Brain Imaging and Behavior (2019) 13:660–668
https://doi.org/10.1007/s11682-018-9872-6

ORIGINAL RESEARCH

Preliminary evidence of altered gray matter volume in subjects with internet gaming disorder: associations with history of childhood attention-deficit/hyperactivity disorder symptoms

Deokjong Lee[1,2] · Kee Namkoong[2,3] · Junghan Lee[2] · Young-Chul Jung[2,3]

Published online: 11 May 2018

Abstract

Attention-deficit/hyperactivity disorder (ADHD) is commonly comorbid with Internet gaming disorder (IGD). Although childhood ADHD symptoms may decline during late brain maturation, structural alterations in some brain areas may persist into adulthood. This study investigated whether young adults with IGD and a history of childhood ADHD symptoms had gray matter volume (GMV) alterations that were distinct from subjects without a history of childhood ADHD. As an exploratory investigation, we conducted a whole-brain voxel-based morphometry with the diffeomorphic anatomical registration using an exponentiated Lie algebra algorithm and applied an uncorrected threshold at the voxel level for multiple comparisons. GMVs of IGD subjects with a history of childhood ADHD (IGD_{ADHD+} group; $n = 20$; 24.5 ± 2.5 years) were compared to those of subjects without a history of childhood ADHD (IGD_{ADHD-} group; $n = 20$; 23.9 ± 2.5 years) and controls (n = 20; 22.7 ± 2.4 years). Compared with controls, both IGD groups had a smaller GMV in the right anterior cingulate cortex, the left inferior frontal gyrus, and the left insula, yet had a larger GMV in the right angular gyrus. The IGD_{ADHD+} group had a larger GMV in the right precuneus than the IGD_{ADHD-} group and controls. When controlling for other comorbid psychiatric symptoms, the IGD_{ADHD+} group also had a smaller GMV in the right inferior frontal gyrus. In conclusion, we found that young adults with IGD and a history of childhood ADHD symptoms had characteristic GMV alterations, which may be linked with their manifestation of childhood ADHD.

Keywords Attention-deficit/hyperactivity disorder · Gray matter volume · Internet gaming disorder · Voxel-based morphometry

Introduction

Internet gaming disorder (IGD) is characterized by uncontrollable use of Internet games during adolescence and young adulthood, and this condition is noted as requiring further study in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)(Petry and O'brien 2013). Over the past decade, considerable neuroimaging research has explored the mechanisms underlying the loss of control in excessive Internet game use (Kuss and Griffiths 2012). Of note, structural imaging studies in individuals with IGD showed structural abnormalities within the brain regions underlying executive control and reward processing, including the anterior cingulate cortex (ACC), the insula, the dorsolateral prefrontal cortex (DLPFC), and the orbitofrontal cortex (OFC) (Weng et al. 2013; Yuan et al. 2011; Zhou et al. 2011). Although these neurobiological results have provided important insight into the pathophysiology of IGD, interpretation of the relationship between structural abnormalities and excessive gaming still requires careful consideration, due to a lack of longitudinal investigation. Furthermore, the complex interactions between psychosocial factors and high rates of comorbidity with other psychiatric conditions make it difficult to identify a distinct pathophysiology for IGD (Kim et al. 2016; Ko et al. 2012). Several psychiatric disorders, including depression (Morrison and Gore 2010), anxiety disorder (Lo et al. 2005), and attention-deficit/hyperactivity disorder

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11682-018-9872-6) contains supplementary material, which is available to authorized users.

✉ Young-Chul Jung
eugenejung@yuhs.ac

[1] Department of Psychiatry, Ilsan Hospital, National Health Insurance Corporation, 10444, Goyang, South Korea

[2] Institute of Behavioral Science in Medicine, Yonsei University College of Medicine, 03722, Seoul, South Korea

[3] Department of Psychiatry, Yonsei University College of Medicine, 03722, Seoul, South Korea

(ADHD)(Yen et al. 2007), have been associated with IGD. These comorbid conditions may be predisposing factors for the development and maintenance of IGD (Brand et al. 2016). To understand the link between structural abnormalities and excessive gaming, the influence of predisposing comorbid psychiatric conditions on IGD and resulting structural alterations needs to be defined.

Evidence is accumulating for a strong relationship between IGD and ADHD (Kim et al. 2017; Yen et al. 2017). There is a high rate of comorbidity between IGD and ADHD in both children and adolescents (Yen et al. 2007). Because the onset of ADHD is typically during early childhood (Kieling et al. 2010), childhood ADHD can be considered one of the most important predisposing psychiatric conditions for IGD. Previous studies have revealed that alterations in reward processing and inhibitory control persist into adolescence, even when the ADHD phenotype declines with time (Halperin et al. 2008; McAuley et al. 2014). Due to these persistent alterations, subjects with remitted ADHD who met diagnostic criteria in childhood, but not in adolescence and adulthood, may have an increased risk of negative psychosocial conditions (Yoshimasu et al. 2012), including addictive disorders (Shaw et al. 2012). The vulnerability of subjects with remitted ADHD may be related to altered structural changes during their brain development. Neuroanatomic studies have indicated that cortical development is delayed in individuals with childhood ADHD, compared with typically developing controls (Shaw et al. 2007). Although childhood ADHD symptoms may decline during the late maturation of brain regions related to cognitive control, structural alterations in some brain regions are reported to persist into adulthood (Cortese et al. 2013; Proal et al. 2011). We speculate that young adults with IGD and a history of childhood ADHD may have brain structural alterations associated with childhood ADHD symptoms, even if they do not meet the diagnostic criteria for ADHD in adulthood. Given that ADHD involves the impairment of executive control (Fosco et al. 2015; Weigard et al. 2016) and reward processing (Sonuga-Barke 2003), these brain structural alterations may also be closely related to the pathophysiology and clinical features of IGD.

The purpose of this study is to investigate the impact of a history of childhood ADHD on gray matter volume (GMV) alterations in IGD. We assumed the following hypotheses about the pattern of GMV alterations in subjects with IGD. First, we expect both IGD subjects with and without a history of childhood ADHD symptoms to have a common pattern of GMV alterations related to IGD pathophysiology. Consistent with previous studies (Weng et al. 2013; Yuan et al. 2011; Zhou et al. 2011), we expected that IGD subjects would have a smaller GMV in the ACC, the insula, the DLPFC, and the OFC than controls. Second, we expected that IGD subjects with a history of childhood ADHD symptoms to have a distinct pattern of GMV alteration, which may be linked with their manifestation of childhood ADHD symptoms. Our previous functional imaging study of IGD suggested that a history of childhood ADHD may affect functional connectivity of the default mode network (DMN) in individuals with IGD (Lee et al. 2017). Based on this previous study and the important role of DMN abnormalities in ADHD pathophysiology (Fassbender et al. 2009), we anticipated that GMVs in hubs of the DMN are specifically altered in IGD subjects with a history of childhood ADHD symptoms. To test our hypotheses, we employed voxel-based morphometry (VBM) analysis using an exponentiated Lie algebra algorithm (DARTEL) to explore GMV in young male adults with IGD. We then compared alterations in the GMV of IGD subjects with a history of childhood ADHD symptoms with that of IGD subjects without a history of childhood ADHD symptoms and with healthy controls.

