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FULL-LENGTH REPORT

Differences in resting-state functional connectivity according to the level of impulsiveness in patients with internet gaming disorder

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ABSTRACT

Background and aims: Impulsiveness is an important factor in the pathophysiology of Internet gaming disorder (IGD), and regional brain functions can be different depending on the level of impulsiveness. This study aimed to demonstrate that different brain mechanisms are involved depending on the level of impulsiveness among patients with IGD. *Methods:* Resting-state functional MRI data were obtained from 23 IGD patients with high impulsivity, 27 IGD patients with low impulsivity, and 22 healthy controls, and seed-based functional connectivity was compared among the three groups. The seed regions were the ventromedial prefrontal cortex (vmPFC), dorsolateral prefrontal cortex, nucleus accumbens (NAcc), and amygdala. *Results:* Connectivity of the vmPFC with the left temporo-parietal junction (TPJ) and NAcc-left insula connectivity were significantly decreased in the patients with high impulsivity, compared with the patients with low impulsivity and healthy controls. On the other hand, amygdala-based connectivity with the left inferior frontal gyrus showed decreases in both patient groups, compared with the healthy controls. *Conclusion:* These findings may suggest a potential relationship between impulsivity and deficits in reward-related social cognition processes in patients with IGD. In particular, certain interventions targeted at vmPFC-TPJ connectivity, found to be impulsivity-specific brain connectivity, are likely to help with addiction recovery among impulsive patients with IGD.

KEYWORDS

Internet gaming disorder, impulsiveness, resting-state functional connectivity, ventromedial prefrontal cortex, temporo-parietal junction

INTRODUCTION

Patients with Internet gaming disorder (IGD) tend to have difficulties in controlling excessive internet game playing despite significant academic/occupational, psychological and interpersonal negative consequences (Müller et al., 2015; Petry, Rehbein, Ko, & O'Brien, 2015). IGD is one of the disorders classified as a tentative disorder that requires further research on the fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (American Psychiatric Association, 2013), and is officially listed as one of medical illnesses in the name of "Gaming Disorder" in the 11th revision of the International Classification of Diseases (ICD-11) (World Health Organization, 2019). Considerable research results have been reported to support the diagnostic importance of IGD. The resting-state functional connectivity (rsFC) study is an example. Previous studies in patients with IGD using this

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methodology have reported dysfunctional interhemispheric connectivity of the prefrontal cortices (Wang et al., 2015) and dysfunctional connectivity of the dorsolateral prefrontal cortex (dlPFC) with the insula and striatum (Han et al., 2018; Jin et al., 2016), the insula and nucleus accumbens (NAcc) with the prefrontal cortices (Chen et al., 2016), and the amygdala with the prefrontal cortices and insula (Ko et al., 2015).

Distress in patients with IGD is associated with various psychological and social factors, such as loneliness, personal experiences of failure, escape from reality, anger, and preexisting mental disorders including depression and anxiety (Snodgrass, Zhao, Lacy, Zhang, & Tate, 2019). Impulsiveness or impulsivity, which represents making hasty decisions and acting without consideration about the consequences of behavior as a result of failure of cognitive control (Dalley & Robbins, 2017) and contributes to the development and relapse of addictive disorder (Hanson, Luciana, & Sullwold, 2008), may also be another important factor in patients with IGD. Previous studies have demonstrated that patients with IGD showed premature impulsive responses during the information sampling task (Irvine et al., 2013), the stop-signal or go-nogo task (Choi et al., 2014; Irvine et al., 2013; Little et al., 2012), and the game of dice task (Pawlikowski & Brand, 2011). A previous longitudinal study has shown that impulsivity plays an important role in the transition of gamers to pathologic gamers (Gentile et al., 2011). Impulsivity-related neural processes may underlie addiction processes in IGD (Ding et al., 2014). In addition, IGD and attention deficit hyperactivity disorder (ADHD) are a common comorbidity among young adults (Dalbudak & Evren, 2014), and impulsivity mediates the association between these two disorders (Yen et al., 2017).

It has been known that impulsiveness involves several cortical and subcortical regions. A typical region is the ventromedial prefrontal cortex (vmPFC). Individuals with damage to the vmPFC reveal personality changes with increased impulsivity and aggression (Berlin, Rolls, & Kischka, 2004), and make more impulsive decisions while performing inhibition tasks (Bechara, Tranel, & Damasio, 2000). The close relationship between impulsiveness and the vmPFC has also been consistently reported in structural and functional imaging studies. For example, there is a significant correlation between low impulse control and decreased vmPFC volume (Boes et al., 2009; Matsuo et al., 2009), vmPFC activity is significantly associated with behavioral impulsivity during the intertemporal decision-making task (Jimura, Chushak, & Braver, 2013), and reward-related VMPFC activation is attenuated in highly impulsive individuals (Diekhof et al., 2012). The role of the vmPFC in impulsiveness is related to its involvement in three domains of psychological function through interactions with cortical or subcortical connections: the representation of reward- and value-based decision making, the generation and regulation of negative emotion, and multiple aspects of social cognition (Hiser & Koenigs, 2018). These three functions are also main areas where pathological changes are frequently observed in patients with IGD (Paulus, Ohmann, von Gontard, & Popow, 2018).

