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Altered Functional Connectivity of the Nucleus Accumbens and Amygdala in Cyber Addiction: A Resting State Functional Magnetic Resonance Imaging Study

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Objective: Cyber addiction, which is more vulnerable in adolescents, is defined as the excessive use of computers and the Internet that causes serious psychological, social, and physical problems. In this study, we investigated the resting-state functional connectivity (rsFC) in adolescents with cyber addiction.
Methods: We collected and analyzed resting-state functional neuroimaging data of 20 patients with cyber addiction, aged 13−18 years, and 27 healthy controls. Based on previous studies, the seed regions included the dorsolateral prefrontal cortex, medial orbitofrontal cortex, lateral orbitofrontal cortex, dorsal anterior cingulate cortex, insula, hippocampus, amygdala, nucleus accumbens, and the ventral tegmental area. Seed-to-voxel analyses were performed to investigate the differences between patients and healthy controls. A correlation analysis between rsFC and cyber addiction severity was also performed.
Results: Patients with cyber addiction showed the following characteristics: increased positive rsFC between the left insular−right middle temporal gyrus; increased positive rsFC between the right hippocampus−right precentral gyrus; increased positive rsFC between the right amygdala−right precentral gyrus and right parietal operculum cortex; increased negative rsFC between the left nucleus accumbens−right cerebellum crus II and right cerebellum VI.
Conclusion: Adolescents with cyber addiction show altered functional connectivity during the resting state. The findings of this study may help us better understand the neuropathology of cyber addiction in adolescents.

KEY WORDS: Internet addiction disorder; Functional MRI; Adolescent; Reward; Decision making; Emotional regulation.

INTRODUCTION

The development of computers and the Internet has brought many conveniences to our society [1-3]. However, the excessive use of computers and the Internet, defined as cyber addiction, causes serious psychological, physical, and social problems. Moreover, cyber addiction in adolescents is more important considering the clinical and developmental perspectives. Adolescence is a critical period of neurobiological development with a high susceptibility to affective disorders and addiction disorders [4,5].

Although most clinicians agree that cyber addiction is a phenomenon that is rapidly increasing with the development of technology [6], there is no consensus on the terminology, diagnosis, and treatment of cyber addiction. Researchers proposing the independent pathology of cyber addiction have suggested a hypothesis based on neuroimaging studies; they suggest that cyber addiction may have major neurobiological changes in cognitive domains, including reward processing and decision making [7]. In addition to the abnormal functioning of the prefrontal cortex, orbitofrontal cortex (OFC), and reward circuits, which are cognitive domains associated with addictive disorders, the anterior cingulate cortex and insula are involved in the regulation of cognitive domains in cyber addiction by processing emotional stimuli involving emotionally induced contexts. For example, in a task-related functional magnetic resonance imaging (fMRI) study involving game

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pictures, Ko *et al.* [8] reported higher activation of the right OFC, right dorsolateral prefrontal cortex (DLPFC), right caudate nucleus, and bilateral anterior cingulate cortex (ACC) in cyber addiction patients than in controls. In a task-related fMRI study simulating a continuous and extreme win-loss situation, Dong *et al.* [9] reported that patients with cyber addiction showed hyperactivation of the inferior frontal cortex, insula, and anterior cingulate during continuous win attempts. Another proposed neurobiological change for cyber addiction is an alteration of the fronto-limbic circuit, including the DLPFC, ACC, hippocampus, and amygdala, which has been reported in substance use disorders. Cheng and Liu [10] suggested an alteration of amygdala connectivity in patients with cyber addiction using resting-state fMRI (rs-fMRI), considering that the fronto-limbic circuit, a key circuit related to emotion-cognition interaction, is involved in addictive disorders.

The neurobiological foundations of various opinions on cyber addiction are largely based on the results of task-related functional changes in brain regions. Most rs-fMRI studies have investigated temporal homogeneity in the blood-oxygen-level-dependent signal in brain regions [11-14], and studies on resting-state functional connectivity (rsFC) in the key regions of cyber addiction are limited. Furthermore, the results of non-gaming cyber addiction studies are limited because of the small number of patients.

