NEUROBIOLOGICAL PERSPECTIVES IN BEHAVIORAL ADDICTION

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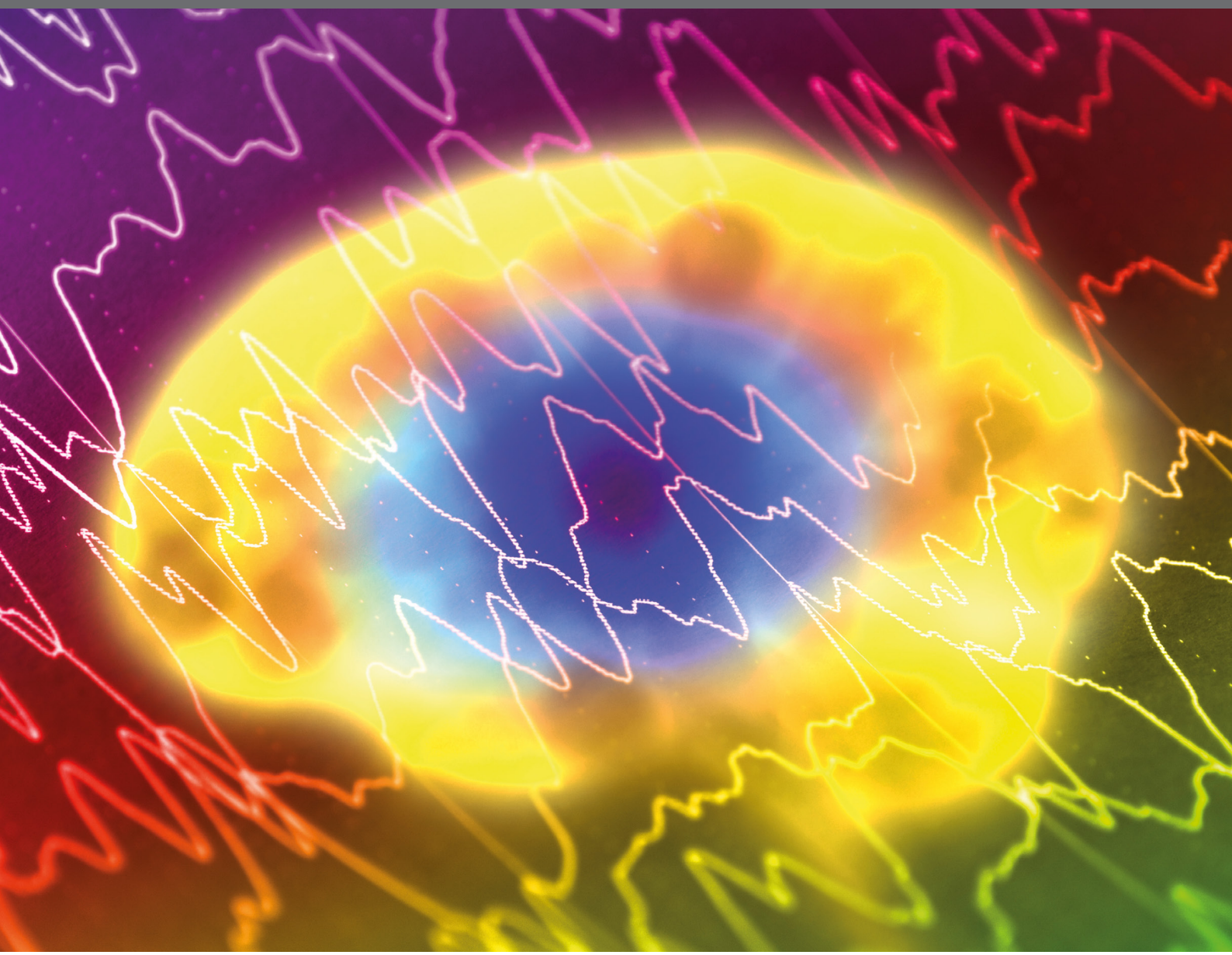

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NEUROBIOLOGICAL PERSPECTIVES IN BEHAVIORAL ADDICTION

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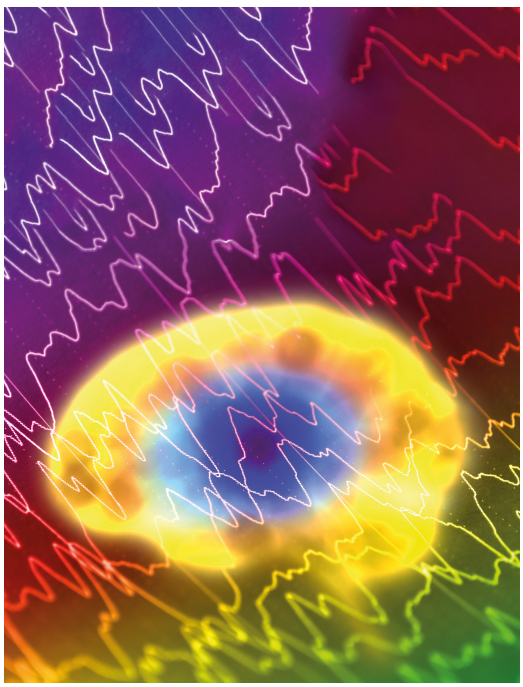

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Some classes of behaviors, including gambling, Internet gaming, and sexual behaviors, may lead to compulsive engagement for a minority of individuals. In extreme cases where individuals may feel unable to control these behaviors without external influence, these behaviors may be considered non-substance or behavioral addictions. Many such behaviors may occur predominantly online, such as gaming, social media, shopping, and pornography, and may be driven by constant accessibility via smartphone and other mobile device technologies. This Research Topic presents diverse papers on neurobiological evidence of behavioral addictions, encompassing gambling disorder, Internet-based disorders, including Internet gaming disorder and smartphone addiction, and compulsive sexual behaviors.

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EDITORIAL
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Editorial: Neurobiological Perspectives in Behavioral Addiction

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Editorial on the Research Topic

Neurobiological Perspectives in Behavioral Addiction

Some classes of behaviors, including gambling, Internet gaming, and sexual behaviors, may lead to compulsive engagement for a minority of individuals. In extreme cases where individuals may feel unable to control these behaviors without external influence, these behaviors may be considered non-substance or behavioral addictions. Many such behaviors may occur predominantly online, such as gaming, social media, shopping, and pornography, and may be driven by constant accessibility via smartphone and other mobile device technologies. The diagnostic criteria for gambling disorder and Internet gaming disorder (IGD) in the DSM-5 are similar to substance use disorder, referring to symptoms of withdrawal and tolerance, continued use despite negative consequences, and loss of control over the activity. However, some behaviors such as compulsive buying and compulsive sexual behaviors do not have specific diagnostic categories in DSM-5. Many of these behaviors, including emerging online behaviors, will continue to be the subject of discussion among international authorities, such as the World Health Organization (WHO), including calls for more research evidence on behavioral addictions. This Research Topic presents diverse papers on neurobiological evidences of behavioral addictions, encompassing gambling disorder, Internet-based disorders, including Internet gaming disorder and smartphone addiction, and compulsive sexual behaviors.

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NEUROBIOLOGICAL MECHANISM UNDERLYING BEHAVIORAL ADDICTIONS

The field of behavioral addictions is continually seeking to identify and understand the important neurobiological mechanisms that drive repetitive, maladaptive behaviors. Animal studies of substance addiction, for example, may help to guide research on the neurobiological mechanisms underlying behavioral addictions. Alcohol withdrawal-anxiety syndrome refers to symptoms that have been shown to depend on molecular and cellular adaptations that lead to persistent, long-term plastic changes in transcription, translation, and synaptic morphology. However, the molecular mechanism underlying the anxiogenic effects of ethanol withdrawal require further study. In the first paper in this Topic, Hou et al. reported that changes in synaptic ultrastructure may be associated with withdrawal anxiety in alcohol dependence.

Impulsivity is considered an important feature associated with the development of addictions. Cho et al. used a rodent version of the gambling task (rGT) to examine how impulsive action and impulsive choice are differentially influenced by difference in age at exposure (i.e., late adolescents/young adults vs. mature adults) to rGT in rats. The results indicated that impulsive action and choice are distinct aspects of impulsivity, which are differentially influenced in rats by the age at the first exposed to gambling task.

One of the major neural networks that play a crucial role in behavioral addiction is the salience network, which mediates the "switching" between neural networks to guide appropriate responses. Alterations in the salience network have been implicated in directing aberrant salience to stimuli associated with addiction, resulting in craving and impaired control over addictive behaviors. Wang et al. reported that increased insular cortical thickness correlated with symptom severity in individuals with IGD. In another study, Lee et al. reported that subregions of the anterior cingulate cortex, another key node of the salience network, formed different functional connectivity patterns in subject with IGD with comorbid depression.

Problematic Internet game play is often accompanied by major depressive disorder (MDD). Depression seems to be closely related to altered functional connectivity (FC) within (and between) the default mode network (DMN) and salience network. In addition, serotonergic neurotransmission may regulate the symptoms of depression, including impulsivity, potentially by modulating the DMN. Hong et al. reported that the SS allele of 5HTTLPR genotype group showed greater FC within the DMN and salience network, and between these networks, compared to the SL + LL allele group. The results suggest that the short allele of 5HTTLPR may increase FC within the DMN and salience network, which may subsequently aggravate impulsive Internet game play in patients with MDD.