Another prefrontal region engaged in impulsiveness is the dlPFC, which plays a role in the process of response inhibition and exerts executive control functions that suppress impulsive responses (Bari & Robbins, 2013; Oldrati, Patricelli, Colombo, & Antonietti, 2016). It has been suggested that both the vmPFC and dlPFC play an important role in the aspect of the top-down cognitive control over the impulse drive. In particular, emotional processing for immediate small rewards relies on the regulation of the vmPFC, whereas rational processing for later larger rewards relies on the regulation of the dlPFC (Manuel, Murray, & Piguet, 2019; Peters & Buchel, 2011). Additionally, important regions related to the impulse drive include the NAcc and amygdala. The NAcc has a well-established role of reward processing in various addictions (Koob & Volkow, 2010), and a function of the region includes a reward-based control of impulsiveness with its interaction with the prefrontal cortex (Behan, Stone, & Garavan, 2015). The amygdala is another representative subcortical region related to impulsiveness, which has been known to process behavioral disinhibition during primary reward anticipation (Kerr et al., 2015) or impulsive aggression (da Cunha-Bang, Fisher, Hjordt, Holst, & Knudsen, 2019).

All four of these regions related to impulsiveness have been reported to be dysfunctional in patients with IGD (Weinstein, 2017). In addition, several other regions, including the anterior cingulate cortex, posterior cingulate cortex, inferior parietal lobule, and insula, have also been reported to be brain areas associated with functional impairments in IGD (Meng, Deng, Wang, Guo, & Li, 2015; Weinstein, 2017). IGD has heterogeneous manifestations with various intertwined factors, such as game types and sociocultural variations, as well as psychiatric comorbidities, and thus can be classified into several subtypes that share a common phenomenology (Lee, Lee, & Choo, 2017). From this perspective, differential characteristics of regional neural activity or structures in subgroups of patients with IGD based on a specific phenomenon have been investigated. For example, there was a report that hippocampal activity while performing a card sorting task differed depending on the presence or absence of depression among adolescents with IGD (Han et al., 2016). Despite the importance of impulsiveness in IGD, however, there is no neuroimaging study showing differences in the brain functions between patient subgroups classified based on this factor. The rsFC study has been used to evaluate circuit-level abnormalities in various mental disorders, including addictive disorders (Sutherland, McHugh, Pariyadath, & Stein, 2012), and can also be a plausible way to investigate subgroup differences among patients with IGD.

This study aimed to demonstrate that different brain mechanisms are involved depending on the level of impulsiveness among patients with IGD. For this purpose, resting-state functional MRI data were obtained in IGD patients with high impulsivity, IGD patients with low impulsivity, and healthy controls. Four regions, such as the vmPFC, dlPFC, NAcc, and amygdala, which have been reported to be related to impulsiveness through previous neuroimaging

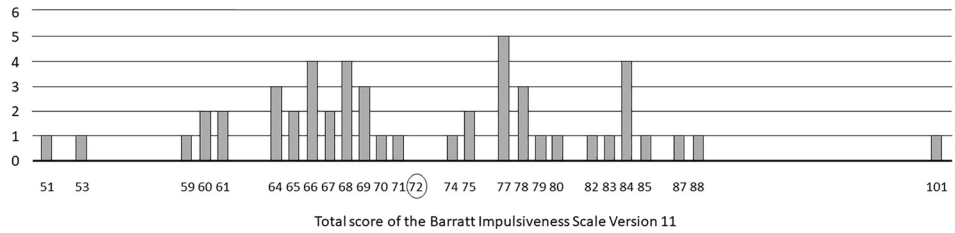

Fig. 1. Frequency distribution of the Barratt Impulsiveness Scale Version 11 in 50 patients with Internet gaming disorder. The divisional baseline score between the high and low impulsivity groups was 72, and the patients showed a bimodal distribution above and below this score

studies, were selected and used as the seed in the rsFC analysis, and rsFC was compared among the three groups. We hypothesized that in terms of overall brain connectivity changes in IGD patients, both the high and low impulsive patient groups would show differences in these regions-based connectivity compared to healthy controls, whereas in terms of examining connectivity of the impulsiveness-related regions, IGD patients with high impulsivity would show a significantly different rsFC pattern than those with low impulsivity as well as healthy controls. In particular, based on a variety of impulsiveness-related behaviors and heterogeneous manifestations in patients with IGD and multifaceted roles of the vmPFC, known as a key region of impulsiveness, we predicted that IGD patients with high impulsivity would show impaired connectivity with the three target networks: (1) network of reward-based decision making, (2) negative emotion-related network, and (3) social cognition-related network.