Method

Participants

Participants were recruited using online advertisements, flyers, and word-of-mouth. The Institutional Review Board at Severance Hospital, Yonsei University, approved all protocols. All participants provided written informed consent before enrollment. Sixty young male adults participated in the study, all of whom were right-handed and between 19 and 29 years old (mean: 23.7 ± 2.5 years). All subjects were assessed for Internet use patterns and screened for IGD using the Internet addiction test (IAT) (Young 1998). Subjects who spent less than 2 h per day on gaming and scored below 50 points on the IAT were classified as healthy controls ($n = 20$; 22.7 ± 2.4 years). Subjects whose main Internet use was gaming and scored above 50 points on the IAT were assigned to the IGD group. To confirm the diagnosis of IGD, we performed the clinician-administered interview according to the proposed criteria of IGD in the DSM-5 (Petry and O'brien 2013). These IGD subjects were further subdivided into two groups according to their history of childhood ADHD symptoms, as assessed by the Wender Utah rating scale (WURS) (Ward 1993): IGD subjects with a history of childhood ADHD symptoms (IGD_{ADHD+} group, n = 20; 24.5 ± 2.5 years) and IGD subjects without a history of childhood ADHD symptoms (IGD_{ADHD-} group, n = 20; 23.9 ± 2.5 years).

To confirm the absence of other mental disorders, we conducted the Structured Clinical Interview from the DSM Fourth Edition (DSM-4) (SCID) (First et al. 1995). Intelligence quotient (IQ) was estimated through the Korean version of the Wechsler adult intelligence scale IV (WAIS-IV) (Wechsler 2014). Psychopathological state was assessed using self-reported questionnaires, including the alcohol use disorders identification test (AUDIT) (Reinert and Allen 2002), the

Beck depression inventory (BDI) (Beck et al. 1961), the Beck anxiety inventory (BAI) (Beck et al. 1988), and the Barratt impulsiveness scale version 11 (BIS-11) (Patton and Stanford 1995). Adult ADHD symptoms were measured using the Conners' adult ADHD rating scales (CAARS) (Conners et al. 1999), which consists of four subscales: inattention/memory problems, hyperactivity/restlessness, impulsivity/emotional lability, and problems with self-concept. No participants met the DSM-IV criteria for ADHD at the time of assessment using the SCID interview.

The exclusion criteria for all groups included: the existence of a neurological disorder or medical illness, major psychiatric illness other than IGD, history of substance dependence, mental retardation, or radiological contra-indications in a magnetic resonance imaging (MRI) scan. All participants were psychiatric medication-naïve at the time of evaluation.

Structural image acquisition and pre-processing

Structural images were acquired using a 3 T Siemens Magnetom MRI scanner equipped with an eight-channel head coil. MRI data were recorded using a T1-weighted spoiled gradient echo sequence (TE = 2.19 ms, TR = 1780 ms, flip angle = 9°, field of view = 256 mm, matrix = 256 × 256, transverse slice thickness = 1 mm). Data were analyzed using SPM8 (Welcome Department of Imaging Neuroscience, UK) on a MATLAB 8.5 platform (MathWorks, Natick, MA). During VBM processing, we applied diffeomorphic anatomical registration using an exponentiated Lie algebra algorithm (DARTEL) to improve inter-subject registration of the structural images (Ashburner 2007). First, T1-weighted MRI images were segmented into gray matter (GM), white matter, and cerebrospinal fluid (CSF) probability maps using a Bayesian image segmentation algorithm. After segmentation, a study-specific template was created by inter-subject alignment of structural images, and each voxel was resampled to $1.5 \times 1.5 \times 1.5$ mm^3. Individual GM images were warped to the study-specific template and then normalized into Montreal Neurological Institute (MNI) standard space for analysis. The normalized and modulated GM images were smoothed using 8-mm full-width at half maximum kernel (FWHM).

Statistical analysis

To examine the differences between groups using demographic and clinical variables, one-way analysis of variance (ANOVA) tests were conducted in SPSS 24.0, with p-value = 0.05 considered to be significant. Post hoc Bonferroni analysis was conducted to detect differences between groups.

We constructed statistical parametric maps using the general linear model in SPM8. Then, GMV estimates were compared between groups using ANOVA at each voxel. Age, IQ, and total intracranial volume (TICV) of each subject were entered as covariates because of their previously established impact on VBM (Frangou et al. 2004; Pell et al. 2008). Statistical inferences for the exploratory whole-brain were set at an uncorrected p-value height threshold of 0.001 and an extent threshold of k = 10. Subsequently, we extracted the mean GMV values of clusters with group differences using the MarsBaR toolbox (http://marsbar.sourceforge.net/). We performed the analysis of covariance (ANCOVA), while controlling for age, IQ, and TICV as covariates, to test for group differences in the mean GMV value for each cluster. Bonferroni post hoc tests were conducted to detect differences between groups.

Then, we added several covariates into the ANOVA model for whole-brain voxel-wise analysis, in order to test whether GMV differences would remain significant after controlling for other comorbid psychiatric symptoms. Because alcohol use and GMV are known to be closely related (Benegal et al. 2007), AUDIT scores were firstly added as a covariate. Then, BDI and BAI scores were also entered as covariates. To elaborate on the clinical interpretation of altered GMV in IGD subjects, we also conducted correlation analyses to investigate the relationships of GMV alterations to the severity of IGD using IAT, the adult ADHD symptoms using CAARS, and impulsivity using BIS.

Results

Demographic and clinical participant variables

There was no significant difference in age or IQ score between controls and subjects with IGD (Table 1). Subjects with IGD had significantly higher IAT scores than controls. The IGD_{ADHD+} group had significantly higher WURS scores than the IGD_{ADHD-} group or controls. Both the IGD_{ADHD-} and IGD_{ADHD+} groups differed from controls when comparing self-reported current ADHD symptoms (e.g. inattention/memory problems and impulsivity/emotional lability). Self-reported hyperactivity/restlessness was higher in the IGD_{ADHD+} group than in controls, but not in the IGD_{ADHD-} group. The IGD_{ADHD+} group scored significantly higher on depression tests than controls. The IGD_{ADHD+} group also scored significantly higher on our anxiety tests than the IGD_{ADHD-} group and controls.

