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FULL-LENGTH REPORT



# Altered connectivity in the right inferior frontal gyrus associated with self-control in adolescents exhibiting problematic smartphone use: A fMRI study

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## ABSTRACT

**Background:** With the continued spread of smartphones and development of the internet, the potential negative effects arising from problematic smartphone use (PSU) in adolescents are being reported on an increasing basis. This study aimed to investigate whether altered resting-state functional connectivity (rsFC) is related to the psychological factors underlying PSU in adolescents. **Methods:** Resting-state functional magnetic resonance images were acquired from 47 adolescents with PSU and 46 healthy control adolescents (the CON group). Seed-based functional connectivity analyses were then performed to compare the two groups with respect to rsFC in the right inferior frontal gyrus, associated with various forms of self-control, and rsFC in the left inferior frontal gyrus. **Results:** Compared to the CON group, the PSU group exhibited a reduction in rsFC between the right inferior frontal gyrus and limbic areas, including the bilateral parahippocampal gyrus, the left amygdala, and the right hippocampus. In addition, a reduction in fronto-limbic rsFC was associated with the severity of PSU, the degree of self-control, and the amount of time the subjects used their smartphones. **Conclusion:** Adolescents with PSU exhibited reduced levels of fronto-limbic functional connectivity; this mechanism is involved in salience attribution and self-control, attributes that are critical to the clinical manifestation of substance and behavioral addictions. Our data provide clear evidence for alterations in brain connectivity with respect to self-control in PSU.

## KEYWORDS

problematic smartphone use, adolescent, functional magnetic resonance imaging, resting-state functional connectivity, inferior frontal gyrus, self-control

## INTRODUCTION

With the widespread adoption of the internet and the development of mobile technology, the popularity of smartphones has rapidly increased over the last year. It is estimated that almost 90% of adults in South Korea owned a smartphone in 2019 (Pew Research Center, 2019). As

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smartphones are becoming an essential part of the lives of people, there are growing concerns related to the negative influence of problematic smartphone use (PSU), especially regarding physical and mental health. Furthermore, it has been reported that PSU has dramatically increased due to the self-isolation and social distancing caused by the rapid worldwide spread of coronavirus disease 2019 (COVID-19) (Caponnetto et al., 2021). In response to the accumulating negative consequences of PSU, particularly during the COVID-19 pandemic, there has been a substantial increase in the volume of research literature pertaining to PSU (Alabdulkader, 2021; Ratan, Zaman, Islam, & Hosseinzadeh, 2021).

Addiction is a state characterized by compulsive and repetitive engagement in rewarding stimuli despite adverse consequences (Philibin & Crabbe, 2015). The term addiction was once limited to the use of drugs or substances; however, the scope of addiction has expanded to gambling, compulsive buying, excessive use of the internet, and other behavioral addictions (Grant, Potenza, Weinstein, & Gorelick, 2010). The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) included “Internet Gaming Disorders (IGD)” as a condition for further study while the 11<sup>th</sup> edition of the International Classification of Diseases (ICD-11) also included “Gaming disorder” as a clinically recognizable and clinically significant syndrome. Based on these guidelines, neuroimaging studies relating to IGD or gaming disorders have thrived over recent years and have provided evidence of neurobiological alterations that are typically related to addictions. Unlike IGD, which has reached a consensus of appropriate terminology and distinct clinical diagnostic classification, there is still significant scientific debate as to whether PSU should be regarded as an addictive behavior (Billieux, Maurage, Lopez-Fernandez, Kuss, & Griffiths, 2015; Chóliz, 2010). Thus, there have been few neuroimaging studies related to PSU (Choi et al., 2021; Chun et al., 2017, 2018; Horvath et al., 2020; Hu, Long, Lyu, Zhou, & Chen, 2017). It has been mentioned in the previous studies that “compulsive use (Lin et al., 2017)”, “excessive use (Chun et al., 2017, 2018; Ha, Chin, Park, Ryu, & Yu, 2008)”, “addictive use (Chóliz, 2010, 2012; De-Sola Gutierrez, Rodriguez de Fonseca, & Rubio, 2016; Kim, Lee, Lee, Nam, & Chung, 2014; Kim et al., 2016; Mahapatra, 2019; van Deursen, Bolle, Hegner, & Kommers, 2015)”, or “habitual use (van Deursen et al., 2015; Wilmer, Sherman, & Chein, 2017)” of smartphones is a problematic behavior with negative consequences for individuals. Moreover, it is a fact that social problems caused by PSU have increased rapidly, especially among the adolescents. Therefore, there is a clear need to develop a universally accepted diagnostic instrument for PSU and perform neuroimaging studies to identify circuit-based evidence underlying PSU.

According to a pathways model of problematic mobile phone use, personality traits related to impulsivity such as lack of planning or low self-control lead to uncontrolled mobile phone use (Billieux, Maurage et al., 2015). A previous study demonstrated that the habitual use of smartphones is a crucial contributor to addictive smartphone behavior, and

that the loss of self-control appears to lead to a higher risk of addictive smartphone behavior (van Deursen et al., 2015). Self-control is described as the ability to ignore one’s inner responses, to interfere with undesired behavioral tendencies, and to refrain from acting upon such tendencies (Tangney, Baumeister, & Boone, 2004). Indeed, individuals with high levels of self-control are likely to achieve better outcomes in a variety of aspects, including a higher grade point average, lower incidence of binge eating and alcohol abuse, and a better degree of psychological adjustment (Tangney et al., 2004). The previous survey study reported that female individuals with high levels of impulsivity and low levels of self-control are prone to engage in smartphone approach behavior (Kim et al., 2016). Factor analysis investigating the psychological factors related to media use revealed that self-control had a significant influence on internet use, video games, and mobile phones (Khang, Kim, & Kim, 2013). The critical role of self-control has been investigated not only in the survey studies but also in neuroscience studies related to substance and behavioral addiction (Chun, Choi, Cho, Lee, & Kim, 2015; Ko, Liu, Yen, Yen, et al., 2013; Montag et al., 2018; Park et al., 2017; Wang et al., 2009). These findings were consistent with the previous research’s finding that the chronically addictive state is associated with profound disruptions in the brain among the interacting motivational drive and self-control circuits (Nora D. Volkow & Baler, 2013). Collectively, existing studies clearly demonstrate that a low level of self-control is one of the most critical factors underlying addiction-like behaviors including PSU.

