Diminished goal-directed executive control in gaming disorders: A real-time heart rate variability analysis approach

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Diminished goal-directed executive control in gaming disorders: A real-time heart rate variability analysis approach

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ABSTRACT

Diminished goal-directed executive control in gaming disorders: A real-time heart rate variability analysis approach

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Objectives: Loss of control over online game use in gaming disorder (GD) is associated with diminished goal-directed executive control. Executive control can be measured as vagally-mediated heart rate variability (HRV) which corresponds to variability in the in the intervals between heart beats. We hypothesized that individuals with GD would show different HRV responses during real-time gaming than those without GD, reflecting their diminished goal-directed executive control.

Methods: Heart rate variability was assessed in 33 young males with GD and 29 controls while playing their favorite online game. Seed-based functional connectivity (FC) was evaluated to assess functional abnormalities in brain neural networks. A voxel-based morphometry (VBM) with diffeomorphic anatomical registration using an exponentiated Lie algebra algorithm was conducted to assess gray matter volume (GMV). Afterwards, we tested

associations between HRV and alterations in FC and GMV.

Results: Game-related reactivity for high frequency (HF) HRV were significantly different between subjects with GD and the control group. Game-related HF-HRV reactivity was correlated with the severity of GD and commission errors in continuous performance test. Compared with the control group, subjects with GD showed decreased FC between the right dorsolateral prefrontal cortex (DLPFC) and the right inferior frontal gyrus (IFG), corresponding to the central executive network. Subjects with GD showed increased FC between the left dorsal caudal putamen and both sides of the postcentral gyrus, and also between the left dorsal rostral putamen and the left postcentral gyrus, reflecting increased FC in the sensorimotor network. Game-related HF-HRV reactivity was correlated with DLPFC-IFG connectivity and dorsal caudal putamen-postcentral gyrus connectivity. Compared with control group, subjects with GD had smaller GMV in the right DLPFC.

Discussion: Young males with GD had phasic HF-HRV suppression during real-time gaming. This characteristic HRV was associated with the severity of GD, impulsivity, and FC alterations involving an imbalance between diminished FC in the central executive network and enhanced FC in the sensorimotor network. Our findings suggest that HRV measurements in young males with GD during real-time gaming reflect their habitual gaming behavior

under diminished goal-directed executive control.

Key words: executive control, functional connectivity, gaming disorder, heart rate variability

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I. INTRODUCTION

Gaming disorder (GD) refers to excessive, uncontrolled online game use despite negative psychosocial consequences.[1] GD is a form of behavioral addiction which shares many cognitive and behavioral symptoms seen in other addictive disorders.[2] However, physiological symptoms of addiction such as tolerance or withdrawal are not prominent in GD.[3] Studies have shown that individuals with GD are characterized by diminished executive control[4] which refers to the ability to exploit several higher order cognitive functions to perform goal-directed actions appropriately.[5] Executive control dysfunction is related to clinical characteristics such

as high impulsivity, disinhibition, and impaired decision making.[6] Studies on GD have demonstrated high impulsivity[7], impaired inhibition[8], and altered risk/reward decision-making[9], which are features associated with diminished executive control. Neuroimaging studies have demonstrated that structural/functional brain abnormalities in executive control-related cortical regions are involved in GD.[10] Structural neuroimaging studies demonstrated that individuals with GD have low gray matter volume (GMV) in the anterior cingulate cortex (ACC), the dorsolateral prefrontal cortex (DLPFC), and the orbitofrontal cortex (OFC).[11-13] Functional neuroimaging studies have demonstrated reduced that functional connectivity (FC) within the central executive network (CEN) in GD.[14] This evidence suggests that diminished goal-directed executive control plays a crucial role in the development and maintenance of GD.[15] However, the precise link between executive control dysfunction and the loss of control over game use has not yet been fully elucidated.

Studies have indicated that the amount of time spent playing games is not a firm criterion for GD diagnosis.[16] In some cases of recreational online game-users or professional gamers, psychosocial impairment or executive control dysfunction is not prominent, even if the time spent gaming is extensive.[17,18] Confirming a diagnosis of GD depends not only on the duration of time spent gaming, but also on the behavior patterns associated with the gaming. Addictive behavior begins with a voluntary, goal-directed pattern at first, which gradually becomes a habitual and compulsive pattern.[19,20] This process involves several neurobiological changes, including weakened prefrontal cortical control and strengthened dorsal striatal control.[21,22] We assume that

GD is founded and maintained through a similar pathophysiological process. Initially, most gaming takes place as a goal-directed action that includes complex cognitive processes dominated by executive control, such as predicting the outcome of behavior and receiving feedback based on the outcome. However, in some cases (especially those with vulnerability to addiction), gameplay behavior gradually changes from goal-directed to stimulus-driven habits as the gamer becomes more proficient. With this change, the influence of executive control may be gradually weakened, and the outcome of the game may be dominated by coincidence and fortune. We speculate that these changes in the behavioral patterns of gaming may be related to the loss of control over the game and the progression to GD. Gameplay in a goal-directed manner is not likely to progress to behavioral addiction even if it takes place for long periods of time. However, habitual gaming repeated over an extended period of time may have an increased likelihood to progress to GD. We speculate that the progression to GD may be based on neurobiological changes that are gradually governed by the dorsal striatum rather than the prefrontal regions.

Although there have been numerous efforts to measure loss of control over gaming behaviors, there is currently no screening and diagnostic tool to objectively evaluate GD. Therefore, clinicians and researchers still rely on self-report questionnaires.[23] In psychophysiology, behavioral patterns are analyzed by monitoring physiological responses to certain behaviors.[24] Behavioral patterns of gaming in GD are reflected in bio-signals extracted during gaming, may be an important indicator of habitual gaming with diminished goal-directed executive control. Heart rate variability

(HRV), which refers to variation in time intervals between heart beats, encodes autonomic functions and cognitive processes.[25] The neuro-visceral integration model suggests that brain networks relate to autonomic and cognitive functions and are associated with the regulation of cardiac vagal function.[26] Heart rate variability in the resting state and during mental load is related to the efficiency of cognitive regulation.[27,28] Especially, vagally-mediated HRV (i.e. high frequency [HF] HRV) involves prefrontal neural functions and related executive control.[29] Resting-state vagally-mediated HRV reflects an individual's capacity for executive functioning.[30,31] Furthermore, a steeper decrease in vagally-mediated HRV during mental loading has been correlated with diminished executive control over behavioral tasks.[32] Given the associations between HRV and executive control, measuring HRV during real-time online gaming could be valuable for assessing the level of difficulty exerting goal-directed executive control during gaming. Furthermore, HRV features identified through this experiment may be applied as objective indicators for the diagnosis of GD, or to monitor the progression of treatment.