Therefore, the aim of this study was to investigate rsFC in adolescents with cyber addiction and healthy controls (HCs), using rs-fMRI. We focused on cognitive domains related to reward processing, decision making, and emotional regulation, which are known to be key regions of addiction. Consistent with previous evidence, we hypothesized that there are alterations in the functional connectivity between these domains and other brain regions in adolescents with cyber addiction. We also hypothesized that the intensity of the altered rsFC in these adolescents would correlate with the severity of cyber addiction. We aimed to find neuroimaging changes in a group of patients with cyber addiction that were not limited to Internet gaming disorders.

METHODS

Participants and Clinical Measures

Patients with cyber addiction, such as Internet, game, or smartphone addiction, were recruited from the Department of Pediatric Psychiatry in Guro Hospital, Korea University, between December 2016 and October 2019. There is no diagnostic standard for cyber addiction, including the Internet, game, and smartphone addiction. Therefore, all patients were diagnosed with cyber addiction using the modified criteria for Internet gaming disorders in Section III of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, by a child and adolescent psychiatrist [15]. The modified diagnostic criteria for cyber addiction include: (1) preoccupation with the Internet, game, or smartphone; (2) withdrawal symptoms when Internet, game, or smartphone is taken away; (3) the need to spend increasing amounts of time engaged in Internet, game, or smartphone; (4) unsuccessful attempts to control Internet, game, or smartphone participation; (5) loss of interest in previous hobbies and entertainment as a result of, and exception for Internet, game, or smartphone; (6) continued excessive use of the Internet, game, or smartphone despite knowledge of psychosocial problems; (7) deceived family members, therapists, or others regarding the amount of Internet, game, or smartphone; (8) use of Internet, game, or smartphone to escape or relieve a negative mood; and (9) jeopardized or lost a significant relationship, job, or educational or career opportunity because of participation in the Internet, game, smartphone [15]. Five of these nine criteria must be met over 12 months for the diagnosis of cyber addiction. All patients were also assessed using the Internet Addiction Test (IAT) [16], Korean Internet Addiction Scale (K-scale) [17], Korean Internet Game Addiction Scale (G-scale) [18], and Korean Smartphone Addiction Scale (S-scale) [19] to evaluate the severity of cyber addiction. For comparisons between groups, we recruited HCs from middle and high schools in the same local area through advertisements. Since it was confirmed that the recruited HCs did not meet the diagnostic criteria for cyber addiction through an interview with a child and adolescent psychiatrist, the HCs' severity of cyber addiction was not evaluated.

Twenty-nine patients and twenty-eight HCs participated in the study. All participants were assessed for meeting the following enrollment criteria: (1) between the ages of 13 and 18 years, (2) intelligence quotient (IQ) score above 70 on the Korean Wechsler Intelligence Scale, (3) without a family history of psychosis or personality disorder, (4) without a psychiatric or neurological impairment and head trauma resulting in loss of consciousness (for the patients: no major psychiatric disorders), (5) without history of smoking and alcohol intake, and (6) without a history of psychotropic prescription. All participants were assessed using the Korean Wechsler Intelligence Scale and the Korean version of the Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime [20]. Written consent was obtained from all participants and their legal guardians. This study was approved by the Institutional Review Board of the Korea Medical University (2016GR0037).

Functional MRI Image Acquisition

The participants were instructed to close his or her eyes and relax, but not to fall asleep, move, and think about anything during the scan. We used a 3.0-Tesla Siemens MR scanner (Magnetom Skyra; Siemens Healthineers) at the Korea University Guro Hospital to acquire the image data. Structural scans were obtained using a T1-weighted magnetization-prepared rapid gradient-echo sequence (repetition time, 2,300 ms; echo time: 2.32 ms; inversion time, 900 ms; flip angle, 8°; field of view, 230 mm; voxel size: 0.9 mm isotropic; 192 slices; generalized auto-calibrating partially parallel acquisition acceleration factor: factor of two along the phase-encoding direction; received bandwidth per pixel: 200 Hz/pixel; echo spacing: 7.1 ms). The rs-fMRI scans were constituted of 240 contiguous echo-planar imaging volumes of the whole brain (repetition time: 2,000 ms; echo time: 3.0 ms; flip angle: 70°; field of view: 224 mm; voxel size: 2.0 mm isotropic; multi-slice mode; interleaved; simultaneous multi-slice factor: three; phase encoding shift factor: two; received bandwidth per pixel: 1,786 Hz/pixel; echo spacing: 0.67 ms). MR images were manually inspected for the presence of artifacts due to head motion or dental materials.