The inferior frontal gyrus (IFG) has been widely investigated due to its multifunctional role in human behavior. Moreover, the functional connectivity of the IFG with other regions of the brain is known to be asymmetrical when compared between the right and left hemispheres (Du et al., 2020). Studies involving neuroimaging and lesion-mapping in humans have suggested that the right-lateralized IFG is a region that is commonly activated when subjects are engaged in various forms of self-control (Aron, Robbins, & Poldrack, 2004; Cohen & Lieberman, 2010; Garavan, Ross, Murphy, Roche, & Stein, 2002; McClure, Laibson, Loewenstein, & Cohen, 2004; Rubia, Smith, Brammer, & Taylor, 2003). Lesion-mapping studies in humans have shown that damage to the right IFG (R.IFG) were correlated with reduced levels of response inhibition, which is one of aspects of self-control (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003). A transcranial magnetic stimulation (TMS) study further showed that TMS-induced temporal disruption in the R.IFG led to reduced levels of inhibition in the stop-signal task (Chambers et al., 2006); this could be inferred as a reduced level of self-control performance.

Resting-state functional magnetic resonance imaging (rs-fMRI) measures the spontaneous blood oxygen-level dependent (BOLD) signal changes within different brain regions in the absence of task stimuli (Biswal, Yetkin, Haughton, & Hyde, 1995). Furthermore, rs-fMRI allows us to investigate functional brain connectivity by reflecting intrinsic interactions between functionally connected brain regions of interest (ROIs) (Friston, Frith, Liddle, & Frackowiak, 1993).

Resting-state functional connectivity (rsFC) has been used to study a range of addictions, including substance addiction and behavioral addiction, including internet addiction and IGD. Considering there have yet been rsFC studies concerning self-control in PSU, the investigation of rsFC in adolescents with PSU will enhance our knowledge of brain function during the early stages of PSU and will allow us to take the first steps forward in preventing developmental alterations that may continue into adulthood.

A recent study reported a strong relationship between PSU and the loss of self-control (Khang et al., 2013; Kim et al., 2016; van Deursen et al., 2015). Although these findings were mostly derived from surveys, the specific neural correlates underlying self-control and PSU have not been investigated yet. Therefore, investigating right-lateralized IFG connectivity underlying self-control ability will help us to understand the neurological aspects of smartphone use. In this study, rs-fMRI was used to investigate the neural correlates underlying self-control in adolescents with PSU. Based on previous studies, which supported the role of the R.IFG in self-control (Aron et al., 2004; Cohen & Lieberman, 2010; Miller & Cohen, 2001), we selected the R.IFG as a seed ROI. In addition, we analyzed the rsFC in the L.IFG to confirm the role of the R.IFG in self-control. As such, we hypothesized that adolescents demonstrating PSU would show a reduced rsFC within the R.IFG. In addition, we hypothesized that altered functional connectivity within the R.IFG would be associated with the severity of PSU symptoms and reduced levels of self-control.

## METHODS

### Participants

A total of 632 adolescents (13–18 years-of-age) participated in this survey after being recruited online. Of these, 51 adolescents were classified as PSU according to the Smartphone Addiction Proneness Scale (SAPS; for further details, see ‘Group Categorization’) for Youths (Kim et al., 2014). The 51 adolescents with PSU were subsequently recruited for fMRI experiments. Fifty-one age-matched adolescents were also recruited as healthy controls (the CON group).

All participants underwent a structured interview from the Korean Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS-PL) to screen out adolescents with major medical disorders, neurological, or psychiatric disorders. All participants were right-handed, as determined by the Edinburgh Inventory (Oldfield, 1971). Four participants in the PSU group, and one participant in the CON group, were excluded due to their IQs being below 80, as assessed using subtests of the Korean Wechsler Intelligence Scale for Children, 4<sup>th</sup> edition (K-WISC-IV) (O’Donnell, 2009). Prior to scanning, all participants were assessed for MRI safety. Four participants in the PSU group were excluded from the final analysis due to the poor quality of the acquired imaging data. Therefore, our final analysis included 47 adolescents

with PSU (25 males and 22 females) and 46 CON adolescents (26 males and 20 females).

### Group categorizations

PSU was evaluated with the Korean Smartphone Addiction Proneness Scale (SAPS) for Youths (Kim et al., 2014). The SAPS consisted of 15 items scored on a four-point Likert scale ranging from 1 (not at all) to 4 (always). The reliability test of the scale yielded a Cronbach’s alpha of 0.880. This scale consists of four factors: the disturbance of adaptive functions, virtual life orientation, withdrawal, and tolerance. The participants were diagnosed with PSU in the following cases: if the total score exceeded 42 or if the subscale scores for the disturbance of adaptive function, withdrawal, and tolerance exceeded 14, 12, and 13, respectively.

In addition, we also used the Smartphone Addiction Scale (SAS) (Kwon et al., 2013) in order to enhance the reliability and validity of this study. The SAS was developed by Kwon et al. (2013) and is based on the Internet Addiction Scale and smartphone characteristics; Cronbach’s alpha for the SAS was 0.967.

