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Females are more vulnerable to Internet gaming disorder than males: Evidence from cortical thickness abnormalities

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ABSTRACT

Background: Male predominance is a well-known feature of Internet gaming disorder (IGD), with a reported male to female ratio of 3:1. Because of the overwhelming focus on males, little is known about the neural basis of sex differences in IGD, especially neuroanatomical features. Thus, investigations on sex differences with an adequate sample size are critical for improving the understanding of biological mechanisms underlying IGD.
Methods: Structural magnetic resonance imaging data were acquired from 62 IGD subjects (29 males, 33 females) and 71 recreational game users (RGUs) (37 males, 34 females) with well-matched age and education levels. Group-by-sex interaction in cortical thickness was analyzed, and the correlations between cortical thickness and addiction severity were calculated.
Results: We detected a group-by-sex interaction in the bilateral rostral middle frontal gyri (MFG), left superior frontal gyrus (SFG), left supramarginal gyrus (SMG), right posterior cingulate cortex (PCC), and right superior parietal lobule (SPL). Post-hoc analyses revealed that, compared with same-sex RGUs, male IGD subjects had increased cortical thickness and female IGD subjects had reduced cortical thickness beside their right PCC. By contrast, male IGD subjects had reduced cortical thickness and female IGD subjects had increased cortical thickness in their right PCC. Moreover, only females showed significant negative correlations between the cortical thickness and their self-reported cravings and Internet addiction test scores.
Conclusions: For female IGD subjects, the reduced cortical thickness, combined with the negative correlations of addiction severities, suggests the great effect created by IGD in the brain regions. Males and females may be affected differently by IGD, with females being more vulnerable to it.

1. Introduction

Unlike substance addiction, Internet gaming disorder (IGD) has been conceptualized as a type of behavioral addiction because no chemical intake is involved (Dong and Potenza, 2014, 2016; Dowling, 2014; Petry et al., 2015; Rehbein et al., 2015). In 2013, the *Diagnostic and Statistical Manual of Mental Disorders-5* (DSM-5) committee generated criteria for diagnosing IGD and appealed for further studies on the disorder (Cooper and Michels, 1980; Griffiths et al., 2014; Petry et al., 2015). Natural and social science researchers have demonstrated that addiction and its consequences differ in terms of biological sex and gender (Becker and Hu, 2008; Becker and Koob, 2016; Becker et al., 2012; Hartwell and Ray, 2013). However, neurological effects or behavioral alterations within IGD subjects, as modulated by sex, are still unknown.

Structural imaging of the brains of IGD subjects has demonstrated an abnormal gray matter volume (GMV) in many brain regions. In general, these abnormal brain regions are involved in cognitive control and reward/loss processing, but the results have not been entirely consistent (Hong et al., 2013b; Lee et al., 2017; Lin et al., 2015; Yuan et al., 2013; Yuan et al., 2011; Zhou et al., 2011). Previous studies have found that individuals with IGD showed low gray matter density (GMD) in the dorsolateral prefrontal cortex (DLPFC), superior parietal cortex (SPC), and orbitofrontal cortex (OFC), which are related to executive controls (Wang et al., 2015; Weng et al., 2013; Yuan et al., 2011). Other studies detected decreased GMD in the insula and posterior cingulate cortex (PCC), which is related to reward/loss processing (Lin, 2015; Zhou et al., 2011). All these studies used voxel-based morphometry

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(VBM), which involves voxel-wise tissue classification, normalization to a standard atlas, and statistical comparisons to determine differences in cortical volume. Although volume represents one dimension of cortical macrostructure, VBM does not account for the complex folding patterns of the cortex or variations in its columnar architecture. In contrast to VBM, surface-based algorithms model sulci and gyri topologies and provide measures of cortical thickness (Fischl and Dale, 2000). By using a similar surface-based modeling, Makris et al. (2008) presented cortical thinning in cocaine-dependent subjects in a reward network in the brain. The reward network comprises the orbitofrontal, insula, cingulate, and DLPFC. Durazzo et al. (2011) demonstrated cortical thinning in similar brain regions in alcoholics (ALCs) compared with controls. Yuan et al. (2013) found a thinning of the cortex in the left lateral OFC in adolescents and young adults with IGD compared with healthy controls. In another study, Hong et al. (2013a) focused on the changes in OFC, which was implicated in the pathology of drug and behavioral addictions. The results demonstrated that male adolescents with IGD had significantly reduced cortical thickness in the right lateral OFC but not the left lateral OFC, which contradicted the findings of Yuan's study. Our previous study also found a thinning in the cortex of the left lateral OFC (Wang et al., 2018).

Another possible important reason for the inconsistent results is that most brain morphometry studies focus on male addiction. Although previous studies have tried to control the influence of sex differences by using same-sex subjects, evidence suggest that sex is an important modulator of drug-related behavior, brain structure, and function (Greenfield et al., 2010; Volkow et al., 2011). Sex differences in cortical thickness have been observed in healthy controls (Sowell et al., 2007). Furthermore, alterations in brain structure and function differ in female compared with male substance users. For example, Tanabe et al. (2013) detected differences in the insula morphology of substance-dependent individuals (SDI) and controls, and the differences were modulated by sex. Compared with same-sex healthy controls, female SDI had smaller insula, whereas male SDI had larger insula. Kogachi et al. (2015) found that male methamphetamine (meth) users had larger right superior frontal gyrus (SFG), compared with female meth users. Male meth users with large frontal volumes and female meth users with small frontal cortices had greater cognitive impulsivity. Previous studies have also detected a correlation between sex differences among cocaine-dependent (CD) patients, revealing lower GMV (Rando et al., 2013) and greater motivation for cocaine among female patients (Kerstetter et al., 2013). Medina et al. (2008) found that compared with healthy same-sex controls, the prefrontal cortex volume in young female alcohol users was smaller than that in young male alcohol users. Sawyer et al. (2017) revealed a significant gender interaction in the association between alcoholism and total reward network volumes, with ALC men having smaller reward network volumes than their non-ALC control (NC) counterparts and ALC women having larger reward network volumes than NC women. Men and women are also known to have different vulnerabilities and treatment responses to drugs and alcohol (Greenfield et al., 2010). Compared with men, women tend to progress more rapidly from initial experience to addiction (Bobzean et al., 2014). The rapid escalation after the initiation of behavior or drug use in women has been replicated in other drugs of abuse (Richmondrakerd et al., 2016). In addition, sex differences influence dependence and addiction and the side effects of drugs (Sanchis-Segura and Becker, 2016). Women appear to be more vulnerable to the side effects induced by medications used to treat substance use disorders compared with men (Agabio et al., 2016). Therefore, a better understanding of sex differences in addiction problems can help further improve clinical efficiency in intervention and treatment. The purpose of this study is to investigate the sex differences of cortical thickness in young adults by using an advanced surface-based method for a precise thickness measurement of the complex cerebral cortex structure and localized regional mapping.

To the best of our knowledge, this is the first study to examine the effects of sex differences in cortical thickness using a cortical surface model in IGD patients. In this study, we mainly focused on two aspects that may differentiate IGD patients from the controls: executive control and reward processing (Dong and Potenza, 2014). Previous studies have shown that sex differences exist in certain regions of the brain involved in executive control, such as the DLPCE, ACC, and IFG (Ide et al., 2014; Konova et al., 2016; Medina et al., 2008; Zanchi et al., 2016). Therefore, we hypothesized that sex differences in cortical thickness among IGD patients are found in the regions of the brain involved in executive control, such as the OFC, and in the regions involved in reward systems, such as the insula and PCC (Sawyer et al., 2017; Tanabe et al., 2013).

2. Methods and materials

The study was approved by the Zhejiang Normal University Subcommittee on Human Studies and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to participation in the study.