Brain Image Preprocessing and Analysis

CONN-fMRI Functional Connectivity toolbox v18b [21] (http://www.nitrc.org/projects/conn), MATLAB R2019a (MathWorks), and SPM12 (Wellcome Department of Cognitive Neurology; http://www.fil.ion.ucl.ac.uk/spm/software/spm12) were used to preprocess and analyze the data. All image sequences were pre-processed using the default pipeline of the CONN toolbox. Preprocessing procedures included (1) resampling to 2-mm voxels, (2) unwarping, (3) centering, (4) slice time correction, (5) normalization through the Montreal Neurological Institute (MNI) echo-planar imaging (EPI) template, (6) smoothing through an 8-mm full-width at half-maximum isotropic Gaussian kernel, and (7) outlier detection through artifact detection tools. For denoising to reduce noise effects, signals from the cerebrospinal fluid, white matter, and motion parameters were regressed from the functional data and processed with a band-pass filter of 0.008−0.09 Hz. Further image scrubbing was conducted using the ART method in the CONN toolbox with a frame-wise displacement threshold of 0.5, and linear de-trending was applied.

Based on previous studies, we set the following seed regions of interest (ROIs) that were known to belong to cognitive domain related to reward processing, decision making, and emotional regulation: dorsolateral prefrontal cortex (44, 35, 20; −42, 34, 20) [22]; medial orbitofrontal cortex (6, 37, −12; −6, 37, −12); lateral orbitofrontal cortex (26, 39, −6; −26, 39, −6) [23]; dorsal anterior cingulate cortex (5, 14, −42; −5, 14, 42) [24]; insula (39, −9, −9; −36, −12, 15) [25]; hippocampus (24, −18, −18; −24, −18, −18) [26]; amygdala (23, −5, −12; −23, −5, −12) [27]; nucleus accumbens (9, 9, −8; −9, 9, −8) [25]; and ventral tegmental area (3, −17, −12; −2, −15, −13) [28]. The ROIs were established as a sphere, with a 4-mm radius, which was centered on the MNI coordinates defined by the Harvard-Oxford Subcortical Structural Probability Atlas in Functional Magnetic Resonance Imaging of the Brain Software Library.

Statistical Analysis

A Seed-to-voxel analysis was performed. The mean time series from each seed was used as a predictor in the multiple regression general linear model for each voxel. T-statistic volumes imported into SPM12 for whole-brain investigation of between-group seed-to-voxel maps were created using the toolbox. Analysis of covariance controlling for sex ratio, age, IQ, and the presence of comorbid disorders was conducted between patients and HCs. Cluster-extent based thresholding was used [29]. The results reported here were thresholded with a primary threshold of voxel-wise $p < 0.001$, and the cluster-level extent threshold was set as $p < 0.05$ using family-wise error correction to assess statistical significance. SPSS version 23 (IBM Co.) was used for statistical analyses. Differences in demographic factors between the patients and HCs were assessed using the chi-square test and Mann−Whitney U test. The significance level for the analysis was set at $p \leq 0.05$. In addition, clusters that confirmed altered rsFC were used for ROI-to-ROI analysis in the patients. We generated the mean ROI-to-ROI Z-scores of rsFC for each patient using the CONN toolbox and estimated Spearman's correlation coefficients between the rsFC and the severity of cyber addiction (IAT, K-scale, G-scale, and S-scale) of patients.

RESULTS

Demographics and Clinical Characteristics

Of the 29 patients, seven were excluded because their IQ or MR images were not measured. One patient was excluded from the analysis due to poor image quality due to dental materials. Another patient was excluded because of his IQ. Of the 28 HCs enrolled, one patient was excluded due to poor image quality due to dental materials. As a result, 20 patients with cyber addiction (14 males, 6 females) and 27 HCs (5 males, 22 females) were included in the final analysis. We recruited adolescents between the ages of 13 and 18 years in both the patients and HCs, but there were significant differences in age between the two groups in the final analysis. There were also significant differences in the sex ratio and IQ between the patients and HCs. Considering these differences, we controlled for sex, age, IQ, and the presence of comorbid disorders as covariates in the seed-to-voxel analysis. Detailed results are presented in Table 1. The IAT, K-scale, S-scale, and G-scale scores evaluated in the patient group are also presented in Table 1.