### Clinical assessments

Self-control was assessed by the Brief Self-Control Scale (BSCS) (Tangney et al., 2004). The concept of self-control measured by this scale refers to the ability to override or change an individual’s inner responses while avoiding undesirable behaviors such as impulses (Tangney et al., 2004). This scale consists of 13 items that measure general self-control. Participants rate each item using a 5-point Likert scale ranging from 1 (not at all like me) to 5 (very much like me). Higher scores on the BSCS indicate higher levels of self-control. Cronbach’s alpha for this scale was 0.85.

The intellectual ability of each participant was assessed using the Vocabulary and Block Design subtests of the K-WISC-IV (O’Donnell, 2009). We compared the subtest scores on the K-WISC-IV between PSU and CON groups in order to control the potential effect of intelligence.

### Acquisition of imaging data

Functional and structural MRI data were acquired with a 3-Tesla MAGNETOM Verio system (Siemens, Erlangen, Germany) equipped with a 16-channel head coil. The participant’s head was cushioned with earmuffs to minimize head motion. During scanning, participants were instructed to keep their head still and their eyes fixated on a crosshair. Functional images were obtained with a T2\* weighted gradient echo-planar imaging sequence with the following parameters: repetition time (TR) = 2,000 ms; echo time (TE) = 30 ms; voxel size = 2.0 × 2.0 × 4.0 mm; matrix size = 96 × 96; and slice number = 28. Structural images were obtained with a resolution of 1.0 × 1.0 × 1.0 mm and were acquired with a 3D T1-weighted gradient echo sequence (TR = 2,300 ms, TE = 2.22 ms, and image matrix = 256 × 256, 176 slices).



## Functional connectivity analysis

Resting-state fMRI data were preprocessed and analyzed with the CONN toolbox v.18b ([www.nitrc.org/projects/conn](http://www.nitrc.org/projects/conn)) implemented on MATLAB (Mathworks, Inc., MA, USA). Functional images were corrected for slice-timing and head motion and were normalized to the Montreal Neurological Institute (MNI) common Atlas space. Subsequently, the anatomical data were segmented to produce gray matter, white matter, and cerebrospinal fluid maps for each participant that were then spatially smoothed with a Gaussian kernel of 6 mm (full width at half maximum). The time course for each participant's standard motion parameters, along with the time course for artifact detection tool-based "scrubbed" signal artifacts, were included as first-level covariates for rs-fMRI data. Nuisance regression and band-pass filtering (0.008–0.09 Hz) were applied to remove unwanted effects from the BOLD signal, including motion, physiological, and other artifactual effects.

Functional connectivity analyses were performed to investigate differences between the two groups; these analyses were performed using a seed-based ROI-to-ROI approach implemented in the CONN toolbox v.18b ([www.nitrc.org/projects/conn](http://www.nitrc.org/projects/conn)). Whole-brain functional connectivity analysis was performed in the left and right IFG across all other cortical and subcortical areas using the Harvard-Oxford Atlas in FSL (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012), defined as *a priori* in the CONN toolbox. Correlation coefficients for the time series between the left and the right IFG, and the entire whole brain region, were calculated and then transformed into z-values using Fisher's r-to-z transformation. To control for potential confounding factors, we used IQ, age, and sex, as covariates of no interest for each of these analyses. We compared the resulting correlation coefficients for each participant using a two-sided independent samples *t*-test to evaluate between-group differences in ROI-to-ROI connectivity. The significance level was determined at  $P < 0.05$ , and false discovery rate (FDR) correction was applied to correct for multiple tests, as required.

## Statistical analyses

All statistical analyses involving demographic variables, clinical variables, and mean rsFC, were conducted in IBM SPSS Statistics for Windows, version 20 (IBM Corp., Armonk, NY). We conducted a two-sample *t*-test for group comparisons for the demographic and clinical variables. In addition, we performed one-tailed Pearson's correlation analysis, merging the PSU and CON groups to investigate the relationships between relative rsFC strength and clinical measures, including SAPS and BSCS scores.

Previous studies demonstrated that alterations in the function of the R.IFG were related to low levels of self-control (Aron et al., 2003, 2004; Cohen & Lieberman, 2010; Liakakis, Nickel, & Seitz, 2011) and that a low level of self-control was a key trait underlying PSU. On this basis, we conducted mediation analysis to investigate the specific relationships between three variables: rsFC within the R.IFG, self-control, and the severity of PSU. Mediation analysis was performed in SPSS using the PROCESS module (Hayes, 2013). The strength of rsFC within the R.IFG was used as the causal variable, with SAPS scores as the outcome variable, and BSCS scores as the mediator variable.

## Ethics

All participants, and their parents, provided written informed consent in accordance with the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board of Seoul St. Mary's Hospital. All experiments were performed in accordance with the guidelines and regulations.

## RESULTS

### Demographics

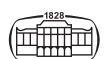
Table 1 describes the demographic and clinical characteristics of the participants. There were no significant differences

Table 1. Demographic characteristics of the PSU and CON groups

	PSU ( $n = 47$ )		CON ( $n = 46$ )		<i>t</i> -score
	Mean	SD	Mean	SD	
Age	15.68	1.48	14.98	1.61	2.19
K-WISC	104.38	13.15	105.37	11.73	−0.381
Gender					
Male	53.2% ( $n = 25$ )		56.5% ( $n = 26$ )		$\chi^2 = 0.10$
Female	46.8% ( $n = 22$ )		43.5% ( $n = 20$ )		
Time spent on smartphone use per week (h)	29.35	14.51	17.51	11.80	4.29**
SAPS	39.40	7.82	21.96	3.54	13.80**
Disturbance of adaptive function	13.98	2.93	7.50	1.38	13.59**
Withdrawal	9.64	3.21	5.52	1.68	7.72**
Tolerance	11.85	2.62	6.59	1.68	11.50*
SAS	114.43	33.99	60.13	16.14	9.81**
BSCS	35.81	6.09	44.70	5.43	−7.42**

\* $P < 0.01$ , \*\* $P < 0.001$ .

