Aberrant brain functional connectivity and executive dysfunction in adolescents with internet gaming disorder

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Aberrant brain functional connectivity and executive dysfunction in adolescents with internet gaming disorder

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ABSTRACT

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The clinical significance of internet gaming disorder (IGD) is spreading worldwide, but the neural mechanisms still remain unclear. As problems in cognitive control are repeatedly mentioned in IGD, this study aimed to identify alteration in brain functional connectivity associated with executive dysfunction through two different ways using functional magnetic resonance imaging (fMRI): task related analysis and resting state analysis. This study included 18 male adolescents with IGD and 18 age-matched male adolescents as healthy control (HC). Stroop Match-to-Sample task with emotional interference was applied for task fMRI. As a result, aberrant functional connectivity which is related to executive dysfunction was identified in adolescents with IGD both during task performance and resting state. Adolescents with IGD demonstrated weaker dorsal anterior cingulate cortex (dACC) activation and stronger anterior insular cortex (AIC) activations during stroop task. The functional connectivity of posterior superior temporal sulcus (pSTS) was stronger with salience network and weaker with default mode network in resting state in adolescents with IGD. Our findings suggest that aberrantly stronger functional connectivity associated with salience network in IGD might disturb top-down executive function in both task-related situation and resting state.

Key words: internet gaming disorder, executive function, salience network, brain functional connectivity

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I. INTRODUCTION

Internet gaming disorder (IGD) is a pattern of gaming behavior characterized by impaired control over gaming, increasing priority given to gaming over other activities, and continuation or escalation of gaming despite of the occurrence of negative consequences that result in personal, familial, social, occupational impairments for more than 12 months [1]. Internet gaming disorder was first proposed as a condition for further study in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [2]; With spread of the clinical significance of IGD worldwide, the World Health Organization recognized 'gaming disorder' as a mental health condition in the 11th Revision of the International Classification of Diseases (ICD-11). However, the neural mechanism of IGD still remains controversial [3].

Diverse attempts have been tried to unveil the neurobiology of IGD [4]. For example, IGD in some cases showed dysfunctional striatal circuits which is related to reward processing [5, 6], others suggesting problems in emotion processing in IGD [7], and cognitive control was also stressed out to be impaired in IGD [8, 9]. Especially, Studies about psychological characteristics of IGD revealed that self-control is negatively correlated with IGD [10, 11]. Self-control includes the ability to control an impulse, emotion, or temptation. In the same sense, aggression is thought to be one of characteristics related to IGD [10]. Considering aggression is the motor counterpart of the affect of rage, anger, or hostility [12], it might be the consequence of a failure of emotion regulation[13]. Problems in self-control or emotion regulation are frequently mentioned in various psychiatric illnesses [14, 15], and brain structures in prefrontal area such as dorsolateral prefrontal cortex, ventrolateral prefrontal cortex and dorsomedial prefrontal cortex are frequently announced to be related to the problems [16]. Taken together, considering that self-control and emotion regulation are involved in executive function [17], IGD seems to be associated with executive dysfunctions according to previous researches [18-20].

As prevalence of IGD seems highest in adolescence [21], the development of adolescent brain should be also considered in understanding neural mechanism of IGD. Heterogeneous developmental trajectory of each brain regions can explain why adolescents behave unlike adults, and why they are more vulnerable to several psychiatric illness [22-24]. Especially, adolescents show some distinctive characteristics on decision-making [25]. Adolescents tend to make risky decisions despite of predicted serious consequences, which are due to slow development of prefrontal cortex responsible for cognitive control and subsuming response selection [26]. Similarly, the function of executive control network which support decision making and inhibitory control might be insufficient in early adolescence as the network continues to mature during adolescence [27]. “Dual system model” by Steinberg et al. [28] explains risk-taking behaviors of adolescents as linked to relatively strong socio-emotional system than cognitive control system for the reason of gap in developmental trajectory

[29], implying that socio-emotional brain networks other than executive control network also plays an important role in decision-making of adolescents. Especially, networks related to social cognition and mentalization might be crucial in adolescents' decision making, because adolescents regard social contexts as salient clue in decision making than adults because of differences in mentalizing network between two groups [25]. Unlike executive functions, social brain is known to develop in infancy and childhood. Two different systems suggested in "Dual system model" might be related to each other rather than working independently, as social dysfunction is known to be associated with default mode network, executive control network and salience network [30]. As risky decision making and impulsivity followed by neurodevelopmental differences seems to underlie the addiction vulnerability in adolescence, it would also let adolescents to fall easily into internet gaming [31].

In this study, we aimed to identify the alteration of functional connectivity related to executive dysfunction in adolescents with IGD using functional magnetic resonance imaging (fMRI). To attain our purpose, we performed two different approaches in brain fMRI analysis. To investigate top-down emotional regulation, we proceeded task fMRI using an emotional stroop Match-to-Sample task (STUDY 1). Our task required the subjects to ignore emotional inference and concentrate on a stroop Match-to-Sample task. The purpose of using emotional Match-to-Samples task was to confirm emotional influence on top-down control according to previous studies. Among various emotional stimuli, we chose negative emotional stimuli in our study considering that negative emotional words showed significant overlap in brain activations with alcohol-related word in alcohol dependence [32]. Moreover, we selected angry faces because angry emotion is closely associated with aggression which is known as one of psychological characteristics of IGD [10]. Previous studies reported that the dorsal anterior cingulate cortex (dACC) is a key region for top-down cognitive control and selective attention while performing a stroop task [33-35]. The dACC is the principal locus of conflict monitoring [36, 37] and has been implicated in top-down control signaling to adjust behavior and guide performance [38, 39]. In addition, we conducted functional connectivity analysis to examine the interplay between the neural correlates that are involved in emotional processing. Functional connectivity refers to the functionally integrated relationship between spatially separated brain regions. Unlike structural connectivity which looks for physical connections in the brain, functional connectivity measures the temporal correlation of activations in remote brain regions [40]. We also analyzed functional connectivity of large-scale intrinsic networks during resting state to identify the alteration of network functional connectivity related to executive dysfunction in adolescents with IGD (STUDY 2). We selected default mode network, salience network, and executive central network, as previous studies have demonstrated that the interactions between these major large-scale networks underlie in wide range of psychopathologies including executive dysfunctions [41]. We hypothesized that both approaches would present aberrant functional connectivity accompanied by executive dysfunction in adolescents with IGD. First, we hypothesized that adolescents with IGD would be more disturbed by the emotional interference, while demonstrating compromised dACC activation and functional connectivity during the stroop Match-to-Sample task. Second, we hypothesized that adolescents with IGD would demonstrate different functional connectivity pattern among these large-scale intrinsic networks which might be associated with executive dysfunction.

II. MATERIALS AND METHODS

1. Participants

Participants consisted of 18 male adolescents with IGD (Age range: 12 to 15 years) and 18 age-matched male adolescents (Age range: 12 to 15 years) as healthy controls (HC). Participants were recruited from the local community through announcements, flyers, or word of mouth. Only male adolescents whose main purpose of using internet was playing multiplayer-online game called 'League of Legend' were included in study. Each participant was assessed through a structured interview, including the Korean Internet Addiction Proneness scale which is standardized in Korea with high reliability, a coefficient alpha of 0.838 [42]. Participants were excluded if their main purpose of using internet were other than playing online game such as social networking and watching videos, or in case they had history of current or past psychiatric disorders, neurological illness, traumatic brain injury, any radiological contraindications for MRI scanning. A psychiatrist confirmed the diagnosis of IGD based on the proposed criteria of Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5).

Participants self-reported several psychometric tests. To evaluate the previously reported psychological characteristics of IGD such as self-control and aggression, participants were asked to complete Barratt Impulsiveness Scale version 11 [43], Conners-Wells Adolescent Self-report Scale [44], Aggression Questionnaire [45]. To rule the confounding factors for executive functions out, Beck Depression Inventory [46], and Beck Anxiety Inventory [47] were used. Barratt Impulsiveness Scale version 11 measures impulsivity and possesses subscales of cognitive impulsiveness, motor impulsiveness, and non-planning impulsiveness [43]. Aggression was assessed by the aggression questionnaire which contains four subscales : Physical aggression, Verbal aggression, Anger, and Hostility [45]. Conners-Wells Adolescent Self-report Scale is developed to screen adolescents with Attention-deficit hyperactivity disorder (ADHD), we used short-form of Conners-Wells Adolescent Self-report Scale with 27 items. Short-form of Conners-Wells Adolescent Self-report Scale contains cognitive problem (coefficient alpha≥ 0.80), hyperactivity problem (coefficient alpha≥ 0.80), and conduct problem (coefficient alpha=0.73) as subscales [44, 48]. This study was carried out under the guidelines for the use of human participants established by the Institutional Review Board at Severance Mental Health Hospital, Yonsei University. Following a complete description of the scope of the study to all participants, written informed consent was obtained.