2.1. Participants

We recruited 62 IGD subjects (29 males, 33 females) and 71 recreational game users (RGUs) (37 males, 34 females) through posters and online advertisements (Table 1). All subjects fitted the following criteria: must be right-handed university students, have normal or corrected-to-normal vision, have no reported history of illegal drug use, scored lower than 5 on the Beck Depression Inventory questionnaire (Beck et al., 1967), and have no Axis-I psychiatric disorders as per assessment from a 15-minute structured psychiatric interview (MINI) (Lecrubier et al., 1997). On the day of the scanning process, all participants were instructed to not use any addictive substance, including tobacco and caffeinated drinks.

2.1.1. Definition and selection of the IGD group

The subjects who were categorized into the IGD group should satisfy two criteria: First, they should have scored 50 or more on Young's online IAT (62.89 ± 10.77). Second, they should have exhibited at

Table 1
Demographic information and group differences.

	IGD (n = 62)		RGU (n = 71)		F	P
	M (n = 29)	F (n = 33)	M (n = 37)	F (n = 34)		
Age (mean ± SD)	21.1 ± 1.43	20.7 ± 1.76	21.7 ± 2.05	20.9 ± 1.99	1.695	0.171
IAT score (mean ± SD)	63.6 ± 11.65	62.3 ± 10.07	41.3 ± 10.05	38.1 ± 16.02	42.960	0.000
DSM-5 score (mean ± SD)	5.7 ± 1.07	5.2 ± 1.47	2.4 ± 1.34	2.7 ± 1.86	44.117	0.000
Game playing per week (hours) (mean ± SD)	19.2 ± 9.70	20.4 ± 10.27	20.7 ± 9.99	12.9 ± 8.01	5.019	0.003
Gaming history (months) (mean ± SD)	25.7 ± 8.77	25.1 ± 9.30	24.1 ± 3.31	30.2 ± 11.39	3.315	0.022
Educations (years) (mean ± SD)	14.2 ± 2.42	14.4 ± 1.89	14.4 ± 1.54	14.8 ± 1.95	0.581	0.628
Self-reported craving (mean ± SD)	50.4 ± 16.18	53.2 ± 19.75	35.7 ± 14.06	34.0 ± 20.38	10.231	0.000

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

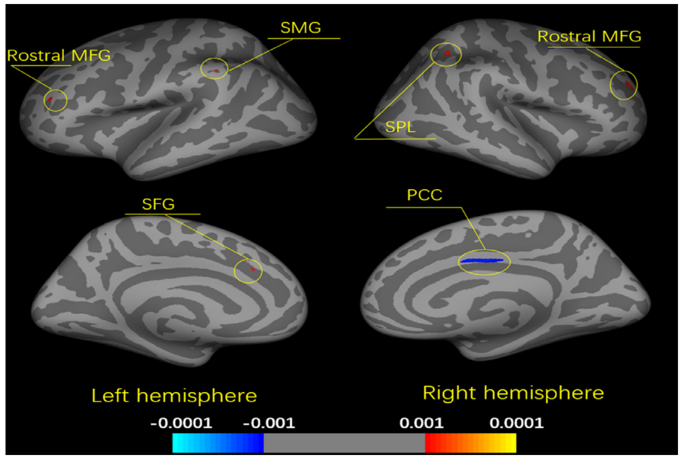

Fig. 1. Vertex-based analysis of interactions after controlling for the age.
Group-by-sex interaction was found in the bilateral rostral MFG, left SMG, SFG, right PCC, and SPL ($p \leq 0.001$).

least five of the nine IGD diagnostic criteria in the DSM-5 (5.45 ± 1.31) (Petry et al., 2014).

2.1.2. Definition and selection of the RGU group

The RGUs are those who frequently play online games without developing game addiction. The selection criteria for the RGUs are consistent with our previous study (Dong et al., 2017). First, the subjects should have played online games as frequently as the IGD subjects (at least five out of seven days and more than two hours per day in the last years). Second, the RGU subjects should have no symptoms of physical or psychological dependence on online gaming as confirmed by their test scores (scored less than 50 on the Young's IAT and exhibited fewer than four of the nine items in DSM-5 criteria of IGD).

2.2. Magnetic resonance imaging data acquisition

Magnetic resonance imaging (MRI) was conducted with a Siemens Trio 3T scanner (Siemens, Erlangen, Germany). Whole-brain T1-weighted MR images were collected via a T1-weighted three-dimensional spoiled gradient-recalled sequence in 384 s (176 slices, repetition time = 1700 ms, echo time = 3.93 ms, slice thickness = 1.0 mm, skip = 0 mm, flip angle = 15, inversion time = 1100 ms, field of view = 240 × 240 mm, in-plane resolution = 256 × 256). Head motions were minimized by filling the empty space around the subjects' heads with sponge and fixing their lower jaws with tape.

2.3. Image data analysis

Cortical reconstruction was performed using the FreeSurfer software package (Version 5.3.0, http://surfer.nmr.mgh.harvard.edu) based on procedures described in previous publications (Dale et al., 1999; Fischl and Dale, 2000; Fischl et al., 1999). Before the analysis of the cortical thickness, we visually checked the quality of raw data and used the TkMedit command (https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/TroubleshootingDataV6.0) to modify errors. None of the subjects' scanned images were excluded due to excessive distortions or artifacts.

2.4. Whole-brain analyses

Vertex-wise general linear modeling (GLM) using FreeSurfer's statistical tools Query, Design, Estimate, Contrast tested the main effects of group, sex, and their interactions on cortical thickness based on Desikan–Killiany atlas (Desikan et al., 2006). Moreover, age was entered as covariates. The subjects' cortical surface data were smoothed with a 10 mm full-width-half-maximum Gaussian smoothing. A statistical threshold of $p \leq 0.001$ was used for the correction of imaging results according to previous studies on sex differences (Tanabe et al., 2013). The average values of cortical thickness were then extracted to conduct post-hoc analysis and specify the form of interaction.

2.5. Correlation analyses

Correlations were further conducted to investigate the relationship between cortical thickness and IGD level (measured by craving ratings and IAT scores). The average values of the cortical thickness with significant differences were extracted to calculate the correlation coefficients. All tests were two tailed, and the level of significance was $p < .0083$ (.05/6) (Bonferroni corrected).

3. Results

3.1. Demographic information and group differences (Table 1)

All groups were similar in age ($F = 1.695$, $p = 0.171$) and education ($F = 0.581$, $p = 0.628$) but had significant differences in game playing per week (hours) ($F = 5.019$, $p = 0.003$), gaming histories (months) ($F = 3.315$, $p = 0.022$), IAT scores ($F = 42.960$, $p = 0.000$), DSM-5 scores ($F = 44.117$, $p = 0.000$), and self-reported cravings ($F = 10.231$, $p = 0.000$) (Table 1). After a simple-effect analysis, we found that the IGD group's IAT and DSM scores and self-reported cravings, regardless of gender, were higher than the RGU group. In addition, the gaming histories of female RGUs were longer compared with those of other groups, but their hours of game playing per week is shorter.

3.2. Vertex-based analysis of interaction effect

Whole brain analyses indicated a group-by-sex interaction on the bilateral rostral middle frontal gyri (MFG), left supramarginal gyrus (SMG), SFG, right PCC, and superior parietal lobule (SPL) (Fig. 1 and Table 2). Sex difference was found to have a main effect on SFG thickness but no main effect on the groups (IGD and RGU). Furthermore, women were found to have thicker SFGs than men.