Voxel-based morphometry results

In the whole-brain voxel-wise analysis, we found multiple clusters with significant GMV differences between groups (Table 2). Post hoc tests revealed that both IGD groups had a smaller GMV in the right ACC, the left inferior frontal gyrus (IFG), and the left insula (Fig. 1a–c) than controls. The GMV in the right angular gyrus was larger in both IGD groups than in controls (Fig. 1d). The IGD_{ADHD-} and IGD_{ADHD+} groups

Table 1 Demographic and clinical variables of subjects

	Controls (n = 20)	IGD_{ADHD-} (n = 20)	IGD_{ADHD+} (n = 20)	Test	P-value	Post Hoc Test
Age	22.7 ± 2.4	23.9 ± 2.5	24.5 ± 2.5	F(2,57) = 2.788	0.070	
Full Scale IQ	107.0 ± 18.0	106.2 ± 14.2	101.7 ± 12.1	F(2,57) = 0.720	0.491	
IAT	31.3 ± 12.8	58.6 ± 9.3	65.6 ± 9.6	F(2,57) = 57.814	<0.001	IGD_{ADHD-}, IGD_{ADHD+} > Controls
WURS	23.1 ± 10.1	22.7 ± 13.1	60.6 ± 11.5	F(2,57) = 69.690	<0.001	IGD_{ADHD+} > Controls, IGD_{ADHD-}
CAARS						
Inattention/memory	49.3 ± 4.9	55.0 ± 6.6	54.9 ± 4.0	F(2,57) = 7.778	0.001	IGD_{ADHD-}, IGD_{ADHD+} > Controls
Hyperactivity/restlessness	46.8 ± 5.5	48.8 ± 4.3	52.4 ± 5.5	F(2,57) = 6.227	0.004	IGD_{ADHD+} > Controls
Impulsivity/emotional lability	47.6 ± 4.2	54.1 ± 6.1	54.4 ± 4.9	F(2,57) = 11.317	<0.001	IGD_{ADHD-}, IGD_{ADHD+} > Controls
Problems with self-concept	63.5 ± 8.3	68.2 ± 9.2	69.5 ± 9.6	F(2,57) = 2.389	0.101	
BAI	4.3 ± 3.6	9.5 ± 7.0	15.8 ± 8.1	F(2,57) = 15.403	<0.001	IGD_{ADHD+} > IGD_{ADHD-} > Controls
BDI	6.5 ± 4.0	11.7 ± 7.6	16.2 ± 8.2	F(2,57) = 10.029	<0.001	IGD_{ADHD+} > Controls
AUDIT	9.2 ± 4.6	10.9 ± 8.6	15.4 ± 10.5	F(2,57) = 3.035	0.056	
BIS	47.4 ± 11.2	51.6 ± 12.5	54.9 ± 11.8	F(2,57) = 2.015	0.143	

Data are expressed as mean ± standard deviation. All *p* values are calculated with one-way analysis of variance (ANOVA) tests. Post hoc tests were conducted using the Bonferroni correction

IGD, Internet gaming disorder; ADHD, attention-deficit/hyperactivity disorder; IQ, intelligence quotient, IAT, Internet addiction test; WURS, Wender Utah rating scale; CAARS, Conners' adult ADHD rating scales; BAI, Beck anxiety inventory; BDI, Beck depression inventory; AUDIT, alcohol use disorders identification test; BIS, Barratt impulsiveness scale

also showed distinct GM alterations in some other regions. For example, compared with the IGD_{ADHD+} group and controls, the IGDADHD- group exhibited a smaller GMV in the left middle occipital gyrus (MOG) and the left lingual gyrus (Fig. 2a, b). Compared with the IGD_{ADHD-} group and controls, the IGD_{ADHD+} group had a larger GMV in the right precuneus (Fig. 2c).

Most of the results remained valid even when AUDIT was added as a covariate; however, GMV differences in the left insula were not significant after including AUDIT as a covariate (Supplement Table 1). Most of the results also remained valid when BDI, BAI, and AUDIT were included as covariates (Table 3). But GMV differences in the right ACC and the right precuneus were not significant after controlling for BDI, BAI, and AUDIT. Notably, GMV in the right IFG was smaller in the IGD_{ADHD+} group than in other groups (Fig. 3) after controlling for BDI, BAI, and AUDIT. In correlation analyses, there were no statistically significant relationships between the extracted GMV values and the scores on self-reporting questionnaires.

Discussion

We investigated alterations in the GMV of IGD subjects with and without a history of childhood ADHD symptoms, using

Table 2 Whole-brain voxel-based morphometry (VBM) results

Region	Side	k_E	Z-score	x	y	z	Post Hoc Test
Anterior cingulate cortex	Right	171	3.55	3	26	18	Controls > IGD_{ADHD-}, IGD_{ADHD+}
Middle occipital gyrus	Left	43	3.52	−44	−84	14	Controls, IGD_{ADHD+} > IGD_{ADHD-}
Inferior frontal gyrus	Left	27	3.44	−56	5	15	Controls > IGD_{ADHD-}, IGD_{ADHD+}
Angular gyrus	Right	12	3.39	42	−68	32	IGD_{ADHD-}, IGD_{ADHD+} > Controls
Insula	Left	11	3.39	−45	12	−5	Controls > IGD_{ADHD-}, IGD_{ADHD+}
Lingual gyrus	Left	22	3.31	−17	−98	−17	Controls, IGD_{ADHD+} > IGD_{ADHD-}
Precuneus	Right	10	3.18	6	−53	59	IGD_{ADHD+} > Controls, IGD_{ADHD-}

Brain regions in which gray matter volumes (GMVs) showed significant differences between groups (uncorrected $p < 0.001$, in conjunction with an extent threshold of k = 10)

The effects of age, intelligence quotient and total intracranial volume were controlled as covariates. The coordinates of each cluster are indicated by the Montreal Neurological Institute (MNI) system. Post hoc tests were conducted using the Bonferroni correction

ADHD, attention-deficit/hyperactivity disorder; IGD, Internet gaming disorder; k_E; number of cluster voxels