METHODS

Participants

Fifty participants with IGD and 22 healthy controls were recruited via advertisement on the bulletin boards of online university communities. Participants were interviewed by a psychiatrist for IGD diagnosis according to DSM-5 section 3 (American Psychiatric Association, 2013) and for psychiatric comorbidity with the Mini-International Neuropsychiatric Interview (MINI 5.0) (Sheehan et al., 1998). Participants were excluded if they have any history of other psychiatric or neurological illness or current use of psychotropic medication and are left-handed or not suitable for MRI scanning. All participants submitted the Barratt Impulsiveness Scale Version 11 (BIS-11), that is a 30-item 4-point self-report Likert questionnaire and includes six first-order factors (attention, motor, self-control, cognitive complexity, perseverance, and cognitive instability impulsiveness) and 3 s-order factors (attentional, motor, and non-planning impulsiveness) (Patton, Stanford, & Barratt, 1995). A previous review article about the BIS-11 suggested to classify individuals who scored 72 or above as highly impulsive through college sample data (Stanford et al., 2009), and our patient participants showed a bimodal frequency distribution with peaks on each side higher and lower than this score (Fig. 1). Therefore, based on this scale score, participants diagnosed as IGD were divided into two groups; 23 participants who scored 72 or above were allocated as the "IGD with high impulsivity" (IGD-HI) group and 27 participants who scored less than 72 were assigned as the "IGD with low impulsivity" (IGD-LI) group.

Psychological assessment and analysis

All participants were evaluated for sociodemographic characteristics and internet use patterns. Estimated full intellectual functioning (IQ) was obtained using the short form of the Wechsler Adults Intelligence Scale-IV (Hwang & Oh, 2017). The severity of IGD was assessed by the Internet Addiction Test (IAT), a 20-item scale with a 5-point score, ranging from 1 (very rarely) to 5 (very frequently) (Young, 1998). Anxiety and depression symptoms were evaluated using the Hospital Anxiety and Depression Scale (HADS), a 14-item scale with scores between 0 and 21 for either anxiety or depression (Zigmond & Snaith, 1983). Demographic variables and the psychological scale scores were compared among the IGD-HI, IGD-LI, and control groups using one-way analysis of variance (ANOVA), and post-hoc *t*-tests were used to identify the inter-group differences. Statistical significance was accepted at a threshold of Bonferroni-corrected $P < 0.05$. All data were analyzed using the Statistical Package for the Social Sciences 25.0 (SPSS Version 25.0; IBM Corporation, Armonk, NY, USA).

MRI acquisition and pre-processing

MRI scanning was performed on a 3.0-Tesla MR scanner (Magnetom Verio, Siemens Medical Systems, Erlangen, Germany). The functional data were acquired through a T2*-weighted gradient echo-planar pulse sequence (echo time = 30 ms, repetition time = 2,000 ms, flip angle = 90°, field of view = 240 mm, in-plane matrix = 64 × 64, slice thickness = 3.5 mm, bandwidth = 2,232 Hz/Px). During the acquisition of functional MRI data, participants were directed to look at a cross in the center of a screen for 6 minutes without any cognitive, lingual, or motor activities. A structural image was obtained using a T1-weighted gradient echo sequence (echo time = 2.46 ms, repetition time = 1,900 ms, flip angle = 9°, field of view = 250 mm, matrix size = 256 × 256, slice thickness = 1 mm, bandwidth = 170 Hz/Px).

Functional MRI data was pre-processed using Statistical Parametric Mapping 12 (SPM12, http://www.fil.ion.ucl.ac.uk/spm/). The first five volumes were discarded to allow for magnetization stabilization. After slice-timing correction, we realigned a time-series of images acquired from the same subject using a least squares approach. Head movement artifacts were assessed in individual subjects to confirm that the maximum head motion in each axis was <3 mm. After the realignment, functional MRI images were co-registered to structural images and spatially normalized into the Montreal Neurological Institute (MNI) coordinate system through 12-parameter affine transformation and nonlinear iterations. Finally, normalized images were smoothed using a 6-mm full-width at half maximum kernel. To remove confounding effects, we regressed out artifacts from head motions and physiological noises from the white matter and cerebrospinal fluid, and the waveform of each voxel was filtered using a bandpass filter (0.008 Hz < f < 0.09 Hz) to reduce low-frequency drift and high-frequency noise effects.

Seed-based resting-state functional connectivity analysis

We calculated the functional connectivity strengths between the seed regions and the other gray matter using a correlation approach. Based on previous studies that examined the neural mechanism of trait impulsivity and impulsive behavior (Dalley & Robbins, 2017; Diekhof & Gruber, 2010; van der Laan, Barendse, Viergever, & Smeets, 2016), the seeds were defined as the four regions of interest (ROIs): bilateral vmPFC, bilateral dlPFC, bilateral NAcc, and bilateral amygdala. Each ROI was extracted from the Autonomic Anatomical Labeling (AAL) Atlas 3 (Rolls, Huang, Lin, Feng, & Joliot, 2020). Seed-to-voxel functional connectivity maps for each subject were constructed using CONN-fMRI toolbox v.18a (www.nitrc.org/projects/conn) implemented on MATLAB (Mathworks, Inc., MA, USA). Correlation coefficients were calculated and converted to z-values using Fisher r-to-z transform to estimate the functional connectivity strengths.