PSU = problematic smartphone use; CON = control; K-WISC = Korean Wechsler Intelligence Scale for Children; SAPS = Smartphone Addiction Proneness Scale; BSCS = Brief Self-Control Scale. The three subscales used for SAPS cut-off are specified.



between the two groups in terms of age, sex, or K-WISC scores. The participants with PSU spent significantly more time on their smartphones per week [ $t(91) = 4.29$ ,  $P < 0.001$ ] and had significantly higher scores on the SAPS [ $t(91) = 13.80$ ,  $P < 0.001$ ] and the SAS [ $t(91) = 9.81$ ,  $P < 0.001$ ] when compared to the CON group. In addition, the PSU group had significantly lower scores on the BSCS [ $t(91) = -7.42$ ,  $P < 0.001$ ] than the CON group.

## MRI results

Figure 1 and Table 2 demonstrate group differences in ROI-to-ROI functional connectivity. With regards to functional connectivity, the PSU group showed significantly reduced rsFC between the R.IFG and the left parahippocampal gyrus (L.PHG) [ $t(88) = 4.39$ , corrected  $P < 0.05$ ; Fig. 1A], and between the R.IFG and the right parahippocampal gyrus (R.PHG) [ $t(88) = 3.26$ , corrected  $P < 0.05$ ; Fig. 1B]. In

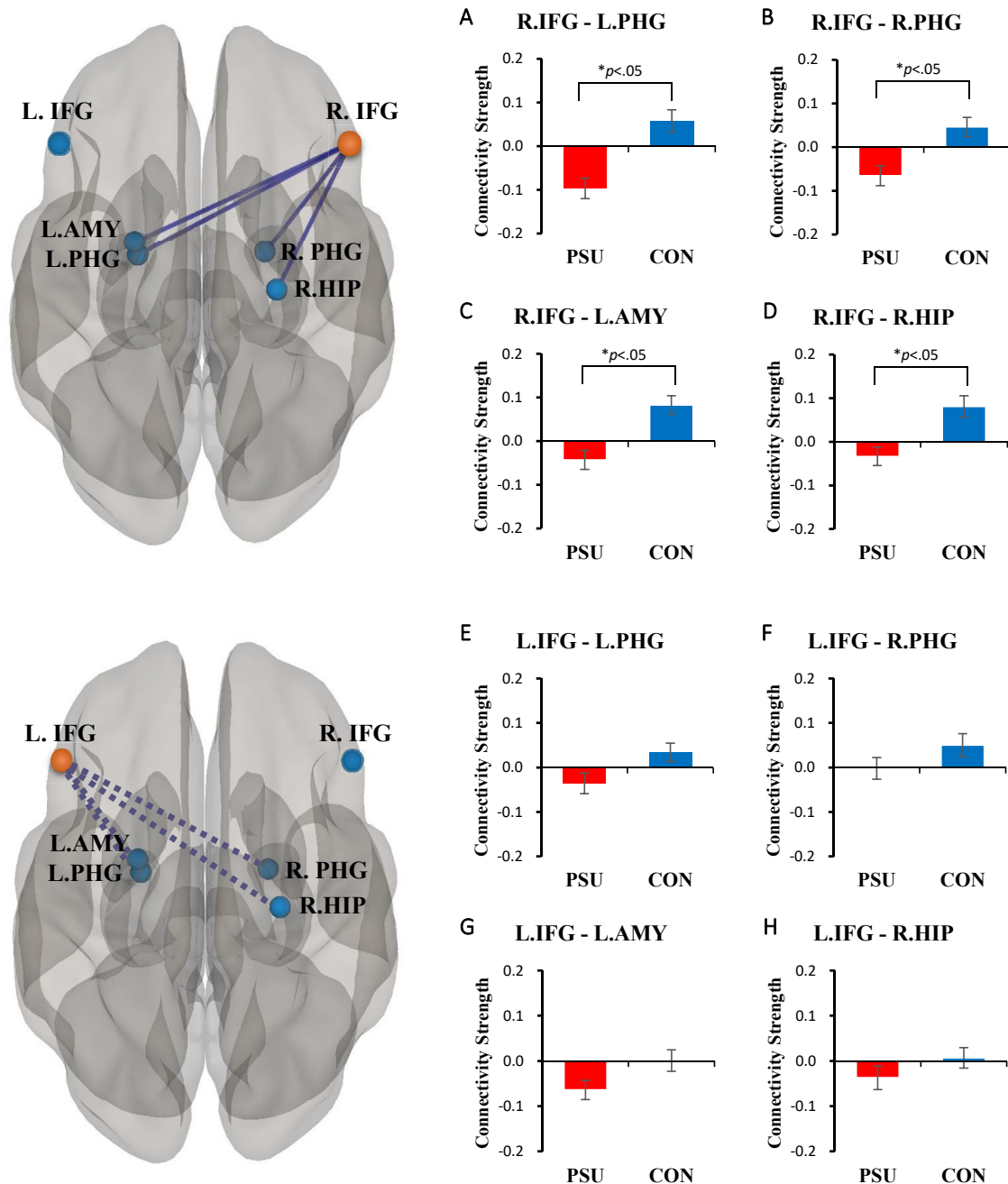


Fig. 1. Group Differences in ROI-to-ROI functional connectivity. Note: Orange circles characterize the seed ROIs. The bar graphs illustrate the mean resting-state functional connectivity strength between (A) the right IFG and the left PHG, (B) the right IFG and the right PHG, (C) the right IFG and the left amygdala, (D) the right IFG and the right hippocampus (E) the left IFG and the left PHG, (F) the left IFG and the right PHG, (G) the left IFG and the left amygdala, and (H) the left IFG and the right hippocampus. PSU = problematic smartphone use; CON = control; IFG = inferior frontal gyrus; PHG = parahippocampal gyrus; AMY = amygdala