2. Stimuli and Experimental Design

A. Stroop Match-to-Sample task

The subjects underwent a Stroop Match-to-Sample Task [49] during MRI scanning. Stimuli were created and presented with E-prime software (Psychology Software Tools, Inc.). Subjects matched the color of a 'cue (XXXX)' to the meaning of the 'target word' or the font color of the 'target word' (Figure 1). The colors of the cue and target words were red, yellow or blue. The cue's color either matched or did not match the Target's color, which was either congruent (the word 'RED' was written in red font) or incongruent (the word 'BLUE' was written in yellow font). Subjects pressed a YES key for when cue-target color matches and a NO key for non-matches using their right hand, yielding accuracy and reaction time (RT) measures. To test the effect of emotional interference on cognitive control and selective attention, we designed the trails in two different conditions. In trials with emotional interference, angry faces were presented between the cue and target word during the inter-stimulus interval for 1700ms, whereas trials without emotional interference presented grey squares during the inter-stimulus interval. The angry faces were six grey-scale images of emotionally expressive faces selected from a standard set of pictures of facial affect [50]. Total duration of each trial was 4400 ms and the inter-trial interval was 1200ms. The task was composed of 8 blocks with emotional interference and 8 blocks without emotional interference, which were presented in pseudo-random order. Total number of trials was 96 (1 block = 6 trials, duration of each block = 26.4 sec). The subject performed a practice session before entering the scanner. The percentage of correct response (accuracy) and reaction time data were recorded for each trial and subject. Subjects had to make at least 80% correct response to be included for further analyses.

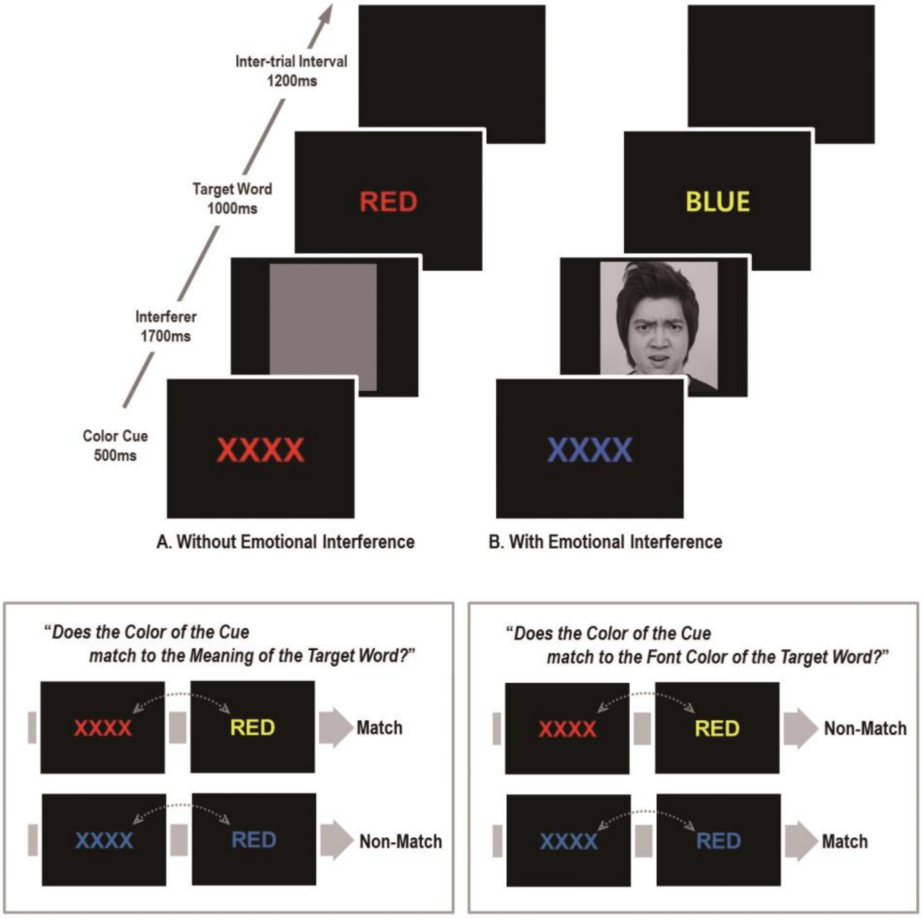

Figure 1. Stroop Match-to-Sample task. In trials without emotional interference (A), gray squares were presented during the inter-stimulus interval. In trials with emotional interference (B), angry faces were presented between the cue and target word.

B. Resting state

Participants were indicated to fixate their eyes on white cross on black background for 15 minutes to obtain reliable resting state images [51].

C. Image acquisition and pre-processing

MR imaging was conducted on a 3T Siemens Magnetom MRI scanner (Siemens AG, Erlangen, Germany) equipped with an 8-channel head coil. Subject motion was minimized by following best practices for head fixation, and structural image series were inspected for residual motion. Whole-brain fMRI data were acquired with a T2*-weighted gradient echo planar pulse sequence (TE=30ms, TR=2200ms, flip angle=90°, field of view=240mm, matrix =64x64, slice thickness=4 mm) during the Stroop task and during passively viewing block scan. High resolution anatomical images were acquired with a T1 weighted spoiled gradient-echo sequence (TE=2.19ms; TR =1780ms, flip angle=9°, field of view=256mm, matrix=256x256, slice thickness=1mm) to serves as an anatomical underlay for the functional MRI data .

Spatial pre-processing and statistical analysis of functional images were performed using SPM8, SPM12 (Welcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm). Motion artifacts of each participants were monitored through visual inspection of realignment parameter estimations, to ensure that maximum head motion in each axis was <3 millimeters (mm) without any abrupt head motion. The anatomical volume was segmented into gray matter, white matter, and cerebrospinal fluid. Then gray matter image was used for determining the parameters of normalization onto the standard Montreal Neurological Institute template. The spatial parameters were applied into the realigned and unwarped functional volumes that were finally re-sampled to voxels of 2x2x2 millimeters. At the end of pre-processing, Images were smoothed with an 8-mm full-width at half-maximum kernel.

3. Analysis

A. STUDY 1 (Task fMRI analysis)

(A) Functional contrast analysis

Individual statistics were computed using a general linear model approach as implemented in SPM8. In order to reveal the activity of the blood oxygenation level dependent (BOLD) responses related to the emotional interference, individual contrast was generated by contrasting ‘angry face’ blocks with ‘grey plate’ blocks at the first-level analysis. The resulting set of contrast images were then entered into a second-level analysis using a full factorial model. To compare the contrast angry face> grey square between groups, we created exclusive masks for each group with SPM maps with a threshold at $p<0.05$. Statistical inferences were thresholded using an uncorrected $p < 0.001$, $k_E>50$ voxels for the whole brain.

(B) Functional connectivity analysis

The CONN-fMRI functional connectivity toolbox (http://www.nitrc.org/projects/conn) was used to create individual seed-to-voxel functional connectivity maps. We defined a right anterior insular cortex (AIC) seed consisted of 5mm radium sphere centered on coordinates (x=46, y=4, z=14) that was identified in the contrast "Angry Face>Grey Plate." Before averaging individual voxel data, the waveform of each brain voxel was filtered using a bandpass filter (0.008 Hz $<f<$0.09 Hz) to reduce the effect of low-frequency drift and high-frequency noise. Signals from the ventricular regions and signal from the white matter were removed from the data through linear regression. To compare the functional connectivity between groups, we created exclusive masks for each group with SPM maps with a threshold at $p<0.05$. Statistical inferences were thresholded using an uncorrected $p<0.001$, $k_E>50$ voxels for the whole brain. The seed-to voxel functional conductivity maps were created according to both positive correlations and negative correlations individually.

(C) Statistical analysis

For between-group comparisons, behavioral performances were conducted with repeated measures analyses of variance (ANOVA). The ANOVAs were defined by one repeated measure factor (with emotional interference vs. without emotional interference), and one between-subjects factor (IGD group vs. HC group).