3.3. Simple-effect analysis

3.3.1. Bilateral rostral MFG

In the vertex-based analysis, bilateral rostral MFG showed a group-by-sex interaction. In the left rostral middle frontal gyrus, female IGD subjects show significantly reduced cortical thickness, but male IGD subjects show relatively increased cortical thickness compared with the

Table 2
Cortical thickness comparison of interaction effect

Cortex Area	Cluster size (mm^{2})	Talairach coordinates max vertex			*p* value
		x	y	z	
Left					
rostral middle frontal gyrus	62.17	−38.3	41.3	17.8	0.001
supra marginal gyrus	35.51	−56.1	−42.5	39.6	0.001
superior frontal gyrus	21.68	−13.0	25.1	31.0	0.001
Right					
rostral middle frontal gyrus	96.21	23.8	44.9	26.5	0.001
posterior cingulate cortex	230.34	4.7	0.0	35.9	0.001
superior parietal lobule	90.41	31.2	−52.3	38.7	0.001

Results from GLM testing for group-by-sex interaction, controlling for age.

RGU subjects (Fig. 2a and b). In the right rostral middle frontal gyrus, the female IGD subjects show significantly reduced cortical thickness, whereas male IGD subjects show significantly increased cortical thickness compared with the RGU subjects (Fig. 3a and b). In addition, low craving scores were associated with thick bilateral rostral middle frontal cortical thickness in the female group (left: $r = -0.359$, $p = 0.003$) (Bonferroni corrected); right: $r = -0.290$, $p = 0.018$ (uncorrected)) but not in the male group (Figs. 2c and 3c).

3.3.2. Left SMG

In the vertex-based analysis, the left SMG showed a group-by-sex interaction, with female IGD subjects showing significantly decreased cortical thickness and male IGD subjects showing relatively increased cortical thickness compared with the RGU subjects (Fig. 4a and b).

3.3.3. Left SFG

In the vertex-based analysis, the left SFG showed a group-by-sex interaction, with female IGD subjects showing significantly decreased cortical thickness and male IGD subjects showing relatively increased cortical thickness compared with the RGU subjects (Fig. 5a and b).

3.3.4. Right PCC

In the vertex-based analysis, the right PCC showed a group-by-sex interaction, with female IGD subjects showing significantly increased cortical thickness and male IGD subjects showing relatively thinner cortical thickness compared with the RGU subjects (Fig. 6a and b). In addition, high IAT scores were associated with thick right PCC in the female group ($r = 0.283$, $p = 0.021$) (uncorrected) (Fig. 6c).

3.3.5. Right superior parietal lobule

In the vertex-based analysis, the right SPL showed a group-by-sex interaction with female IGD subjects showing significantly reduced cortical thickness and male IGD subjects showing significantly increased cortical thickness compared with the RGU subjects (Fig. 7a and b). In addition, high IAT scores were associated with thick right superior parietal cortical (SPC) in the male group ($r = 0.307$, $p = 0.012$) (uncorrected) (Fig. 7c).

4. Discussions

The current study examined the group-by-sex interaction of brain cortical thickness in IGD subjects. Our hypotheses were partially supported: (1) cortical thickness related to cognitive control and reward/loss processes between men and women may be affected differently by IGD, and (2) sex-specific brain alterations in females are associated with self-reported cravings or scores on the Young's IAT.

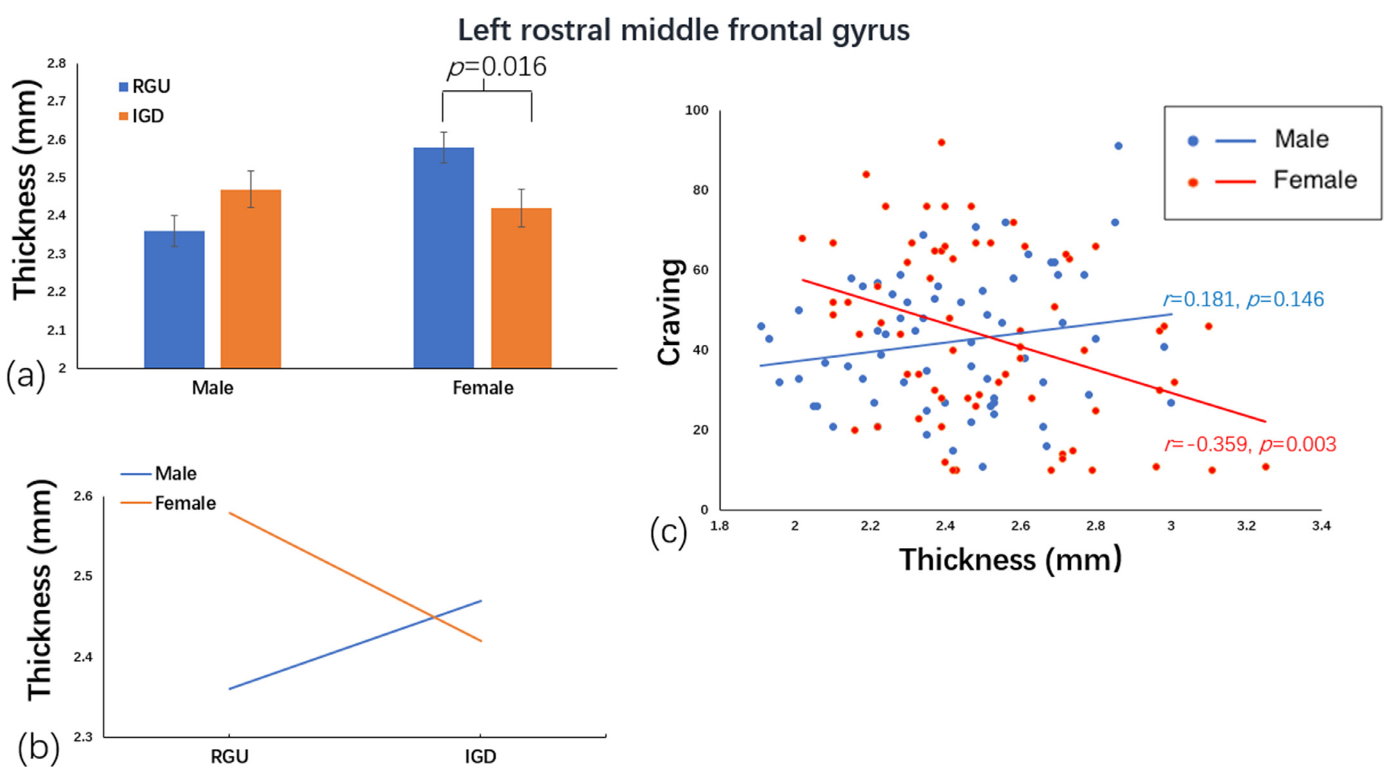

Fig. 2. Group-by-sex interaction and association with self-reported craving scores in left rostral MFG.
(a) GLM analysis showing significant interaction effects ($p = 0.001$) with the female IGD group showing smaller left rostral MFG thickness compared with the female RGU group ($p = 0.016$), whereas the male IGD group had larger thickness compared with the male RGU group (not significant). (b) Line chart showing the change tendency of males and females. (c) Self-reported craving scores were significant and negatively associated with left rostral MFG thickness in the female group ($r = -0.359$, $p = 0.003$) (Bonferroni corrected).