Group-level comparison, one-way ANOVA, was conducted to compare functional connectivity estimates among the IGD-HI, IGD-LI, and control groups. The anxiety and depression scores from the HADS were added as covariates in these second-level analyses. Statistical inferences for these whole-brain analyses were conducted at a threshold of false discovery rate corrected P < 0.05 at the cluster level with a cluster-defining threshold of P < 0.001. Then, reflecting the multiple comparison issue with the use of four seeds, we defined the threshold of P <0.0125 (0.05/4) as statistically significant by Bonferroni correction. For the significant clusters observed in one-way ANOVA, post-hoc t-tests were performed to identify the direction of the differences in all pair-wise group comparisons. Additionally, Pearson correlation analyses were conducted to examine the associations between the IAT scores and rsFC strengths in the significant regions identified by one-way ANOVA. Significant differences in these post-hoc analyses were obtained at a threshold of Bonferroni-corrected P < 0.05.

Ethics

The study was approved by the Institutional Review Board of Yonsei University Gangnam Severance Hospital (approval number: 3-2015-0718-010), and written informed consent was obtained from all participants after they had received a detailed explanation of the study.

RESULTS

Demographic and clinical characteristics

Table 1 summarizes the demographic and clinical data of the IGD-HI, IGD-LI, and control groups. The BIS-11 score showed a significant group difference ($F_{2,69}$ = 55.99, P < 0.001); in post-hoc analysis, the IGD-HI group scored significantly higher than the IGD-LI (t_{48} = 10.75, $Pcorr$ < 0.001) and control groups (t_{43} = 8.62, $Pcorr$ < 0.001), and there was no significant difference between the IGD-LI and control groups. Age, education years, and IQ showed no significant difference among the three groups. The IAT score, HADS anxiety score, and HADS depression score showed significant group differences ($F_{2,69}$ = 259.21, P < 0.001; $F_{2,69}$ = 11.63, P < 0.001; $F_{2,69}$ = 15.12, P < 0.001, respectively). In post-hoc analysis, the IGD-HI and IGD-LI groups scored significantly higher in the IAT score than the control groups (t_{43} = 31.59, $Pcorr$ < 0.001; t_{47} = 16.65, $Pcorr$ < 0.001, respectively), and the IGD-HI group showed

Table 1. Demographic and clinical characteristics of participants (mean ± standard deviation)

	Control (n = 22)	IGD-LI (n = 27)	IGD-HI (n = 23)	F	P
BIS-11	60.77 ± 9.51	64.63 ± 4.86	81.04 ± 5.94	55.99	<0.001
Age (year)	23.50 ± 1.26	23.30 ± 2.32	24.30 ± 2.62	1.45	0.241
Education (year)	15.45 ±1.52	14.33 ± 1.39	15.22 ± 2.50	2.55	0.086
Estimated K-WAIS	107.32 ± 10.10	113.93 ± 14.07	115.39 ± 16.51	2.17	0.122
IAT	24.55 ± 5.94	72.63 ± 12.42	80.30 ± 5.90	259.21	<0.001
HADS					
Anxiety	3.23 ± 2.49	6.93 ± 4.00	8.48 ± 4.40	11.63	<0.001
Depression	3.55 ± 2.43	7.33 ± 4.26	8.91 ± 2.91	15.12	<0.001

IGD-LI, Internet gaming disorder with low impulsivity; IGD-HI, Internet gaming disorder with high impulsivity; BIS-11, Barratt Impulsiveness Scale Version 11; K-WAIS, Korean version of the Wechsler Adults Intelligence Scale; IAT, Internet Addiction Test; HADS, Hospital Anxiety and Depression Scale.

significantly higher IAT score than the IGD-LI group (t_{48} = 2.71, *Pcorr* = 0.010). The IGD-HI and IGD-LI groups scored significantly higher in both the HADS anxiety (t_{43} = 4.90, *Pcorr* < 0.001; t_{47} = 3.78, *Pcorr* = 0.003, respectively) and depression (t_{43} = 6.71, *Pcorr* < 0.001; t_{47} = 3.70, *Pcorr* = 0.001, respectively) scores than the control group, but there were no significant differences in the HADS anxiety and depression scores between the IGD-HI and IGD-LI groups.