To examine brain-behavior relationships, we calculated the functional connectivity strength by extracting the Fisher-transformed Z-value measures of functional connectivity between the right AIC seed and the target regions that were identified through functional connectivity analysis of the task runs. Pearson correlation analysis tested relations between the functional seed-target connectivity and behavioral performance. Statistical analyses were conducted by using SPSS (Chicago, IL) with $p<0.05$ two-tailed.

B. STUDY 2 (Resting state fMRI analysis)

(A) Functional connectivity analysis

Functional connectivity maps of seed-to-voxel analysis were obtained using the CONN-fMRI functional connectivity toolbox version 18.b (http://www.nitrc.org/projects/conn). We used five region of interests (ROI) as seed regions, posterior cingulate cortex (PCC) [52] for the default mode network, bilateral AIC [53, 54] for the salience network, and the bilateral dorsolateral prefrontal cortex (DLPFC) [53, 54] for the executive control network. All seed regions were defined as a 5-mm radium sphere centered on previously reported coordinates [52-54]. Using bandpass filter, the waveform of each brain voxel was temporally filtered (0.008Hz < f < 0.09Hz) to exclude effects of low-frequency drift and high-frequency noise. Signals from white matter and ventricular regions were also eliminated through linear regression [55]. To reduce the artifacts by head motion, estimated subject-motion parameters [56] implemented in

CONN's default denoising guideline were applied to the linear regression. The strength of functional connectivity, correlation coefficients were converted to z-values using Fisher's r-to-z transformation. In between-group analysis, independent-sample t-tests were performed using threshold of an uncorrected p-value <0.001, minimum cluster extent of 100 contiguous voxels. Afterward we made additional seed region, a 5-mm radium sphere centered on left posterior superior temporal sulcus (pSTS) from our seed-to-voxel result of right AIC (MNI coordinates -60 -54 6) and proceeded seed-to-seed analysis to identify within-group correlation of ROIs (PCC, bilateral AIC, bilateral DLPFC and an additional ROI from seed-to-voxel result). The within-group significance was determined using one-sample t tests with false discovery rate (FDR) correction (p-value<0.05). Furthermore, group independent component analysis (ICA) was done to clarify if the result of seed-to-voxel analysis can reflect interrelationship of functional connectivity networks not just informing relationship between clusters.

(B) Group independent component analysis

Group independent component analysis (group ICA) was performed to investigate spatially independent network using group ICA of fMRI toolbox (GIFT ver.3.0b, http://mialab.mrn.org/software/gift). Preprocessed data were reduced through two stages of principal component analysis [57]. Following the modified minimal description length criteria, thirty-eight ICA components were estimated with infomax algorithm [58]. Using ICASSO algorithm [59], ICA analysis was repeated 20 times for stability of the result. As a result, 38 independent functional spatial maps for every participant were obtained.

For the selection of ICA components of interest, we performed stepwise estimations. First, each component was correlated with prior probabilistic maps of white matter and cerebrospinal fluid within a standardized brain space provided by MNI templates in SPM8. If components show spatial correlation greater than $r^2=0.025$ in both white matter and cerebrospinal fluid, they were discarded from analysis because they can be considered as artifacts. Second, to sort out the candidates of large-scale intrinsic networks, components survived from first step were correlated with network atlas of default mode network, salience network, and left, right executive control network [60]. Among candidates, we selected most suspected default mode network, salience network, and executive control network by inspecting conscientiously focusing on coactivated brain regions in components. Third, brain regions from seed-to-voxel analysis results were used as a mask to correlate with ICA components. Components with high spatial correlation with the mask were regarded as candidates of network of interest.

One-sample t tests and two-sample t tests of selected components were done to analyze within- and between-group differences. Analysis were completed using SPM 12 with the help of 'SPM stat' function in the GIFT toolbox. To compare correlations between selected components, participants' spatial maps of selected components were converted to Z values. Functional network connectivity was computed to evaluate correlations between components in the GIFT toolbox, FNC matrix and connectogram were generated.

(C) Statistical analysis

Independent t-tests were performed to compare demographic and clinical variables between IGD group and HC group. To examine relationship between results of clinical assessments and functional connectivity, Pearson correlation analysis tested relations between the functional seed-target connectivity and behavioral performance. Statistical analyses were conducted by using SPSS (Chicago, IL) with $p<0.05$ (two-tailed).

III. RESULTS

1. Demographic and Clinical Assessments

Among 18 participants in IGD group, one participant was excluded in resting state analysis because of disrupted resting fMRI data. There were no differences in age, verbal IQ and performance IQ between IGD group and HC group. Scores of the Beck depression inventory (p=0.023), cognitive impulsiveness in Barratt's impulsiveness scale (p=0.036), Conners-Wells adolescent self-report scale (p=0.001) were significantly high in IGD group (Table 1).

Table 1. Demographic and clinical characteristics of participants

	IGD Group	HC Group	T	p
Age (years)	13.6 (0.9)	13.4 (1.0)	0.350	0.729
Verbal IQ[a]	8.6 (2.6)	10.3 (3.3)	-1.771	0.086
Performance IQ[b]	10.4 (3.0)	10.8 (3.3)	-0.420	0.677
BDI[c]	11.5 (11.5)	4.4 (4.6)	2.392	**0.023**
BAI[d]	8.9 (9.0)	5.0 (6.2)	1.491	0.145
BIS[e]	65.1 (18.4)	56.2 (12.4)	1.700	0.098
Cognitive impulsiveness	18.2 (5.4)	14.8 (3.7)	2.189	**0.036**
Motor impulsiveness	20.9 (7.2)	18.0 (4.7)	1.428	0.162
Non-planning impulsiveness	26.1 (7.5)	23.4 (5.9)	1.157	0.255
Aggression Questionnaire	76.6 (27.8)	58.6 (11.4)	2.532	**0.016**
Physical aggression	23.9 (10.7)	16.7 (4.4)	2.674	**0.011**
Verbal aggression	13.2 (5.5)	12.8 (3.2)	0.296	0.769
Anger	17.2 (6.6)	14.9 (4.9)	1.199	0.239
Hostility	22.2 (9.0)	14.3 (3.8)	3.412	**0.002**
CASS	30.6 (16.0)	14.7 (8.6)	3.637	**0.001**
Cognitive problem	15.8 (8.0)	7.2 (5.7)	3.686	**0.001**
Hyperactivity problem	10.1 (6.3)	4.9 (2.4)	3.208	**0.004**
Conduct problem	4.8 (3.0)	2.6 (2.7)	2.213	**0.034**

Note. Values are expressed as mean (SD). Verbal Intelligence Quotient (IQ) was assessed with vocabulary in Wechsler Adult Intelligence Scale, and performance IQ was assessed with the Block design of Wechsler Adult Intelligence Scale. BDI: Beck depression inventory; BAI: Beck anxiety inventory; BIS: Barratt impulsiveness scale; CASS: Conners/Wells adolescent self-report scale.

2. STUDY 1 (Task fMRI results)

A. Behavioral performance: Accuracy and reaction time

The behavioral performances are presented in Table 2. Repeated measure ANOVA revealed no significant difference between the two groups in accuracy ($F_{1, 34}$=0.12, p=0.913). There was no significant effect of condition (emotional interference; $F_{1, 34}$=1.235, p=0.274) and the group-by-condition interaction was not significant ($F_{1, 34}$=1.089, p=0.304).

Repeated measure ANOVA revealed no significant difference between the two groups in reaction time ($F_{1, 34}$=0.072, p=0.791). There was no significant effect of condition ($F_{1, 34}$=3.326, p=0.077) and the group-by-condition interaction was not significant ($F_{1, 34}$=2.090, p=0.157).

Table 2. Behavioral Performance of Subjects

	IGD Group	HC Group	T	p
Accuracy (%)				
Without emotional interference[a]	93.9 ± 4.7	92.5 ± 6.0	0.723	0.475
With emotional interference[a]	91.3 ± 5.6	92.4 ± 7.1	-0.488	0.629
Reaction Time (ms)				
Without emotional interference	501.6 ± 80.4	510.4 ± 80.4	-0.363	0.719
With emotional Interference	534.9 ± 82.9	514.3 ± 58.9	0.860	0.396

[a]In trials with emotional interference, angry faces were presented between the cue and target word during the inter-stimulus interval. By contrast,in trials without emotional interference, grey squares were presented during the inter-stimulus interval.