The purpose of this study is to investigate whether measured bio-signals of game addicts during real-time gameplay can reflect their addiction to the game and diminished goal-directed executive control. The current study was composed of two parts. First, we hypothesized that people with GD would have a characteristic HRV response during real-time gaming, associated with their addictive gaming behavior. To test this hypothesis, we measured the HRV of young males with GD and without GD while playing an online game that they were familiar with to a similar level. We

compared the HRV of participants with and without GD during gaming. Second, we hypothesized that characteristic HRV in young males with GD would be related to their habitual game use under diminished executive control, and that this relationship would be mediated by weakened prefrontal control and strengthened dorsal striatal control. To test this hypothesis, we tested associations between HRV, clinical variables, and neuroimaging results. Clinical variables in this study included several self-reported questionnaires for GD symptoms and impulsivity, and behavioral performances in a continuous performance test to measure capacity of executive control. Neuroimaging studies in this study included brain magnetic resonance imaging (MRI) to analyze the structural and functional properties of the brain. Whole brain voxel-based morphometry (VBM) analysis was performed to assess GMV. Whole brain seed-based FC analysis was conducted to evaluate FC within or between functional networks.

II. MATERIALS AND METHODS

1. Participants

This study was conducted from August 2016 to June 2018. The protocol was approved by the Institutional Review Board at Severance Hospital, Yonsei University. Each participant signed a written informed consent before participating in the study. Subjects were recruited through online advertisements, flyers, and word of mouth. Sixty-two, right-handed males, aged between 16 and 27 years (mean age: 22.6 ± 2.8

years) participated in the study. All subjects were interviewed for their socio-demographic characteristics and Internet use patterns. In this study, subjects played "League of Legends (LOL)" (Riot Games, 2009) which is the most popular online game in South Korea. To reduce confounding effects caused by differences in familiarity or proficiency, only those who meet the "gold tier" by ranking system of LOL were recruited. The tier in LOL is determined by the ranked games between the players with a game level of 30 or higher (reachable after playing about 150 games). The Elo rating system, which was originally used in the chess, determines the tier to which the player belongs by calculating the relative skill levels of players[33]. The gold tier is within the top 13% of the players, which means that the level of proficiency in LOL is high.

The severity of GD was assessed using the Internet Addiction Test (IAT).[34] Subjects with GD were classified as those who use the Internet mainly for gaming purposes and scored more than 50 points in the IAT[35,36] (n = 33; age, 23.1 ± 2.8 years). A board-certified psychiatrist conducted psychiatric interviews based on the diagnostic criteria for Internet gaming disorder in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).[37] Subjects with an IAT score less than 50 and not experiencing difficulties controlling their gaming were classified as healthy controls (n = 29; age, 22.0 ± 2.8 years).

All subjects were assessed for comorbid psychiatric illness using a structured clinical interview from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (SCID-IV).[38] The Korean version of the Wechsler Adult Intelligence Scale IV (WAIS-IV)[39] was applied to estimate intelligence quotient (IQ). Several self-

report questionnaires were used to assess subjects' psychological characteristics: the Beck Depression Inventory (BDI)[40] for depression, the Beck Anxiety Inventory (BAI)[41] for anxiety, the Alcohol Use Disorders Identification Test (AUDIT)[42] for alcohol-related problems, the Wender Utah Rating Scale (WURS)[43] for childhood symptoms of attention-deficit/hyperactivity disorder (ADHD), and the Barratt Impulsiveness Scale, version 11 (BIS-11)[44] for impulsivity.

To assess the capacity of executive control, the Conners Continuous Performance Test (CPT)[45] was also performed. Because different versions of the CPT were performed during the early period of research (August 2016 to October 2016), the data were not valid for a substantial proportion of the control group (n = 9). So only the CPT data in subjects with GD is presented in the current study. The CPT consisted of 18 blocks and each block was composed of 20 trials (for a total of 360 trials). Subjects were instructed to press a keyboard button, except for the "X" key, as quickly as possible when a stimulus was displayed. Each stimulus was presented for 250 ms and the interstimulus intervals were block-randomized (1, 2, or 4 s). Behavioral performance variables included omission error and commission error.

The following exclusion criteria precluded volunteers from participation in this study: psychiatric illness other than GD, neurological disorder or medical illness that could cause changes in HRV (e.g., cardiac disease or endocrine disease), low intelligence or difficulty understanding the research process, and taking medications that could cause changes in HRV (e.g., beta blockers or anticholinergics). All subjects were psychiatric medication-naïve when participating in this study.

2. HRV analysis

Electrocardiogram (ECG) signals were obtained through a standard 3-channel ECG instrument and monitoring system (MP150 BIOPAC Systems, Santa Barbara, CA, USA). After at least 10 minutes rest, Ag-AgCl electrodes were attached to subjects' chest according to the Einthoven triangle superimposed on the subjects' thorax region.[46] The anode was attached to the left lower abdomen, the cathode to the right shoulder, and the ground electrode to the left shoulder.[47] In a comfortable sitting position a resting ECG recording was performed for 5 minutes to establish the baseline HRV. Heart rate variability was then recorded while subjects played the online game for the first 5 minutes of the game. The first five minutes was used to reduce confounding effects of the progression of the game such as the outcome of the battle.