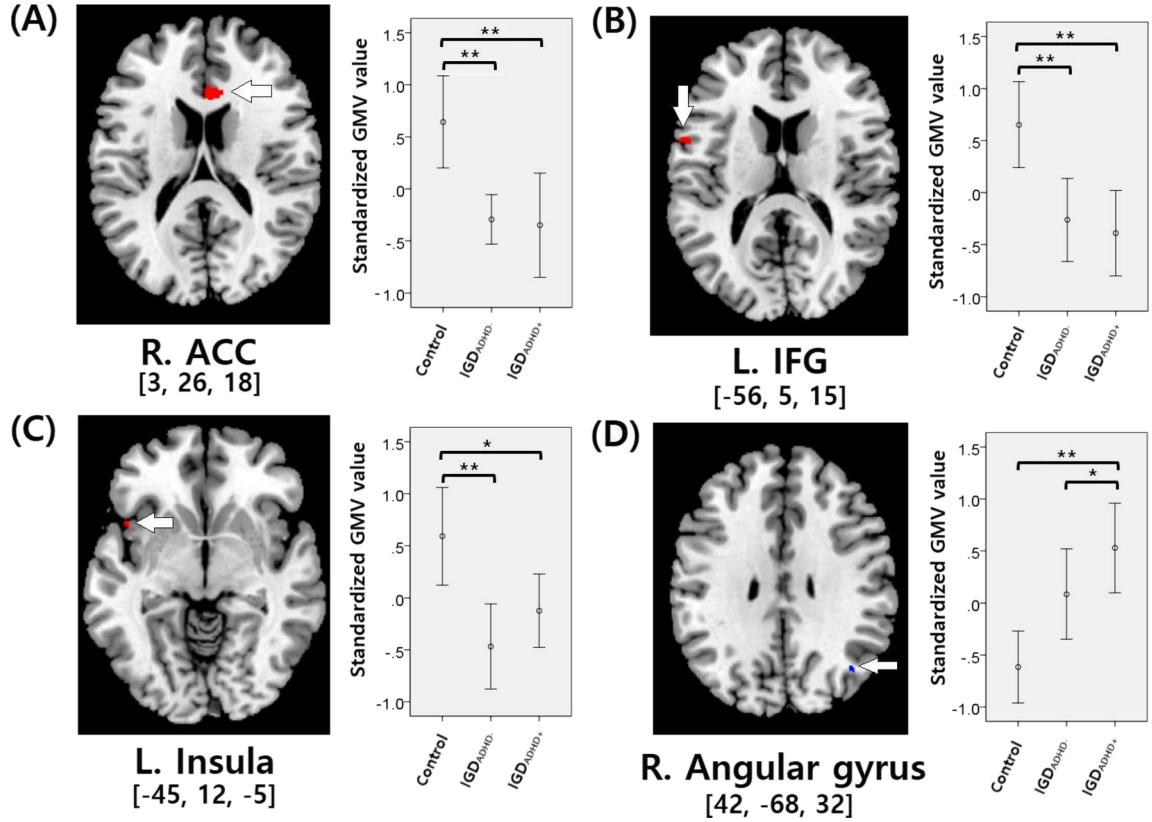

Fig. 1 Brain regions showing the same gray matter volume (GMV) pattern in the IGD_{ADHD-} and IGD_{ADHD+} groups compared to controls. (**a**) right anterior cingulate cortex (ACC), (**b**) left inferior frontal gyrus (IFG), (**c**) left insula, (**d**) right angular gyrus. The coordinates of each cluster are indicated by the Montreal Neurological Institute (MNI) system. The analysis of covariance (ANCOVA), controlling for age, intelligence quotient, and total intracranial volume as covariates, tested for group differences in the extracted GMV value for each cluster. Post hoc tests were conducted to detect differences across groups using the Bonferroni correction. * $p < 0.05$ ** $p < 0.01$

VBM analysis. Whole-brain analysis revealed that both IGD groups (IGD_{ADHD-} and IGD_{ADHD+}) had a significantly smaller GMV in the right ACC, the left insula, and the left IFG than controls. Both IGD groups also had a significantly larger GMV in the right angular gyrus than controls. These findings are consistent with our expectation of similar patterns of GMV alteration in both IGD groups. This also coincided with our expectation that these GMV alterations include smaller GMV in the ACC and the insula. Additionally, IGD subjects with and without a history of childhood ADHD symptoms displayed distinct GM changes in some other regions. For example, the IGD_{ADHD+} group had a larger GMV in the right precuneus than other groups. This finding is consistent with our expectation that the IGD_{ADHD+} group would have altered GMV in DMN-related regions, reflecting an association with childhood ADHD. The IGD_{ADHD+} group also showed a

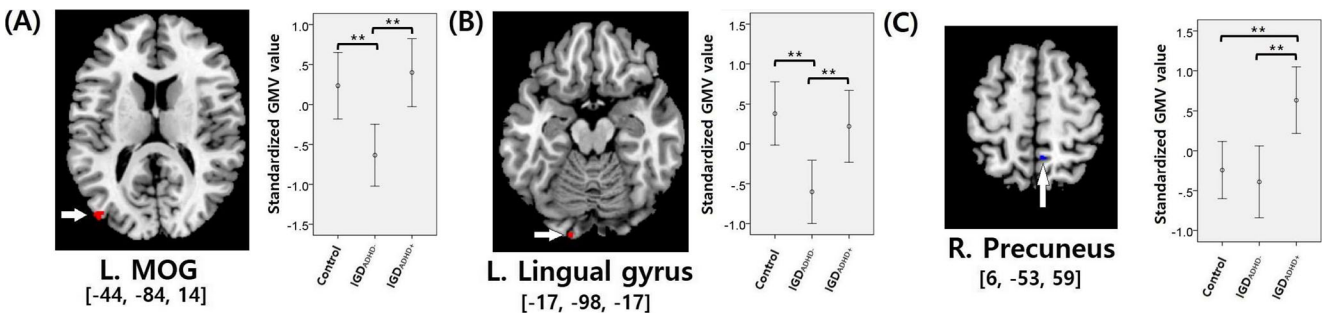

Fig. 2 Brain regions showing different gray matter volume (GMV) patterns in the IGD_{ADHD-} and IGD_{ADHD+} groups. (**a**) left middle occipital gyrus (MOG), (**b**) left lingual gyrus, (**c**) right precuneus. The coordinates of each cluster are indicated by the Montreal Neurological Institute (MNI) system. The analysis of covariance (ANCOVA), controlling for age, intelligence quotient, and total intracranial volume as covariates, tested for group differences in the extracted GMV value for each cluster. Post hoc tests were conducted to detect differences across groups using the Bonferroni correction. * $p < 0.05$ ** $p < 0.01$