Table 2. Group Differences in ROI-to-ROI functional connectivity (PSU<CON)

Seed	Locus Region	Peak <i>T</i>	<i>p</i>	
			Uncorrected	FDR corrected
R. IFG	L. PHG	4.39	0.0000	0.0033
	L. Amygdala	3.89	0.0002	0.0100
	R. PHG	3.26	0.0016	0.0471
	R. Hippocampus	3.22	0.0018	0.0471
L. IFG	None	-	-	-

PSU = problematic smartphone use; CON = control; FDR = false discovery rate; IFG = inferior frontal gyrus; PHG = parahippocampal gyrus.

addition, there was weaker levels of connectivity between the R.IFG and the left amygdala (L.amygdala) [ $t(88) = 3.89$ , corrected  $P < 0.05$ ; Fig. 1C] and between the R.IFG and the right hippocampus (R.hippocampus) [ $t(88) = 3.22$ , corrected  $P < 0.05$ ; Fig. 1D] in the PSU group than in the CON group. Although we observed a reduced rsFC in the R.IFG seed, there was no significant group difference with regards to the rsFC in the L.IFG seed (Fig. 1E-H).

**The relationship between rsFC and the characteristics of PSU**

ROI-to-ROI connectivity analysis was performed for both sides of the IFG; however, there was no significant difference with regards to the rsFC in the L.IFG when compared between the two groups. Therefore, Pearson’s correlation analysis was performed only between the rsFC of the R.IFG seed, BSCS, and smartphone-related characteristics (Table 3). The SAPS scores were negatively correlated with BSCS scores when considered across all participants. Higher SAPS scores were associated with lower rsFC values between the R.IFG seed and the limbic regions (i.e., the bilateral PHG, the L.amygdala, and the R.hippocampus). The rsFC between the R.IFG and the R. hippocampus was negatively correlated with the amount of time spent using

smartphones. Correlations between the BSCS scores and the rsFC of the R.IFG seed are shown in Fig. 2. We identified positive correlations between BSCS scores and R.IFG/L.PHG connectivity (Fig. 2A), R.IFG/R.PHG connectivity (Fig. 2B), and R.IFG/L. amygdala connectivity (Fig. 2C). As BSCS increased, the rsFC of the R.IFG/R.hippocampus also tended to increase, although this was not statistically significant (Fig. 2D).

We also conducted correlation analysis between SAPS, BSCS, and rsFC strength, in each group separately; however, these analyses did not identify any significant differences between the two groups.

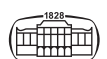
We also used mediation analysis to investigate whether the lower levels of self-control associated with the rsFC strength of the R.IFG seed were linked to the severity of PSU (Fig. 3). Four rsFCs of the R.IFG seed were shown to exhibit significant differences between the two groups: R.IFG/L.PHG, R.IFG/R.PHG, R.IFG/L.amygdala, and R.IFG/R.hippocampus. Consequently, we conducted mediation analysis to investigate each of these rsFCs. First, when using the rsFC of the R.IFG/L.PHG as a causal variable (Fig. 3A), mediation analysis revealed that the rsFC of the R.IFG/L.PHG had an indirect influence on the severity of PSU via self-control (Fig. 3A), with a standardized indirect effect of  $-0.13$ , as revealed by a 95% bootstrap confidence interval (CI) that was below zero (CI:  $-0.25$  to  $-0.03$ ). Second, when using the rsFC of the R.IFG/R.PHG as a causal variable (Fig. 3B), mediation analysis showed that the rsFC of the R.IFG/R.PHG also had an indirect effect on the severity of PSU via self-control (95% CI:  $-0.29$  to  $-0.06$ ). Third, as shown in Fig. 3C, when the rsFC of the R.IFG/L.amygdala was used as a causal variable, mediation analysis revealed that the rsFC of the R.IFG/L.amygdala had an indirect influence on the severity of PSU via self-control (95% CI:  $-0.28$  to  $-0.04$ ). Finally, when the rsFC of the R.IFG/R.hippocampus was used as a causal variable (Fig. 3D), the R.IFG/R.hippocampus did not predict self-control to be a mediator. In this case, the mediation model could not be tested according to Baron and Kenny’s method (Hayes, 2013) since the causal variable could not predict the mediator.

Table 3. Pearson's correlations between the rsFC of the right IFG and variables related to PSU and personality, while merging data from the PSU and CON groups

	rsFC				BSCS
	R. IFG-L.PHG	R. IFG-R.PHG	R. IFG-L.AMY	R. IFG-R.HIP	
SAPS	-0.330**	-0.358**	-0.293**	-0.339**	-0.671**
Disturbance of adaptive function	-0.375**	-0.287**	-0.325**	-0.258*	-0.659**
Withdrawal	-0.205*	-0.324**	-0.190	-0.301**	-0.488**
Tolerance	-0.312**	-0.333**	-0.305**	-0.349**	-0.662**
SAS	-0.229*	-0.265*	-0.183	-0.343**	-0.0597**
Time for smartphone use per week (h)	-0.162	-0.189	-0.056	-0.285**	-0.407**
BSCS	0.213*	0.279**	0.251*	0.140	1

\* $P < 0.01$ , \*\* $P < 0.001$ .

SAPS = Smartphone Addiction Proneness Scale; SAS = Smartphone Addiction Scale; BSCS = Brief Self-Control Scale. The three subscales used for SAPS cut-off are specified.