ECG signals were preprocessed through filters to eliminate interference caused by movement, breathing, and the electrical activity of skeletal muscles. Third-order Butterworth high pass filtering with a 0.1 Hz cutoff frequency, third-order Butterworth low pass filtering with a 15 Hz cutoff frequency, and sixth-order Butterworth notch filtering were applied.[48,49] Next, RR intervals on ECG data were identified using the Pan & Tompkins algorithm.[50] First, ECG signals were sampled with a frequency of 200 Hz. Beats with a more than 10% difference in consecutive RR intervals were eliminated. Then, ECG signals were resampled with a frequency of 10 Hz using cubic spline interpolation.[51]

Different HRV parameters were obtained from the ECG data. In the time

domain analyses of HRV, the square root of the mean of the sum of the squares of differences between consecutive RR intervals (RMSSD) and the standard deviation of the R-R interval (SDNN) were analyzed. While SDNN measures the overall trend of HRV, RMSSD is particularly sensitive to parasympathetic activity.[52] High frequency (HF-HRV: 0.15-0.40 Hz) and low frequency (LF-HRV: 0.04-0.15 Hz) components of HRV were analyzed using autoregressive spectral analyses.[53] While the HF-HRV is sensitive to parasympathetic activity, the LF-HRV represents both sympathetic and parasympathetic activity.[54] To adjust for skewed distributions of values, natural logarithms of HF-HRV and LF-HRV were computed (lnHF for HF-HRV, lnLF for LF-HRV).

3. VBM analysis

Brain MRI data were acquired by a 3T MRI scanner (Siemens, Magnetom) equipped with an eight-channel head coil. The 3-D structural MRI data were obtained through a T-1 weighted spoiled gradient echo sequence (echo time = 2.19 ms, repetition time = 1780 ms, flip angle = 9°, field of view = 256 mm, matrix = 256 × 256, transversal slice thickness = 1 mm). Structural MRI data were analyzed using MATLAB 8.5 (MathWorks, Natick, MA) and SPM8 (Welcome Department of Imaging Neuroscience, UK). Preprocessing was performed according to standardized procedure.[55] Briefly, images were aligned along the anterior-posterior commissure line. Images were then segmented into gray matter, white matter, and cerebrospinal fluid probability maps

using the Bayesian method. For accurate inter-subject alignment of images, diffeomorphic anatomical registration using an exponentiated Lie algebra algorithm (DARTEL) was performed.[56] For this, flow fields were created that parameterized each subject's brain deformations during template creation. Then, a study-specific template was generated by including all subjects' images. Gray matter images of each subject were wrapped to the study-specific template and then spatially normalized to the Montreal Neurological Institute (MNI) standard brain coordinate system. In the normalization process, flow fields of each subject were applied to gray matter images and Jacobian modulation was conducted to preserve the regional volume data. Voxel size was resampled to 1.5 × 1.5 × 1.5 mm during normalization. Finally, normalized images were smoothed using 8 mm full-width at half maximum kernel.

After adjusting for age, IQ, and intracranial volume (ICV), analysis of covariance (ANCOVA) was performed for each voxel, to compare GMVs between the groups. Age and IQ were entered into as covariates because of their known influence over GMV.[57] ICV was estimated by the sum of gray matter, white matter, and cerebrospinal fluid volume. Whole brain analysis was performed to locate clusters showing group differences in GMVs. Statistical inferences for whole brain analysis were set at a height threshold of $p < 0.001$, uncorrected, and an extent threshold of $k > 100$ voxels, based on previous VBM studies on addiction.[58,59]

4. FC analysis

The fMRI data were obtained through a single-shot T2-weighted gradient echo planar pulse sequence (echo time = 30 ms, repetition time = 2,500 ms, flip angle = 90°, field of view = 240 mm, matrix = 64 × 64, slice thickness = 3.5 mm). Subjects were directed to look at a white cross in the center of a black background for six minutes, without any cognitive, verbal, or athletic activity. Preprocessing of the data was preformed using MATLAB 8.5 (MathWorks, Natick, MA) and SPM8 (Welcome Department of Imaging Neuroscience, UK). To avoid variations caused by head movement, each subject's realignment parameter estimates were examined and checked to ensure that the maximum head movement of each axis was less than 2 mm and there were no unexpected head movements. Three subjects (two subjects with GD, one control) were excluded in FC analysis because of large head movements during functional MRI. Functional brain scans were realigned and co-registered to structural brain scans. Co-registered data were spatially normalized into the MNI standard brain coordinate system through 12-parameter affine transformation and non-linear iterations. Voxel size was resampled to 1.5 × 1.5 × 1.5 mm during the normalization step. Finally, normalized images were smoothed using 8 mm full-width at half maximum kernel.

Seed-to-voxel FC maps for each subject were configured using the CONN-fMRI FC toolbox (http://www.nitrc.org/projects/conn). To evaluate for FC of the CEN, prefrontal seed regions were selected based on data from previous resting-state FC studies [60,61]. The following spherical seeds with a 6-mm radius were selected: the right DLPFC (x = 38, y = 41, z = 22) and the left DLPFC (x = -40, y = 39, z = 26). Based on data from previous resting-state FC studies[62], dorsal striatum-based FC was

investigated. The following spherical seeds with a 4-mm radius were selected: dorsal caudate (DC; x = ±13, y = 15, z = 9), dorsal caudal putamen (DCP; x = ±28, y = 1, z = 3); dorsal rostral putamen (DRP; x = ±25, y = 8, z = 6).

The waveform of each brain voxel was filtered using a bandpass filter (0.008 Hz < f < 0.09 Hz) to avoid low-frequency drift and high-frequency noise effects. A linear regression model was used to minimize signals from white matter and ventricular regions.[63] Motion parameters were applied into the linear regression model to reduce variations caused by head movement. Correlation coefficients were calculated and converted to z-values using Fisher's r-to-z transform to extract FC estimates. An analysis of variance (ANOVA) was used on each voxel to compare FC estimates between the groups. Statistical inferences for whole brain analysis was set at a height threshold of $p < 0.001$, uncorrected; and an extent threshold of the false discovery rate (FDR)-corrected $p < 0.05$.

5. Statistical analysis

Statistical analyses were conducted using SPSS 24.0 (SPSS Inc., Chicago IL, USA) and thresholds for statistical significance were set at $p < 0.05$. Demographic and clinical variables were compared using a two-sample t-test. Absolute values of HRV parameters (lnHF, lnLF, SDNN, and RMSSD) at baseline and during gaming were compared between groups using a two-sample t-test. Gaming-related HRV reactivity was calculated by subtracting the baseline HRV values from the HRV values during

gaming and compared between groups.[64] After controlling for age, IQ, and BDI, partial correlation analyses was performed to determine whether HRV parameters that differed between groups correlated with clinical variables, FC, or GMV estimates.