Seed-based resting-state functional connectivity analysis

Table 2 shows significant results from one-way ANOVA for the seed-based rsFC among the IGD-HI, IGD-LI and control groups. The group effect of vmPFC-based rsFC was shown at a significant level in the left temporo-parietal junction (TPJ). It was also observed in the right superior temporal gyrus (STG) and left amygdala, but these results did not survive correction for multiple comparisons according to the use of the four seeds. Post-hoc tests showed that vmPFC-left TPJ connectivity was significantly decreased in the IGD-HI group compared with the IGD-LI (t_{48} = −4.00, *Pcorr* = 0.002) and control groups (t_{43} = −3.56, *Pcorr* = 0.001) (Fig. 2A1). Likewise, vmPFC-left amygdala connectivity and vmPFC-right STG connectivity were significantly decreased in the IGD-HI group compared with the IGD-LI (t_{48} = −3.35, *Pcorr* = 0.005 and t_{48} = −3.76, *Pcorr* = 0.001, respectively) and control groups (t_{43} = −3.12, *Pcorr* = 0.015 and t_{43} = −3.80, *Pcorr* = 0.004, respectively) (Fig. 2A2 and A3). No group effect of dlPFC-based rsFC was found in any brain regions.

The significant group effect of NAcc-based rsFC was found in the left insula (Fig. 3A); rsFC was significantly decreased in the IGD-HI group compared with the IGD-LI and control groups (t_{48} = −6.12, *Pcorr* < 0.001; t_{43} = −3.30, *Pcorr* = 0.008, respectively), whereas it was significantly increased in the IGD-LI group compared with the control group (t_{47} = 2.60, *Pcorr* = 0.022). In addition, although the group effect of NAcc-based rsFC was not enough to survive

Table 2. Statistical comparisons of resting-state functional connectivity among the group of Internet gaming disorder with high impulsivity, group of Internet gaming disorder with low impulsivity, and control group using one-way analysis of variance

Seed	Target region	MNI coordinate			N_{vox}	*F*	P_{FDR}
		x	*y*	*z*			
vmPFC	Lt. temporo-parietal junction	−56	−50	32	96	12.2	0.002
	Rt. superior temporal gyrus	54	−36	22	45	18.5	0.038
	Lt. amygdala	−22	−4	−20	50	17.1	0.037
dlPFC	no significant results						
NAcc	Lt. superior temporal gyrus	−60	−34	10	39	10.6	0.029
	Rt. superior temporal gyrus	46	−30	14	44	12.4	0.029
		60	−32	20	41	12.2	0.029
		38	0	−22	49	10.9	0.029
	Lt. insula	−38	6	−26	98	11.7	0.001
Amygdala	Lt. inferior frontal gyrus	−42	26	−2	73	15.1	0.008

MNI, Montreal Neurological Institute; Nvox, number of voxels within a cluster; FDR, false discovery rate; vmPFC, ventromedial prefrontal cortex; dlPFC, dorsolateral prefrontal cortex; NAcc, nucleus accumbens; Lt., left; Rt., right.

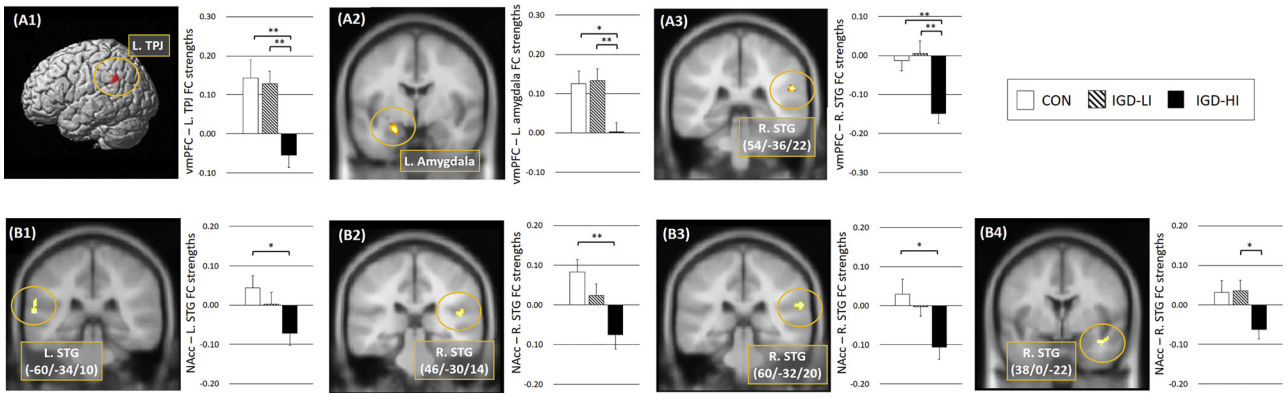

Fig. 2. Seed-based resting-state functional connectivity (rsFC) and the post-hoc comparisons showing significantly decreased connectivity in the group of Internet gaming disorder with high impulsivity (IGD-HI) compared with the group of Internet gaming disorder with low impulsivity (IGD-LI) or control (CON) group. (A) Ventromedial prefrontal cortex (vmPFC)-based rsFC showed the group effect in the left temporo-parietal junction (L. TPJ), left amygdala, and right superior temporal gyrus (STG). (B) Nucleus accumbens (NAcc)-based rsFC showed the group effect in four regions of the STG.
* $P < 0.05$; ** $P < 0.01$

