	*P*
	M (n=23)	F (n=23)	M (n=29)	F (n=29)		
Age (mean±SD)	23.0±1.14	22.7±1.41	23.4±1.47	22.6±1.68	1.491	0.222
IAT score (mean±SD)	63.7±11.13	67.0±10.18	41.6±9.60	36.9±9.25	55.705	0.000
DSM-5 score (mean±SD)	6.0±1.14	5.8±1.19	2.6±1.34	2.5±1.30	59.406	0.000
Game playing per week (hours) (mean±SD)	22.5±7.59	16.9±5.06	18.1±7.50	15.7±4.71	4.725	0.004
Gaming history (years) (mean±SD)	2.9±1.19	2.1±0.71	2.1±0.57	2.0±0.46	6.591	0.000
Educations (years) (mean±SD)	14.1±2.42	14.4±1.89	14.4±1.54	14.7±1.95	0.581	0.627

IGD: Internet gaming disorder; RGU: recreational game user; IAT: Internet addiction test; DSM-5: Diagnostic and Statistical Manual of Mental Disorders-5.

Table 2: Sex-by-group interactions in different comparisons

[a] Peak MNI Coordinates.

Cluster Number	x,y,z[a]	Peak Intensity	Cluster Size[b]	Region [c]	Brodmann's Area
1	12,-57,18	19.01	155	R Posterior Cingulate	31
2	-24,-84,15	19.71	220	L Middle Occipital Gyrus	18
3	39,-75,18	28.07	192	R Middle Temporal Gyrus	19
4	63,-12,18	15.05	257	R Postcentral Gyrus	6

[b] Number of voxels. Alphasim correction, p<0.01; Cluster size >150 voxels.

[c] The brain regions were referenced to the software Xjview (http://www.alivelearn.net/xjview8) and verified through comparisons with a brain atlas.