III. RESULTS

1. Participants characteristics

There were no statistically significant differences between the GD and control groups in age and full-scale IQ (Table 1). The GD and control groups did not significantly differ in their self-reported anxiety, alcohol-related problems, or childhood ADHD symptoms. Compared to the control group, subjects with GD exhibited significantly higher levels of Internet addiction, depression, and cognitive impulsiveness (IAT; $p < 0.001$, BDI; $p = 0.003$, and cognitive subscale of BIS; $p = 0.025$, respectively). Subjects with GD spent significantly more time playing Internet games daily than healthy controls ($p = 0.001$).

Table 1. Demographics and clinical variables of participants

	GD (n = 33)	***Control (n = 29)***	***t test***	***p-value***
Age (years)	23.1 ± 2.8	22.0 ± 2.8	1.521	0.133
Full Scale IQ[1]	107.9 ± 12.9	110.2 ± 12.9	-0.728	0.470
IAT	64.6 ± 8.3	31.2 ± 11.7	13.108	<0.001*
Time for gaming per day (hours)	3.8 ± 1.6	2.5 ± 1.5	3.329	0.001*
BDI	8.9 ± 5.4	5.4 ± 3.3	3.095	0.003*
BAI	8.2 ± 7.0	9.5 ± 14.9	-0.428	0.670
AUDIT	7.7 ± 4.9	9.4 ± 5.4	-1.299	0.199
WURS[2]	27.8 ± 17.9	25.9 ± 16.0	0.451	0.654
BIS				
Non-planning	22.1 ± 3.3	21.0 ± 3.2	1.309	0.196
Motor	15.0 ± 4.1	14.3 ± 2.5	0.823	0.414
Cognitive	14.7 ± 2.8	13.0 ± 3.1	2.298	0.025*
CPT[3]				
Omission (%)	0.5 ± 1.3			
Commission (%)	16.3 ± 12.8			

Values are expressed as means ± SD. AUDIT, Alcohol Use Disorders Identification Test, BAI, Beck Anxiety Inventory, BDI, Beck Depression Inventory, BIS, Barratt Impulsivity Scale, CPT, Continuous Performance Test, GD, gaming disorder, IAT, Internet Addiction Test, IQ, intelligence quotient, WURS, Wender Utah Rating Scale

[1]IQ was assessed using the Wechsler Adult Intelligence Scale.

[2]Wender Utah Rating Scale was used to assess childhood attention-deficit/hyperactivity disorder (ADHD) symptoms.

[3]For Conners' CPT, only GD group data were presented because of insufficient control group data.

* $p<0.05$.

2. HRV analysis results

Baseline HRV and game-related HRV parameters were not significantly different between groups (Table 2). However, game-related reactivity of lnHF was significantly different between subjects with GD and the control group ($p = 0.014$).

Correlation analysis revealed that the game-related reactivity of lnHF was significantly correlated with the severity of GD assessed by IAT scores (Fig. 1A; r=-0.370, p=0.044). Game-related reactivity of lnHF was also significantly correlated with commission errors in the CPT (Fig. 1B; r=-0.501, p=0.005).

Table 2. Comparison of HRV parameters between subjects with GD and controls

	Baseline HRV				*During game HRV*				*Game-related reactivity*[1]			
	GD (n=33)	*Control (n=29)*	*t Test*	*p-value*	*GD (n=33)*	*Control (n=29)*	*t Test*	*p-value*	*GD (n=33)*	*Control (n=29)*	*t Test*	*p-value*
lnLF	5.67 ± 0.90	5.47 ± 0.89	0.913	0.365	5.49 ± 1.02	5.53 ± 0.88	-0.146	0.885	-0.18 ± 0.85	-0.06 ± 0.87	-1.114	0.270
lnHF	4.63 ± 0.96	4.20 ± 0.90	1.822	0.073	4.15 ± 0.93	4.12 ± 0.87	0.132	0.896	-0.48 ± 0.65	-0.08 ± 0.60	-2.537	0.014*
RMSSD	42.95 ± 26.24	32.64 ± 21.75	1.672	0.100	36.39 ± 21.21	34.51 ± 17.46	0.377	0.707	-6.57 ± 18.48	1.87 ± 14.76	-1.968	0.054
SDNN	39.85 ± 18.72	33.87 ± 16.57	1.322	0.191	36.03 ± 15.55	35.71 ± 14.24	0.083	0.934	-3.82 ± 14.95	1.84 ± 13.95	-1.533	0.130

Values are expressed as means ± SD. HRV, heart rate variability, GD, gaming disorder, lnLF, natural logarithm of low frequency, lnHF, natural logarithm of high frequency, RMSSD, square root of the mean of the sum of the squares of differences between consecutive normal-to-normal intervals, SDNN, standard deviation of the normal-to-normal interval

[1]Computed by subtracting 'baseline HRV' from 'during game HRV'

* $p < 0.05$

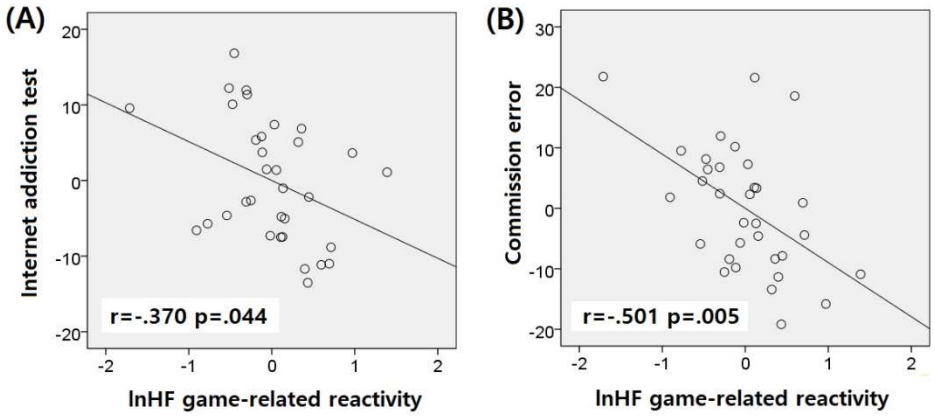


Fig 1. Partial correlation analyses between clinical variables and HRV. Age, intelligence quotient (IQ), and Beck Depression Inventory (BDI) scores were controlled as covariates. Variables were regressed to covariates using linear regression to describe the partial correlation. Computed non-standardized residuals were used to create scatter plots. (A) Game-related reactivity of lnHF was significantly correlated with the severity of GD assessed by IAT scores (r=-0.370, p=0.044). (B) Game-related reactivity of lnHF was significantly correlated with commission errors in the CPT (r=-0.501, p=0.005).