Seed-to-voxel Analysis between Patients and Healthy Controls

Compared with HCs, the positive rsFC between the left insula and a cluster in the right middle temporal gyrus was increased in patients. The patients had an increased pos-

Table 1. Demographic comparison between patients with cyber addiction and healthy controls

Variable	Patients (n = 20)	HCs (n = 27)	p value
Sex (male/female)	14/6	5/22	0.001
Age	14.80 ± 1.64	15.96 ± 1.02	0.004
IQ	103.00 ± 18.05	123.44 ± 12.94	0.000
Severity of cyber addiction			
IAT	41.05 ± 15.01		
K-scale	32.35 ± 5.99		
G-scale	29.50 ± 8.69		
S-scale	33.90 ± 8.28		
Comorbid disorder			
Other specified depressive disorder	10		
Social anxiety disorder	2		
Tic disorder	1		
ADHD	1		

Values are presented as number only or mean ± standard deviation.
HCs, healthy controls; IQ, intelligence quotient; IAT, Internet addiction test; K-scale, Korean Internet Addiction Scale; G-scale, Korean Internet Game Addiction Scale; S-scale, Korean Smartphone Addiction Scale; ADHD, attention deficit hyperactivity disorder.

Table 2. Seed to voxel analysis of resting state functional connectivity between patients with cyber addiction and healthy controls

Seed	Regions	Peak (MNI) x, y, z	Number of voxels	t	p value (FWE-corrected)
Patients > HCs					
Insula l	Middle temporal gyrus r	54, −60, 10	220	4.34	0.011
Hippocampus r	Precentral gyrus r	16, −18, 66	155	4.16	0.039
Amygdala r	Precentral gyrus r	12, −14, 58	2,679	5.86	0.000
	Parietal operculum cortex r	36, −18, 22	264	4.83	0.003
Nucleus accumbens l	Cerebellum curs 2 r	28, −78, −46	639	−6.22	0.000
	Cerebellum 6 r	8, −72, −22	236	−4.71	0.005

HCs, healthy controls; r, right; l, left; MNI, Montreal Neurological Institute; FWE, family-wise error rate.

itive rsFC between the right hippocampus and a cluster in the right precentral gyrus. The positive rsFC between the right amygdala and a cluster belonging to the right precentral gyrus and another cluster belonging to the right parietal operculum cortex were also increased in patients compared to HCs. Furthermore, the patients had an increased negative rsFC between the left nucleus accumbens and a cluster that included the right cerebellum crus II and right cerebellum VI (Table 2, Figs. 1, 2).

Correlation between Intensity of Abnormal rsFC and Clinical Variables

There were no significant associations between the connectivity intensity in regions that showed significant alterations in rsFC and the severity of cyber addiction (IAT, K-scale, G-scale, and S-scale).

DISCUSSION

This study compared rsFC in key regions of cognitive domain-related reward processing, decision making, and emotional regulation between patients with cyber addiction