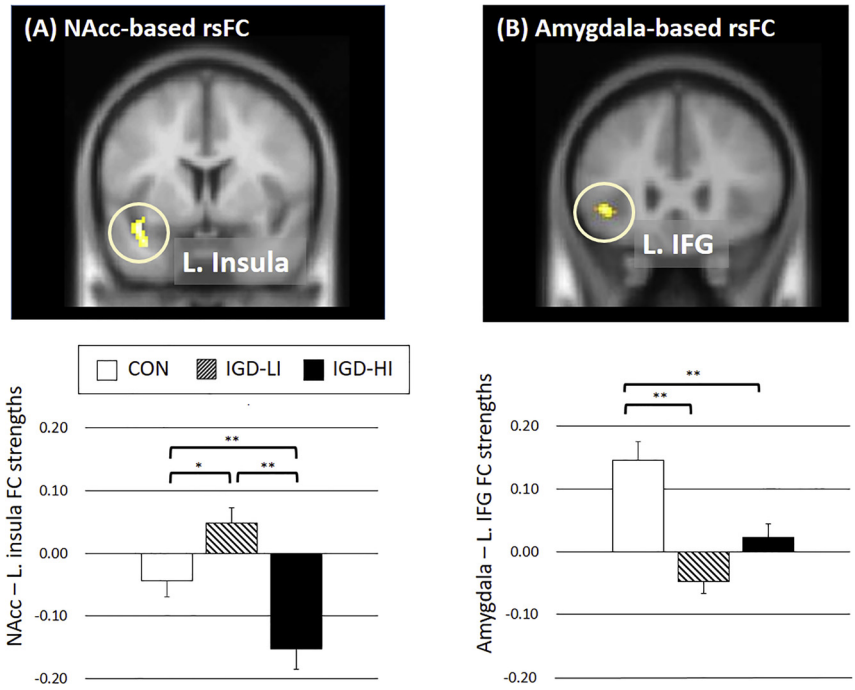

Fig. 3. Seed-based resting-state functional connectivity (rsFC) and the post-hoc comparisons illustrating that compared with the control (CON) group, the group of Internet gaming disorder with high impulsivity (IGD-HI) and the group of Internet gaming disorder with low impulsivity (IGD-LI) showed a change in the opposite or same pattern. (A) Nucleus accumbens (NAcc)-based rsFC showed the group effect in the left (L.) insula, whereas (B) amygdala-based rsFC showed the group effect in the left inferior frontal gyrus (L. LFG).
* $P < 0.05$; ** $P < 0.01$

correction for multiple comparisons, it was found in the bilateral STG (Fig. 2B1–B4). Post-hoc tests showed that the connectivity strengths between the NAcc and four STG regions were significantly decreased in the IGD-HI group compared with the control group ($x/y/z$ = −60/−34/10: t_{43} = −2.69, *Pcorr* = 0.033; 46/−30/14: t_{43} = −3.33, *Pcorr* = 0.004; and 60/−32/20: t_{43} = −2.75, *Pcorr* = 0.012) or the IGD-LI group (38/0/−22: t_{48} = −2.69, *Pcorr* = 0.033).

The significant group effect of amygdala-based rsFC was shown only in the left inferior frontal gyrus (IFG) (Fig. 3B); rsFC was significantly decreased in both the IGD-HI and IGD-LI groups compared with the control group (t_{43} = −3.40, *Pcorr* = 0.002; t_{47} = −5.63, *Pcorr* < 0.001, respectively). Meanwhile, correlations between the regional rsFC strengths in the significant clusters and IAT scores showed no statistical significance in any group.

DISCUSSION

In this study, we divided patients with IGD into groups with low impulsivity and high impulsivity to find the distinct functional neural correlates that depend on the level of impulsivity. This is the first study to compare functional connectivity of the brain by dividing patients with IGD according to their impulsivity levels. Since the purpose of the study was not to find brain regions related to impulsiveness among IGD patients, but to suggest the possibility that different pathophysiology may be involved depending on the level of impulsiveness, the three-group design including two patient groups and controls was used rather than a correlation approach exploring the relationship between functional connectivity and impulsiveness. It is unlikely that the differences in functional connectivity between the IGD-HI and IGD-LI groups were due to other psychological variables, such as anxiety or depression, rather than impulsivity, because the variables showed no significant difference between the two groups and were included in the imaging analysis as covariates.