B. Brain activations associated with emotionally interfering angry faces

The HC group demonstrated significant BOLD responses to emotionally interfering angry faces in the dACC, primary motor cortex, superior temporal sulcus and posterior parietal cortex. By contrast, the IGD group showed significant BOLD responses to emotionally interfering angry faces in the right AIC, supplementary motor area, and fusiform gyrus (Table 3, Figure 2).

Table3. Brain activations[a] associated with emotionally interfering angry faces

Region		BA	k_E	T_{max}	x	y	z
Healthy Control Group > Internet Gaming Disorder Group							
Anterior cingulate cortex		24	110	3.64	0	22	40
Supplementary motor area	Left	6	60	3.80	-26	-6	46
Dorsolateral prefrontal cortex	Left	4	91	3.92	-52	-6	34
Superior temporal gyrus	Right	22	62	3.54	66	-8	10
Posterior cingulate cortex	Left	23	503	4.78	-6	-26	28
Posterior parietal cortex	Right	7	103	4.00	8	-82	48
Internet Gaming Disorder Group > Healthy Control Group							
Anterior insular cortex	Right	48	57	4.18	46	4	14
Supplementary motor area	Right	6	115	4.64	2	-6	68
	Left	6	404	4.70	-18	-10	72
Fusiform gyrus	Left	37	81	3.86	-44	-60	-22

[a] To compare the contrast [angry face> grey square] between groups, we created exclusive masks for each group with SPM maps with a threshold at $p<0.05$. Statistical inferences were thresholded using an uncorrected $p < 0.001$, $k_E>50$ voxels for the whole brain.

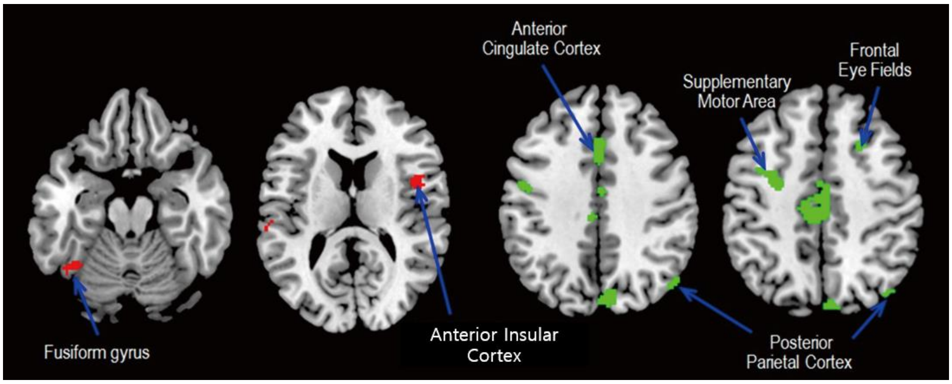

Figure 2. Brain activations associated with emotionally interfering angry faces. Green: Brain activations stronger in HC group than in the IGD group. Red: Brain activations stronger in the IGD group than in the HC group.

C. Functional connectivity between the right AIC and the dorsal attention network

The AIC activations synchronized with activations negatively in the dorsolateral prefrontal cortex, middle temporal gyrus, cerebellum and posterior parietal cortex in IGD group (Table 4, Figure 3A).

Table 4. Brain regions[a] exhibiting negative functional connectivity with the right AIC in IGD group

Region		BA	k_E	T_{max}	x	y	z
Dorsolateral prefrontal cortex	Right	9	59	4.71	16	38	54
			61	7.10	42	18	58
	Left		202	5.08	-36	18	56
Middle temporal gyrus	Left	21	261	5.43	-50	-2	-24
	Right		558	7.74	68	-26	-12
Fusiform gyrus	Left	37	64	5.66	-44	-40	-6
Posterior parietal cortex	Left	39	196	6.00	-44	-68	42
	Right	7	88	4.54	40	-72	50
Cerebelum	Right		146	4.61	40	-66	-50
	Left		376	6.02	-34	-66	-42
	Left		204	6.51	-6	-82	-34

[a] Statistical inferences were thresholded using an uncorrected $p < 0.001$, $k_E>50$ voxels for the whole brain.

D. Correlation between functional connectivity and behavioral performance

In IGD group, delayed reaction time correlated with stronger negative functional connectivity between right AIC and right dorsolateral prefrontal cortex (Pearson r=-0.609, p=-0.007, Fig. 3B). Higher cognitive impulsivity score also correlated with stronger negative functional connectivity between right AIC and right dorsolateral prefrontal cortex (Pearson r=-0.467, p=-0.051, Fig.3C)

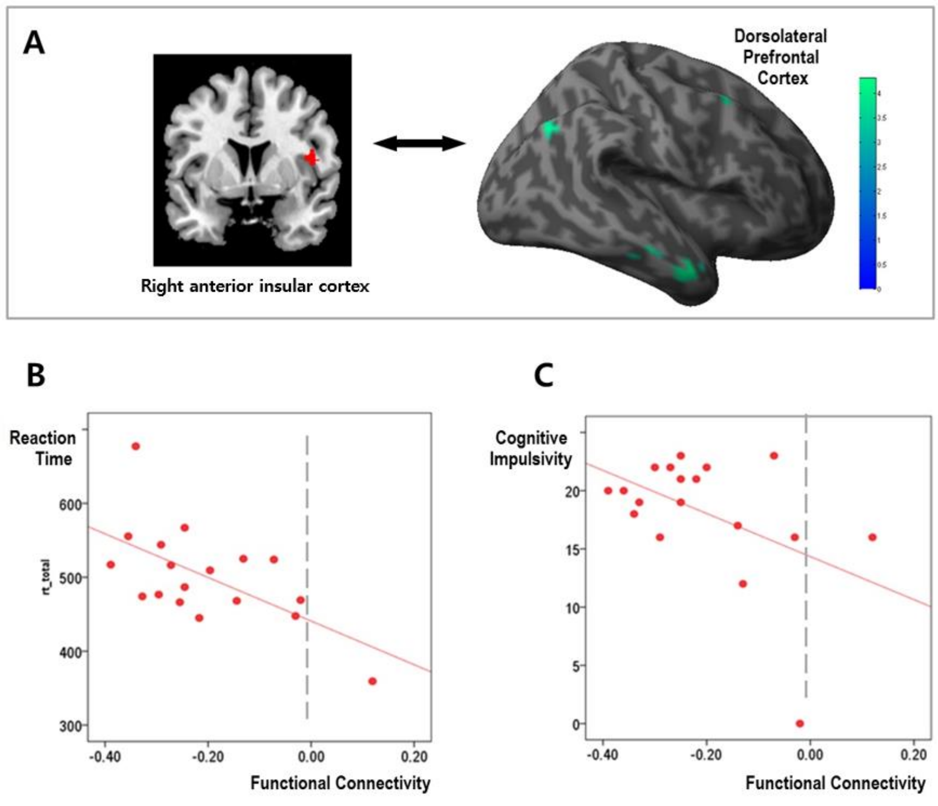

Figure 3. Brain-behavior relationship in the IGD group. (A) Brain regions exhibiting negative functional connectivity with the right AIC activation. (B) Correlation between AIC-prefrontal functional connectivity and reaction time. (C) Correlation between AIC-prefrontal functional connectivity and cognitive impulsivity.

3. STUDY 2 (Resting state fMRI results)

A. Functional connectivity analysis

In seed-to-voxel analysis, the IGD group showed stronger positive functional connectivity between the right AIC and left pSTS than HC group. In contrast, HC group showed significant positive functional connectivity between PCC and left pSTS compared to IGD group (Figure 4a, Table 5). Regarding that the PCC and AIC were selected to represent the default mode network and salience network respectively, the pSTS was positively correlated with salience network in IGD while presenting negative correlation with salience network in HC group (t: 4.219, p-value<0.001). On the other hand, pSTS was negatively correlated with default mode network in IGD opposite to HC group (t: -4.411, p-value<0.001) (Figure 4b). There was a negative correlation between the PCC-pSTS functional connectivity strength and the AIC-pSTS functional connectivity strength (Pearson’s r=-0.464, p-value=0.005) (Figure 4c).

In seed-to-seed analysis, the pSTS functional showed different pattern in the IGD group. The pSTS showed additional functional connectivity with left DLPFC, right AIC only in IGD and altered functional connectivity with PCC in IGD compared to HC group. Moreover, functional connectivity between PCC and right DLPFC in healthy control was not observed in IGD group (Figure 5).