3. VBM analysis results

Compared to the control group, subjects with GD exhibited smaller GMV in the right DLPFC (Fig.2; peak MNI coordinate: 36, 27, 42; cluster size k = 158). This difference remained statistically significant even after adding BDI to the ANCOVA as a covariate (p=0.001). There were no brain areas in which subjects with GD showed significantly larger GMV than that of the controls. On correlation analyses, there were no statistically significant relationships between GMV values and HRV parameters.

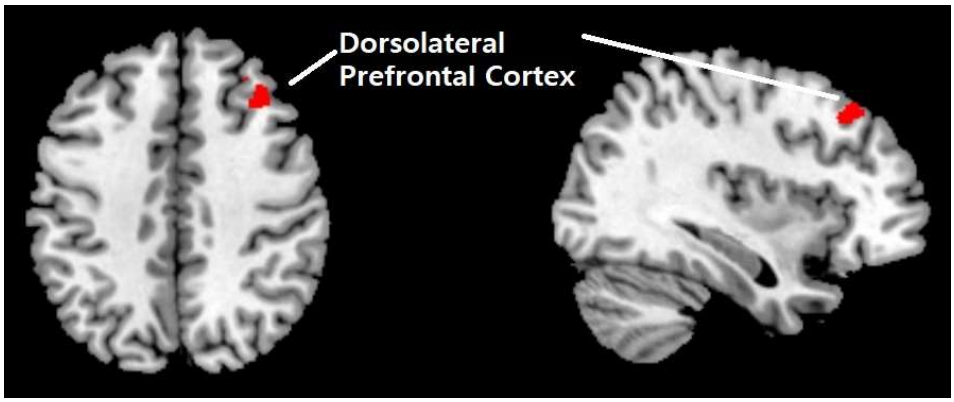
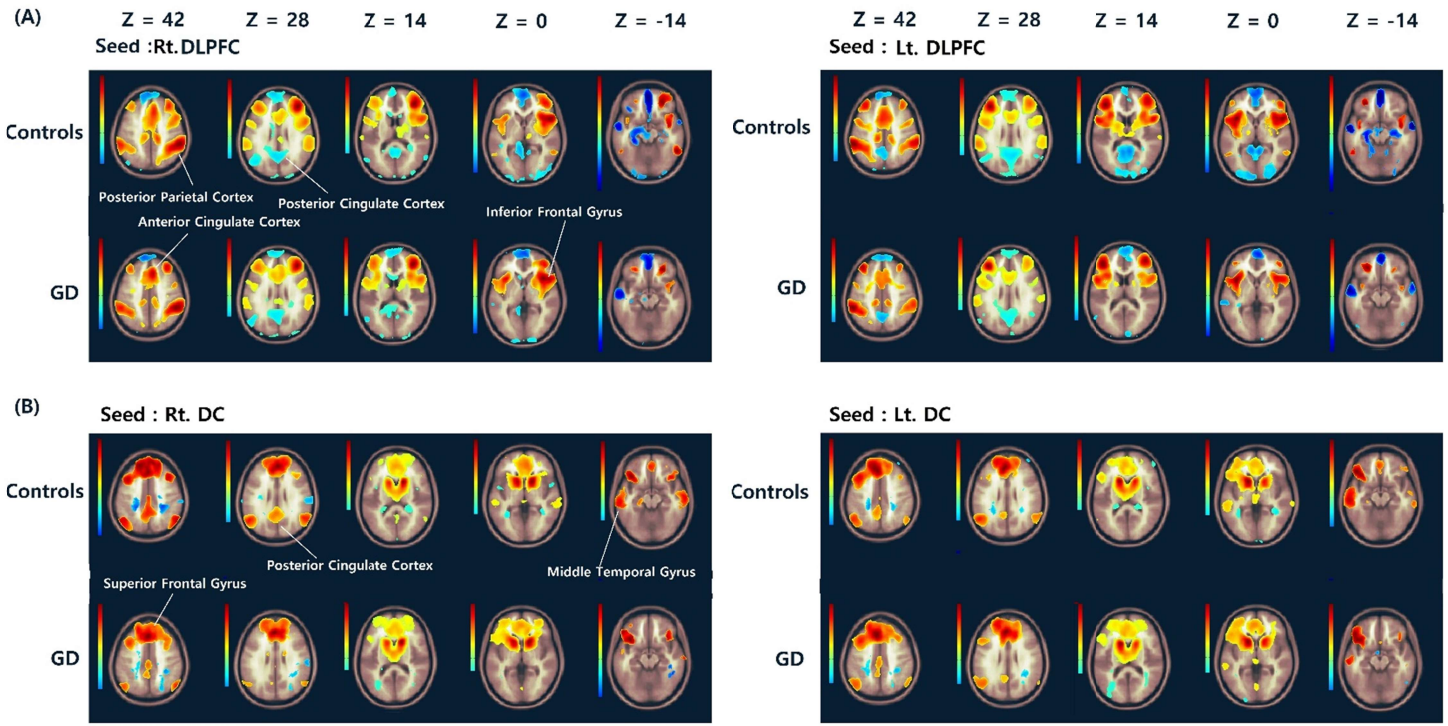


Fig 2. Image of brain regions in which voxels showed significantly smaller GMV in the GD group compared with the control group. Thresholds for cluster forming were set at uncorrected $p < 0.001$, in conjunction with an extent threshold of $k = 100$. Analysis of covariance (ANCOVA), controlling for age, IQ, and total intracranial volume as covariates, tested for group differences in the GMV value for each cluster. Peak Montreal Neurological Institute (MNI) coordinate was $x = 36$, $y = 27$, $z = 42$.