In the prefrontal connections, vmPFC-based rsFC showed a significant change in the left TPJ. In this region, decreased connectivity was observed only in the IGD-HI group compared with the IGD-LI and control groups, suggesting the close relationship between these connections and impulsivity and supporting the existence of an impulsivity-specific brain mechanism within patients with IGD. Behavioral impulsivity is related to the ability to control immediate reward desiring in the vmPFC (Diekhof et al., 2012), and higher impulsivity for acting for immediate reward is associated with diminished control of the vmPFC on physiological arousal to external stimulation (Economides, Guitart-Masip, Kurth-Nelson, & Dolan, 2015; Zhang et al., 2015). Therefore, decreased vmPFC-based rsFC in the IGD-HI group suggests the existence of abnormal impulsivity-related reward processes. Both of the vmPFC and dlPFC were selected as prefrontal seeds because they were expected to be related to impulsivity, but unlike vmPFC-based rsFC, no significant result was found in dlPFC-based

rsFC. This is inconsistent with the previous reports that patients with IGD showed decreased dlPFC-based connectivity with various cortical regions (Han et al., 2018; Jin et al., 2016). This discrepancy may have been due to a difference in sample characteristics or the definition of the seed. Since the dlPFC is a large area, the results may vary depending on how a seed is defined within the dlPFC. Therefore, based only on the current negative finding, it cannot be concluded that dlPFC-based connectivity is unrelated to impulsivity or IGD.

Decreased vmPFC-TPJ connectivity in the IGD-HI group is considered to be the most notable result. The TPJ is one of the core brain regions related to the theory of mind (ToM) process, which enables individuals to represent the internal thoughts, beliefs and desires of others and differentiate them from one's own (Saxe & Kanwisher, 2003), and corresponds to the third target - social cognition-related network - in our study hypothesis. The ToM process is known to be damaged in individuals with addictive disorders (Innamorati et al., 2017; Onuoha, Quintana, Lyvers, & Guastella, 2016; Preller et al., 2014). Regarding gaming, problems that are most likely related to the ToM process have also been reported. For example, pathological game players reported lower scores on empathy than non-pathological players (Gentile et al., 2011; Tejeiro, Gómez-Vallecillo, Pelegrina, Wallace, & Emberley, 2012). In IGD, gaming addiction was negatively associated with emotional intelligence (Che et al., 2017). Impaired ToM inevitably causes a variety of conflicts and psychological stresses in the interpersonal relationship, which can reciprocally influence on one's addictive behavior. This may be why patients with IGD are immersed in gaming without being conscious of others' eyes. In addition, both the vmPFC and TPJ are engaged in social reward-related behaviors (Lo Gerfo et al., 2019) and positive social emotion regulation (Koush et al., 2019). Previous studies have shown that vmPFC-TPJ connectivity is involved in both of the emotion mentalizing and intention mentalizing processes (Atique, Erb, Gharabaghi, Grodd, & Anders, 2011) and reflect individual differences in subjective value for social rewards (Smith, Clithero, Boltuck, & Huettel, 2014). Therefore, high impulsivity in patients with IGD may interrupt the ToM process by cutting down decision time in social situations and decreased vmPFC-TPJ connectivity may reflect this disturbance.

Decreased vmPFC-amygdala connectivity in the IGD-HI group was out of a significant level after correction for multiple comparisons, and thus it is not enough to be given an important meaning, but it is worth further study. The amygdala is a critical limbic region in processing negative affect and fear conditioning (Phelps & LeDoux, 2005), corresponding to the second target – negative emotion-related network - in our study hypothesis. This region also plays an important role in reward-related social cognition, such as learning about the beneficial biological value of stimuli (Baxter & Murray, 2002) and computing observational rewards and observational expected reward values (Aquino et al., 2020). Interactions between the vmPFC and amygdala are critical for reward anticipation, and an alteration in this function can lead to an inability to wait for rewards or impulsivity (Churchwell, Morris, Heurtelou, & Kesner, 2009). In fact, there is a report that weakened vmPFC-amygdala connectivity underlies impaired sensitivity to others' emotions in impulsive individuals (Waller et al., 2019). It has also been reported that these two regions are part of the altered structural correlates of impulsivity in patients with IGD (Du et al., 2016). Taken together, if vmPFC-amygdala connectivity diminishes in the IGD-HI group, it is likely to be associated with deficits in reward-related social cognition processes along with decreased vmPFC-TPJ connectivity.

Although all the group differences in the STG did not survive correction for multiple comparisons, the vmPFC-right STG or NAcc-bilateral STG connectivity strengths were possibly decreased in the IGD-HI group compared with the IGD-LI or control group, suggesting that the relationship between these interregional connections and impulsivity needs to be further studied. There are few reports of functional changes of the STG, part of the auditory cortex, in IGD. Decreased STG homogeneity in the resting state (Dong, Huang, & Du, 2012; Kim et al., 2015) and increased STG activation during task shifting (Dong, Lin, Zhou, & Lu, 2014) have been found in patients with IGD, suggesting that long-term persistence of gaming behaviors may have caused changes in the excitability of auditory regions. In addition, given that esthetic rewards arise from the interaction between reward valuation of the NAcc and perceptual analysis and valuation of auditory cortices (Salimpoor et al., 2013), it is possible that NAcc-STG connectivity may be affected by chronic exposure to music and audio cues as rewards provided by game programs. It is uncertain, however, what functions vmPFC-STG or NAcc-STG connectivity and why such connectivity is likely to decrease only in patients with high impulsivity. Impulsivity is associated with auditory processing of voluntary attentional control (Mathias & Stanford, 1999) and involuntary preattention (Franken, Nijs, & Van Strien, 2005), and thus the possibility that impulsive people may have had a more specific reduction in connectivity to the auditory cortex is of value as a topic for future research.