Kim and Kang investigated different reward systems implicated in IGD. For monetary reward, the IGD group exhibited stronger functional connectivity within the brain regions involved in motivational salience, whereas the group showed reduced functional connectivity the widely distributed brain areas involved in learning or attention. These differences in functional connectivity of reward networks, suggest that IGD is associated with an increased incentive salience or "wanting" process, which may serve as the neurobiological mechanisms underlying impaired goal-directed behavior.

Attentional bias toward addiction-related cues is also associated with incentive salience, but the pathophysiology of attentional bias in IGD is not well-understood, such as its relationship to compulsivity. Kim et al. used the electrophysiological marker of late positive potential (LPP) to compare attentional bias in IGD and obsessive compulsive disorder (OCD). Increased LPPs in response to disorder-specific cues (game-related and OCD-related) were found in both IGD and OCD groups, respectively. These results indicate that LPP is a candidate neurophysiological marker for cue-related craving in IGD and OCD.

Impairment of self-regulation is one of the major psychopathologies of addiction. Self-regulation ability is related to how well basic psychological needs are satisfied. These basic psychological needs, consisting of autonomy, competence, and relatedness, are important factors affecting individual growth and integration. Some individuals may rely on and overuse social media networks, as well as Internet games, in an attempt to meet basic psychological needs. Kim et al. investigated the neural correlates underlying the distorted self of individuals with IGD in relation to their satisfaction with basic psychological needs. Individuals with IGD had a negative ideal and actual self-image. Neurobiologically, dysfunction in the inferior parietal lobule associated with emotional regulation and negative self-evaluation was found in IGD. Recognizing that IGD often develops in adolescence, this self-concept problem should be noted and addressed with appropriate therapy approaches.

Neurobehavioral phenotypes are epigenetically controlled by non-coding RNAs including microRNAs (miRNAs). Since miRNAs can be detected in blood (plasma or serum), circulating miRNAs have a definite advantage as non-invasive biomarkers in neuropsychiatric disorders. Lee et al. identified IGD-associated miRNA markers by observing differentially expressed plasma miRNAs between the IGD and control groups. Through genome-wide screening of miRNA expression profiles and independent validation, three IGD-associated miRNAs (hsa-miR-200c-3p, hsa-miR- 26b-5p, and hsa-miR-652-3p) were discovered. Individuals with downregulation of all three miRNA are at high risk of IGD.

Autonomic nerve system (ANS) dysfunction has also been associated with substance abuse and behavioral addiction. As the ANS responds to internal and external stimuli to maintain homeostasis, its function is closely related to adaptive adjustments in behavior strategies. ANS dysfunction likely contributes to the development and maintenance of loss of control over gaming, as individuals with IGD are unable to adjust their behavior strategies despite negative outcomes. ANS function can be assessed non-invasively by measuring heart rate variability (HRV). Hong et al. demonstrated that individuals with IGD were characterized by reductions in high-frequency heart rate variability while the subjects were playing their favorite online game. Their results suggest that an altered HRV response to specific gaming situations is related to addictive patterns of gaming and may reflect the diminished executive control of individuals with IGD while playing Internet games.

As smartphone adoption and use has grown rapidly, there has been increased interest in the potential negative impact of excessive smartphone use. Chun et al. investigated altered brain connectivity associated with excessive smartphone use, and the relations between withdrawal symptoms, cortisol concentrations, and frontostriatal connectivity. They found that adolescents with excessive smartphone use had reduced functional connectivity in these regions related to cognitive control. Furthermore, Internet use withdrawal symptoms appear to elicit cortisol secretion, and this psychophysiological change may affect frontostriatal connectivity. These results provide important insights into the effects of excessive use of smartphones on brain functional connectivity in adolescence.

Gaming disorder and compulsive sexual behavior (CSB) disorder were recently included in the latest International Classification of Diseases (ICD-11). However, the WHO purposefully decided to classify compulsive sexual behavior disorder as an impulse control disorder, while gaming disorder was included to addictive disorders. Seok and Sohn found that individuals with problematic hypersexual behavior have diminished executive control and impaired functionality in the right dorsolateral prefrontal cortex, which is a core feature shared across both addictive disorders and impulsive control disorders. In addition, Gola and Draps reported that CSB is related to

increased ventral striatal reactivity during the anticipation of erotic stimuli, in support of the theory of incentive salience. They suggested that further studies should be undertaken to examine neurobiological differences in these two disorders.

LONGITUDINAL CHANGES OF NEUROBIOLOGICAL CORRELATES IN BEHAVIORAL ADDICTIONS

This Research Topic also presents a series of novel studies that employ longitudinal designs, a design approach that historically has been quite limited in the IGD field. Lee et al.'s study aimed to identify the neuropsychological factors that promote improved recovery from IGD. They reported that individuals with IGD who had not improved at 6-month follow-up were more likely to have higher aggression and harm avoidance at baseline, indicating that gaming problems among these more complex cases appear less likely to resolve spontaneously. The assessment of aggression and harm avoidance levels may help predict the course of IGD.

Park et al. investigated neural connectivity associated with treatment responses in patients with IGD using resting-state electroencephalography (EEG) coherence analyses. Compared with healthy controls (HCs), patients with IGD showed increased beta and gamma intrahemispheric coherence and increased delta intrahemispheric coherence of the right hemisphere at baseline. After 6 months of outpatient management including selective serotonin reuptake inhibitors, patients with IGD exhibited improvements in IGD symptoms compared with baseline, but they continued to show increased beta and gamma intrahemispheric coherence compared with that of HCs. These findings suggest that significantly greater intrahemispheric fast-frequency coherence may be an important neurophysiological trait marker of IGD.

DIAGNOSTIC AND TREATMENT APPROACH

The final category of studies in this Research Topic involved neurobiological diagnostic and treatment approaches. Kim et al. investigated the relative value of behavioral, temperamental, and physical factors in predicting risk/problematic Internet use (ARPIU) in adolescents. They found that, among boys, severity of Internet addiction correlated inversely with the 2D:4D digit ratio and novelty-seeking, and positively with reward dependence scores when controlling for depression scores. These relationships were not found in girls, suggesting the need for gender-sensitive approaches to prevent ARPIU in youth.

The paper by Kim and Hodgins proposes a transdiagnostic treatment model of addictions that targets underlying similarities between behavioral and substance use addictions. Their model highlights various component vulnerabilities, each with intervention possibilities, including: lack of motivation, urgency, maladaptive expectancies, deficits in self-control, deficits in social support, and compulsivity. In another paper relevant to this topic, Blum et al. introduced the "Precision Addiction Management" (PAM)^{TM}, the customization of neuronutrient supplementation based on the Genetic Addiction Risk Score test result, along with a behavioral intervention. Finally, Bae et al. examined bupropion as a treatment modality for IGD and gambling disorder. Bupropion showed promise for improving problematic behaviors in both IGD and GD, however there were differing pharmacodynamics across the two groups.

In conclusion, the presented collection of original articles encompasses diverse research reports and review articles, with broad coverage of neurocognitive, neurophysiological, neurochemical, and neuroimaging research techniques. Together these articles demonstrate that the study of behavioral addictions from a neurobiological perspective is continuing to flourish and that there will be many exciting advances in this area that will improve our understanding, assessment, and treatment of individuals affected by these conditions.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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ORIGINAL RESEARCH
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Synaptic Ultrastructure Might Be Involved in HCN[1]-Related BDNF mRNA in Withdrawal-Anxiety After Ethanol Dependence

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Withdrawal from ethanol dependence has been associated with heightened anxiety and reduced expression of Brain-derived neurotropic factor which promotes the synaptic transmission and plasticity of synapses. Hyperpolarization-activated cyclic nucleotide-gated channel 1 regulates expression; however, whether Hyperpolarization-activated cyclic nucleotide-gated channel 1-related Brain-derived neurotropic factor is involved in the synaptic ultrastructure that generates withdrawal-anxiety has been poorly perceived. Sprague–Dawley rats were treated with ethanol 3–9% (v/v) for a period of 21 days. Conditioned place preference and body weight were investigated during ethanol administration. Rats were subjected to behavioral testing and biochemical assessments after ethanol withdrawal, which was induced by abrupt discontinuation of the treatment. The results showed that the ethanol administration induced severe ethanol dependence behaviors, with higher body weight and more time in the ethanol-paired compartment. After withdrawal, rats had a higher total ethanol withdrawal score and explored less. Additionally, increased Hyperpolarization-activated cyclic nucleotide-gated channel 1 protein and gene expression and decreased Brain-derived neurotropic factor protein and gene expression were detected in the Ethanol group. Eventually, there was a negative correlation between the level of Brain-derived neurotropic factor mRNA and Hyperpolarization-activated cyclic nucleotide-gated channel 1 protein. Importantly, the synaptic ultrastructure changed in the Ethanol group, including increased synaptic cleft width and reduction in postsynaptic density thickness or synaptic curvature. The synthesis of the Brain-derived neurotropic factor mRNA could be down-regulated by higher Hyperpolarization-activated cyclic nucleotide-gated channel 1 protein expression. Changes in synaptic ultrastructure may be induced by lower Brain-derived neurotropic factor protein, which could be associated with the withdrawal-anxiety that is experiences after ethanol dependence.

Keywords: ethanol withdrawal, anxiety, BDNF, HCN1, synaptic ultrastructure

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INTRODUCTION

Alcohol dependence is chronic relapsing disorder characterized by repeated episodes of withdrawal and then relapse with resumption of heavy alcohol consumption (1). Abrupt cessation of regular alcohol intake in a dependent person causes withdrawal syndrome that is characterized by tremors, increased risk of convulsions, and anxiety (2). Ethanol withdrawal-anxiety syndrome refers to symptoms that have been shown to depend on molecular and cellular adaptations that lead to persistent, long-term plastic changes in transcription, translation, and synaptic morphology (3). However, the molecular mechanism underlying the anxiogenic effects of ethanol withdrawal has not yet been completely elucidated.