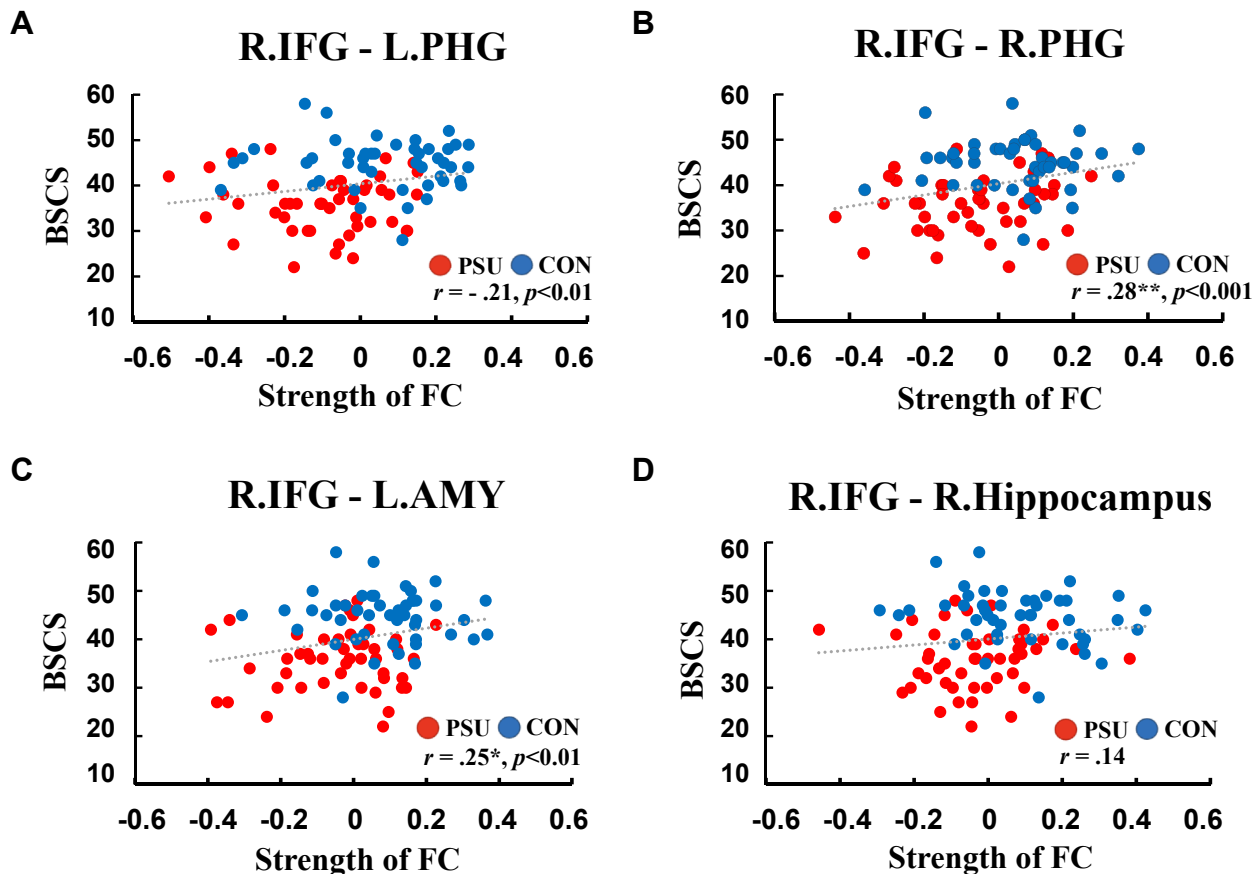


Fig. 2. Correlations between fronto-limbic rsFC strength and BSCS score. Positive associations between (A) R.IFG/L.PHG rsFC and BSCS ( $r = 0.21$ ,  $P < 0.01$ ), (B) R.IFG/R.PHG rsFC and BSCS ( $r = 0.28$ ,  $P < 0.001$ ), (C) R.IFG/L.AMY rsFC and BSCS ( $r = 0.25$ ,  $P < 0.01$ ), and between (D) R.IFG/R.Hippocampus and BSCS ( $r = 0.14$ ). PSU = problematic smartphone use; CON = control; IFG = inferior frontal gyrus; PHG = parahippocampal gyrus; AMY = amygdala

## DISCUSSION

To our knowledge, this is the first study to demonstrate alterations in the rsFC of the right IFG in adolescents with PSU. In addition, this study showed that alterations in rsFC in the R.IFG were correlated with self-control ability and the severity of PSU. Furthermore, we found a mediating effect of self-control in the relationship between rsFC within the R.IFG and the severity of PSU.

Our findings demonstrated that adolescents with PSU showed significantly lower levels of self-control and reduced fronto-limbic rsFC than the CON group. The self-control ability of adolescents tends to be lower than that of adults; this phenomenon is known to be related to the development of the brain during adolescence. The prefrontal cortex is associated with decisions to delayed rewards, engaging in the quantitative analysis of economic options and the assessment of future opportunities for reward (Dixon & Christoff, 2012), and undergoes gradual developmental changes during adolescence and young adulthood (Kelley, Schochet, & Landry, 2004). Limbic and paralimbic cortical structures, known to be rich in dopaminergic innervation, are associated with decisions to approach rewards that are immediately

available (McClure et al., 2004) and appear to mature earlier than the prefrontal area (Casey, Jones, & Hare, 2008). This discrepancy in development rates between the prefrontal and limbic regions is deemed to increase the chances of risk-taking behaviors (Balogh, Mayes, & Potenza, 2013) and promotes poor decision-making (Somerville, Jones, & Casey, 2010). Adolescents tend to be more impulsive and lack self-control; in addition to this, our group of PSU adolescents exhibited a reduced fronto-limbic rsFC when compared to the control group. This suggests that the ability to regulate smartphone use in adolescents with PSU is prone to be significantly lower than the ability of adults with PSU. Moreover, the fact that smartphones are portable devices makes adolescents more vulnerable to unrestrained smartphone use.