NAcc-left insula connectivity was decreased in the IGD-HI group compared to controls, while it was increased in the IGD-LI group. Although the insula was not adopted as a seed in our research, this region has also been reported to be highly related to impulsivity in IGD (Chen et al., 2010; Shin, Kim, Kim, & Kim, 2020). In the addiction process, the insula may contribute to converting somatic signals into craving, increasing sensitivity toward addiction-related stimuli, and impeding the action of inhibitory resources (Garavan, 2010; Naqvi & Bechara, 2009). A previous study showed that deep brain stimulation of the NAcc evoked activation in the insula (Knight et al., 2013), suggesting the direct connection between these two regions for functional coupling in a reward process. The role of the insula in addiction can be estimated through the phenomena that addictive behaviors involve physiological states with strong interoceptive signals and faulty decision processes for immediate rewards at the expense of long-term negative consequences (Droutman,

Read, & Bechara, 2015), and thus this region corresponds to the first target - network of reward-based decision making - in our study hypothesis. Therefore, our finding of decreased NAcc-insula connectivity in the IGD-HI group suggests that the reward calculation process may be skipped in IGD patients with high impulsivity. On the other hand, increased NAcc-insula connectivity in the IGD-LI group suggests that IGD patients with low impulsivity may fall into gaming, motivating themselves to enjoy rewards rather than impulsiveness. This is consistent with a previous finding that increased NAcc-insula connectivity was reported in patients with IGD, regardless of impulsivity (Chen et al., 2016).

Changes in amygdala-based connectivity was found in the left IFG. Previous studies reported that the level of impulsivity was correlated with amygdala-dlPFC connectivity (Ko et al., 2015; Zheng, Chen, Wang, & Zhou, 2019), but the result in the dlPFC was not found in our study. Post-hoc test showed that amygdala-based connectivity was decreased with the left IFG in both the IGD-HI and IGD-LI groups compared to controls. Since there was no difference between the two IGD groups, such changes may be attributed to the characteristics of IGD rather than the level of impulsivity. Considering the wide range of amygdala functions in the interaction of emotion and cognition (Pessoa, 2008), there is sufficient likelihood that amygdala-based connectivity will be affected by long-term gaming behaviors regardless of impulsivity. In particular, effective amygdala-IFG connectivity is closely related to successful emotion regulation (Morawetz, Bode, Baudewig, & Heekeren, 2017). The IFG, one of the regions where structural abnormalities have been reported in patients with IGD (Takeuchi et al., 2016), is responsible for the self-control process of associating between advantageous actions and outcomes (Ernst & Paulus, 2005) and the inhibiting process of giving up immediate gratification and seeking for long-term interests (Garavan, Ross, Murphy, Roche, & Stein, 2002). Taken together, decreased amygdala-IFG connectivity in the patient groups may reflect impairments in self-control and emotion regulation by long-term gaming behaviors.

There are several limitations in this study. First, this study was conducted only in young male adult participants. It needs caution to generalize the results from this study to the general population. Second, only self-report questionnaire was used for measuring impulsivity. Self-reports are likely to be inaccurate reports if the participants lack their insight or have the intent of unfaithfully responding. Third, the patient groups were divided based on the cut-off score of the BIS-11 used in a previous study. Accordingly, both groups included patients with the scores near this cut-off score. It would have been more desirable to examine the BIS-11 for more patients, to exclude patients with moderate scores, and to include patients with extreme scores in the grouping. Lastly, there were no adjustments for ADHD symptoms which is closely associated with impulsivity. Although participants with ADHD were excluded, adjustment of the extent of ADHD propensity within the normal range is considered necessary.

In summary, this study classified heterogeneous patients with IGD into two groups based on the level of impulsivity and aimed to demonstrate the involvement of impulsivity-specific brain mechanisms. Connectivity of the vmPFC with the left TPJ and connectivity of the NAcc with the left insula were decreased only in the IGD-HI group compared with controls, suggesting deficits in reward-related social cognition processes and reward calculation processes in IGD patients with high impulsivity. NAcc-left insula connectivity was increased only in the IGD-LI group compared with controls, reflecting reward-seeking behaviors in IGD patients with low impulsivity. Decreased amygdala-left IFG connectivity was found in both patient groups, suggesting impairments in self-control processes by long-term gaming behaviors. These findings provide evidence of the differences in impulsivity-specific brain connectivity among patients with IGD. In particular, certain interventions targeted at vmPFC-TPJ connectivity are likely to help with addiction recovery among impulsive patients with IGD.

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