Previous studies found that changes in the synaptic ultrastructure and morphology in the nucleus accumbens (NAc) and hippocampus (Hip) are involved in various behavioral sequelae, including movement control, motivation, and addiction (4, 5). Ethanol withdrawal is accompanied by molecular and cellular adaptations that lead to persistent, long-term plastic changes in transcription, translation, and synaptic morphology (3, 6). In particular, withdrawal syndrome after drug administration is manifested by the induction of rapid changes in synaptic ultrastructure and morphology (7). However, there have been few if any reports describing whether an association exists between withdrawal anxiety and changes in synaptic ultrastructure.

Brain-derived neurotrophic factor (BDNF), a neuromodulator in the mammalian nervous system, seems to contribute to the neuroadaptive changes set in motion by drug withdrawal (8). Abstinence from chronic ethanol exposure also affects the expression of BDNF in the dentate gyrus and CA3 region of the Hip (9). Additionally, the production of BDNF mediates the anxiety induced by drug withdrawal (10). Importantly, BDNF plays a crucial role in regulating synaptic transmission and plasticity at adult synapses. A lower level of BDNF in all brain structures could lead to an increase in the synaptic cleft width and reduction in postsynaptic density thickness (11).

It has been found that BDNF could be up- regulated by a lentivirus-based silencing RNA system using short hairpin RNA (shRNA)-hyperpolarization-activated cyclic nucleotide-gated channel 1 (HCN1), which reduced the expression of HCN1 protein, increased the neuronal excitability, and produced anxiety- and depressive-like behavior (12). Studies conjectured that hyperpolarizing membrane was generated by Ih current when HCN1 channel excessively activated, which inhibited calcium inward current of the presynaptic membrane. And the BDNF released from presynaptic vesicles into the synaptic cleft, dependent intracellular calcium concentration, were prevented in the neuron which might lead to the anxiety (13). Additionally, HCN1-related BDNF played a crucial role in the pathogenesis of anxiety were explored in our previous study which found there was a negative correlation between the level of BDNF and HCN1 in the brain (14).

HCN1 is known to play a fundamental role in controlling several important cellular functions including dendritic integration, synaptic transmission, plasticity phenomena, and rhythmic activity in the central nervous system (15, 16). Additionally, HCN1 is expressed at the highest levels in the NAc and Hip, which are the most important brain regions involved in the process of drug addiction (17, 18). One *in vitro* study reported that withdrawal from repeated methamphetamine administration increased HCN1 mRNA levels (19). Repeated ethanol exposure *in vivo* down-regulated Ih in the HCN1 (20). Although Mala observed that inactive HCN1 channels might be enhanced when the BDNF protein releases from presynaptic vesicles into the synaptic cleft (13), the molecular mechanisms by which reduced HCN channel function augmented BDNF are still not clearly understood. Additionally, the potential effect of HCN1 in ethanol withdrawal has not been reported.

Based on this background, the present study hypothesized that changes in synaptic ultrastructure, which could be induced by a reduction of BDNF due to an increase in HCN1 expression in the Hip and NAc, might be associated with ethanol withdrawal-induced anxiety. An attempt was carried out to further understand this potential mechanism regarding ethanol withdrawal-induced anxiety. This study was conducted to establish an ethanol-dependent rat model (21). After ethanol withdrawal, we examined the withdrawal syndrome using behavioral tests, as well as variations in the expression of BDNF and HCN1 proteins in the prefrontal cortex (PFC) by biochemical tests. Additionally, the synaptic ultrastructure and morphology were observed by transmission electron microscopy (TEM).

MATERIALS AND METHODS

Animals

The male Sprague–Dawley rats (6 weeks old, 180 ± 20 g) utilized in this study were purchased from the animal center at WeiFang Medical University. The animals were housed five per cage (53.5 × 39 × 20 cm) with a 12-h light/12-h dark cycle (lights on at 06:00 a.m.) at a relatively constant room temperature (23 ± 1°C) and humidity (45%). Food was available *ad libitum*. Sterilized drinking water or ethanol solutions were available *ad libitum*, with the exception of the periods determined for withdrawal as follows. Before the experiments, the rats were undisturbed for 7 days to acclimate to the environmental conditions. All experiments were performed between 9:00 a.m. and 14:00 p.m. during the light cycle. The experiments were conducted according to the National Institutes of Health Guidelines (Care and Use of Laboratory Animals) and were approved by the WeiFang Medical University Animal Care and Use Committee.

Ethanol Administration

The control group ($n = 20$) animals received water *ad libitum* for 23 days. The ethanol group ($n = 20$) received ethanol starting with a solution of 3% ethanol (v/v) that was gradually increased every 3 days to 6% (days 7–9) and then 9% (days 10–24). Then, the ethanol solution (9%) was removed and returned the next day (day 24) for 2 h. After that, the animals received water until day 26, thereby ensuring a 48 h abstinence period. Previous studies showed that anxiety-like behavior after this period of

abstinence from ethanol was robust (22). Therefore, a period of 48 h after ethanol withdrawal was chosen in this study. A short period of treatment using a low dose of ethanol was chosen to avoid any systemic or vascular effects of the ethanol. The choice of treatment for 21 days with ethanol (3–9%) was based on a previous study (21) (See **Figure 1**).

Determination of the Effect of Ethanol

Body Weight

All animals were weighed once daily throughout the 21 days of ethanol treatment.

Conditioned Place Preference

The reward effect was assessed by conditioned place preference (CPP) testing with a two-compartment CPP apparatus (23). In brief, the apparatus consisted of two wooden chambers identical in size (30 × 30 × 30 cm). The first chamber had white walls with a large textured grid floor, whereas the second chamber was black with a smooth floor, and they were connected to the other two compartments via removable doors. Both black and white compartments had a ceiling lamp. General activity was monitored via a video recorder for 15 min, and the time spent in each compartment was recorded using Smart3.0 software (Version 3.0, Panlab SL, Barcelona, Spain). CPP consisted of a 3-day schedule with two distinct phases: a pre-conditioning test (pre-CPP) on Day 1–3 and a post-conditioning test (post-CPP) on Day 22–24.

To identify any pre-existing bias toward the individual compartments, each rat was initially placed in the middle chamber and allowed to freely explore the entire apparatus for a 15-min session for three consecutive days before ethanol administration. The time spent in each compartment on the third day was used as the pre-conditioning data. The most preferred compartment was designated as the preferred compartment, and the other as the non-preference compartment. Each animal received individual CPP training. In the post-CPP session, each rat was allowed to freely explore the entire apparatus for a 15-min session repeatedly on Day 22–24 in an ethanol-free state. The amount of time spent in the non-preference (ethanol-paired) compartment was recorded as the post-conditioning data.

Ethanol Withdrawal Symptoms

Erden's Score

The symptoms of ethanol withdrawal were tested for 4 min 4 and 6 h after ethanol withdrawal. At each observation time, the rats were simultaneously assessed for the following behavioral conditions: stereotyped behaviors (grooming, sniffing, head weaving, gnawing, and chewing), agitation, tail stiffness, abnormal posturing, and abnormal gait. These behaviors were measured in the open-field test (OFT) (40 × 40 × 35 cm). Before the start of the experiment, the rats were put in the open field arena for 30 s. The symptoms of ethanol withdrawal were scored using a rating scale prepared by Erden (24). The behavior scores were recorded and summed for the individual observation period.

Open-Field Test

Exploratory locomotor activity and anxiety were tested in the OFT as previously reported (25). The area consisted of an enclosed square arena (100 × 100 × 50 cm). The field was divided into 25 squares with computer virtual grid lines for analysis using Smart3.0 software. Each rat was placed in the central area and was allowed to explore for 5 min. Their behaviors, including the number of crossings (with all four paws placed in a new square), upright posture (both front paws raised from the floor), carding, and fecal grains were recorded by a digital camera.

Elevated Plus-Maze Test

The standard EPM test was used to assess anxiety-like behavior (26). The EPM apparatus was composed of two open arms (50 × 10 cm) and two closed arms (50 × 10 × 40 cm) connected by a central platform (10 × 10 cm). The EPM was made of dark gray plastic and positioned 100 cm above the floor. The rats were individually placed in the central platform, facing the closed arms, and allowed to explore the arena freely for 5 min. The behaviors, including the number of entries into the open and closed arms, as well as the percentage of time spent in the open and closed arms were recorded by a digital camera.