4. FC analysis results

For each group of the current study, the results of the seed-based FC of both sides of the DLPFC, the DC, the DCP, and the DRP were consistent with of previous studies (Fig. 3). Right DLPFC-based FC analysis showed that subjects with GD exhibited weaker FC with the right inferior frontal gyrus (IFG) compared with the control group (Table 3). Left DCP-based FC analysis showed that subjects with GD exhibited stronger FC on both sides of the postcentral gyrus compared with the control group. Left DRP-based FC analysis showed that subjects with GD exhibited stronger FC on the left postcentral gyrus compared with the control group. The statistical significance of FC differences remained after adding BDI to the ANCOVA as a covariate ($p<0.001$). Results of the correlation analysis indicated that game-related HF-HRV reactivity was significantly correlated with the DLPFC-IFG connectivity (Fig. 4A; $r=0.443$, $p=0.018$) and also significantly correlated with FC strength between the left DCP and the right postcentral gyrus (Fig. 4B; $r=-0.397$, $p=0.036$).


(A)
Z = 42
Z = 28
Z = 14
Z = 0
Z = -14
Seed :Rt. DLPFC
Seed : Lt. DLPFC
Controls
GD
Posterior Parietal Cortex
Anterior Cingulate Cortex
Posterior Cingulate Cortex
Inferior Frontal Gyrus
(B)
Seed : Rt. DC
Seed : Lt. DC
Superior Frontal Gyrus
Posterior Cingulate Cortex
Middle Temporal Gyrus

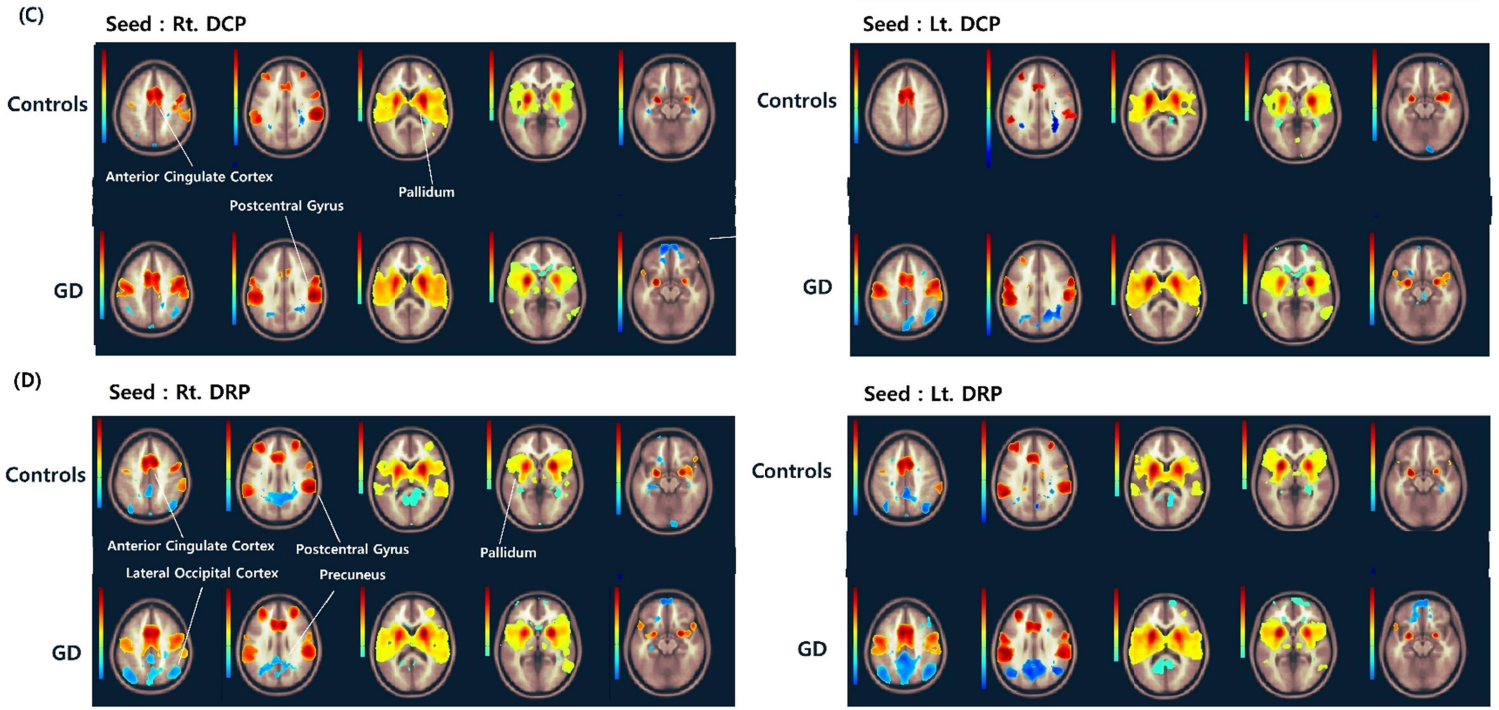


Fig 3. Height threshold of uncorrected $p<0.001$ was applied to depict functional connectivity (FC) results. (A) GD and control groups, the dorsolateral prefrontal cortex (DLPFC) were positively correlated with both sides of the inferior frontal gyrus, both sides of the posterior parietal cortex, and the anterior cingulate cortex. In both groups, the DLPFC was negatively correlated with the medial prefrontal cortex. (B) In both groups, the dorsal caudate (DC) was positively correlated with both sides of the superior frontal gyrus, both sides of the middle temporal gyrus, and the posterior cingulate cortex. (C) In both groups, the dorsal caudal putamen (DCP) was positively correlated with both sides of the postcentral gyrus, both sides of the pallidum, and the anterior cingulate cortex. (D) In both groups, the dorsal rostral putamen (DRP) was positively correlated with both sides of the postcentral gyrus, both sides of the pallidum, and the anterior cingulate cortex. In both groups, the left DRP was negatively correlated with both sides of the lateral occipital cortex and the precuneus.

Table 3. Between-group comparisons of FC (height threshold of uncorrected p-value < 0.001, extent threshold of the FDR-corrected p-value < 0.05).