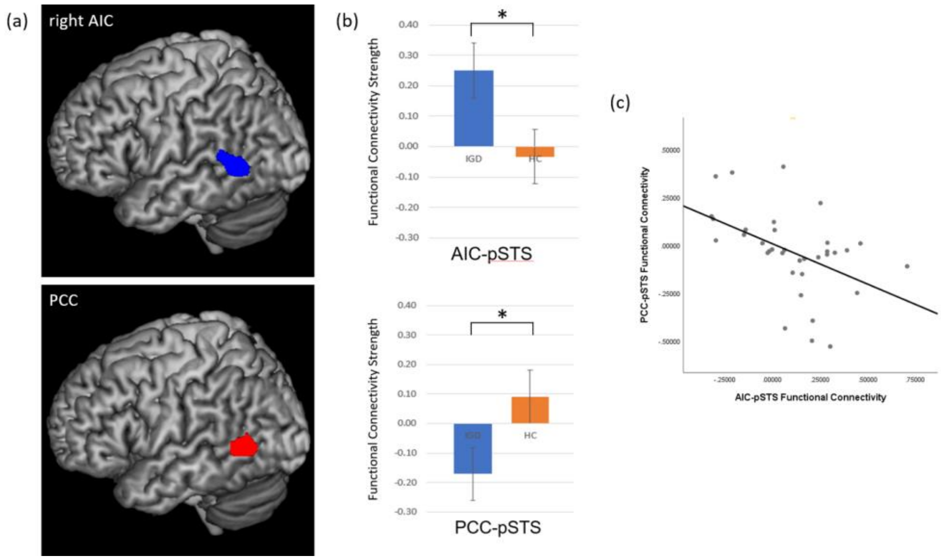

Figure 4. Seed-to-voxel analysis and its functional connectivity strengths. The statistical inferences were thresholded using an uncorrected p value<0.001. Coordinates indicate the locations of the brain slices according to the Montreal Neurological Institute system. (a) Between group differences in seed-to-voxel analysis results. Compared to HC group, right AIC of IGD showed significantly positive functional connectivity with left STS (-60 -54 6) (kmax=357, T=5.35). PCC of HC group showed significant positive functional connectivity with left STS (-58 -58 6) (kmax=175, T=5.00) than IGD group. (b) Between group comparison of functional connectivity strength. AIC-pSTS functional connectivity showed significant difference, presenting positive functional connectivity in IGD and negative functional connectivity in HC (t:4.219, p-value<0.001). PCC-pSTS functional connectivity between two groups was also significantly different while IGD showing negative functional connectivity, HC showing positive functional connectivity (t:-4.411, p-value<0.001). (c) Pearson correlation analysis for AIC-pSTS functional connectivity and PCC-pSTS functional connectivity. Two functional connectivity showed significant anticorrelation (r=-0.464, p=0.005).

Table 5. Brain regions with significant differences in seed-to-voxel functional connectivity

Region	Side	K	T	X	Y	Z
Seed: right Insula (IGD>HC)						
Superior Temporal Sulcus	Left	467	5.35	-60	-54	6
Amygdala	Right	247	5.52	36	-2	-20
Seed: Posterior Cingulate Cortex (HC>IGD)						
Superior Temporal Sulcus	Left	175	5.00	-58	-58	6

Statistical inferences were thresholded using an uncorrected p value<0.001. Coordinates indicated the location of the brain slices according to the Montreal Neurological Institute system. IGD group presented stronger positive functional connectivity of PCC with left pSTS and right amygdala than HC group. HC group showed stronger positive functional connectivity between PCC and pSTS compared to IGD group.

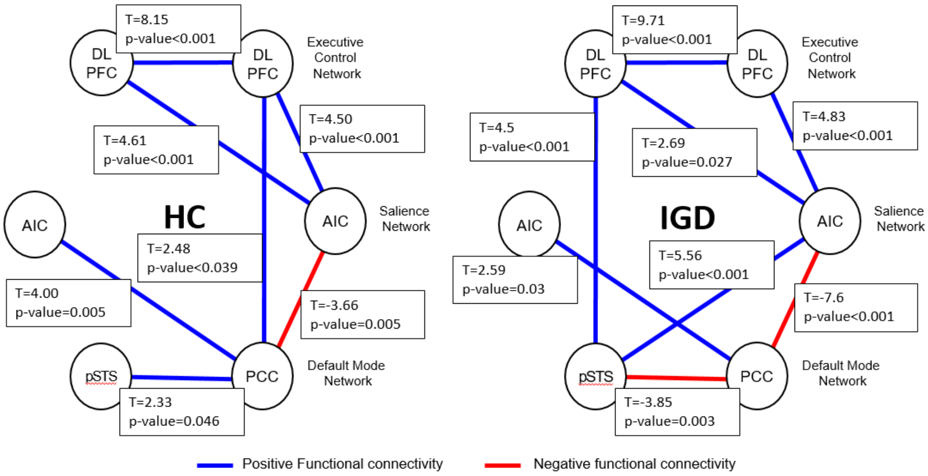

Figure 5. Results of seed-to-seed functional connectivity within group analysis. The statistical inferences were thresholded using an FDR-corrected p value<0.05 **(**Blue line: positive functional connectivity; Red line: negative functional connectivity). In IGD group, functional connectivity of pSTS to left DLPFC and right AIC was newly identified which were not observed in HC group, while alteration in pSTS-PCC functional connectivity (positive to negative) was also found in IGD. Functional connectivity of PCC with right DLPFC shown in HC was not significant in IGD.

B. Correlation between functional connectivity strength and psychometric measures

The AIC-pSTS functional connectivity strength correlated with higher scores of Korean Internet Addiction Proneness Scales (Pearson's r=0.346, p-value=0.042). The AIC-pSTS functional connectivity strength also correlated with higher scores of the cognitive problem subscale of the Conners-Wells Adolescent Self-report Scale (Pearson's r=0.455, p-value=0.006) (Figure 6). After Bonferroni correction, the AIC-pSTS functional connectivity strength was significantly correlated only with high scores of the cognitive problem subscale of the Conners-Wells Adolescent Self-report Scale (Adjusted p-value=0.0125). When analysis was restricted to IGD group, the correlations between functional connectivity in AIC-pSTS and psychometric measures were not significant. There was no significant correlation between the PCC-pSTS functional connectivity strength and any psychometric measures.

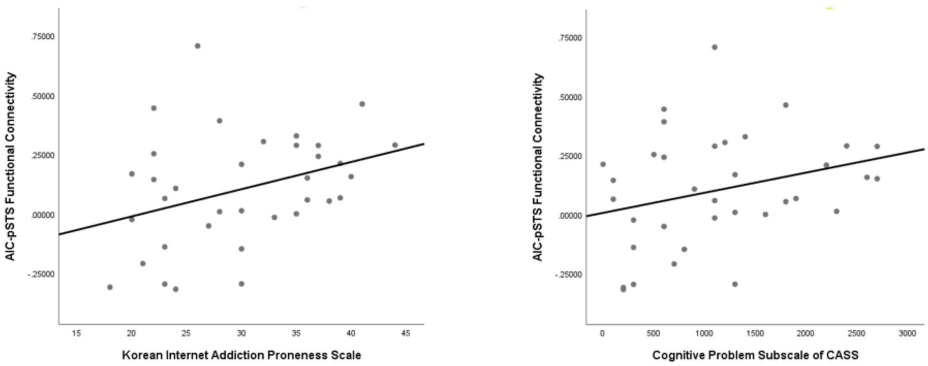

Figure 6. Correlation of functional connectivity strength with clinical variables. Pearson correlation analysis for clinical correlation of functional connectivity. We identified positive correlation between AIC-pSTS functional connectivity and total score of Korean Internet Addiction Proneness Scale (r=0.346, p=0.042), and positive correlation between AIC-pSTS functional connectivity and cognitive problem subscale of Conners-Wells Adolescents Self-report Scale (r=0.455, p-value=0.006).

C. Group independent component analysis

Six out of 38 Independent component (IC; IC 15, IC 17, IC 24, IC 26, IC 29, IC 34) passed our selection criteria. Four among six components were highly correlated with grey matter and Stanford templates respectively: default mode network: IC 34, salience network: IC 17, left executive control network: IC 15, right executive network: IC 24 (Figure 7). Though both IC 26 and IC 29 seemed to be related to the activation of left pSTS, IC 29 was excluded from our analysis because it showed restricted BOLD signal activation only in both pSTS. The IC 26 was composed of left pSTS, bilateral DLPFC, and right temporoparietal junction in within-group analysis of component (FWE-adjusted p-value=0.05, extended voxel >100) (Figure 8). Based on these regions, we identified IC 26 as the social brain network [61, 62]. In two-sample t test of social brain network, the left pSTS was hyperactivated in IGD group compared to HC group (Figure 9).