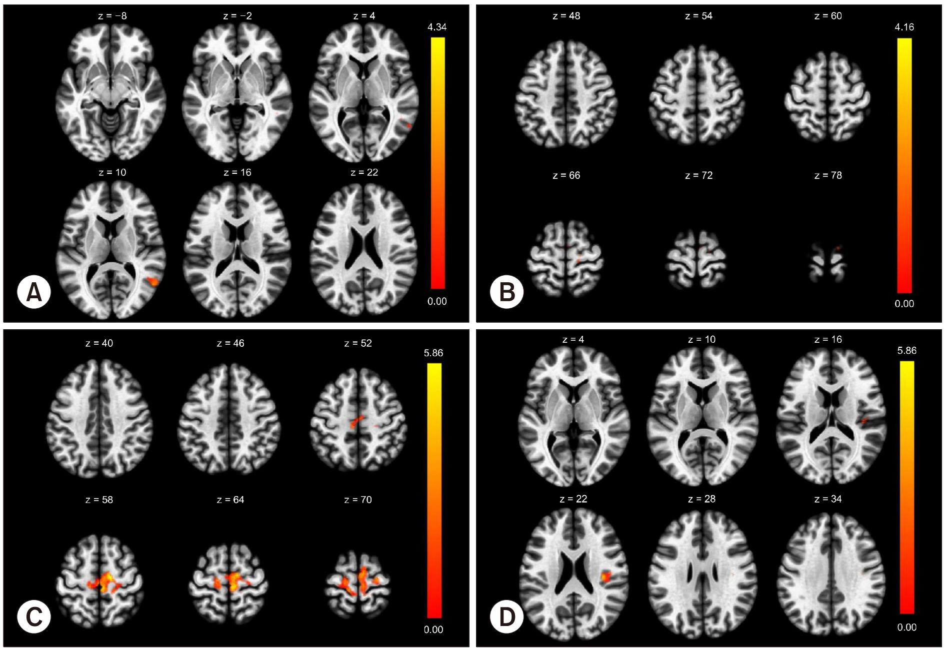

Fig. 1. Regions that showed increased positive functional connectivity in patients with cyber addiction compared to healthy controls. These figures are the results of seed-to-voxel analysis with the left insula (A), right hippocampus (B), and right amygdala (C, D) as seeds. The color scale is the *t* values.

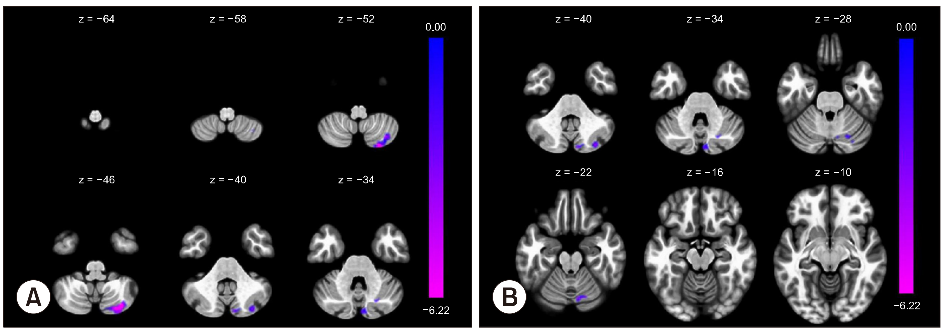

Fig. 2. Regions that showed increased negative functional connectivity in patients with cyber addiction compared to healthy controls. These figures are the results of seed-to-voxel analysis with the left nucleus accumbens (A, B) as a seed. The color scale is the *t* values.

and HCs. The main findings of this study were that patients with cyber addiction showed increased positive rsFC in (1) left insula−right middle temporal gyrus, (2) right hippocampus−right precentral gyrus, (3) right amygdala−right precentral gyrus, and right amygdala−right parietal operculum cortex; they also showed increased negative rsFC in (4) left nucleus accumbens-right cerebellum crus II, and right cerebellum VI compared to HCs.

Among our results, alteration in connectivity between the nucleus accumbens and cerebellum suggests that cyber addiction has biological similarities with other addictive disorders. The nucleus accumbens is known to mediate the rewarding effect of addictive disorders and natural rewards such as food or sexual behavior [30]. Repeated studies [31-33] on functional changes in the nucleus accumbens play a role in the formal inclusion of behavioral addictions, such as gambling disorder, as an addictive disorder. Studies [8,25,34] on functional changes in the changes in the nucleus accumbens have also been reported in cyber addiction. In addition, although the results are limited to internet gaming disorder, regions such as the DLPFC, insula, and precuneus show functional connectivity alteration along with the nucleus accumbens in the rs-fMRI analysis [25]. However, to the best of our knowledge, no studies have reported changes in the functional connectivity of the nucleus accumbens and cerebellum in cyber addiction-related studies, including Internet gaming disorder. Meanwhile, accumulating evidence suggests that the cerebellum is a potentially important region of addiction. In particular, it is very interesting that specific structures of the posterior cerebellar hemispheres, such as cerebellum VI and crus II, which showed significant changes in our study, have been repeatedly reported in addictive disorders [35,36]. Moulton *et al.* [37] suggested that the cerebellum is a mediator between reward, executive control, motivational drive, memory, and stress/interoception, and that there are impaired connections with the brain regions related to these functions in addictive disorders. In particular, Moulton *et al.* [37] mentioned the importance of the cerebellar vermis, VI, VIIb, crus I, and II regions. Therefore, our findings on the alteration in functional connectivity between the nucleus accumbens and the posterior part of the cerebellum in cyber addiction may be meaningful.