Immunohistochemistry

Immunohistochemistry was performed as previously described (27). The rats were deeply anesthetized and transcardially perfused with normal saline followed by paraformaldehyde in

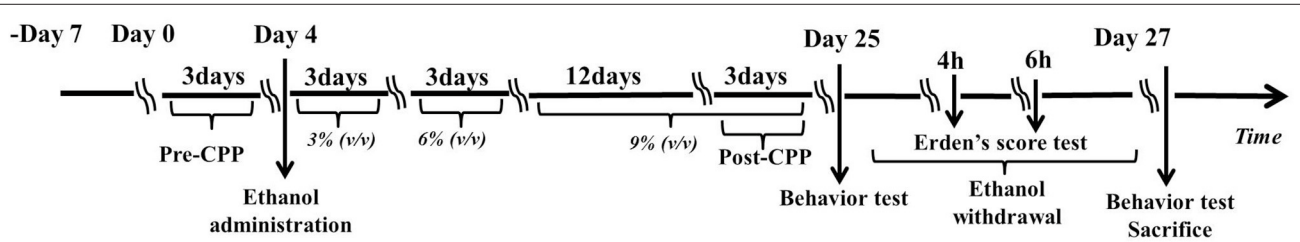

FIGURE 1 | Experimental schedule for developing the ethanol dependence and withdrawal model. On day 0, rats were identified any pre-existing bias toward the individual compartments in the pre-conditioning test for 3 days. On day 4, the rats were administrated a solution of 3% ethanol (v/v) that was increased gradually every 3 days to 6% (day 7–9) and to 9% (day 10–24). The post-conditioning test was developed on the days 22, 23, and 24. The Erden's score was tested for 4 min on hours 4 and 6 after ethanol withdrawal. Then, behavioral assessments, including the open field test (OFT) and the elevated plus maze (EPM) test were administered on day 25 and day 27. All the rats were sacrificed immediately after behavioral assessments on day 27.

phosphate buffer. Then, coronal cryotome sections (20 μm) were cut through the Hip and NAc using a cryostat and collected on poly-L-lysine-coated slides. After drying overnight at room temperature, the sections were treated with 0.3% H_2O_2 in methanol. After rinsing in phosphate-buffered saline (PBS) three times, the sections were blocked in 5% normal goat serum at room temperature. Next, the brain sections were incubated overnight at 4°C in primary antibody (anti-HCN1, 1:500, ab84816; anti-BDNF, 1:500, ab108319; both from Abcam, Cambridge, MA, USA) solutions with Primary Antibody Dilution Buffer. After repeated washing, the brain sections were incubated at room temperature with secondary antibody (Peroxidase-Conjugated Affinipure Goat Anti-mouse IgG (H+L), 1:200 dilution, ZB-2305, ZSGB-BIO, 1:200 dilution; Peroxidase-Conjugated Affinipure Goat Anti-Rabbit IgG (H+L), 1:200 dilution, ZB-2301; ZSGB-BIO, Beijing, China) and reacted with a 3,3′-diaminobenzidine (DAB) kit (ZLI-0931, ZSGB-BIO) for the color reaction. The Hip and NAc sections were examined with an Olympus Fluo View 1200 confocal microscope system (Olympus Corp., Tokyo, Japan), and photomicrographs of representative Hip and NAc areas were obtained.

Western Blot Assay

The western blot assay was conducted as previously described (28). The Hip and NAc were rapidly dissected, and the proteins were extracted with radioimmunoprecipitation (RIPA) buffer (P0013B; Beyotime, Shanghai, China) containing a protease inhibitor cocktail (ST506; Beyotime) on ice. The protein concentration of the supernatant fraction was determined using a bicinchoninic acid (BCA) assay (P0012; Beyotime). Sample proteins were subjected to 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). Then, the proteins were transferred to a polyvinylidene fluoride (PVDF) membrane using the Trans-Blot wet transfer system. The PVDF membrane was incubated in a blocking solution at room temperature. The PVDF membrane was probed overnight at 4°C using anti-rat HCN1 monoclonal antibody (1:1,000) and anti-BDNF (1:1,000). The next day, the membrane was washed three times, 10 min each time, with PBS-T and incubated at room temperature with secondary antibodies, including anti-HCN1 [Peroxidase-Conjugated Affinipure Goat Anti-mouse IgG (H + L), 1:200] and anti-BDNF [Peroxidase-Conjugated Affinipure Goat Anti-Rabbit IgG (H + L), 1:200], and reacted with the Immobilon western chemiluminescent HRP substrate (WBKLS0500; Millipore, Bedford, MA, USA) for the color reaction. Then, the gray values of the immunoreactivity were quantified with ImageJ software.

Quantitative Real-Time Polymerase Chain Reaction

The rats were euthanized after treatment, and the Hip and NAc were extracted from each group and analyzed. Total RNA was isolated using TRIzol reagent (Cat# 15596–026, Invitrogen, Carlsbad, CA, USA). The RNA concentration and purity (OD260/280) were determined using a NanoDrop ND1000 spectrophotometer (NanoDrop Technologies, Inc., Wilmington, DE, USA). First-strand cDNA synthesis was performed using the RevertAid™ First Strand cDNA Synthesis Kit (Code No. RR047A; TaKaRa, Ohtsu, Japan) in a 20-μL reaction volume with 1 μg template RNA. The PCR reaction mix was prepared according to the manufacturer's protocol. The PCR primer sequences are shown in **Table 1**. The amplification reactions were performed in 96-well plates using the 7900HT Fast Real-Time PCR System (Cat# 4346906; Applied Biosystems, Foster City, CA, USA). The thermocycling conditions were set according to the manufacturer's protocol. The specificity of amplification was confirmed using a melting curve analysis. Differential gene expression between the drug and saline groups was calculated using the $2^{-\Delta\Delta CT}$ method with β-actin as an endogenous control.

Transmission Electron Microscopy

The TEM test was carried out as described by Marcelo (29). The Hip and NAc tissues were immediately separated, and immersion fixation was completed at ∼1 mm3 size. The samples were rinsed in cold PBS and placed in 2.5% glutaraldehyde. The samples were post-fixed with 1% aqueous osmium tetroxide in 0.2 M cacodylate buffer for 2 h. Then, the tissue was rinsed with distilled water before dehydration in a gradually increasing ethanol series and infiltrated using a mixture of half acetone and half resin overnight at 4°C. Following post-fixation in osmium tetroxide and dehydration in an ascending ethanol series followed by propylene oxide, the samples were embedded in Araldite resin (Agar Scientific, Essex, UK) overnight. The 70-nm-thick ultrathin sections were stained with 3% uranyl acetate for 20 min and 0.5% lead citrate for 5 min and were observed with the JEOL 1200EX at 120 kV (JEOL, Inc., Tokyo, Japan). Ultrastructural changes in Hip and NAc synapses were observed under TEM (HT7700-SS, Hitachi, Tokyo, Japan). Bouton parameters, including synaptic cleft width, postsynaptic density (PSD), and curvature of the synaptic interface, were quantified using ImageJ, in accordance with previous methods (30, 31).

Statistical Analysis

All measurements were obtained by an independent investigator blinded to the experimental conditions. Total ethanol withdrawal scores in the different groups were compared using the Mann–Whitney *U*-test. Between-group differences in body weight were analyzed using repeated-measures analysis of variance (ANOVA). Other data are expressed as the mean ± standard error. Student's *t*-test was used to compare the differences between the control and ethanol groups using SPSS 22.0 software (SPSS Inc., Chicago, IL, USA). The correlation between the

TABLE 1 | The PCR primer sequences designed by Primer Premier 5.0.

Gene	Primer sequence(5′-3′)	
	Forward	Reverse
BDNF	CAGCGCGAATGTGTTAGTGGTTA	CAGTGGACAGCCACTTTGTTTCA
HCN1	CTGGGATGGCTGTCTTCAGTTTC	GCGCCAGTAACCAATGCAC
β-actin	GGAGATTACTGCCCTGGCTCCTA	GACTCATCGTACTCCTGCTTGCTG

HCN1 protein and BDNF mRNA as well as the BDNF protein was tested by correlation analysis. A $P < 0.05$ was considered significant.

RESULTS

Determination of the Ethanol Effect

The rats in the ethanol group gained significantly more weight than rats in the Control group ($F = 25819.874$, $P < 0.001$; **Figure 2A**). After the 21-day ethanol administration procedure, the weight of rats in the ethanol group (240.29 ± 10.96 g) increased by 28.87% compared with that of rats in the control group (230.14 ± 5.43 g).

No significant difference was observed in the time spent between the water-paired and ethanol-paired sides in the pre-CPP between the Control and Ethanol groups ($t = 1.372$, $P > 0.05$; **Figure 2B**). The time spent in the ethanol-paired compartment by the ethanol group was significantly higher during the post-CPP than that of the Control group ($t = 5.007$, $P < 0.001$; **Figure 2B**).

Ethanol Withdrawal Symptoms

Ethanol Withdrawal Score

The total ethanol withdrawal score in the Control group was significantly lower than that in the Ethanol group after 4 h of ethanol withdrawal ($U = 400$, $P < 0.001$; **Figure 2C**) and after 6 h of ethanol withdrawal ($U = 392.5$, $P < 0.001$; **Figure 2C**).

Ethanol Withdrawal Anxiety Behaviors

The effect of the ethanol administration procedure on anxiety-like behaviors was shown by the OFT (**Figures 3C,F**). The number of cardings, fecal grains, crossings, and upright postures did not decrease in the Ethanol group compared with those in the Control group before withdrawal (0 h; carding: $t = 0.206$, $P > 0.05$; **Figure 3E**; fecal grains: $t = 0.686$, $P > 0.05$; **Figure 3D**; crossing: $t = 0.294$, $P > 0.05$; **Figure 3A**; up-right posture: $t = 0.730$, $P > 0.05$; **Figure 3B**). However, after 48 h of ethanol withdrawal, the rats in the Ethanol group exhibited more anxious behavior, including adding to the number of fecal grains and carding, as well as decrease in the number of crossings and up-right postures compared to those before withdrawal (48 h; carding: $t = 2.390$, $P < 0.05$; **Figure 3E**; fecal grains: $t = 3.130$, $P < 0.001$; **Figure 3D**; crossing: $t = 4.001$, $P < 0.001$; **Figure 3A**; upright posture: $t = 2.789$, $P < 0.05$; **Figure 3B**). The rats in the Ethanol group exhibited more anxious behavior after ethanol withdrawal, compared with that in the Control group (carding: $t = 2.448$, $P < 0.05$; **Figure 3A**; fecal grains: $t = 3.983$, $P < 0.001$; **Figure 3D**; crossing: $t = 3.189$, $P < 0.05$; **Figure 3E**; upright posture: $t = 2.957$, $P < 0.05$; **Figure 3B**).