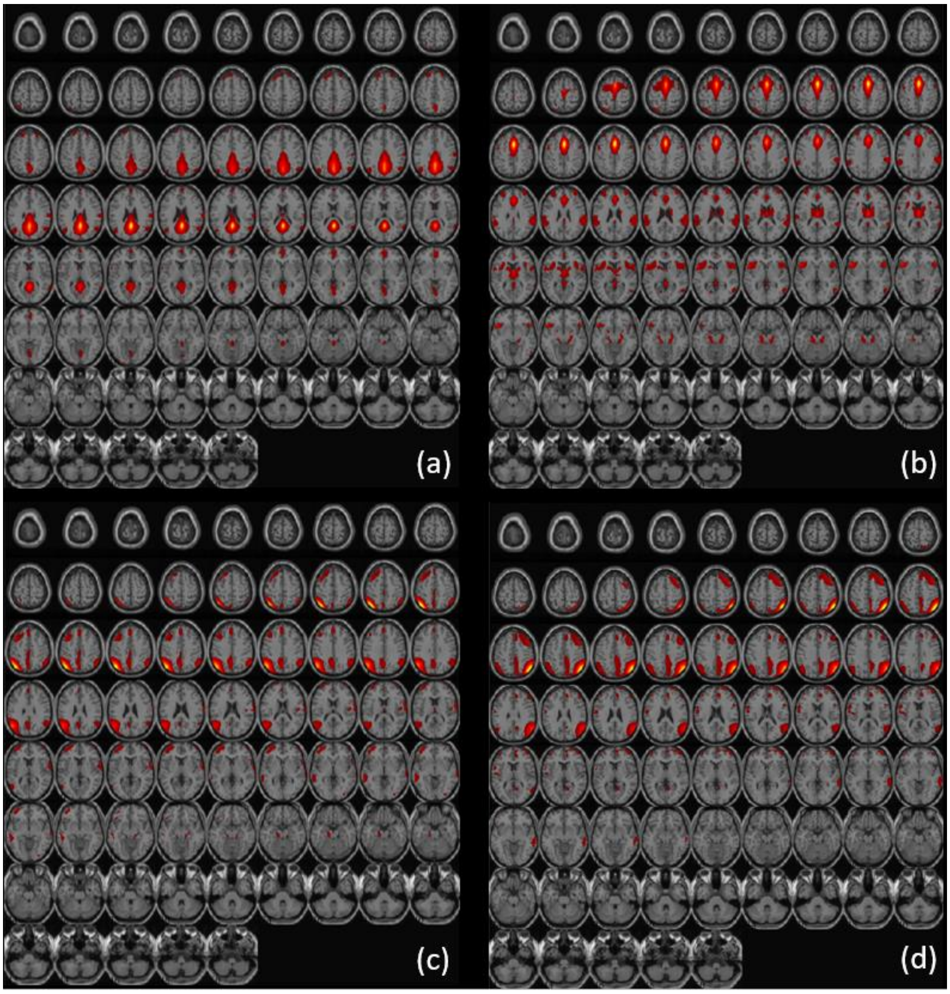

Figure 7. Independent components representing large-scale intrinsic networks. (a) Default mode network (IC 34) (Stanford template correlation: r^2=0.320; White matter correlation: r^2=0.011, Cerebrospinal fluid: r^2=0.033); (b) Salience network (IC 17) (Stanford template correlation: r^2=0.434; White matter correlation: r^2=0.023, Cerebrospinal fluid: r^2=0.075); (c) Left executive control network (IC 15) (Stanford template correlation: r^2=0.490; White matter correlation: r^2=0.031, Cerebrospinal fluid: r^2=0.111); (d) Right executive control network (IC 24) (Stanford template correlation: r^2=0.421; White matter correlation: r^2=0.009, Cerebrospinal fluid: r^2=0.093)

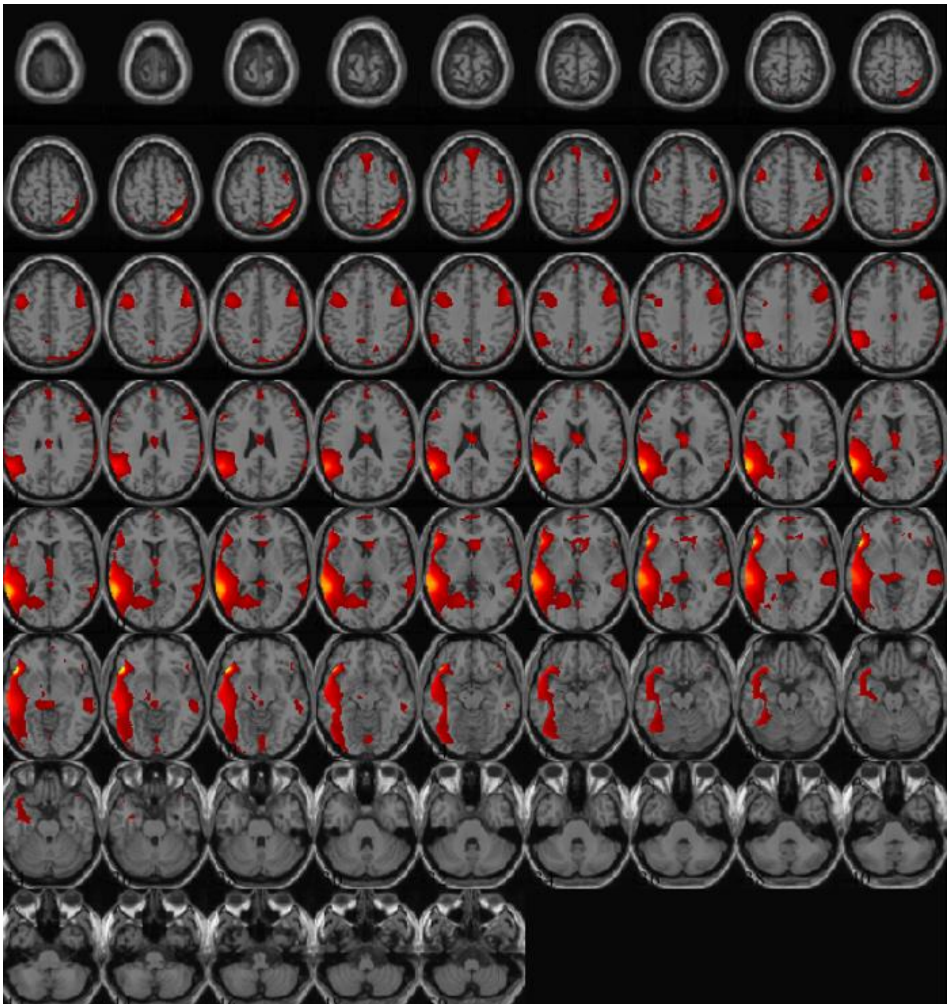

Figure 8. Independent components related to left posterior superior temporal gyrus. IC 26 (r^2=0.126; White matter correlation r^2=0.026; Cerebrospinal fluid correlation r^2=0.064). Activations included left pSTS, bilateral dorsolateral prefrontal cortex, right temporoparietal junction in one-sample t test (FWE-adjusted p-value=0.05, extended voxel>100).

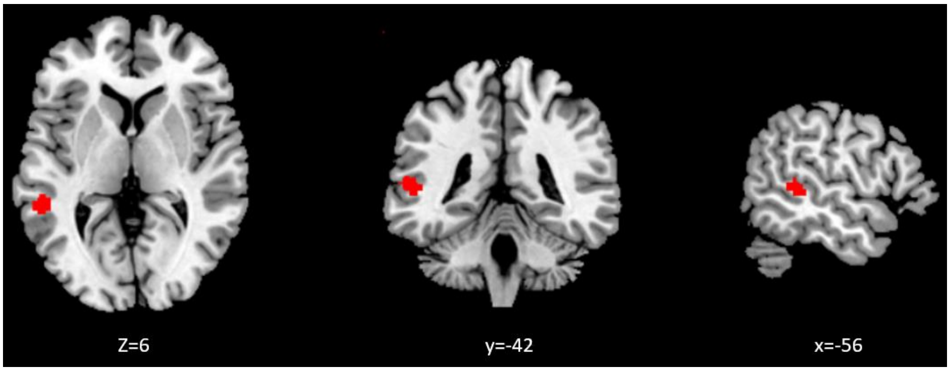

Figure 9. Between-group differences in independent component 26. Compared with HC group, IGD group showed significantly higher activation in left posterior superior temporal gyurs (-56 -42 6) (kmax=109, T=4.76). Threshold was defined uncorrected p-value < 0.001.