Table 3 Whole-brain voxel-based morphometry (VBM) results after controlling for psychiatric comorbid conditions

Region	Side	k_E	Z-score	x	y	z	Post Hoc Test
Inferior frontal gyrus	Left	454	4.12	−60	14	17	Controls > IGD_{ADHD-}, IGD_{ADHD+}
Angular gyrus	Right	81	3.81	41	−68	32	IGD_{ADHD+} > IGD_{ADHD-} > Controls
Insula	Left	32	3.66	−47	14	−5	Controls > IGD_{ADHD-}, IGD_{ADHD+}
Middle occipital gyrus	Left	20	3.34	−44	−84	14	Controls, IGD_{ADHD+} > IGD_{ADHD-}
Inferior frontal gyrus	Right	48	3.29	51	14	12	Controls, IGD_{ADHD-} > IGD_{ADHD+}
Lingual gyrus	Left	12	3.19	−15	−98	−15	Controls, IGD_{ADHD+} > IGD_{ADHD-}

Brain regions in which gray matter volumes (GMVs) showed significant differences between groups (uncorrected $p < 0.001$, in conjunction with an extent threshold of $k = 10$)

The effects of age, intelligence quotient, total intracranial volume, the alcohol use disorders identification test (AUDIT), the Beck depression inventory (BDI) and the Beck anxiety inventory (BAI) were controlled as covariates. The coordinates of each cluster are indicated by the Montreal Neurological Institute (MNI) system. Post hoc tests were conducted using the Bonferroni correction

ADHD, attention-deficit/hyperactivity disorder; IGD, Internet gaming disorder; k_E, number of cluster voxels

smaller GMV in the right IFG than other groups, after controlling for comorbid psychiatric symptoms. Unlike the IGD_{ADHD+} group, the IGD_{ADHD-} group had a smaller GMV in the left MOG and the lingual gyrus, which are associated with visual processing and selective attention (Mangun et al. 1998). These findings are consistent with previous studies on IGD that reported brain structural alterations in the occipital lobe (Han et al. 2012; Lin et al. 2012) and may be related to the altered neural activity in response to gaming-related cues (Zhang et al. 2016).

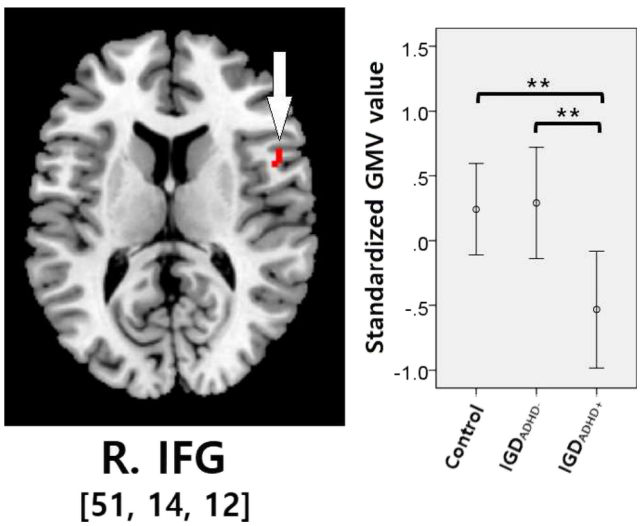

Fig. 3 A newly detected brain region showing different gray matter volume (GMV) patterns between groups, after controlling for comorbid psychiatric symptoms. The brain region corresponds with the right inferior frontal gyrus (IFG). The coordinates of each cluster are indicated by the Montreal Neurological Institute (MNI) system. The analysis of covariance (ANCOVA), controlling for age, intelligence quotient, total intracranial volume, the Beck depression inventory (BDI), the Beck anxiety inventory (BAI), and the alcohol use disorders identification test (AUDIT) as covariates, tested for group differences in the extracted GMV value for each cluster. Post hoc tests were conducted to detect differences across groups using the Bonferroni correction. * $p < 0.05$ ** $p < 0.01$

We found that both IGD groups had a smaller GMV in the right ACC and the left insula than healthy controls. The ACC region is known to be involved in executive control (Bush et al. 2000). In particular, it is responsible for conflict monitoring (Botvinick et al. 2001) and response inhibition (Barch et al. 2001). Numerous studies have demonstrated executive control problems in individuals with IGD and have suggested that structural or functional alterations of the ACC contribute to impaired executive control (Ko et al. 2014; Wang et al. 2016a). On the other hand, the insula is considered to be a major node of the salience network (Menon and Uddin 2010) and is suggested to play an important role in risky decision-making (Xue et al. 2010) by reflecting signals of risk and risk prediction error (Preuschoff et al. 2008). Individuals with IGD have problems making appropriate decisions under risky conditions (Dong and Potenza 2016), and functional alteration of the insula has been implicated in their risky decision-making deficit (Lee et al. 2016). Our findings of a smaller GMV in the ACC and the insula in IGD may be associated with clinical features of IGD, such as diminished executive control and altered risky decision-making.

Both IGD groups showed a significantly larger GMV in the right angular gyrus than controls. Although some previous studies have indicated that parietal regions are involved in IGD (Feng et al. 2013; Yuan et al. 2013), the evidence for altered GMV in parietal regions in IGD is less than for other brain regions. The angular gyrus is suggested to be involved in bottom-up control of attention (Ciaramelli et al. 2008). A previous functional brain imaging study revealed that individuals with IGD were easily distracted from gaming cues and could not perform normal top-down control of attention (Liu et al. 2014). Further studies should provide additional evidence, but we speculate that altered GMV of the angular gyrus in IGD is related to dysfunctional interaction between the top-down and bottom-up attention systems.

We observed that both IGD groups have a smaller GMV in the left IFG than healthy controls. The IFG is implicated in

appropriate inhibitory control of behavior (Hampshire et al. 2010). Deficits in inhibitory response control, which are indicative of dysfunctional executive control, are suggested to contribute to the development of uncontrolled Internet game usage (Dong and Potenza 2014). Thus, the smaller GMV in the IFG of IGD subjects may be associated with response inhibition deficits in IGD. In particular, the GMV of the right IFG was found to be significantly smaller only in the IGD_{ADHD+} group. Substantial evidence has demonstrated that the right side of the IFG may be a significant locus for ADHD pathophysiology (Depue et al. 2010; Rubia et al. 1999). The relevant IFG regions in this study correspond with the pars opercularis section of the IFG. Children with ADHD had a thinner bilateral cortex in the pars opercularis of the IFG than healthy controls and a disrupted correlation between cortical thickness in the pars opercularis and inhibitory performance (Batty et al. 2010). Taken together, the present findings of a smaller GMV in the bilateral IFG of the IGD_{ADHD+} group may be related to the neurobiology of childhood ADHD.