The effect of the ethanol administration procedure on different anxiety-like behaviors was shown by the EPM test (**Figures 3I,L**), revealing that rats in the Ethanol group exhibited significantly more time in the closed arms ($t = 8.532$, $P < 0.001$; **Figure 3J**), and significantly more entrances into the closed arms ($t = 3.731$, $P < 0.05$; **Figure 3K**) than rats in the Control group. The time spent in the open arms ($t = 2.734$, $P < 0.05$; **Figure 3G**) and the number of entrances into the open arms by the Ethanol group ($t = 3.900$, $P < 0.05$; **Figure 3H**) markedly decreased compared with those in the Control group after ethanol withdrawal. The rats in the Ethanol group showed anxiety-like behaviors after ethanol withdrawal (time spent in closed arms: $t = 5.789$, $P < 0.001$; **Figure 3J**; number of entries into closed arms: $t = 4.368$, $P < 0.001$; **Figure 3K**; time spent in open arms: $t = 5.889$, $P < 0.001$; **Figure 3G**; number of entries in open arms: $t = 5.756$, $P < 0.001$; **Figure 3H**).

Changes in HCN1 and BDNF Levels in the NAc and Hip After Ethanol Withdrawal

As illustrated in **Figures 4**, **5**, significant decreases in expression of the BDNF gene were detected in the Hip ($t = 6.541$, $P < 0.001$; **Figure 4A**) and NAc ($t = 7.791$, $P < 0.001$; **Figure 5A**) following ethanol withdrawal. However, HCN1 expression significantly increased in the Hip ($t = 5.108$, $P < 0.05$; **Figure 4E**) and NAc ($t = 4.768$, $P < 0.05$; **Figure 5E**) of the ethanol group.

Because BDNF and HCN1 play a key role in ethanol withdrawal-induced anxiety, we performed a western blot analysis of BDNF and HCN1 in the Hip and NAc. As shown in **Figures 4**, **5**, BDNF expression in the Hip ($t = 2.360$, $P < 0.05$; **Figure 4B**) was significantly higher in the Control group than that in the Ethanol group and NAc ($t = 3.585$, $P < 0.001$; **Figure 5B**). The HCN1 level significantly increased in the Hip ($t = 12.909$, $P < 0.001$; **Figure 4F**) and NAc ($t = 2.416$, $P < 0.001$; **Figure 5F**) of the ethanol group compared to that in the control group. Through correlation analysis, it was found that there was a negative correlation between the expression of the BDNF gene and the level of the HCN1 protein in the Hip ($r^2 = 0.7702$, $P < 0.001$) as well as the NAc ($r^2 = 0.4747$, $P < 0.001$). However, the level of the HCN1 protein had no correlation with the BDNF protein in the Hip ($r^2 = 0.3499$, $P > 0.05$) or the NAc ($r^2 = 0.05422$, $P > 0.05$).

The immunohistochemistry results of the ethanol group showed significantly fewer BDNF-positive cells in the Hip ($t = 9.776$, $P < 0.001$, **Figures 4C,D**) and NAc ($t = 6.169$, $P < 0.001$; **Figures 5C,D**) compared to those in the Control group. The ethanol withdrawal procedure significantly increased the numbers of HCN1-positive cells in the Hip ($t = 5.225$, $P < 0.001$; **Figures 4G,H**) and the NAc ($t = 14.618$, $P < 0.001$; **Figures 5G,H**).

Changes in Synaptic Ultrastructure in the NAc and Hip After Ethanol Withdrawal

The synaptic ultrastructure of the Hip and NAc was examined by TEM after ethanol withdrawal, as shown in **Figure 6**. The thickness and curvature of the synaptic interface in the Hip increased in the Ethanol group as compared to those in the control group ($t = 2.668$, $P < 0.05$; **Figure 6C**; $t = 2.330$, $P < 0.05$; **Figure 6E**) and NAc ($t = 3.071$, $P < 0.05$; **Figure 6H**; $t = 3.845$, $P < 0.05$; **Figure 6J**). In addition, the width of the synaptic cleft was markedly augmented in the Hip ($t = 0.923$, $P < 0.05$; **Figure 6D**) and NAc ($t = 0.894$, $P < 0.05$; **Figure 6I**) in the Ethanol group as compared to those in the Control. All the original data of results see in Supplementary Material.

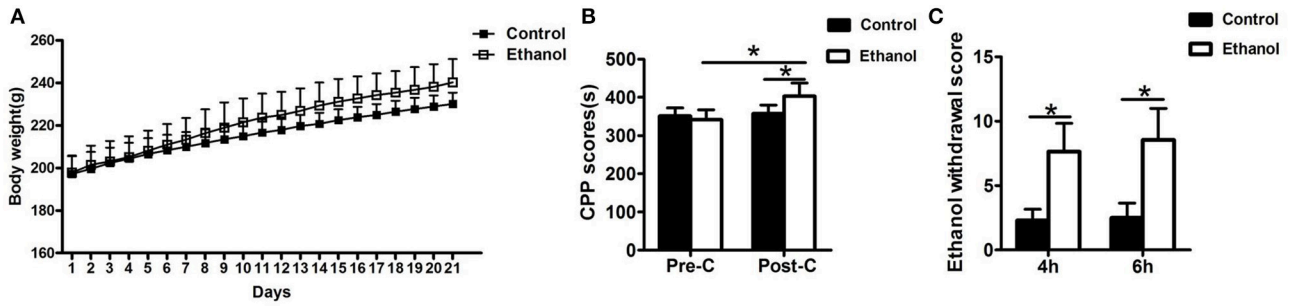

FIGURE 2 | Effects of ethanol dependence on body weight, conditioned place preference (CPP) and total ethanol withdrawal score at hours 4 and 6 of ethanol withdrawal. **(A)** The Ethanol group gained significantly more weight than the group; **(B)** The group exhibited no difference in the Pre-CPP; **(C)** The total ethanol withdrawal score. Data are as mean ± standard error. *$P < 0.05$ was significant.

DISCUSSION

The present study investigated the apparent anxiety behaviors and potential modulation in rats after 48 h of withdrawal from repeated systemic administration of ethanol. The reward effect was assessed by the CPP test, which demonstrated that apparent ethanol addictive behaviors were exhibited in the Ethanol group. As evidenced by the Erden's score results, the rats exhibited ethanol withdrawal symptoms after ethanol was withdrawn. The data for the OFT and EPM tests showed that ethanol withdrawal induced anxiety behaviors. Ethanol withdrawal also increased HCN1 activity and decreased the BDNF level in the Hip and NAc as well as resulted in abnormal changes in synaptic ultrastructure. These results revealed that the Ethanol withdrawal anxious behavior might be based on modulation of synaptic ultrastructure, in which the lowering of BDNF expression down-regulated by higher HCN1 in the Hip and NAc played a potential part.

During the ethanol administration procedure, the body weights of the ethanol group were higher than those of the control, which might have been due to the added calories from ethanol or the positive relationship between ingestion of fat and ethanol, which was hinted at by a previous report (32). However, the developmental trend in body weight observed in the present study differed from that in Rosanne's study, which found that chronic ethanol consumption might cause a thiamine deficiency by inhibiting intestinal absorption of thiamine, leading to weight loss (33), but this difference may have been caused by the different methods of ethanol administration.

The reward properties of ethanol measured by CPP are positively correlated with ethanol consumption (34). The CPP data of the ethanol group suggested that ethanol administration promoted a preference for contextual cues paired with the ethanol experience, which is in accordance with a previous study demonstrating enhanced drug CPP following repeated ethanol consumption (35). However, Tipps reported that contextual association processes are significantly impaired by ethanol intoxication at this dose (36). Considering the changes in body weight and the CPP results, the ethanol-dependent model was established in the present study.

Ethanol withdrawal is known to produce sensitization, tolerance, dependence, craving, and relapse after stopping intake, as shown with other abused drugs (24). The Erden's score of the Ethanol group was significantly higher than that of the Control group, which was interpreted as reflecting the success of ethanol withdrawal.

In the present study, the rats withdrawing from ethanol exhibited a significant decrease in exploratory activity, such as crossing and up-right posturing during the OFT. This decrease in exploratory activity could be interpreted as enhanced anxiety. Furthermore, the evidence of poorer fecal grain and carding performance, which suggests the rat's ability to adapt to a strange environment, implies that the rats were in an anxiety-like state after ethanol withdrawal. These results agree with the study of Bonassoli who also reported that rats exhibit anxious behavior after ethanol withdrawal (22). However, in Bonassoli's study, the rats were habituated to the test apparatus by repeated testing for 3 days, and therefore, the decreased exploration could be considered normal expression rather than confounding of an enhanced anxiety-like state (37).

The EPM has been widely employed to evaluate ethanol withdrawal-induced anxiety-like behavior in rodents (21). Ethanol withdrawal usually decreases exploratory activity on the EPM, indicating the anxiety-like effect of ethanol withdrawal in rodents (37). In the present study, the EPM data from the Ethanol group showed a lower number of entries and percentage of time spent in the open arms compared with those of the control group, which was in accordance with another study describing anxiety-like effects in rodents that were induced with ethanol withdrawal (21). However, Gonzaga reported that the ataxia induced by ethanol also affects exploration during the EPMT (38). Thus, the significant difference in exploration of the closed arms observed in the present study suggesting decreased exploration of the open arms was probably not a result of ethanol withdrawal.