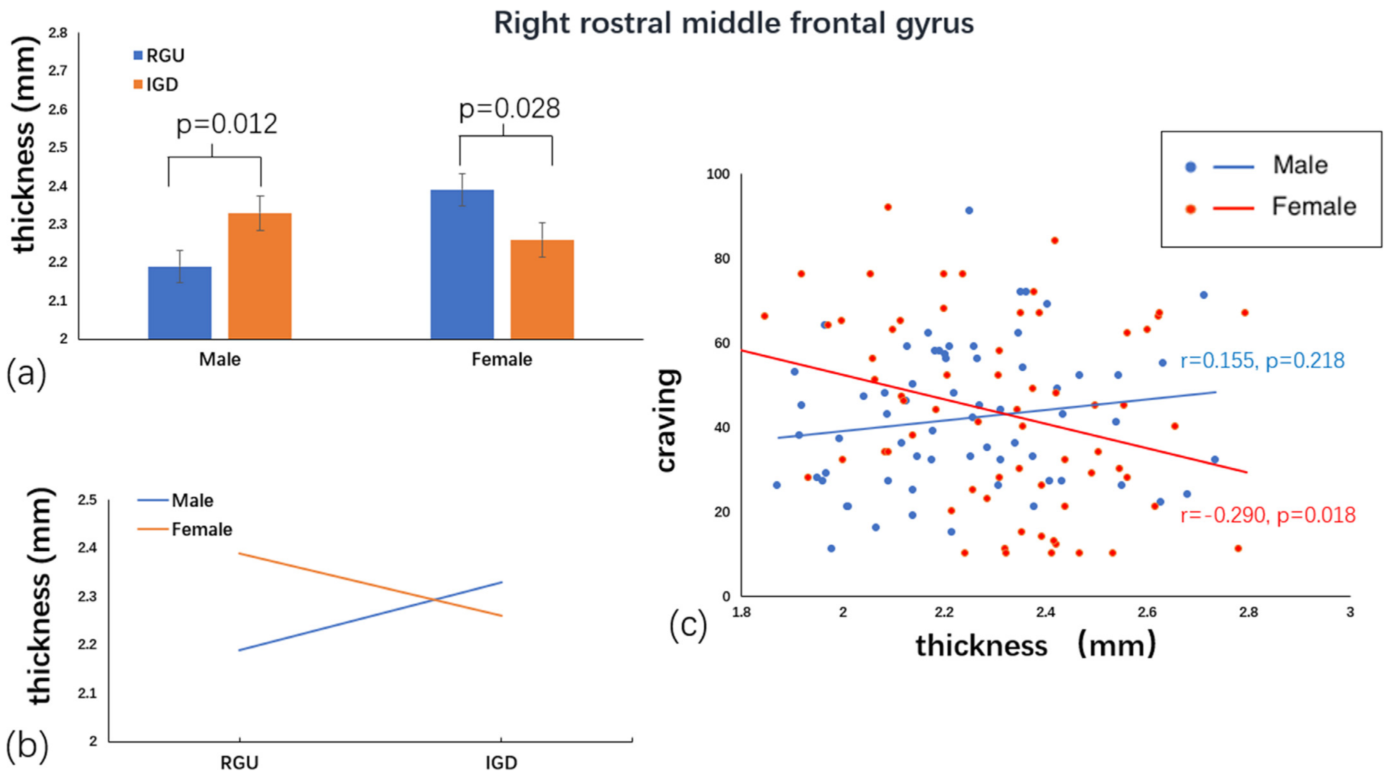

Fig. 3. Group-by-sex interaction and association with self-reported craving scores in right rostral MFG.
(a) GLM analysis showing significant interaction effects (p = 0.001) with the female IGD group showing smaller right rostral MFG thickness compared with the female RGU group (p = 0.028), whereas the male IGD group had larger thickness compared with the male RGU group (p = 0.012). (b) Line chart showing the change tendency of males and females. (c) Self-reported craving scores were significant and negatively associated with left rostral MFG thickness in the female group (r = -0.290, p = 0.018) (uncorrected).

4.1. Sex difference in executive control-related brain regions

In the current study, we detected a group-by-sex interaction in the bilateral rostral MFG, left SFG, SMG and right SPL.

Frontal executive function, including the ability of conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy assessed by the Frontal Assessment Battery (Dubois et al., 2000), was clearly predicted by the volumetric changes of gray matter in the PFC in ALCs, especially from the rostral MFG. In the current study, we detected a group-by-sex interaction in the bilateral rostral MFG. In the left rostral MFG, the female IGD subjects showed significantly reduced cortical thickness and the male IGD subjects showed relatively increased cortical thickness compared with the RGU subjects. In the right rostral MFG, the female IGD subjects showed significantly reduced cortical thickness and the male IGD subjects showed significantly increased cortical thickness

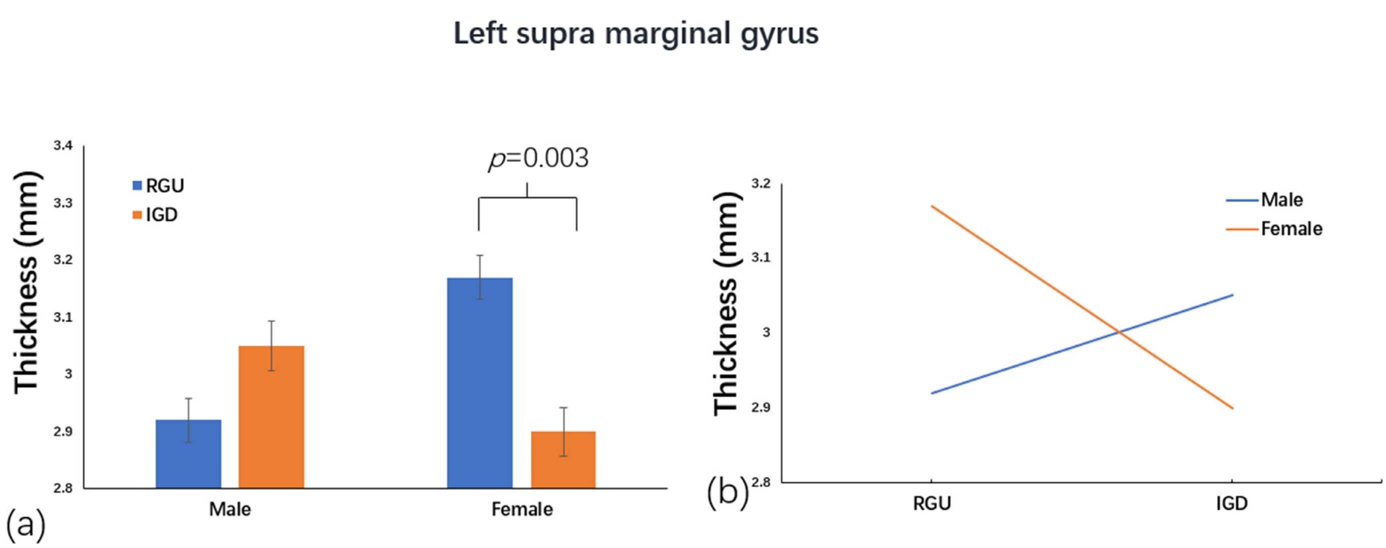

Fig. 4. Group -by-sex interaction in left SMG.
(a) GLM analysis showing significant interaction effects (p = 0.001) with the female IGD group showing smaller left SMG thickness compared with the female RGU group (p = 0.003), whereas the male IGD group had larger thickness compared with the male RGU group (not significant). (b) Line chart showing the change tendency of males and females.