The amygdala and hippocampus play important roles in the acquisition, integration, and retrieval of learning addiction-related cues leading to addictive behavior. These structural and functional changes have been found not only in substance use disorders [30] but also in cyber addiction [10,38]. The precentral gyrus, which showed changes in functional connectivity with the hippocampus and amygdala in our findings, is a somatosensory region associated with motor movement [39]. Some studies [40,41] have reported changes in the precentral gyrus in Internet gaming disorder and smartphone addiction. Through a machine learning model based on resting-state neural patterns, Ye *et al.* [42] found a correlation between the severity of Internet gaming disorder and topological features of the right precentral gyrus. In addition, connectivity of the dorsal anterior cingulate cortex and precentral gyrus and the severity of cyber addiction were related. Ye *et al.* [42] suggested that the precentral gyrus and the connection between this region and other brain regions could be potential therapeutic intervention targets for Internet gaming disorder. From this perspective, changes in the connectivity of the right hippocampus, right amygdala, and right precentral gyrus may at least partially explain cyber addiction. In addition, considering that the parietal operculum cortex also belongs to the somatosensory region along with the precentral gyrus, additional studies on the role of the somatosensory region in cyber addiction are needed.

The insula is known to process somatic interoceptive signals and awareness of emotions and self [43]. The insula has also been shown to play an important role in the decision making process, known as the dynamic interaction between the automatic appetitive system, such as cue-related habitual behavior and executive control [44]. Addictive disorder is related to both the modulation of interoceptive signals and to decision making; therefore, the insula has already been identified as a pathological domain in addictive disorders, particularly behavioral addiction, such as gambling disorders [45]. The function of the middle temporal gyrus, where increased positive rsFC with the insula was observed, is unclear. Studies investigating the functional role of the middle temporal gyrus have reported that it may be related to motion observation, deductive reasoning, and default mode networks in addition to language processing [46]. In a study related to cyber addiction, it was reported that the positive rsFC between the posterior cingulate cortex and bilateral middle temporal gyrus was increased in Internet gaming disorder

[47]. In addition, Yuan *et al.* [48] found an increase in the thickness of the middle temporal cortices in adolescents with Internet gaming disorder. Therefore, additional studies on the function of the middle temporal gyrus and repeated results on the change in connectivity between the left insula and right middle temporal gyrus are necessary; however, these may be meaningful.

Our study had several limitations. First, we may have overlooked other possible resting-state networks, because we used seed-based correlations. Second, it was impossible to determine whether the functional changes in the brain were the result or cause of cyber addiction due to the study's cross-sectional design. Third, quantitative factors known to be important in addiction diseases, such as Internet use time and addiction period, were not investigated. In addition, we did not find any association between cyber addiction severity and altered functional connectivity. Fourth, there was insufficient evaluation and consideration of the symptoms of attention deficit hyperactivity disorder (ADHD). ADHD is one of the most common comorbidities of cyber addiction [49], and it is known to be closely associated with cyber addiction symptoms [50,51]. Fifth, there were differences in the demographic variables between the enrolled patient group and HCs. As for age, we recruited participants of the same age group between 13 and 18 years, but a significant difference of approximately 1 year was observed. To correct for this, we adjusted for demographic variables that showed statistically significant differences between the two comparison groups as confounding factors; however, it is difficult to exclude the influence of differences in age, sex ratio, and intelligence on our results.

In conclusion, we found altered functional connectivity between brain regions that may be related to addictive disorders in adolescents with cyber addiction. Despite the limitations of our study, it may provide a view on the neuropathology of cyber addiction by reporting alterations in functional connectivity between brain regions reported in previous studies on cyber addiction or other addictive disorders. Further research is needed to support our findings, including studies that considered the demographic factors of participants, quantitative factors for cyber addiction, and ADHD symptoms.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Manuscript drafting and data analysis: Minsoo Ko. Data analysis: Su-hyuk Chi, Jong-ha Lee. Acquisition of neuroimaging data and quality check of images: Sang-il Suh. Manuscript organization and drafting: Moon-Soo Lee.

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