Region	*Side*	k_E	*Z*	*X*	*y*	*z*
GD < Controls						
Seed: right DLPFC						
Inferior frontal gyrus	Right	248	4.53	54	12	24
GD > Controls						
Seed: left DCP						
Postcentral gyrus	Left	729	4.99	-54	-8	40
Postcentral gyrus	Right	362	4.45	62	-2	38
Seed: left DRP						
Postcentral gyrus	Left	312	4.01	-56	-18	26

DCP; dorsal cortical putamen, DRP; dorsal rostral putamen, DLPFC; dorsolateral prefrontal cortex, FC; functional connectivity, GD; gaming disorder

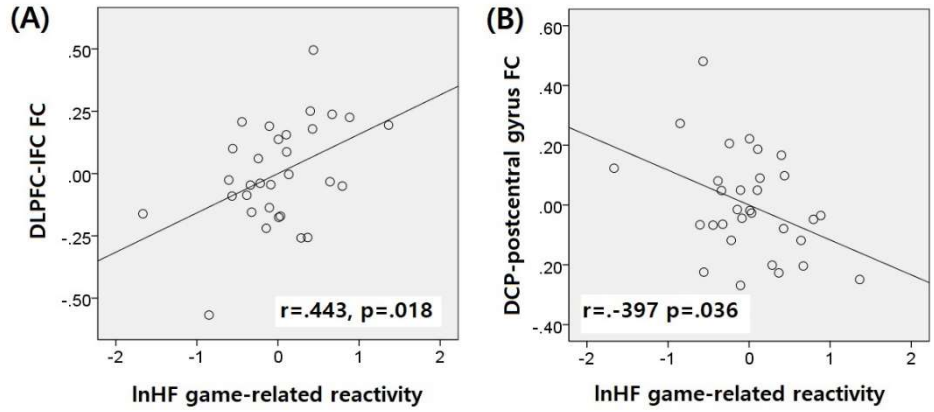


Fig 4. Partial correlation analyses between FC strength and HRV. Age, IQ, and BDI scores were controlled as covariates. Variables were regressed to covariates using linear regression to describe the partial correlation. Computed non-standardized residuals were used to create scatter plots. (A) Game-related reactivity of lnHF was significantly correlated with FC strength between the right dorsolateral prefrontal cortex (DLPFC) and the right inferior frontal gyrus (IFG; r=0.443, p=0.018). (B) Game-related reactivity of lnHF was also significantly correlated with FC strength between the left DCP and the right postcentral gyrus (r=-0.397, p=0.036).

IV. DISCUSSION

The aim of this study was to use bio-signals obtained in real-time to explore the behavioral patterns of online game addicts while playing online games. In the current study, HRV responses were investigated while young males with GD were playing a real-time online game that they were addicted to. Before commencing gaming, there were no differences in HRV parameters between subjects with GD and the control group. However, after starting online gaming, subjects with GD exhibited significantly

decreased lnHF, which was not exhibited by those in the control group. These results are consistent with our hypothesis that young males with GD would exhibit characteristic patterns in HRV measured during real-time gaming. Furthermore, more considerable reduction in lnHF during gaming was significantly correlated with a higher score on the IAT scale. These results are also consistent with our expectation that HRV measurements during gaming would be a significant indicator of addiction to the game. HF-HRV represents parasympathetic tone.[54] According to the neurovisceral model proposed by Thayer et al., HRV mediated by parasympathetic tone can reflect an individual's executive function.[25] Specifically, a large phasic reduction of HF-HRV in response to psychosocial stimuli has been correlated with weakened goal-directed cognitive control over behavior.[29] Although we could not confirm difference in CPT outcomes between the groups in this study, higher commission error rates were significantly correlated with a larger reduction in lnHF during gaming in the GD group. Commission error of CPT represents high impulsivity which is related with diminished executive control.[65] Taken together, the lnHF reduction in the GD group supports that game addicts experience less goal-directed executive control when gaming than those who are not addicted to the game.

We examined the functional brain alterations of subjects with GD to explore the neurobiological background of their addictive game use. The GD group had weaker FC strength between the right DLPFC and the right IFG, compared with the control group. Executive functions involve several areas of the brain, and the prefrontal cortex cooperates with other cortical and subcortical regions to exert executive control.[66] Especially, the DLPFC was found to play a critical role in the neural network sub-serving top-down evaluation of behavioral sequences and associated outcomes.[67] The

relevant region of the right IFG in this study correspond with the right pars opercularis, which is related to the exertion of inhibitory control.[68] Both the Right DLPFC and the right IFG constitute the CEN and are involved in performing goal-directed action by exerting executive control.[69] On the other hand, subjects with GD had stronger FC strength between the left DCP and both sides of the postcentral gyrus, compared with the control group. Subjects with GD also had stronger FC between the left DRP and the left postcentral gyrus, compared with the control group. The postcentral gyrus corresponds to the primary sensorimotor cortex activated in motor performance and motor imagery.[70] Dorsal striatum, such as putamen, has been found to coactivate with sensorimotor cortices, including the primary sensorimotor cortex.[71] Dorsal striatum and sensorimotor cortices are connected to the sensorimotor network and are involved in forming habits via stimulus-response learning.[72] Taken together, our FC analysis results indicate an imbalance between diminished CEN and enhanced sensorimotor network in GD.

The strength of this study is that we collected both neurophysiological data (HRV during gaming) and neuroimaging data and analyzed the correlation between them. In subjects with GD, the lower the DLPFC-IFG connectivity strength, the greater the reduction in HF-HRV response to gaming. On the other hand, the higher connectivity between the left DCP and the right postcentral gyrus, the greater the reduction in HF-HRV in response to gaming. As previously stated, the reduction in HF-HRV during gameplay is an indicator of GD's distinctive gaming behavior, weakly dominated by executive control. Our findings of the significant correlation between HRV and FC suggest that these distinctive game behavior patterns in game addicts are associated with their functional brain alteration. All participants in this study were game

players who were proficient at playing LOL and exposed to the game for a considerable amount of time. However, among the participants, those with a relatively high FC of the CEN associated with goal-directed behavior exerted a control over the game, while those with a relatively high FC of the sensorimotor network associated with stimuli-driven habits did not exercise adequate control over the game. These findings are consistent with our hypothesis that GD may be related to habitual behavioral patterns under diminished goal-directed executive control.