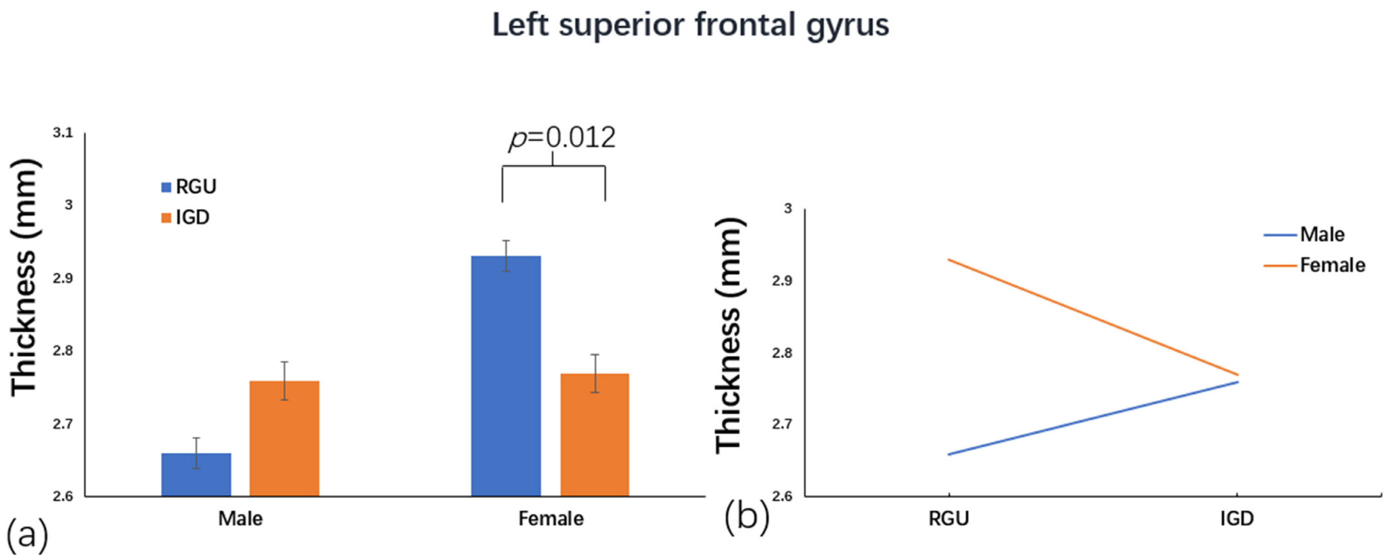

Fig. 5. Group-by-sex interaction in left SFG.
(a) GLM analysis showing significant interaction effects (p = 0.001) with the female IGD group showing smaller left SFG thickness compared with the female RGU group (p = 0.012), whereas the male IGD had larger thickness compared with the male RGU group (not significant). (b) Line chart showing the change tendency of males and females.

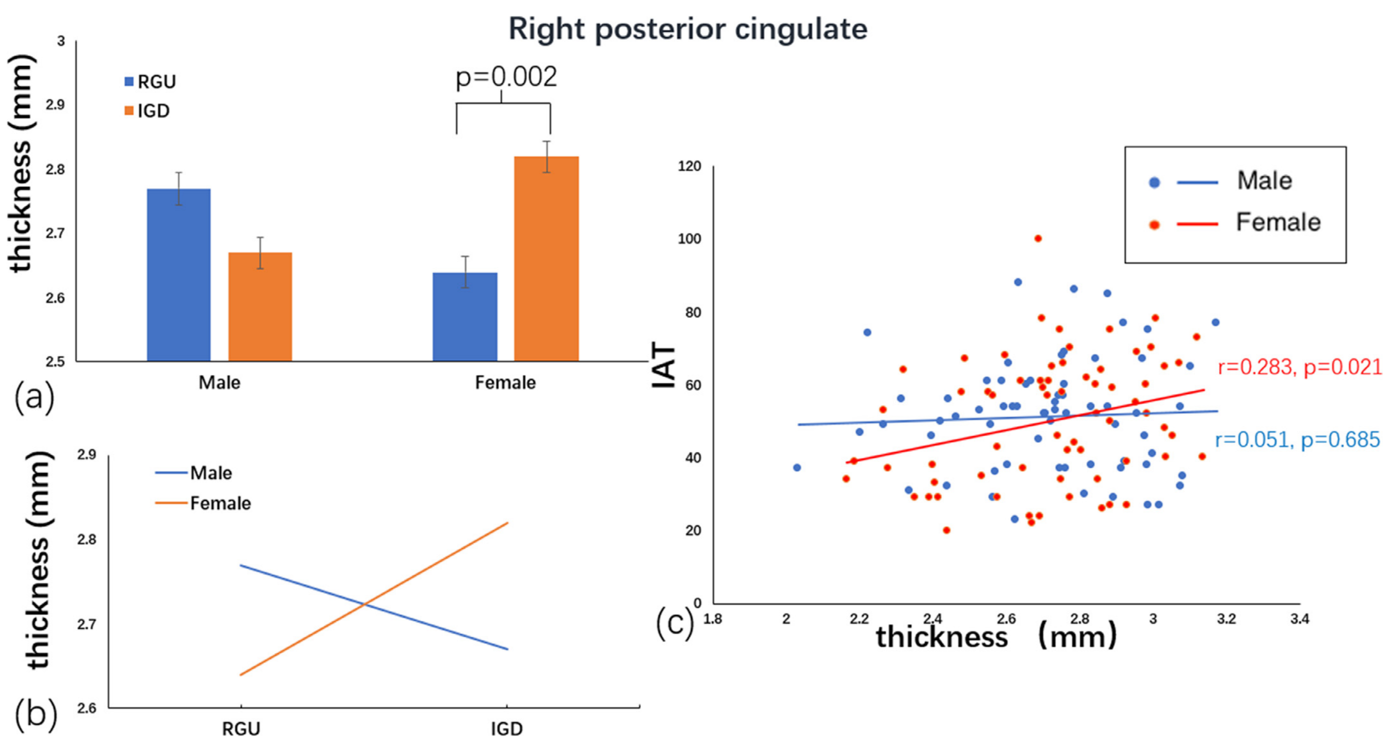

Fig. 6. Group-by-sex interaction and association with self-reported craving scores in right PCC.
(a) GLM analysis showing significant interaction effects (p = 0.001) with the female IGD group showing larger right PCC thickness compared with the female RGU group (p = 0.002), whereas the male IGD group had smaller thickness compared with the male RGU group (not significant). (b) Line chart showing the change tendency of males and females. (c) IAT scores were significant and positive associated with right PCC thickness in the female group (r = 0.283, p = 0.021) (uncorrected).

compared with the RGU subjects. Previous studies have also detected increased cortical thickness in the MFG in male IGD subjects (Yuan et al., 2013). The rostral MFG is partially located in the DLPFC (Rajkowska and GoldmanRakic, 1995) and is reciprocally connected to many brain regions (Fuster, 2008). Direct inputs and outputs to the rostral MFG include the cingulate cortex, thalamus, orbital medial prefrontal cortex, and posterior association cortex. Activities in the rostral MFG have been shown to predict frontal executive performances in ALC subjects (Durazzo et al., 2011). In addition, low craving scores were associated with reduced bilateral rostral MFG thickness in the female group in our study. Craving is an important feature of addiction and has recently been included as an inclusionary criterion for substance-use disorders (Organization, 2013). Craving reflects a motivational state that promotes gaming-seeking cues (Dong et al., 2017). Therefore, abnormal rostral MFG in the female IGD subjects may also account for their lack of self-control, which might have led to their