The abnormal changes in the morphological structure of the PSD may lead to disturbances in long-term synaptic plasticity and dysfunction in synaptic transmission (5). In the present study, the PSD revealed reduced thickness in the anxious rats undergoing ethanol withdrawal. Some authors have hypothesized that changes in PSD thickness during synaptic transmission

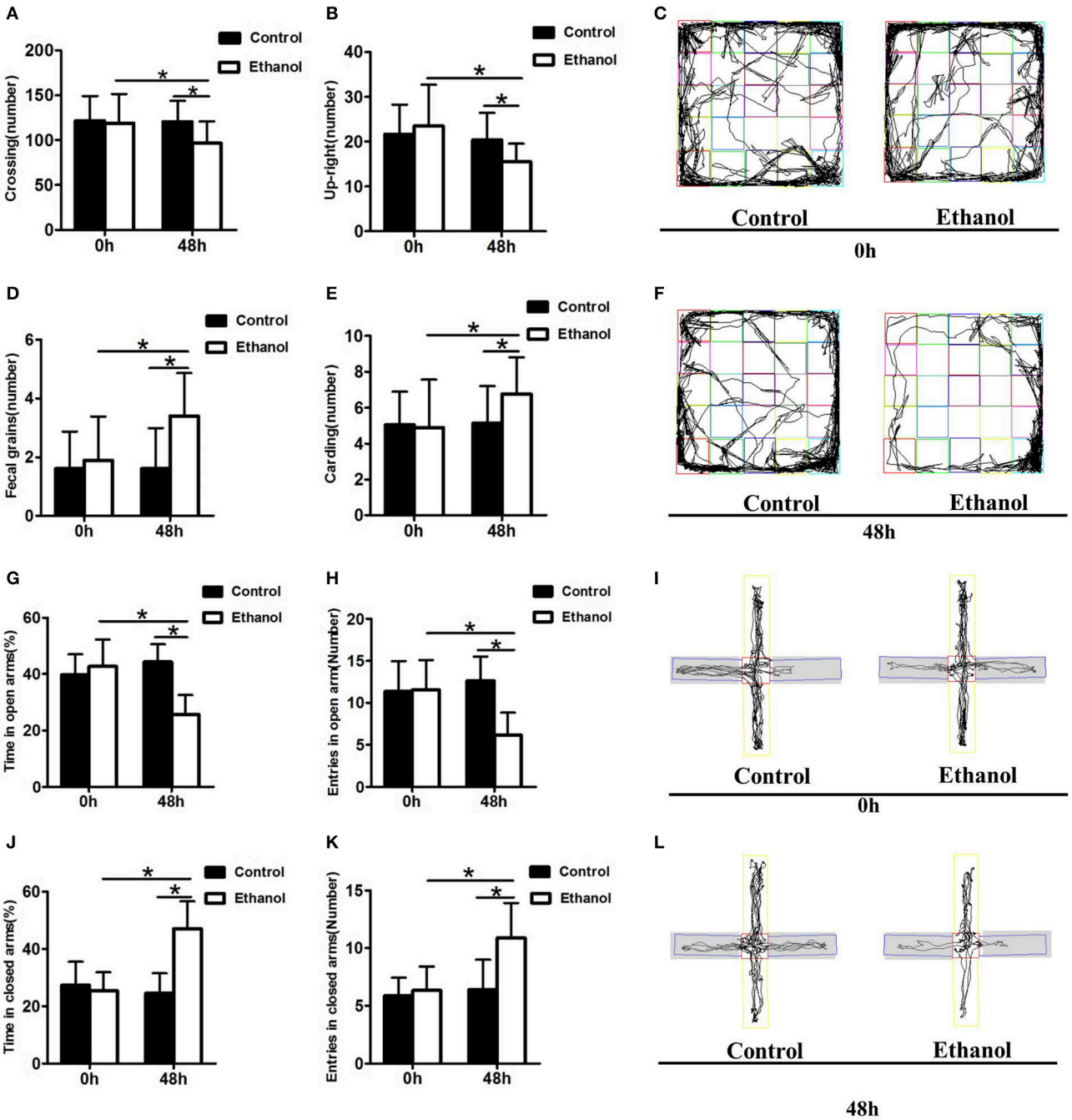

FIGURE 3 | Effect of ethanol withdrawal on the anxiety behaviors. **(A)** The number of crossings in the OFT. **(B)** The number of up-right in the OFT. **(D)** The number of fecal grains in the OFT. **(E)** The number of carding in the OFT. **(C,F)** Representative video tracking images during the last 5 min in the OFT. **(J,G)** Time spent in closed arms and open arms in the EPM. **(K,H)** Number of entries into closed arms and open arms in the EPM. **(I,L)** Representative video tracking images during the last 5 min in the EPM. 0 h: Before ethanol withdrawal period. 48 h: After ethanol withdrawal period. Data are mean ± standard error. *$P < 0.05$ was significant.

underlie some aspects of the ethanol withdrawal syndrome (22). This may also explain why ionotropic glutamate receptors [iGluRs], which are important constituents of the PSD, show decreased expression after ethanol consumption (39). The iGluRs could disturb the postsynaptic membrane response to the signal by causing intense Ca^{2+} loading (40). In addition, these changes in synaptic ultrastructure might lead to ablation of cyclin-dependent kinase 5, a major regulator of synaptic plasticity, which could also enhance the release of gamma aminobutyric acid and decrease anxiety (41). The crucial role of the PSD thickness in the anxiety-like effects after ethanol withdrawal requires further exploration.

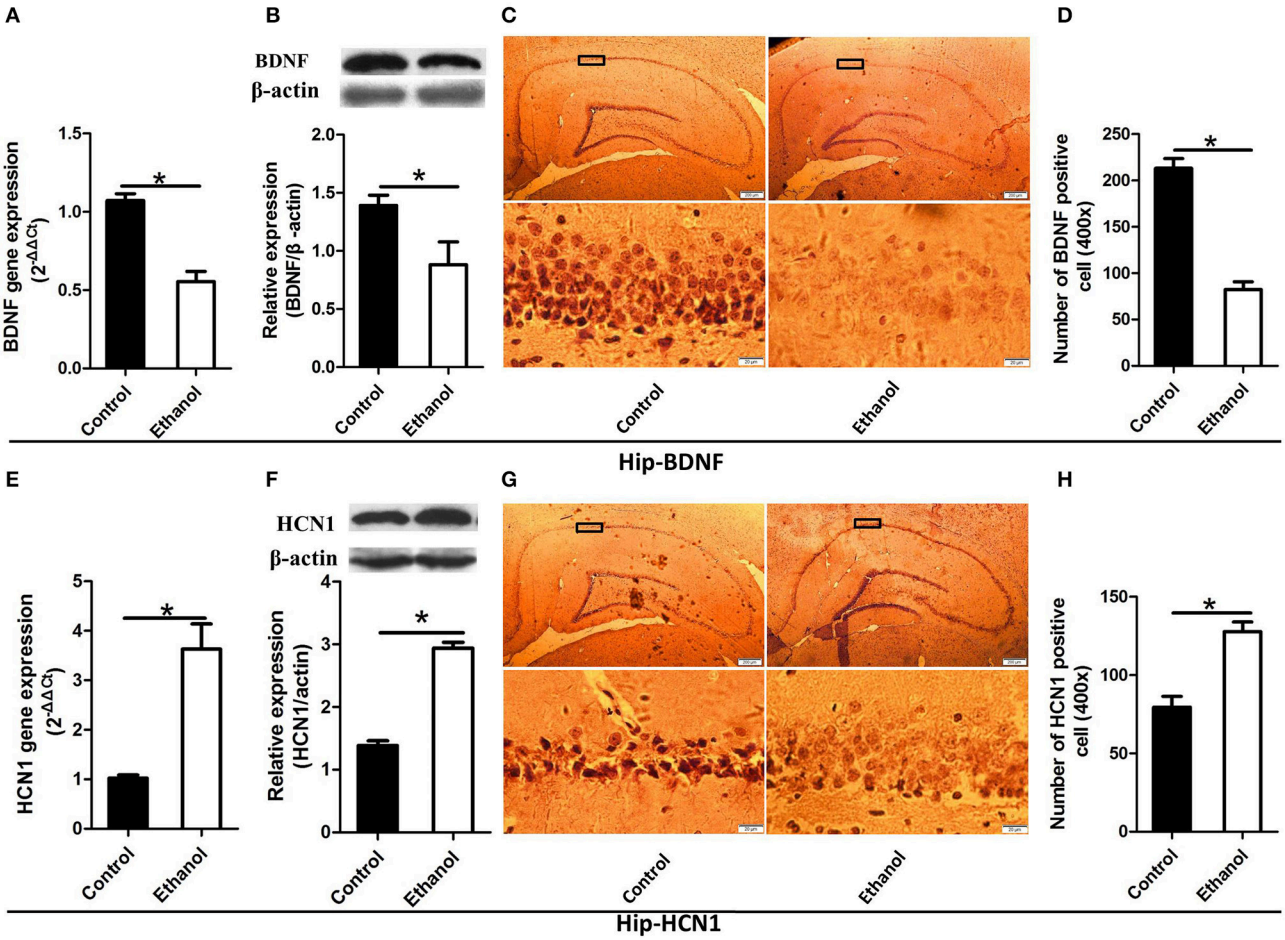

FIGURE 4 | Effects of the ethanol withdrawal procedure on the hyperpolarization-activated cyclic nucleotide-gated cation channel (HCN1) and brain-derived neurotrophic factor (BDNF) protein or gene level changes in the hippocampus (Hip). **(A)** The expression of BDNF BDNF mRNA in the Hip. **(B)** The expression of BDNF-positive cells in the Hip. **(C)** Expression of BDNF positive cells in the Hip. **(D)** The number of BDNF-positive cells in the Hip. **(E)** The expression of HCN1 mRNA in the Hip. **(F)** The expression of HCN1-positive cells in the Hip. **(G)** Expression of HCN1 positive cells in Hip. **(H)** The number of HCN1-positive cells in the Hip. The BDNF- and HCN1-positive cells in the Hip are represented by photomicrographs (400×). Data are mean ± standard error. *$P < 0.05$ was significant.