The IGD_{ADHD+} group showed a larger GMV in the right precuneus than other groups. Previous studies on ADHD found an increased GMV in the precuneus (Nakao et al. 2011). In particular, the precuneus is known to play a major role in the DMN (Utevsky et al. 2014) and dysfunction of the DMN has been suggested as part of the pathophysiology of ADHD (Sonuga-Barke and Castellanos 2007). Thus, our finding of a larger GMV in the right precuneus of the IGD_{ADHD+} group supports the expectation of characteristic gray matter alterations that may be related to the manifestation of childhood ADHD. Previous studies of IGD have reported that DMN abnormalities are also involved in the IGD pathophysiology (Ding et al. 2013; Wang et al. 2016b) and that a history of childhood ADHD symptoms may affect functional connectivity of the DMN in individuals with IGD (Lee et al. 2017). We speculate that altered GMV in the right precuneus of the IGD_{ADHD+} group might influence IGD pathophysiology via changes in the DMN.

There are several limitations in this study. First, this study did not include individuals who had childhood ADHD symptoms but did not develop IGD. Due to this limitation, it is difficult to interpret whether GMV alterations are associated with childhood ADHD or with IGD. Second, we used a cross-sectional study design and retrospectively evaluated childhood ADHD symptoms using self-reporting questionnaires. Although all subjects completed an additional psychiatric interview to confirm the presence of childhood ADHD symptoms, the risk of recall bias remains. A future longitudinal study of individuals who were diagnosed with childhood ADHD would help identify whether GM changes associated with childhood ADHD may contribute to vulnerability to IGD. Third, this study was conducted with a sample of small size and used a liberal statistical threshold. Our findings need to be confirmed by future studies with larger subject samples. Fourth, although we performed additional analyses to control for comorbid psychiatric symptoms by using additional scale scores as covariates, we could not control some variables. For example, smoking status has been reported to affect GMV (Fritz et al. 2014). Furthermore, although most of the results remained valid even after controlling for comorbid psychiatric conditions, we detected some differences that depended on which variables were controlled. Careful consideration of the variables affecting GMV is needed in future studies of IGD. Fifth, our findings are difficult to interpret because of the lack of a significant correlation between GMV alterations and the clinical variables assessed by self-reports. In addition, the study did not include an objective measure of clinical IGD features or an assessment of brain function. Future studies that include assessment for clinical IGD features and its associated brain function would strengthen the current findings.

This study compared the GMV of IGD subjects with and without a history of childhood ADHD symptoms. Regardless of a history of childhood ADHD symptoms, both IGD groups had a smaller GMV in the right anterior cingulate cortex, the left inferior frontal gyrus, and the left insula, yet had a larger GMV in the right angular gyrus. However, IGD subjects with a history of childhood ADHD symptoms also had different patterns of GMV alterations, such as a larger GMV in the right precuneus and a smaller GMV in the right IFG than other subjects. Differences in GMV alterations between IGD subjects with and without childhood ADHD symptoms may suggest that different neurobiological factors underlie the pathophysiology and clinical features of IGD in these two groups. However, due to the limitations of this study design, the clinical significance of these different GMV alterations is unclear. Future studies, including longitudinal studies, are required to build upon these findings.

Author contributions Deokjong Lee and Young-Chul Jung conceived and designed the study. Junghan Lee recruited participants and acquired imaging data. Deokjong Lee drafted the manuscript. Kee Namkoong and Young-Chul Jung provided critical revision of the manuscript and important intellectual content. All authors critically reviewed and approved the final version of this manuscript for publication.

Funding This study was funded by a grant from the Korean Mental Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (HM14C2578).

Compliance with ethical standards

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

Ethical approval All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments, or comparable ethical standards. The experimental protocol was approved by the Institutional Review Board at Severance Hospital, Yonsei University, Seoul, Korea.

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

References

Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *NeuroImage, 38*(1), 95–113.

Barch, D. M., Braver, T. S., Akbudak, E., Conturo, T., Ollinger, J., & Snyder, A. (2001). Anterior cingulate cortex and response conflict: Effects of response modality and processing domain. *Cerebral Cortex (New York, NY), 11*(9), 837–848.

Batty, M. J., Liddle, E. B., Pitiot, A., Toro, R., Groom, M. J., Scerif, G., et al. (2010). Cortical gray matter in attention-deficit/hyperactivity disorder: A structural magnetic resonance imaging study. *Journal of the American Academy of Child & Adolescent Psychiatry, 49*(3), 229–238.

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry, 4*(6), 561–571.

Beck, A. T., Epstein, N., Brown, G., & Steer, R. A. (1988). An inventory for measuring clinical anxiety: Psychometric properties. *Journal of Consulting and Clinical Psychology, 56*(6), 893.

Benegal, V., Antony, G., Venkatasubramanian, G., & Jayakumar, P. N. (2007). Imaging study: Gray matter volume abnormalities and externalizing symptoms in subjects at high risk for alcohol dependence. *Addiction Biology, 12*(1), 122–132.

Botvinick, M. M., Braver, T. S., Barch, D. M., Carter, C. S., & Cohen, J. (2001). Evaluating the demand for control: Anterior cingulate cortex and conflict monitoring. *Psychological Review, 108*(3), 624–652.

Brand, M., Young, K. S., Laier, C., Wölfling, K., & Potenza, M. N. (2016). Integrating psychological and neurobiological considerations regarding the development and maintenance of specific internet-use disorders: An interaction of person-affect-cognition-execution (I-PACE) model. *Neuroscience & Biobehavioral Reviews, 71*, 252–266.

Bush, G., Luu, P., & Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Sciences, 4*(6), 215–222.

Ciaramelli, E., Grady, C. L., & Moscovitch, M. (2008). Top-down and bottom-up attention to memory: A hypothesis (AtoM) on the role of the posterior parietal cortex in memory retrieval. *Neuropsychologia, 46*(7), 1828–1851.

Conners, C., Erhardt, D., Sparrow, E., & Conners, M. (1999). *CAARS adult ADHD rating scales*. New York: MHS.

Cortese, S., Imperati, D., Zhou, J., Proal, E., Klein, R. G., Mannuzza, S., et al. (2013). White matter alterations at 33-year follow-up in adults with childhood attention-deficit/hyperactivity disorder. *Biological Psychiatry, 74*(8), 591–598.