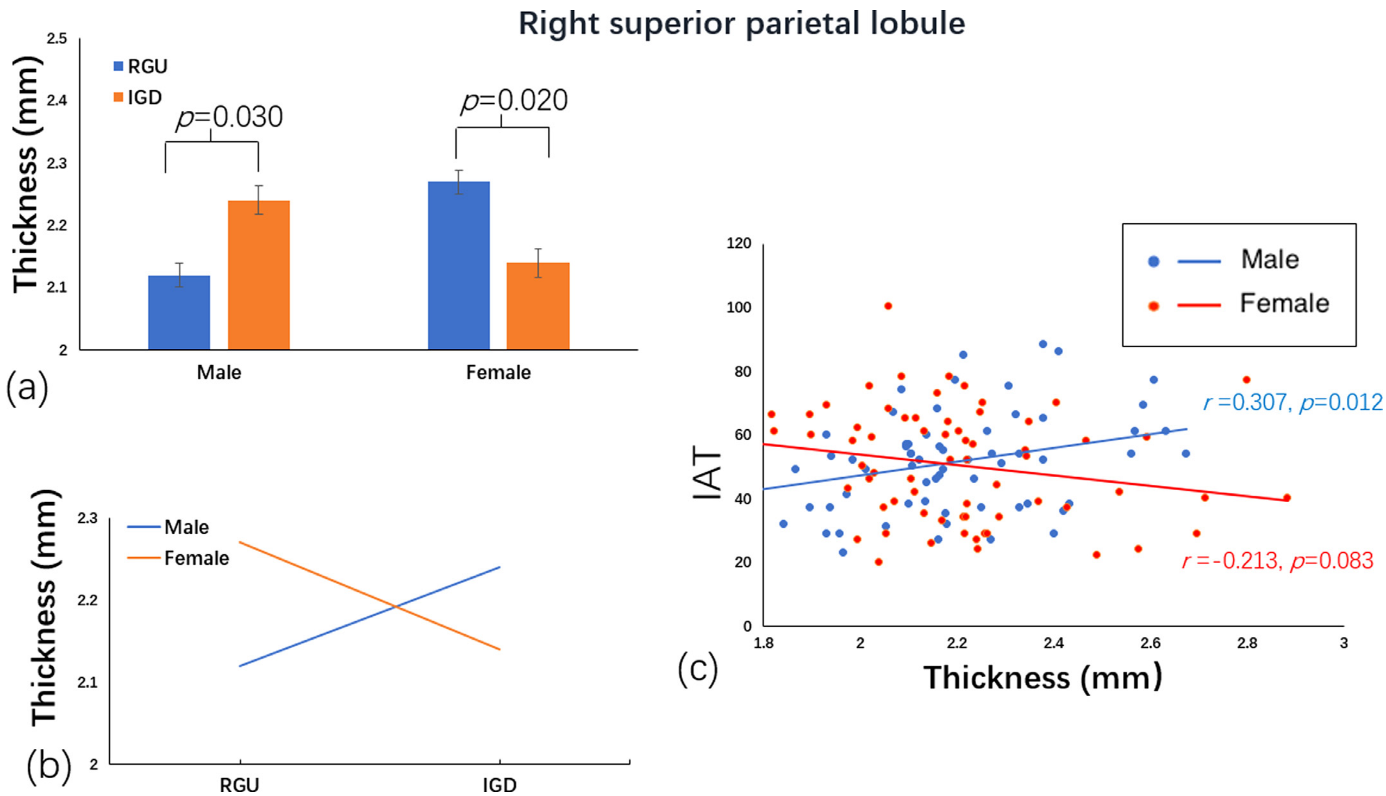

Fig. 7. Group-by-sex interaction and association with self-reported craving scores in right SPL.
(a) GLM analysis showing significant interaction effects (p = 0.001) with the female IGD group showing smaller right SPL thickness compared with the female RGU group (p = 0.020), whereas the male IGD group had larger thickness compared with the male RGU group (p = 0.030). (b) Line chart showing the change tendency of males and females. (c) IAT scores were significant and positively associated with right SPL thickness in the male group (r = -0.307, p = 0.012) (uncorrected).

gaming behaviors.

We also found a group-by-sex interaction in the SFG, with female IGD subjects showing significantly decreased cortical thickness and male IGD subjects showing relatively increased cortical thickness compared with the RGU subjects (Fig. 5a and b). These results were similar with previous studies on cocaine dependence (Ide et al., 2014), which suggested that women may be particularly vulnerable to the influences of cocaine on their SFG. The SFG can predict impulsiveness and reduced inhibitory control with decreased cortical thickness (Schilling et al., 2013). The SMG also plays a role in active saccadic inhibition (Brown et al., 2006) and shows a group-by-sex interaction, with female IGD subjects showing significantly decreased cortical thickness and male IGD subjects showing relatively increased cortical thickness compared with the RGU subjects. Thus, our current findings contribute to the existing literature by highlighting a neural phenotype on the sex differences of IGD.

Moreover, we detected differences in the right SPL of female and male IGD subjects compared with the RGU subjects. Specifically, female IGD subjects showed significantly reduced cortical thickness, whereas male IGD subjects showed significantly increased cortical thickness compared with the RGU subjects. Consistent with our findings, a previous study significantly found increased cortical thickness in the SPL of heroin-dependent male individuals (Li et al., 2014). In addition, high IAT scores were associated with reduced right SPL cortical thickness in the male group. This finding shows that group-by-sex interaction in the right SPL has an opposite impact on males and females. The brains of males and females can differ from each other in more than one way (Becker et al., 2016). Males and females are sometimes referred to as "opposites," and a bimodal distribution of traits exists that typify "male" and "female" brains. The SPL was determined to contribute to cognitive control (Durston et al., 2003; Ko et al., 2013) and visual attention (Salmi et al., 2007), and its activities have been reported to be associated with smoking cues among smokers (Mcclernon et al., 2009).

Furthermore, the gaming histories of the females in the RGU group were longer than those from the other groups, but hours of game playing per week was shorter. Females in the RGU group exhibited better control on Internet gaming compared with the females in the IGD group. We included a subsample comparison that is equated for game time and history (see details from supplementary materials). The results are basically consistent with the original results. We also investigated the correlation of cortical thickness with gaming history and time but yielded no significant results. Overall, the female subjects especially in the IGD group showed reduced cortical thickness in bilateral rostral MFG, SFG, SMG, and SPL whereas the male subjects in the IGD group showed increased cortical thickness in right rostral MFG and SPL, which is related to inhibition. Thinner and thicker cortices are abnormal when compared with the RGU group, and different effects on female and male subjects were observed. Moreover, female subjects may show great influence on the brain regions. Thus, further studies are needed to provide additional insights.

4.2. Sex difference in reward/loss processing-related brain regions

Our study detected that female IGD subjects show significantly increased cortical thickness in the PCC and male IGD subjects show relatively reduced cortical thickness compared with RGU subjects (Fig. 6a and b). In addition, increased IAT scores were associated with increased right PCC cortical thickness in the female group. The results were opposite from previous studies on alcoholism and GMV (Sawyer et al., 2017). Thus, more studies are needed to provide more insights on this topic.

Our results also showed abnormal changes in the PCC, which is unusual in the reward system. Previous studies have suggested that the PCC is associated with the mechanisms of gaming cravings under cue exposure, and it has a prominent role in the processing of emotionally salient stimuli and modulation of memory by emotionally arousing stimuli (Maddock and Richard, 1999). Furthermore, the PCC integrates the reward outcome and motivational information of visual stimuli (Pearson et al., 2011). Thus, our results suggest that PCC might be involved in processing the emotional significance of gaming cues and providing their rewarding significance only in female subjects.

4.3. Limitations

The present study has some advantages, such as the relative equal sample size in all the groups, which allow us to control for a range of possible confounders. However, limitations are also noted. First, data from groups with no gaming experiences can be collected to identify the differences between the three groups (healthy control, IGD, and RGU). The results will be remarkable if a group of non-gamers is included. Second, biological factors, such as genetics and hormonal status in females, could affect the findings, but they were not assessed in this study. Third, the scale used to measure craving is self-reported; hence, the findings may not reflect the actual degree of craving experienced by the subjects due to subjective interpretation of variables or truthfulness. Finally, the study did not assess cognitive functions indicated by performance on cognitive tasks. Additional cognitive measurements, such as reward and memory-related tasks, could complement the explanations of imaging findings in future studies.