Although some studies have shown that PSD is involved in the postsynaptic membrane response to the signal, few studies have investigated the effects of the synaptic cleft and synaptic curvature as they relate to synaptic functions involved in anxiety after ethanol withdrawal (40). In the present study, we found an increase in synaptic cleft width and a decrease in synaptic curvature in the NAc and CA1 of the Hip after ethanol withdrawal. A potential mechanism of the ethanol withdrawal-induced anxiety by changes in synaptic ultrastructure is that an increase in synaptic cleft width could retard delivery of neurotransmitters from the presynaptic membrane to the postsynaptic membrane (42). Furthermore, the change of synaptic curvature could reflect the functional activity of the neuron. Gondre reported that a curved synapse has more mitochondria than a straight synapse, suggesting that a curved synapse is more active (43). The decreased neuronal activity caused by widening of the synaptic cleft and flattening of the synaptic curvature might be why the rats exhibited anxious behaviors after ethanol withdrawal.

BDNF has been implicated in the development of alcohol addiction due to its role in the regulation of synaptic plasticity in the Hip and NAc (8). BDNF gene expression decreased in rats under ethanol withdrawal, and BDNF signaling and the dendritic spines are involved in anxiety-like behaviors during ethanol withdrawal in rats (44). In addition, treatment with BDNF increases the numbers of dendritic spines and synapses in the Hip (45), suggesting a role for BDNF–Arc signaling in the regulation of neuronal architecture.

In the present study, protein levels of BDNF in the Hip and NAc significantly decreased in the Ethanol group compared to those in the Control group after ethanol withdrawal. Here, BNDF decreased in the NAc and CA1 of the Hip after abstinence from chronic ethanol consumption, suggesting that BDNF is involved in ethanol withdrawal-related anxiety and alcohol-drinking behaviors in rats (9, 10). Additionally, BDNF gene expression also decreased in the NAc and CA1 of the Hip in the Ethanol group. This result contrasts with that of Tapia, who found no difference in BDNF mRNA between the Ethanol

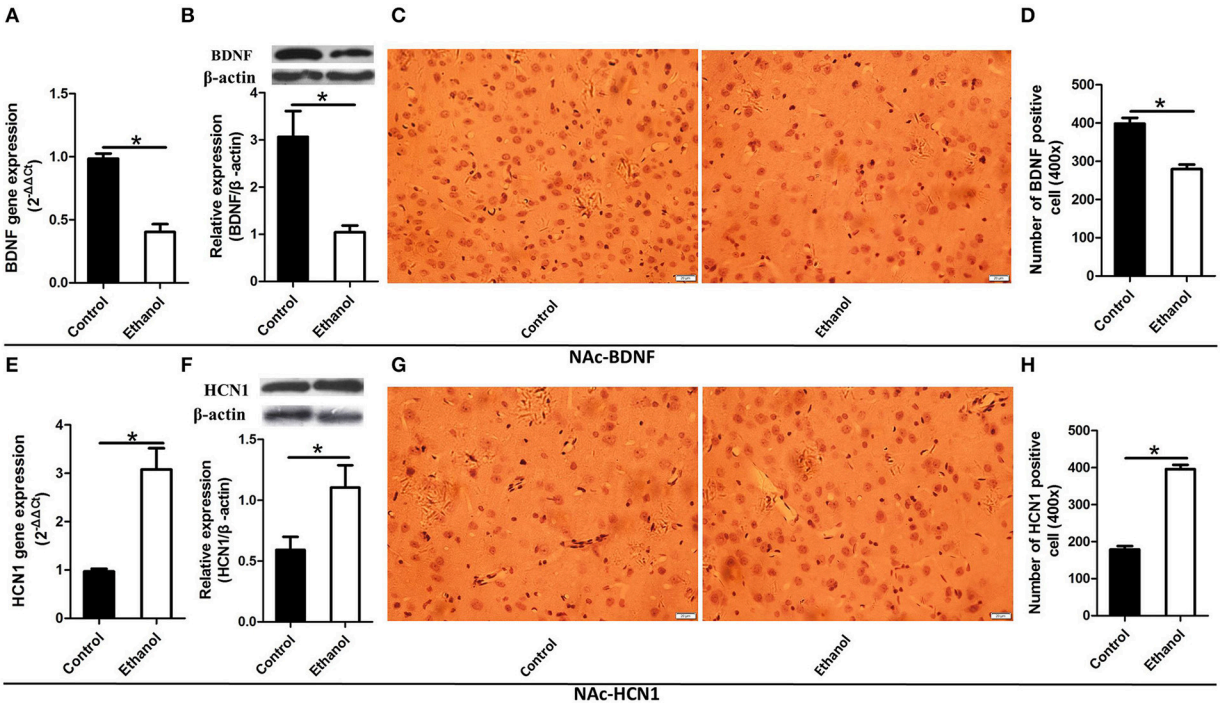

FIGURE 5 | Effects of the ethanol withdrawal procedure on the hyperpolarization-activated cyclic nucleotide-gated cation channel (HCN1) and brain-derived neurotrophic factor (BDNF) protein or gene level changes in the nucleus accumbens (NAc). **(A)** The expression of BDNF BDNF mRNA in the NAc. **(B)** The expression of BDNF-positive cells in the NAc. **(C)** Expression of BDNF positive cells in the NAc. **(D)** The number of BDNF-positive cells in the Hip. **(E)** The expression of HCN1 mRNA in the NAc. **(F)** The expression of HCN1-positive cells in the NAc. **(G)** Expression of HCN1 positive cells in the NAc. **(H)** The number of HCN1-positive cells in the NAc. The BDNF- and HCN1-positive cells in the NAc are represented by photomicrographs (400×). Data are mean ± standard error. *$P < 0.05$ was significant.

withdrawal group and Control group in the CA3 of the Hip 12 h after ethanol withdrawal. The differences in these two studies might be caused by the expression of BDNF mRNA, which was influenced by the different brain regions or the different withdrawal times (46). Some studies show that BDNF signaling promotes the expression of postsynaptic density protein-95 (PSD-95) in synapses and dendritic spines and regulates the post-synaptic localization of PSD-95 via the TrkB signaling pathway (47).

The number of HCN1-positive cells and HCN1 expression levels significantly increased in the Hip and NAc. A more interesting development was that there was a negative correlation between the expression of the BDNF gene and the level of the HCN1 protein, which suggested that level of the HCN1 protein might down regulate the expression of BNDF mRNA. Mala also reviewed the process whereby inhibiting HCN1 channels leads to antidepressant-like effects and enhances the BDNF mRNA level. However, the cellular mechanism (or mechanisms) that reduces HCN1 channel function leading to an increase in BDNF synthesis is unknown (13).

The change in Ih in the HCN1 channel caused by ethanol withdrawal is mediated by increases in cAMP, which binds to a cyclic nucleotide binding domain (CNBD) on the COOH-terminus of the channel. The HCN1 channels are activated by the CNBD (48). However, we found that HCN1 mRNA and protein were expressed, suggesting an unclear mechanism of the ethanol withdrawal effect by the HCN1 gene expression.

LIMITATION AND OUTLOOK

Despite the important role played by Hip and NAc in mediating ethanol withdrawal-induced anxiety, we were unable to ascertain whether or not there is any interaction between Hip and NAc. Additionally, Neuropeptide Y (NPY) is a neuromodulator that is involved in the regulation of alcohol dependence and withdrawal, as well as the BDNF (49, 50). Both ethanol exposure and withdrawal from chronic ethanol consumption has been shown to produce changes in NPY and NPY receptor protein levels. Therefore, whether it plays a critical role in ethanol withdrawal anxiety behaviors has not been observed, and we will continue to explore this important point in future studies.