Depue, B. E., Burgess, G. C., Bidwell, L. C., Willcutt, E. G., & Banich, M. T. (2010). Behavioral performance predicts grey matter reductions in the right inferior frontal gyrus in young adults with combined type ADHD. *Psychiatry Research: Neuroimaging, 182*(3), 231–237.

Ding, W.-n., Sun, J.-h., Sun, Y.-w., Zhou, Y., Li, L., Xu, J.-r., et al. (2013). Altered default network resting-state functional connectivity in adolescents with internet gaming addiction. *PLoS One, 8*(3), e59902.

Dong, G., & Potenza, M. N. (2014). A cognitive-behavioral model of internet gaming disorder: Theoretical underpinnings and clinical implications. *Journal of Psychiatric Research, 58*, 7–11.

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. *Journal of Psychiatric Research, 73*, 1–8.

Fassbender, C., Zhang, H., Buzy, W. M., Cortes, C. R., Mizuiri, D., Beckett, L., et al. (2009). A lack of default network suppression is linked to increased distractibility in ADHD. *Brain Research, 1273*, 114–128.

Feng, Q., Chen, X., Sun, J., Zhou, Y., Sun, Y., Ding, W., et al. (2013). Voxel-level comparison of arterial spin-labeled perfusion magnetic resonance imaging in adolescents with internet gaming addiction. *Behavioral and Brain Functions: BBF, 9*(1), 33.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. (1995). *Structured clinical interview for DSM-IV axis I disorders*. New York: New York State Psychiatric Institute.

Fosco, W. D., Hawk, L. W., Rosch, K. S., & Bubnik, M. G. (2015). Evaluating cognitive and motivational accounts of greater reinforcement effects among children with attention-deficit/hyperactivity disorder. *Behavioral and Brain Functions: BBF, 11*(1), 20.

Frangou, S., Chitins, X., & Williams, S. C. (2004). Mapping IQ and gray matter density in healthy young people. *NeuroImage, 23*(3), 800–805.

Fritz, H.-C., Wittfeld, K., Schmidt, C. O., Domin, M., Grabe, H. J., Hegenscheid, K., et al. (2014). Current smoking and reduced gray matter volume—A voxel-based morphometry study. *Neuropsychopharmacology, 39*(11), 2594–2600.

Halperin, J. M., Trampush, J. W., Miller, C. J., Marks, D. J., & Newcorn, J. H. (2008). Neuropsychological outcome in adolescents/young adults with childhood ADHD: Profiles of persisters, remitters and controls. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 49*(9), 958–966.

Hampshire, A., Chamberlain, S. R., Monti, M. M., Duncan, J., & Owen, A. M. (2010). The role of the right inferior frontal gyrus: Inhibition and attentional control. *NeuroImage, 50*(3), 1313–1319.

Han, D. H., Lyoo, I. K., & Renshaw, P. F. (2012). Differential regional gray matter volumes in patients with on-line game addiction and professional gamers. *Journal of Psychiatric Research, 46*(4), 507–515.

Kieling, C., Kieling, R. R., Rohde, L. A., Frick, P. J., Moffitt, T., Nigg, J. T., et al. (2010). The age at onset of attention deficit hyperactivity disorder. *The American Journal of Psychiatry, 167*(1), 14–16.

Kim, N. R., Hwang, S. S.-H., Choi, J.-S., Kim, D.-J., Demetrovics, Z., Király, O., et al. (2016). Characteristics and psychiatric symptoms of internet gaming disorder among adults using self-reported DSM-5 criteria. *Psychiatry Investigation, 13*(1), 58–66.

Kim, D., Lee, D., Lee, J., Namkoong, K., & Jung, Y.-C. (2017). Association between childhood and adult attention deficit hyperactivity disorder symptoms in Korean young adults with internet addiction. Journal of Behavioral Addictions, 44(0), 1–9.

Ko, C.-H., Yen, J.-Y., Yen, C.-F., Chen, C.-S., & Chen, C.-C. (2012). The association between internet addiction and psychiatric disorder: A review of the literature. *European Psychiatry, 27*(1), 1–8.

Ko, C.-H., Hsieh, T.-J., Chen, C.-Y., Yen, C.-F., Chen, C.-S., Yen, J.-Y., et al. (2014). Altered brain activation during response inhibition and error processing in subjects with internet gaming disorder: A functional magnetic imaging study. *European Archives of Psychiatry and Clinical Neuroscience, 264*(8), 661–672.

Kuss, D. J., & Griffiths, M. D. (2012). Internet and gaming addiction: A systematic literature review of neuroimaging studies. *Brain Sciences, 2*(3), 347–374.

Lee, D., Lee, J., Yoon, K. J., Kee, N., & Jung, Y.-C. (2016). Impaired anterior insular activation during risky decision making in young adults with internet gaming disorder. *Neuroreport, 27*(8), 605–609.

Lee, D., Lee, J., Lee, J. E., & Jung, Y.-C. (2017). Altered functional connectivity in default mode network in internet gaming disorder: Influence of childhood ADHD. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 75*, 135–141.

Lin, F., Zhou, Y., Du, Y., Qin, L., Zhao, Z., Xu, J., et al. (2012). Abnormal white matter integrity in adolescents with internet addiction disorder: A tract-based spatial statistics study. *PLoS One, 7*(1), e30253.

Liu, G.-C., Yen, J.-Y., Chen, C.-Y., Yen, C.-F., Chen, C.-S., Lin, W.-C., et al. (2014). Brain activation for response inhibition under gaming cue distraction in internet gaming disorder. *Kaohsiung Journal of Medical Sciences, 30*(1), 43–51.

Lo, S.-K., Wang, C.-C., & Fang, W. (2005). Physical interpersonal relationships and social anxiety among online game players. *Cyberpsychology & Behavior, 8*(1), 15–20.

Mangun, G. R., Buonocore, M. H., Girelli, M., & Jha, A. P. (1998). ERP and fMRI measures of visual spatial selective attention. *Human Brain Mapping, 6*(5–6), 383–389.

McAuley, T., Crosbie, J., Charach, A., & Schachar, R. (2014). The persistence of cognitive deficits in remitted and unremitted ADHD: A case for the state-independence of response inhibition. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 55*(3), 292–300.

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: A network model of insula function. *Brain Structure & Function, 214*(5–6), 655–667.

Morrison, C. M., & Gore, H. (2010). The relationship between excessive internet use and depression: A questionnaire-based study of 1,319 young people and adults. *Psychopathology, 43*(2), 121–126.