IV. DISCUSSION

1. STUDY 1 (Task fMRI)

We showed that the prefrontal cognitive control of emotional interference was compromised in adolescents with IGD. The adolescents with IGD demonstrated weaker dACC activation and stronger AIC activations to interfering angry facial stimuli, which implied difficulty in emotional regulation. Reciprocal interaction between stronger AIC activation and weaker dorsolateral prefrontal activation correlated with higher cognitive impulsivity in adolescents with IGD.

Our results support our hypothesis that the dACC activation during stroop Match-to-Sample task would be compromised in adolescents with IGD. As a key region for top-down cognitive control and selective attention [63, 64], stronger dACC activation was demonstrated in the HC group compared to the IGD group. In addition, the dorsolateral prefrontal cortex and posterior parietal cortex, which consist the dorsal attention network [65], were significantly activated in HC group compared to IGD group. The dorsal attention network is involved in the cognitive selection of sensory information and responses, and thought to generate and maintain endogenous signals based on current goals [65, 66]. The dACC is a part of the salience network, which initiate switching between other large-scale brain networks to facilitate access to attention and working memory resources when a salient event is detected [67]. Therefore, we speculate that the weaker activation of the dorsal attention network in the IGD group should be linked to the altered activation of the dACC.

The adolescents with IGD showed stronger activation in the right AIC and the fusiform gyrus. The AIC, which is the hub of the ventral attention system, is proposed to function as a link between attention-related problem solving and salience systems during the coordination of task performance [68]. By contrast to the dorsal attention network, the ventral attention network makes important contributions to stimulus-driven reorienting of covert visual spatial attention [66]. Most importantly, stimulus-driven ventral attention network interferes with the top-down dorsal attention network as a ‘circuit breaker’ during task performance coordination [65, 69]. Therefore, the stronger activation of the right AIC could be related to the weaker activation of the dorsal attention network in the IGD group. Taken together, we assume that the adolescents with IGD were more distracted by the emotional interference of the angry facial stimuli. From the same viewpoint, it is noteworthy that fusiform gyrus activation was demonstrated in the IGD group. Previous studies suggest that the fusiform gyrus plays a crucial role in facial recognition, especially invariant aspects of faces [70, 71]. Compared to the healthy control group, the activation in the fusiform gyrus indicates the failure of the IGD to ignore the emotional interfering angry faces during the stroop Sample-to-Match task.

Our speculations that angry face stimulus-driven attention disrupted goal-directed attention of the IGD group were supported the functional connectivity analysis, which demonstrated reciprocal interaction between stronger AIC activation and weaker dorsolateral prefrontal activation. In addition, stronger negative functional connectivity between AIC and dorsolateral prefrontal activation correlated with delayed reaction time and with higher cognitive impulsivity score. Although adolescents with IGD demonstrated a tendency of longer reaction time in emotional interfering conditions, the difference was not significant. Therefore, our findings show the changes of the cortical activation pattern might precede noticeable changes of the behavioral performance in adolescents with IGD.

Our findings are in line with previous studies [72], which report higher incidence of impulsivity and aggression in adolescents with IGD; however, over factors which account for the impulsive and aggressive behaviors in adolescents with IGD should be considered. For instance, top-down control of cortical inhibition is also reduced in attention deficit hyperactivity disorder, which is one of the most common comorbidities in adolescents with IGD [73]. The influence of combined psychiatric disorders should be evaluated in further studies and be treated to prevent their deteriorating effect on the prognosis of adolescents with IGD. Another factor to consider should be the content and type of the internet online game. A meta-analytic review reported that violent video games (in which the predominant goal is to harm another game character) increase aggression, whereas pro-social video games (in which the predominant goal is to benefit another game character) have the opposite effect [74]. Among Korean adolescents, role playing games, first person shooing games, real-time strategy games, and sports games are the most popular types of internet games. In our study, majority of the participants reported to enjoy role playing PC games, especially massively multiplayer online role-playing games (MMORPG), we could not examine the effect of the game type on the behavioral responses or brain activations.

There are several limitations to this study. First, there were no statistically significant differences in behavioral results between groups. Studies with larger population should be followed to ensure tendencies of our results. Second, we couldn't see diverse results following different emotional stimuli, because we used just angry face as emotional interruption. There can be debates about the effects of different emotions, such as fear, on our results. Moreover, with the psychometric results of BDI and BAI, faces with depressive or anxious emotion might be helpful in the interpretation of fMRI results. Third, the data showed significant difference of BDI score between adolescents with internet gaming disorder and healthy control group. This might reflect comorbidity of internet gaming disorder and depression which is reported in previous studies [73, 75]. Fourth, we tried to reveal the problems of top-down control of IGD by using bottom-up stimuli, we did not focus on evaluating the bottom-up skills of participants. Differences in bottom-up skills could alter the degree of interference to top-down control.

2. STUDY 2 (Resting state fMRI)

In line with our hypothesis, we identified aberrant functional connectivity of salience network and default mode network with the pSTS in adolescents with IGD. Moreover, functional connectivity between the salience network and pSTS correlated with proneness to internet addiction and self-reported cognitive problems. Regarding that the pSTS is an essential part of the social brain network, our findings imply that excessive exposure to game-related social stimuli during adolescence might affect the dynamic interaction between the salience network and social brain network, which seems to be associated with executive dysfunction and cognitive problems.

Adolescents with IGD showed different functional connectivity patterns among large-scale intrinsic networks. The PCC and right AIC, which are the hubs of the default mode network and salience network, both showed significant interactions with the left pSTS only in adolescents with IGD. In addition, there was a negative correlation between the PCC-pSTS functional connectivity strength and the AIC-pSTS functional connectivity strength. These findings suggest that the left pSTS was involved in the interaction between these two large-scale intrinsic networks. The pSTS plays an important role in detection of face and eye gaze in humans [76, 77] and is known as a key node of the social brain network including mentalization [61]. To achieve successful theory of mind (higher-level subsystem), it is necessary to recognize socially relevant face and motions (lower-level subsystem), and to prepare cohesive response such as empathy that links preprocessed sensory input to mentalizing response (intermediate-level subsystem). Nodes of social brain network such as medial prefrontal cortex and temporoparietal junction (higher-level subsystem), inferior frontal gyrus (intermediate-level subsystem), and fusiform gyrus (lower-level subsystem) are activated in one or more subsystems in social brain network. As pSTS plays a crucial role in lower- and intermediate-level subsystem in social brain network [78], it is directly affected by external social stimuli. Independent Component Analyses confirmed that the pSTS activation in this study was a part of a larger network (IC 26), the social brain network, which was composed of social brain nodes such as the pSTS, bilateral DLPFC, and right temporoparietal junction. DLPFC can be explained as coactivated region of social brain network due to correlation between social brain network and fronto-striatal connectivity [62]. Besides the pSTS, the AIC also is known to take part in social processing. The AIC helps recognizing social stimuli as salient events and makes individuals to remain attentive to social situations by coactivaiton with other social brain nodes [79]. Furthermore, the functional connectivity of AIC and pSTS is increased when individuals share emotional content such as embarrassment of social target [80], and decreased in autism spectrum disorder facing social stimuli [81]. These findings suggest that the AIC-pSTS functional connectivity is sensitive to social situations.

Our finding provide evidence that excessive online gaming behavior might affect social brain functioning in adolescent with IGD. As online games require real-time communication with peers and other players, adolescents can easily be exposed to enormous social stimuli which cannot be ignored. During playing game, adolescents also need to predict intentions of other players to win the game. Moreover, adolescents are sensitive to social judgments [25], and tend to regard social interaction in online gaming as salient stimuli. Considering that the influence of online social situations is similar to that of face-to-face experience on brain activation [82], we assume that the stronger functional connectivity between the social brain network and salience network in adolescents with IGD might be related to the increased time and heavy loading of social interactions while playing online games. Interestingly, psychiatric illness accompanying social impairments such as ADHD and autism spectrum disorders are known to be closely associated with IGD [83, 84], implying the importance of social component in internet gaming problems.