In this study, PSU adolescents exhibited reduced levels of functional connectivity between the R.IFG and the amygdala. The amygdala has been found to play an essential role in the salience response (Santos, Mier, Kirsch, & Meyer-Lindenberg, 2011) and in guiding goal-directed behavior (Winstanley, Theobald, Cardinal, & Robbins, 2004); on that account, its alterations have been repeatedly reported to be associated with substance and behavioral addiction (Chun

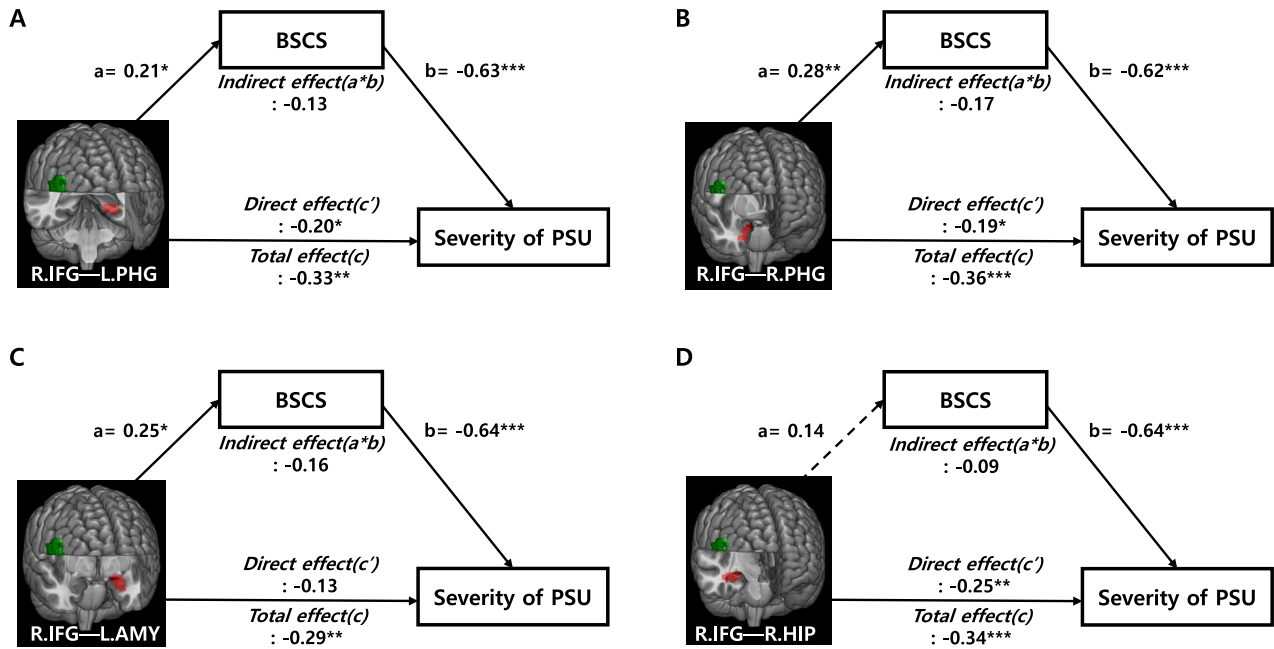


Fig. 3. Mediation analysis between rsFC with right IFG, self-control, and the severity of PSU. Across groups, BSCS scores partially mediated the relationship between (A) rsFC of the right IFG/left PHG and the severity of PSU, (B) rsFC of the right IFG/right PHG and the severity of PSU, and (C) rsFC of the right IFG/left PHG and the severity of PSU. (D) No mediation effect of self-control was found in the relationship between the rsFC of the right IFG/right HIP. Path 'a' is from the rsFC with right IFG (causal variable) to the degree of self-control via BSCS scores (mediator). Path 'b' is from self-control (mediator) to the severity of PSU (outcome variable). The direct effect  $c'$  was calculated by controlling for the mediator. rsFC = resting-state functional connectivity; PSU = problematic smartphone addiction; BSCS = brief self-control scale; IFG = inferior frontal gyrus; PHG = parahippocampal gyrus; AMY = amygdala; HIP = hippocampus.

et al., 2020; Wang, Shen, et al., 2017; Zhang & Volkow, 2019). Accordingly, the reduced R.IFG/amygdala rsFC exhibited by the PSU group could represent alterations in salience and executive networks and could thus lead to the problematic overuse of smartphones.

Moreover, amygdala/PFC connectivity is known to contribute to emotional regulation which plays a key role in negative reinforcement and the motivational effects (Koob & Moal, 2008). Previous surveys have reported higher levels of depression and anxiety in individuals with PSU (Demirci, Akgönül, & Akpınar, 2015; Matar Boumosleh & Jaalouk, 2017). As such, adolescents with PSU, who experience difficulty in coping with their mood, might use their smartphones excessively to escape from a negative emotional state (Elhai & Contractor, 2018). Although the majority of adolescents go online to avoid their psychological problems, it is likely that they can experience adverse outcomes that could exert a negative influence upon their life (Mahapatra, 2019; Young, 1999). Consequently, it is possible that these factors (a reduced amygdala/PFC rsFC, a negative emotional state, and excessive smartphone use) might interlock and reinforce the problematic use of smartphones.

We observed decreased levels of functional connectivity between the right IFG and the bilateral PHG in the PSU group. The PHG is known to evaluate the behavioral significance of sensory information (Salzmann, Vidyasagar, & Creutzfeldt, 1993), and then transfer the contextual information to the inferior frontal lobe (Nora D. Volkow & Baler, 2013). Accordingly, altered levels of activation in the PHG

have been repeatedly reported in cue-induced craving for internet gaming (Han et al., 2011; Ko, Liu, Yen, Chen, et al., 2013), nicotine dependence (Ko, Liu, Yen, Yen, et al., 2013), and pathological gambling (Crockford, Goodyear, Edwards, Quickfall, & el-Guebaly, 2005). A previous study of IGD examined differences in the neural representations of IGD in recreational gaming users during decision-making and revealed reduced neural responses in the PHG, anterior cingulate cortex, medial frontal gyrus, and IFG, in the IGD group, thus suggesting that PHG plays a crucial role in preventing individuals from developing compulsive and addiction-like behaviors (Wang, Wu, et al., 2017). In line with other studies of IGD, the PSU participants in this study exhibited a reduced R.IFG/PHG rsFC; this reduction in rsFC was associated with more severe PSU symptoms, thus suggesting that R.IFG/PHG connectivity could represent a neural-based biomarker for PSU.