5. Conclusions

In conclusion, our results demonstrated that some features of sex differences are exhibited in the brains of individuals with IGD. Sex differences in IGD are associated with cortical regions involved in the two domains of deficits in the disorder, namely cognitive control and reward/loss processing. In addition, structural brain changes in the bilateral rostral MFG and right SPL were associated with the self-reported cravings and IAT scores of the female subjects. Overall, the present study reveals that men and women may be affected differently by IGD in some regions of the brain, indicating the possibility of the differences in brain structure and development between males and females, with greater influence on the regions in females. Furthermore, the current study is the first to identify sex-related structural brain differences in IGD patients compared with RGUs and thus can be considered a starting point for future investigations on the topic.

Contributors

Ziliang Wang analyzed the data and wrote the first draft of the manuscript. Hui Zheng, Kai Yuan and Xiaoxia Du contributed to data collection, data analysis, and figure preparation. Guangheng Dong, and Yanbo Hu contributed in interpreting findings, editing, and revisions. All authors have approved the final manuscript.

Competing interests

The authors declare that no competing interests exist.

Data accessibility

Data are available upon request from the corresponding author at, dongguangheng@zjnu.edu.cn.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2018.11.001.

Reference

Agabio, R., Campesi, I., Pisanu, C., Gessa, G.L., Franconi, F., 2016. Sex differences in substance use disorders: focus on side effects. Addict. Biol. 21, 1030.
Beck, A., Ward, C., Mendelson, M., Mock, J., Erbaugh, J., Mendekson, M., Mendelsohn, M., Medelson, M., Mendelsen, M., Mehdelson, M., 1967. Beck Depression Inventory (BDI): an inventory for measuring depression.
Becker, J.B., Hu, M., 2008. Sex differences in drug abuse. Front. Neuroendocrinol. 29, 36–47.
Becker, J.B., Koob, G.F., 2016. Sex differences in animal models: focus on addiction. Pharmacol. Rev. 68, 242.
Becker, J.B., Mcclellan, M., Reed, B.G., 2016. Sociocultural context for sex differences in addiction. Addict. Biol. 21, 1052.
Becker, J.B., Perry, A.N., Westenbroek, C., 2012. Sex differences in the neural mechanisms mediating addiction: a new synthesis and hypothesis. Biol. Sex Differ. 3, 14.
Bobzean, S.A., Denobrega, A.K., Perrotti, L.I., 2014. Sex differences in the neurobiology of drug addiction. Exp. Neurol. 259, 64–74.
Brown, M.R., Goltz, H.C., Vilis, T., Ford, K.A., Everling, S., 2006. Inhibition and generation of saccades: rapid event-related fMRI of prosaccades, antisaccades, and nogo trials. Neuroimage 33, 644–659.
Cooper, A.M., Michels, R., 1980. Book review, American Psychiatric Association: diagnostic and statistical manual of mental disorders, third ed..
Dale, A.M., Fischl, B., Sereno, M.I., 1999. Cortical surface-based analysis ☆: I. Segmentation and surface reconstruction. Neuroimage 9, 179.
Desikan, R.S., Sã©Gonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., Buckner, R.L., Dale, A.M., Maguire, R.P., Hyman, B.T., 2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 31, 968–980.
Dong, G., Potenza, M.N., 2014. A cognitive-behavioral model of Internet gaming disorder: theoretical underpinnings and clinical implications. J. Psychiatr. Res. 58, 7.
Dong, G., Potenza, M.N., 2016. Risk-taking and risky decision-making in Internet gaming disorder: Implications regarding online gaming in the setting of negative consequences. J. Psychiatr. Res. 73, 1–8.
Dong, G., Wang, L., Du, X., Potenza, M.N., 2017. Gaming increases craving to gaming-related stimuli in individuals with Internet gaming disorder. Biol. Psychiatry Cognit. Neurosci. Neuroimaging 2, 404–412.
Dowling, N.A., 2014. Issues raised by the DSM-5 Internet gaming disorder classification and proposed diagnostic criteria. Addiction 109, 1408–1409.
Dubois, B., Slachevsky, A., Litvan, I., Pillon, B., 2000. The FAB: a frontal assessment battery at bedside. Neurology 55 1621.
Durazzo, T.C., Tosun, D., Buckley, S., Gazdzinski, S., Mon, A., Fryer, S.L., Meyerhoff, D.J., 2011. Cortical thickness, surface area, and volume of the brain reward system in alcohol dependence: relationships to relapse and extended abstinence. Alcohol. Clin. Exp. Res. 35, 1187–1200.
Durston, S., Davidson, M.C., Thomas, K.M., Worden, M.S., Tottenham, N., Martinez, A., Watts, R., Ulug, A.M., Casey, B.J., 2003. Parametric manipulation of conflict and response competition using rapid mixed-trial event-related fMRI. Neuroimage 20, 2135.
Fischl, B., Dale, A.M., 2000. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc. Natl Acad. Sci. 97, 11050.
Fischl, B., Sereno, M.I., Dale, A.M., 1999. Cortical surface-based analysis. II: inflation, flattening, and a surface-based coordinate system. Neuroimage 9, 195–207.
Fuster, J.M., 2008. The prefrontal cortex (fourth ed.).
Greenfield, S.F., Back, S.E., Lawson, K., Brady, K.T., 2010. Substance abuse in women. Psychiatr. Clin. North Am. 33, 339.
Griffiths, M.D., King, D.L., Demetrovics, Z., 2014. DSM-5 Internet gaming disorder needs a unified approach to assessment. Neuropsychiatry 4, 1–4.
Hartwell, E.E., Ray, L.A., 2013. Sex moderates stress reactivity in heavy drinkers. Addict. Behav. 38, 2643–2646.
Hong, S.B., Jae-Won, K., Eun-Jung, C., Ho-Hyun, K., Jeong-Eun, S., Chang-Dai, K., Paul, K., Sarah, W., Murat, Y., Christos, P., 2013a. Reduced orbitofrontal cortical thickness in male adolescents with Internet addiction. Behav. Brain Funct. 9 1(2013-03-12) 911-11.
Hong, S.B., Kim, J.W., Choi, E.J., Kim, H.H., Suh, J.E., Kim, C.D., Klauser, P., Whittle, S., Yűcel, M., Pantelis, C., 2013b. Reduced orbitofrontal cortical thickness in male adolescents with internet addiction. Behav. Brain Funct. 9, 11.
Ide, J.S., Zhang, S., Hu, S., Sinha, R., Mazure, C.M., Li, C.S., 2014. Cerebral gray matter volumes and low-frequency fluctuation of BOLD signals in cocaine dependence: duration of use and gender difference. Drug Alcohol Depend. 134, 51–62.
Rando, K., Tuit, K., Hannestad, J., Guarnaccia, J., Sinha, R., 2013. Sex differences in decreased limbic and cortical grey matter volume in cocaine dependence: a voxel-based morphometric study. Addict. Biol. 18, 147–160.
Kerstetter, K.A., Su, Z.I., Ettenberg, A., Kippin, T.E., 2013. Sex and estrous cycle differences in cocaine-induced approach-avoidance conflict. Addict. Biol. 18, 222–229.
Ko, C.H., Liu, G.C., Yen, J.Y., Chen, C.Y., Yen, C.F., Chen, C.S., 2013. Brain correlates of craving for online gaming under cue exposure in subjects with Internet gaming addiction and in remitted subjects. Addict. Biol. 18, 559.
Kogachi, S., Chang, L., Alicata, D., Cunningham, E., Ernst, T., 2015. Sex differences in impulsivity and brain morphometry in methamphetamine users. Brain Struct. Funct.