Nakao, T., Radua, J., Rubia, K., & Mataix-Cols, D. (2011). Gray matter volume abnormalities in ADHD: Voxel-based meta-analysis exploring the effects of age and stimulant medication. *The American Journal of Psychiatry, 168*(11), 1154–1163.

Patton, J. H., & Stanford, M. S. (1995). Factor structure of the Barratt impulsiveness scale. *Journal of Clinical Psychology, 51*(6), 768–774.

Pell, G. S., Briellmann, R. S., Chan, C. H. P., Pardoe, H., Abbott, D. F., & Jackson, G. D. (2008). Selection of the control group for VBM analysis: Influence of covariates, matching and sample size. *NeuroImage, 41*(4), 1324–1335.

Petry, N. M., & O'brien, C. P. (2013). Internet gaming disorder and the DSM-5. *Addiction (Abingdon, England), 108*(7), 1186–1187.

Preuschoff, K., Quartz, S. R., & Bossaerts, P. (2008). Human insula activation reflects risk prediction errors as well as risk. *The Journal of Neuroscience, 28*(11), 2745–2752.

Proal, E., Reiss, P. T., Klein, R. G., Mannuzza, S., Gotimer, K., Ramos-Olazagasti, M. A., et al. (2011). Brain gray matter deficits at 33-year follow-up in adults with attention-deficit/hyperactivity disorder established in childhood. *Archives of General Psychiatry, 68*(11), 1122–1134.

Reinert, D. F., & Allen, J. P. (2002). The alcohol use disorders identification test (AUDIT): A review of recent research. *Alcoholism: Clinical and Experimental Research, 26*(2), 272–279.

Rubia, K., Overmeyer, S., Taylor, E., Brammer, M., Williams, S. C., Simmons, A., et al. (1999). Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: A study with functional MRI. *The American Journal of Psychiatry, 156*(6), 891–896.

Shaw, P., Eckstrand, K., Sharp, W., Blumenthal, J., Lerch, J., Greenstein, D., et al. (2007). Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proceedings of the National Academy of Sciences of the United States of America, 104*(49), 19649–19654.

Shaw, M., Hodgkins, P., Caci, H., Young, S., Kahle, J., Woods, A. G., et al. (2012). A systematic review and analysis of long-term outcomes in attention deficit hyperactivity disorder: Effects of treatment and non-treatment. *BMC Medicine, 10*(1), 99.

Sonuga-Barke, E. J. (2003). The dual pathway model of AD/HD: An elaboration of neuro-developmental characteristics. *Neuroscience & Biobehavioral Reviews, 27*(7), 593–604.

Sonuga-Barke, E. J., & Castellanos, F. X. (2007). Spontaneous attentional fluctuations in impaired states and pathological conditions: A neurobiological hypothesis. *Neuroscience & Biobehavioral Reviews, 31*(7), 977–986.

Utevsky, A. V., Smith, D. V., & Huettel, S. A. (2014). Precuneus is a functional core of the default-mode network. *The Journal of Neuroscience, 34*(3), 932–940.

Wang, H., Jin, C., Yuan, K., Shakir, T. M., Mao, C., Niu, X., et al. (2016a). The alteration of gray matter volume and cognitive control in adolescents with internet gaming disorder. At Risk for Neuropsychiatric Disorders*:* An Affective Neuroscience Approach to Understanding the Spectrum, 144.

Wang, L., Wu, L., Lin, X., Zhang, Y., Zhou, H., Du, X., et al. (2016b). Dysfunctional default mode network and executive control network in people with internet gaming disorder: Independent component analysis under a probability discounting task. *European Psychiatry, 34*, 36–42.

Ward, M. F. (1993). The Wender Utah rating scale: An aid in the retrospective. *The American Journal of Psychiatry, 1*(50), 885.

Wechsler, D. (2014). Wechsler adult intelligence scale–fourth edition (WAIS–IV).

Weigard, A., Huang-Pollock, C., & Brown, S. (2016). Evaluating the consequences of impaired monitoring of learned behavior in attention-deficit/hyperactivity disorder using a Bayesian hierarchical model of choice response time.

Weng, C.-B., Qian, R.-B., Fu, X.-M., Lin, B., Han, X.-P., Niu, C.-S., et al. (2013). Gray matter and white matter abnormalities in online game addiction. European Journal of Radiology, 82(8), 1308–1312.

Xue, G., Lu, Z., Levin, I. P., & Bechara, A. (2010). The impact of prior risk experiences on subsequent risky decision-making: The role of the insula. *NeuroImage, 50*(2), 709–716.

Yen, J.-Y., Ko, C.-H., Yen, C.-F., Wu, H.-Y., & Yang, M.-J. (2007). The comorbid psychiatric symptoms of internet addiction: Attention deficit and hyperactivity disorder (ADHD), depression, social phobia, and hostility. *Journal of Adolescent Health, 41*(1), 93–98.

Yen, J.-Y., Liu, T.-L., Wang, P.-W., Chen, C.-S., Yen, C.-F., & Ko, C.-H. (2017). Association between internet gaming disorder and adult attention deficit and hyperactivity disorder and their correlates: Impulsivity and hostility. *Addictive Behaviors, 64*, 308–313.

Yoshimasu, K., Barbaresi, W. J., Colligan, R. C., Voigt, R. G., Killian, J. M., Weaver, A. L., et al. (2012). Childhood ADHD is strongly associated with a broad range of psychiatric disorders during adolescence: A population-based birth cohort study. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 53*(10), 1036–1043.

Young, K. S. (1998). *Caught in the net: How to recognize the signs of internet addiction–and a winning strategy for recovery*: John Wiley & Sons.

Yuan, K., Qin, W., Wang, G., Zeng, F., Zhao, L., Yang, X., et al. (2011). Microstructure abnormalities in adolescents with internet addiction disorder. *PLoS One, 6*(6), e20708.

Yuan, K., Cheng, P., Dong, T., Bi, Y., Xing, L., Yu, D., et al. (2013). Cortical thickness abnormalities in late adolescence with online gaming addiction. *PLoS One, 8*(1), e53055.

Zhang, Y., Lin, X., Zhou, H., Xu, J., Du, X., & Dong, G. (2016). Brain activity toward gaming-related cues in internet gaming disorder during an addiction stroop task. *Frontiers in Psychology, 7*.

Zhou, Y., Lin, F.-c., Du, Y.-s., Zhao, Z.-m., Xu, J.-R., & Lei, H. (2011). Gray matter abnormalities in internet addiction: A voxel-based morphometry study. *European Journal of Radiology, 79*(1), 92–95.