In the present study, we observed a reduced rsFC between the R.IFG and the R.hippocampus in the PSU group, and its negative correlation with the amount of time spent using a smartphone. The R.IFG plays a critical role in self-control and makes essential contributions to response suppression and attentional control (Aron et al., 2003; Correas et al., 2019). And it has been well established that the hippocampus is crucial for the memory encoding and retrieval (Eichenbaum, Yonelinas, & Ranganath, 2007; Poppenk, Evensmoen, Moscovitch, & Nadel, 2013) that lead to compulsive addictive behavior (Volkow et al., 2010). The connectivity of prefrontal area and the hippocampus is



known to be involved in a range of memory processes (Howard Eichenbaum, 2017), and the aberrant functional coupling between these regions could contribute to an array of psychiatric disorders (Godsil, Kiss, Spedding, & Jay, 2013; Meyer-Lindenberg et al., 2005), including addiction. In the present study, R.IFG/R.hippocampal connectivity was found to be reduced in adolescents with PSU; this was associated with the amount of hours spent on a smartphone, and also with withdrawal. Therefore, a longer time period spent on a smartphone might influence on rsFC in the fronto-hippocampus, thus leading to an enhanced memory of smartphone-related cues and a deterioration in an individual's ability to suppress intrusive thoughts and memories related to cravings directed towards smartphones.

As mentioned above, previous neuroimaging studies have demonstrated that the right IFG is particularly involved in self-control (Aron et al., 2004; Cohen & Lieberman, 2010; Garavan et al., 2002; McClure et al., 2004; Rubia et al., 2003), and numerous survey studies have revealed that lower self-control is a critical factor that predicts PSU (Khang et al., 2013; Kim et al., 2016; van Deursen et al., 2015). Therefore, mediation analysis was conducted to elucidate the influence of self-control in the relationship between the rsFC of the right IFG and PSU. The mediation analysis further demonstrated that the fronto-limbic rsFC had an indirect influence on the severity of PSU *via* self-control. Lack of self-control and impulsivity were suggested as one of the psychological characteristics leading to dysfunctional involvement in gambling (Blaszczynski & Nower, 2002) and online video games (Billieux, Thorens, et al., 2015), thereby providing neurological evidence in support of pathological gambling and online games being considered behavioral addictions. The results of fMRI and the mediation analysis of the present study could provide neurological evidence for the already existing theoretical model on how an individual's low self-control can lead to PSU, therefore providing a foothold for PSU to be regarded as a behavioral addiction. Volkow (2016) suggested that addiction is a brain disease which consists of profound disruptions in decision-making ability and emotional balance, and preventive interventions should be designed to enhance social skills and improve self-regulation (Volkow, Koob, & McLellan, 2016). These results suggest the possible ways of reducing PSU symptoms; one is strengthening the fronto-limbic rsFC using neuromodulatory, the other is enhancing self-control. Several functional neuroimaging studies have tested the modulation of specific brain regions using transcranial direct current stimulation (tDCS) or repeated high-frequency transcranial magnetic stimulation (rTMS) for smoking cessation (Amiaz, Levy, Vainiger, Grunhaus, & Zangen, 2009; Eichhammer et al., 2003), or the reduction of alcohol (Boggio et al., 2008) and drug (Martinotti et al., 2019; Sharifi-Fardshad et al., 2018) cravings. These treatments significantly attenuated cravings towards addicted substances. On the basis of these previous findings, we suggest the possible involvement of the R.IFG as a target region to develop neuromodulatory treatments for PSU. The other plausible intervention to alleviate PSU symptoms is enhancing self-control through cognitive behavioral therapies (CBTs), implementation intention, or mindfulness training

(van Koningsbruggen, Stroebe, Papies, & Aarts, 2011; von Hammerstein et al., 2018; Young, 2007). In particular, CBTs has revealed to be an effective treatment for behavioral addiction such as pathological gambling (Jiménez-Murcia et al., 2007) and internet addiction (Du, Jiang, & Vance, 2010; Young, 2013), therefore, it is expected to have an effect on the treatment of PSU.

There are several limitations to the current study that need to be considered. First, we did not consider the primary reasons for smartphone use. Because numerous smartphone applications exist, and because user patterns are so diverse and heterogeneous, we did not categorize participants into smaller groups based on their particular preferences for smartphone use. Second, using cross-sectional data, it is difficult to determine whether the alterations in the fronto-limbic rsFC observed in the PSU group fully reflect a predisposition to addiction-like behavior or whether these represent an effect of long-term exposure to smartphones. Thus, a longitudinal imaging study of adolescents is now required to validate the causal mechanisms underlying PSU.

In summary, the present study provides evidence to indicate that adolescents with PSU exhibit multiple rsFC in the fronto-limbic regions. Furthermore, this reduced rsFC was related to the severity of PSU and a lower level of self-control. It is possible, therefore, that the rsFC alterations in the PSU group could be derived from a lower level of self-control, following a functional imbalance within the brain regions associated with executive control and reward-seeking. Understanding the alterations in functional connectivity in adolescents with PSU could guide researchers when developing interventions to control the symptoms of PSU. In addition, evidence supporting the alteration in neurobiology in PSU has been scarce; thus, more research is needed to better understand the epidemiological and neurobiological factors to assist in the intervention of PSU.

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