It is noteworthy that the AIC-pSTS functional connectivity correlated with higher scores of the cognitive problem subscale of the Conners-Wells Adolescent Self-report Scale. Social functions such as social cognition and mentalization are reported to be closely related to executive dysfunction in adolescents [85] as the default mode network and salience network are closely related to social cognition and affect each other [30, 86]. As the cognitive problem subscale in Conners-Wells Adolescent Self-report Scales implies executive functioning such as inhibitory control, organizing work, finishing task [48], our findings, which demonstrated aberrant functional connectivity between the default mode network, salience network and social brain network, might provide further understanding about the neural basis of executive dysfunction and cognitive problems in IGD.

Differences in developmental trajectory of the neural networks are one of the developmental characteristics in adolescence, and the adolescent brain is sensitive to experiential input with synaptic reorganization [87]. The underlying neurodevelopmental vulnerability of adolescent brain, such as functional gaps between networks and insufficient segregation of networks [88], might also play an important role in the neurobiological changes induced by excessive social stimuli. Considering that the social brain network is early-developed compared to other functional networks [62, 89], we suppose that the functional gap between the social network and cognitive network is related to sensitive social perception to excessive social stimuli resulting in increased functional connectivity between salience network and social brain network in IGD. Aberrant functional connectivity of social brain network to other intrinsic networks might also be associated with insufficient segregation during brain maturation. Segregation is one of the key process of brain maturation which is associated with pruning of brain architectures [90]. Children can show distinctive functional connectivity linking two independent large-scale networks compared to adults because of insufficient segregation process [91]. As our participants are in age of early adolescence (mean age 13.7 in IGD group, 13.4 in HC group), segregation of functional networks might be insufficient and changes in patterns of functional connectivity would be possible depending on individual's experience.

There are several limitations to our study. First, as our study was performed in cross-sectional design, we could not conclude whether the aberrant functional connectivity patterns are the result of IGD or a predisposition factor of IGD. To explore this limitation, longitudinal study involving early childhood should be followed. Second, significant difference was observed in Beck Depression Inventory (BDI). Although there was no statistically significant influence on our result as a covariate, effects of depression still cannot be completely excluded. Third, the size of sample was comparatively small. Accordingly, the correlations between AIC-pSTS functional connectivity and psychometric measures in IGD group was not significant. Studies with large sample size should be followed. Fourth, executive functions are evaluated only with self-report scales. Further studies with objective neuropsychological tests evaluating executive function may clarify our results. Fifth, to correlate IGD with social dysfunction, elaborate evaluation on social functioning is necessary, and comorbidities associated with poor social functioning such as autism spectrum disorder and ADHD [92] should also be evaluated with caution. Though we tried to exclude previously diagnosed ADHD and autism spectrum disorder, more detailed evaluation should be followed. Sixth, when the correlation analysis was restricted to IGD group, the correlations between functional between functional connectivity in AIC-pSTS and psychometric measures were not significant. Also, there was no significant correlation between the PCC-pSTS functional connectivity and AIC-pSTS functional connectivity. These results seems to be the consequences of small sample size, further studies with large groups should be followed to ensure the result of this study.

Taken together, the results of both studies are directed to executive dysfunction in IGD and related functional connectivity of brain. Anterior insular cortex, a seed region of salience network, was the common key region of aberrant functional connectivity during task performance and resting state. Salience network seems to work abnormally, and lead to alteration in functional connectivity between networks in IGD. During the task performance, top-down control was easily disturbed by bottom-up stimuli with aberrant salience network affecting dorsal attention network. Altered salience network was also observed in resting state, forming aberrant functional connectivity with other functional networks. Considering that differences in resting state network also can predict executive function of individuals [93], our resting state analysis seems to support the executive dysfunctions in adolescents with IGD. The resting-state results not only support the task-related results but represent that alterations among large intrinsic networks exist consistently even in task-independent situations [94].

Our result should be interpreted with caution because changes of brain functional connectivity could be acquired by other reasons. First, as IGD group showed higher BDI scores, the role of depressive symptom in our result should be considered. Among several comorbid psychiatric disorders, depression might be one of the most important comorbidities in IGD. Depression not only is commonly reported psychiatric conditions in IGD, it also is associated with serious clinical manifestations [95]. Moreover, without IGD, depression itself can harm the executive functions [96, 97]. Impairments of executive functions in depression could confuse the result of correlations between IGD and executive dysfunctions. Previous studies reported decreased functional connectivity of dorsolateral prefrontal cortex with other regions in central executive networks [98, 99]. In our correlation analysis, the BDI scores were not significantly correlated to functional connectivity strength (STUDY 1: right AIC-right DLPFC; STUDY 2: right AIC-right pSTS) in both studies (STUDY 1: $r=-0.373$, $p=0.140$; STUDY 2: $r=0.041$, $p=0.818$). These results partially explain our results wouldn't be the result of depressive symptoms. But still depressive symptoms and other factors such as developmental characteristics of brain should be considered in interpreting the results. Second, differences in the development of brain should also be considered in interpretation. As mentioned, the maturation of brain in early adolescence is still insufficient compared to adult. Delayed neurodevelopment could result in poorer executive function in adolescents. Though there were no age difference and no evident developmental differences between group considering the result of intellectual functioning in our study, still differences in developmental trajectory should be considered. To compensate the problem, longitudinal follow up study in large sample size would be necessary. Third, various functions of AIC should be also taken account in interpretation [100]. Especially, as IGD is regarded one of behavioral addictions [101], the function of AIC reported in addictive disorders [102] could be one of possible interpretations of IGD. AIC is known to take part in increasing subjective sensitivity to addictive stimuli which results in substance seeking and craving [103]. The tripartite model of IGD present that AIC in IGD increases the drive to play the game [104].

V. CONCLUSION

Aberrant functional connectivity which is related to executive dysfunction was identified in adolescents with IGD both during task performance and resting state. Adolescents with IGD demonstrated weaker dACC activation and stronger AIC activations during a stroop task. The functional connectivity of social brain network was stronger with salience network and weaker with default mode network in resting state in adolescents with IGD. Our findings suggest that aberrantly stronger functional connectivity associated with salience network in IGD might disturb top-down executive function in both task-related situation and resting state.

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ABSTRACT(IN KOREAN)

인터넷게임장애 청소년의 뇌 기능적 연결 이상과 실행기능 저하

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이 정 한

인터넷게임장애의 임상적 중요성은 전 세계적으로 널리 알려지고 있으나, 이의 신경 메커니즘은 아직 명확하지 않다. 인터넷게임장애는 인지 조절 문제와 연관이 있다는 것이 여러 차례 사전 연구들을 통해 언급되었는데, 본 연구에서는 뇌 자기공명영상을 이용한 두 가지 방법(과제 관련 분석과 휴지기 분석)을 통해 인터넷게임장애에서의 실행기능과 관련된 뇌 기능적 연결성의 이상을 확인하고자 하였다. 본 연구에는 18명의 인터넷게임장애 청소년과 연령이 동일한 정상대조군 18명이 참여하였으며, 과제 관련 기능적 자기공명영상 촬영시에는 감정간섭을 동반한 스트룹 과제를 시행하였다. 연구 결과, 두 가지 접근 모두에서 실행 기능 이상과 관련된 뇌 기능적 연결성의 이상을 인터넷게임장애 청소년에게서 발견할 수 있었다. 인터넷게임장애 청소년은 스트룹 과제 중 등쪽

전방 대상 피질(dorsal anterior cingulate cortex)의 약한 활성화를 보였으며, 뇌섬엽(insula)에서 더 강한 활성화를 보였다. 또한, 휴지기에는 인터넷게임장애 청소년의 후측 상측두엽 고랑(posterior superior temporal sulcus)이 현출성 네트워크(salience network)와 강한 연결을, 디폴트 모드 네트워크(default mode network)와는 약한 연결을 보였다. 본 연구의 결과는 인터넷게임장애에서의 현출성 네트워크와 연관된 비정상적으로 강한 뇌 기능적 연결성이 하향 조절을 담당하는 실행 기능의 이상을 과제 수행 및 휴지기 모두에서 일으킬 것이라는 것을 시사한다.

핵심되는 말 : 인터넷게임장애, 실행기능, 현출성 네트워크, 뇌 기능적 연결성

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