146, 1–13.
Konova, A.B., Moeller, S.J., Parvaz, M.A., Froböse, M.I., Aliaklein, N., Goldstein, R.Z., 2016. Converging effects of cocaine addiction and sex on neural responses to monetary rewards. Psychiatry Res. 248, 110–118.
Lecrubier, Y., Sheehan, D.V., Weiller, E., Amorim, P., Bonora, I., Sheehan, K.H., Janavs, J., Dunbar, G.C., 1997. The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI. Eur. Psychiatry 12, 224–231.
Lee, D., Namkoong, K., Lee, J., Jung, Y.C., 2017. Abnormal gray matter volume and impulsivity in young adults with Internet gaming disorder. Addict. Biol.
Li, M., Tian, J., Zhang, R., Qiu, Y., Wen, X., Ma, X., Wang, J., Xu, Y., Jiang, G., Huang, R., 2014. Abnormal cortical thickness in heroin-dependent individuals. Neuroimage 88, 295.
Lin, X., 2015. Abnormal gray matter and white matter volume in 'Internet gaming addicts'. Addict. Behav. 40, 137–143.
Lin, X., Dong, G., Wang, Q., Du, X., 2015. Abnormal gray matter and white matter volume in 'Internet gaming addicts'. Addict. Behav. 40, 137–143.
Maddock, Richard, J., 1999. The retrosplenial cortex and emotion: new insights from functional neuroimaging of the human brain. Trends Neurosci. 22, 310.
Makris, N., Gasic, G.P., Kennedy, D.N., Hodge, S.M., Kaiser, J.R., Lee, M.J., Kim, B.W., Blood, A.J., Evins, A.E., Seidman, L.J., 2008. Cortical thickness abnormalities in cocaine addiction–a reflection of both drug use and a pre-existing disposition to drug abuse? Neuron 60, 174–188.
Mcclernon, F., Kozink, R., Am, Rose, J., 2009. 24-h smoking abstinence potentiates fMRI-BOLD activation to smoking cues in cerebral cortex and dorsal striatum. Psychopharmacology (Berl.) 204, 25.
Medina, K.L., Mcqueeny, T., Nagel, B.J., Hanson, K.L., Schweinsburg, A.D., Tapert, S.F., 2008. Prefrontal cortex volumes in adolescents with alcohol use disorders: unique gender effects. Alcohol. Clin. Exp. Res. 32, 386.
Organization, A.P., 2013. Diagnostic and Statistical Manual of Mental Disorders (fifth ed.). American Psychiatric Association.
Pearson, J.M., Heilbronner, S.R., Barack, D.L., Hayden, B.Y., Platt, L.M., 2011. Posterior cingulate cortex: adapting behavior to a changing world. Trends Cogn. Sci. 15, 143–151.
Petry, Rehbein, F., Gentile, D.A., Lemmens, J.S., Rumpf, H.J., Mößle, T., Bischof, G., Tao, R., Fung, D.S., Borges, G., 2014. An international consensus for assessing internet gaming disorder using the new DSM-5 approach. Addiction 109, 1399.
Petry, N.M., Rehbein, F., Ko, C.H., O'Brien, C.P., 2015. Internet gaming disorder in the DSM-5. Curr. Psychiatry Rep. 17, 72.
Rajkowska, GoldmanRakic, 1995. Cytoarchitectonic definition of prefrontal areas in the normal human cortex: I. Remapping of areas 9 and 46 using quantitative criteria. Cereb. Cortex 5, 307–322.
Rehbein, F., Kliem, S., Baier, D., Mößle, T., Petry, N.M., 2015. Prevalence of Internet gaming disorder in German adolescents: diagnostic contribution of the nine DSM-5 criteria in a statewide representative sample. Addiction 110, 842.
Richmondrakerd, L.S., Fleming, K.A., Slutske, W.S., 2016. Investigating progression in substance use initiation using a discrete-time Multiple Event Process Survival Mixture (MEPSUM) approach. Clin. Psychol. Sci. 4, 167–182.
Salmi, J., Rinne, T., Degerman, A., Alho, K., 2007. Orienting and maintenance of spatial attention in audition and vision: an event-related brain potential study. Brain Struct. Funct. 212, 181.
Sanchis-Segura, C., Becker, J., 2016. Why we should consider sex (and study sex differences) in addiction research. Addict. Biol. 21, 995–1006.
Sawyer, K.S., Oscar-Berman, M., Barthelemy, O.J., Papadimitriou, G.M., Harris, G.J., Makris, N., 2017. Gender dimorphism of brain reward system volumes in alcoholism. Psychiatry Res. 263, 15.
Schilling, C., Kühn, S., Paus, T., Romanowski, A., Banaschewski, T., Barbot, A., Barker, G.J., Brühl, R., Büchel, C., Conrod, P.J., 2013. Cortical thickness of superior frontal cortex predicts impulsiveness and perceptual reasoning in adolescence. Mol. Psychiatry 18, 624.
Sowell, E.R., Peterson, B.S., Kan, E., Woods, R.P., Yoshii, J., Bansal, R., Xu, D., Zhu, H., Thompson, P.M., Toga, A.W., 2007. Sex differences in cortical thickness mapped in 176 healthy individuals between 7 and 87 years of age. Cereb. Cortex 17, 1550.
Tanabe, J., York, P., Krmpotich, T., Miller, D., Dalwani, M., Sakai, J.T., Mikulich-Gilbertson, S.K., Thompson, L., Claus, E., Banich, M., Rojas, D.C., 2013. Insula and orbitofrontal cortical morphology in substance dependence is modulated by sex. Am. J. Neuroradiol. 34, 1150–1156.
Volkow, N.D., Tomasi, D., Wang, G.J., Fowler, J.S., Telang, F., Goldstein, R.Z., Aliaklein, N., Wong, C., 2011. Reduced metabolism in brain "control networks" following cocaine-cues exposure in female cocaine abusers. PLoS One 6, e16573.
Wang, H., Jin, C., Yuan, K., Shakir, T.M., Mao, C., Niu, X., Niu, C., Guo, L., Zhang, M., 2015. The alteration of gray matter volume and cognitive control in adolescents with internet gaming disorder. Front. Behav. Neurosci. 9, 64.
Wang, Z., Wu, L., Yuan, K., Hu, Y., Zheng, H., Du, X., Dong, G., 2018. Cortical thickness and volume abnormalities in Internet gaming disorder: evidence from comparison of recreational Internet game users. Eur. J. Neurosci. https://doi.org/10.1111/ejn.13987.
Weng, C.B., Qian, R.B., Fu, X.M., Lin, B., Han, X.P., Niu, C.S., Wang, Y.H., 2013. Gray matter and white matter abnormalities in online game addiction. Eur. J. Radiol. 82, 1308.
Yuan, K., Cheng, P., Dong, T., Bi, Y., Xing, L., Yu, D., Zhao, L., Dong, M., Deneen, K.M.V., Liu, Y., 2013. Cortical thickness abnormalities in late adolescence with online gaming addiction. PLoS One 8, e53055.
Yuan, K., Qin, W., Wang, G., Zeng, F., Zhao, L., Yang, X., Liu, P., Liu, J., Sun, J., Deneen, K.M.V., 2011. Microstructure abnormalities in adolescents with Internet addiction disorder. PLoS One 6, e20708.
Zanchi, D., Brody, A., Borgwardt, S., Haller, S., 2016. Sex effects on smoking cue perception in non-smokers, smokers, and ex-smokers: a pilot study. Front. Psychiatry 7 S703–S703.
Zhou, Y., Lin, F.C., Du, Y.S., Qin, L.D., Zhao, Z.M., Xu, J.R., Lei, H., 2011. Gray matter abnormalities in Internet addiction: a voxel-based morphometry study. Eur. J. Radiol. 79, 92–95.