In this study, we also examined structural brain alterations of subjects with GD via VBM analysis. We observed that subjects with GD had smaller GMV in the right DLPFC, compared with the control group. This is consistent with previous studies, reporting small GMVs in prefrontal areas in GD.[73,74] Given the crucial role of the right DLPFC in executive function[66], altered GMV in the right DLPFC may contribute to the pathophysiology of GD by affecting the capacity of executive control. In many cases, excessive use of online games by game addicts begins in early adolescence and continues into early adulthood. This is a crucial time for cortical maturation in the prefrontal areas.[75] The precise inter-relationship between excessive/uncontrolled online game use and altered structural brain development in the prefrontal areas needs to be clarified by further investigation, including well-designed longitudinal studies.

There are several limitations of this study. First, this study did not include the objective assessment of goal-directed executive control by means of neuropsychological tests. Although CPT was performed, the difference between the groups was not confirmed. There are various factors to be considered when assessing the capacity for executive control. Careful consideration should be given when interpreting the current HRV and neuroimaging findings as an indicator for executive

control deficit in GD. Studies employing behavioral measures of executive function would enhance the interpretation of the current findings and enable the relationships between the HRV alterations and the diminished goal-directed executive control to be further established. Second, this study could not completely exclude the possibility that the HRV and neuroimaging findings may be derived from differences in proficiency or degree of exposure to the game. Although this study was conducted with subjects with similar rankings in the game, further studies would benefit from including other indexes that reflect the proficiency and exposure of the game. Third, we hypothesized that neuroimaging findings operate as vulnerabilities in the process of losing control over game use and that HRV measured during gaming reflects the subject's current behavior patterns due to GD. However, the design of this study was cross-sectional; therefore, it was difficult to determine causal relationships between current HRV and neuroimaging findings, and addiction to online games. Studies of changes in HRV and neuroimaging results should be followed up by longitudinal studies of subjects with GD. Fourth, the present study was carried out with only male subjects. Although previous studies report a higher prevalence of GD in males[76], the rate of Internet game use among females has risen over the last decade, and future studies should include both genders. Fifth, the present study includes only one type of online game. Each online game has complex and various game contexts. To be able to generalize the current results to GD, further research should include other types of online games. Which elements of online games are addictive should also be investigated.

V. CONCLUSION

Young males with GD showed significantly decreased HF-HRV while playing online games indicating diminished goal-directed executive control over gaming. They also had FC alterations suggesting an imbalance between diminished CEN and enhanced sensorimotor network. Notably, HF-HRV suppression during gaming correlated with FC alterations. Individuals with GD may have less prefrontal control, particularly when playing online games, and consequently play games in a habitual manner rather than in a goal-directed manner. Our findings also suggest that measurements of HRV during real-time gaming may be used to indicate the status of addiction to online games and diminished goal-directed executive control.

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ABSTRACT(IN KOREAN)

게임 장애에서의 목표지향적 집행 통제의 약화
: 실시간 심박변이도 분석을 통한 접근

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이덕종

목적: 온라인 게임 사용에 대한 통제력 상실은 목표지향적 집행 통제의 약화와 관련이 있다고 알려져 있다. 심장 박동 사이의 시간 간격 차이가 얼마나 변화하는가를 의미하는 심박변이도, 그 중에서도 부교감 신경계에 의해서 조율되는 심박변이도의 경우 집행 통제력을 반영할 수 있다고 제시되어 왔다. 우리는 게임 장애가 있는 있는 사람과 그렇지 않은 사람 사이에는 게임플레이를 하는 동안의 심박변이도 반응에 있어서 차이가 있을 것이며, 이는 게임 장애에서의 목표지향적 집행 통제의 약화를 반영할 것이라고 가정하였다.

방법: 본 연구에서는 게임 장애가 있는 젊은 성인 남성 33명과, 정상 성인 남성 29명이, 그들이 제일 선호하는 온라인 게임을 하는 동안에 심박변이도를 측정하였다. 또한, 뇌의 신경 연결망의 기능적 이상을 측정하기 위하여 특정영역 중심 휴식상태 기능 연결성 분석을 시행하였으며, 뇌의 회백질 부피 특성을 측정하기 위하여 화소기반 형태분석을 시행하였다. 그리고, 심박변이도 분석 결과와 기능 연결성 분석 결과, 화소기반 형태 분석 결과 사이의 상관관계를 분석하였다.

결과: 게임 장애군과 정상군 사이에는 고주파-심박변이도의 게임에 대한 반응성에서 유의미한 차이가 나타났다. 고주파-심박변이도의 게임에 대한 반응성은 게임 장애의 증상 심각도 및 연속 수행 검사에서의 오경보오류의 빈도와 유의미한 상관관계를 보였다. 게임 장애군의 경우, 우측 등쪽외측 전전두피질과 우측 하전두이랑 사이의 기능적 연결성이 저하되어 있었고, 이는 중심 집행 연결망의 약화를 의미하였다. 게임 장애군은 또한, 좌측 등쪽미상피각과 양측 중심뒤이랑 사이, 그리고 좌측 등쪽입쪽피각과 좌측 중심뒤이랑 사이의 기능적 연결성이 증가되어 있었고, 이는 감각 운동 연결망의 강화를 의미하였다. 우측 등쪽외측 전전두피질과 우측 하전두이랑

사이의 기능적 연결성 및 좌측 등쪽미상피각과 우측 중심뒤이랑 사이의 기능적 연결성의 경우는 고주파-심박변이도의 게임에 대한 반응성과 유의미한 상관 관계를 보였다. 게임 장애군은 또한, 정상군과 비교하여 우측 등쪽외측 전전두피질의 회백질 부피가 감소되어 있음이 확인되었다.

고찰: 게임장애가 있는 젊은 성인 남성은 실시간 게임플레이 중에 고주파-심박변이도가 감소되는 특징을 보였다. 이러한 게임장애에서의 특징적인 심박변이도는 게임 장애의 증상 심각도, 충동성 그리고 뇌의 기능적 연결성 이상-약화된 중심 집행 연결망과 강화된 감각 운동 연결망 사이의 불균형-과 유의미한 상관관계가 있었다. 이러한 연구 결과는, 실시간 게임플레이 중의 심박변이도 측정이, 약화된 목표 지향적 집행 통제로 인한 습과적인 게임 사용을 반영할 수 있는 지표가 될 수 있음을 시사한다.

핵심되는 말: 집행 통제, 기능적 연결성, 게임 장애, 심박변이도