CONCLUSION

In summary, we provide several lines of new evidence for the increase in anxiety-like behaviors exhibited by rats undergoing

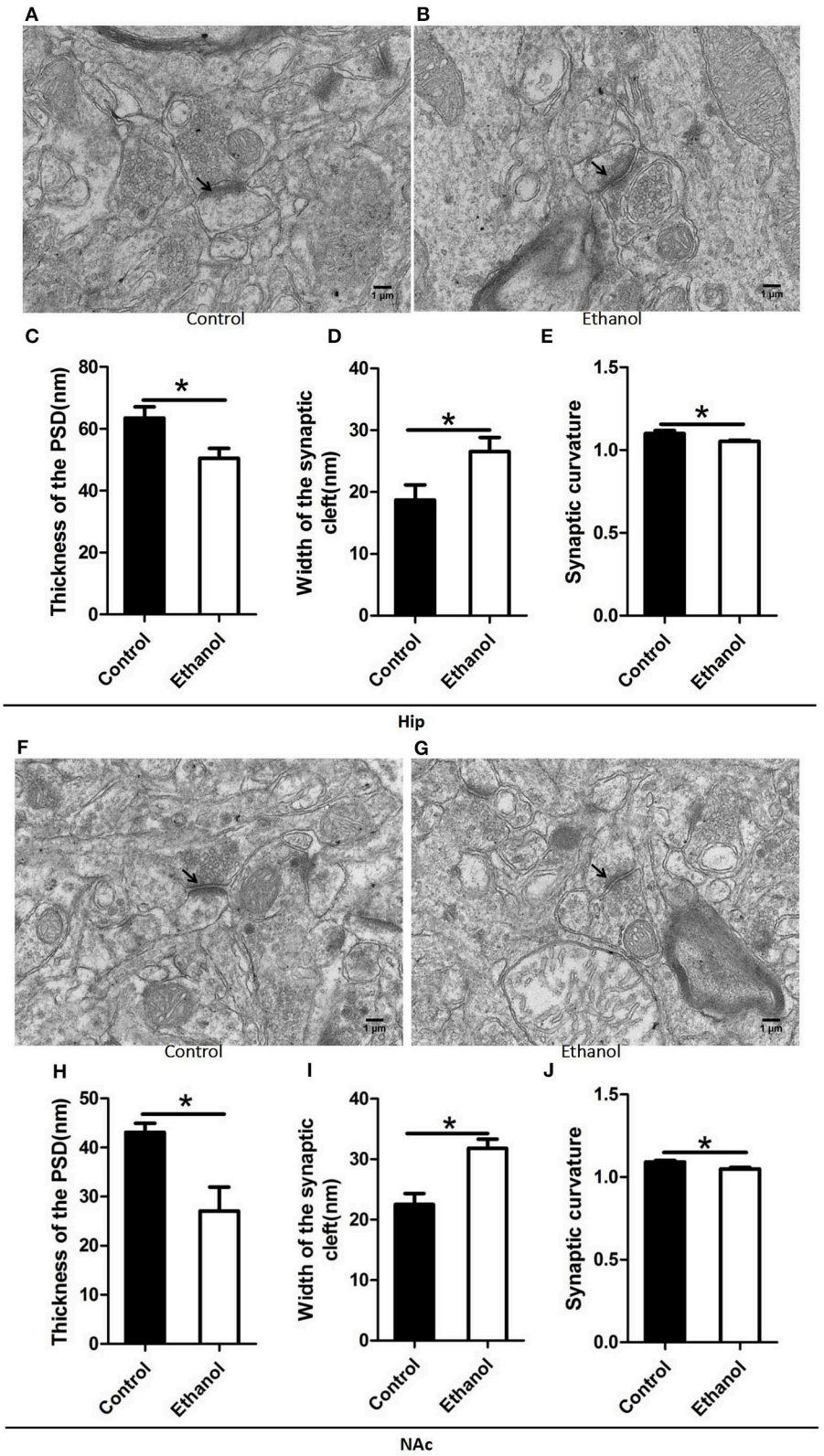

FIGURE 6 | Effects of the ethanol withdrawal procedure on the synaptic ultrastructure in the hippocampus (Hip) and nucleus accumbens (NAc). **(C,H)** Thickness postsynaptic density (PSD) in the Hip and NAc. **(D,I)** Width of the synaptic cleft in the Hip and NAc. **(E,J)** Synaptic curvature in the Hip and NAc. **(A,B,F,G)** Synaptic ultrastructure in the Hip and NAc under ×12,000 magnification. Data are mean ± standard error. *$P < 0.05$ was significant.

ethanol withdrawal that possibly resulted from abnormal changes in synaptic ultrastructure. These findings speculate that the extended synaptic ultrastructure might be regulated by HCN1-related BDNF mRNA expression during ethanol withdrawal-induced anxiety, which might lead to a better understanding of the synaptic systems affected by ethanol withdrawal and provide new perspectives for the development of appropriate therapies for ethanol withdrawal-induced anxiety.

AUTHOR CONTRIBUTIONS

LH, LS, and YG designed the study. LH and YG collected the data. LH analyzed data and drafted the manuscript. BL, YW, CL, GW, QL, JP, HS, and LS reviewed the manuscript. All authors contributed to and have approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2018.00215/full#supplementary-material

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Impulsive Action and Impulsive Choice Are Differentially Expressed in Rats Depending on the Age at Exposure to a Gambling Task

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Impulsivity is considered an important feature associated with the development of numerous psychiatric disorders, including addictions. In the behavioral approach, impulsivity can be broadly divided into two distinct subtypes: impulsive action and choice. In the present study, we used a rodent version of the gambling task (rGT) to examine how impulsive action and impulsive choice are differentially influenced by difference in age at exposure (i.e., late adolescents/young adults vs. mature adults) to rGT. Rats were trained in a touch-screen chamber to learn the relationships between 4 light signals on the window of the screen and accompanying reward outcomes or punishments associated with different magnitudes and probabilities. Depending on their stabilized pattern of preference when allowed free choice, rats were categorized into risk-averse or risk-seeking group. While undergoing a series of experimental schemes, including extinction, re-acquisition, and acute cocaine injection, rats were re-tested for their premature response during inter-trial interval and choice preference toward the 4 different windows in rGT. Notably, rats exposed early, compared with those exposed late, to rGT showed increased impulsive action, particularly during re-acquisition period, in all sub-groups. In contrast, rats exposed late, compared with those exposed early, to rGT showed increased impulsive choice after acute cocaine injection, but these results were only obtained in a sub-group pre-categorized as high impulsive and risk-averse. These results suggest that different aspects of impulsivity can be differentially expressed during decision-making, and differentially influenced by the age at exposure to a gambling task.

Keywords: impulsive action, impulsive choice, decision-making, rat gambling task, cocaine

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INTRODUCTION

Impulsivity is a common and core feature associated with numerous psychiatric disorders, including attention deficit hyperactivity disorder, substance use disorder, and pathological gambling. It has become increasingly evident that impulsivity is a multi-faceted, rather than a unitary, trait (1–3). In the behavioral approach, the two broadly defined major components of impulsivity are impulsive action and impulsive choice (1–5). Impulsive action is behaviorally manifested as the failure to inhibit an inappropriate response, and consequently, showing premature response. By contrast, impulsive choice is manifested as impulsive decision-making

by choosing small immediate rewards over more beneficial delayed rewards. In addition to their behaviorally distinct features, the brain areas mediating impulsive action and impulsive choice are known to be distinct as well (1, 3), and they are also differentially influenced by pharmacological manipulation (4–6), further suggesting that the two components are well-segregated.

In animal studies, impulsive action, expressed as premature response, is widely measured using the 5-Choice Serial Reaction Time Task (5-CSRTT). In contrast, impulsive choice, which involves decision-making, often expressed as devaluing temporally delayed gratification, is frequently measured using delay-discounting task (3, 4, 6). In humans, however, the deficit of decision-making is widely measured using the Iowa Gambling Task (IGT), which simulates real-life decision-making by adding the features of reward, punishment, and uncertainty (3). Similarly, adopting the basic principle of IGT, the rodent version of the gambling task (rGT), which shares many of the features of the human gambling tasks (7), has been developed by a few research groups (8–10). Recently, we adopted one of the previously developed rGT models (10), with a modification of the touch-screen chamber (11), and successfully trained rats to demonstrate decision-making toward risk-preference (12). In rGT, for rats to be trained to perform decision-making behaviors with gambling features, they require pre-training steps with multiple stages, one of which is very similar to the 5-CSRTT. Thus, rGT provides experimenters the advantage of measuring impulsive action and impulsive choice simultaneously in a within-subjects frame.

Adolescence is an extremely important period in development, during which the brain matures and higher order cognitive functions develop to shape adjustable normal behaviors. This period is also vulnerable to the development of many neuropsychiatric disorders and remarkably more prone to risk-taking behavior and impulsiveness (13–15). These behavioral characteristics of adolescence further interact with environmental factors (e.g., stress and drugs of abuse) to determine the onset of neuropsychiatric disorders (13). When considering the laboratory rat, however, it is difficult to precisely compare rat and human age across the different stages of life. Albeit based on a limited number of studies, it is generally considered that approximately postnatal day (PND) 28, after weaning, is the beginning of adolescence, and PND 63–70 is the period when male rats enter into adulthood (13, 16).

Although the two major components of impulsivity are known to exist in segregation, there have been relatively few studies examining their relationship with each other and their differential expression when rats are placed under stressful situations, such as extinction and re-acquisition of a pre-established task; in particular, there is a lack of studies comparing these parameters across different developmental transition periods. To address these issues, in the present study, we exposed rats to rGT at two different ages (i.e., late adolescent/young adult vs. mature adult), and assessed how impulsive action and impulsive choice are expressed under different situations. In addition, as there is ample evidence that maladaptive decision-making is associated with an increase in cocaine usage in both humans and animals (17–20), we also examined how acute cocaine administration influences the expression of impulsivity.

MATERIALS AND METHODS

Animals

Male Sprague-Dawley rats [Crl:CD(SD); PND 21] were obtained from Orient Bio Inc., (Seongnam-si, Korea). The rats were housed three per cage (GR900; 21.3 cm high × 34.6 cm long × 39.6 cm wide; Tecniplast Inc., Buguggiate, VA, Italy) for 1 week to allow habituation to a new colony environment, during which they were handled by experimenters, and had access to food *ad libitum*. Subsequently, they were housed two per cage and simultaneously placed on a restricted diet with 85% of their normal daily food consumption, which was started 2 days before the pre-training experiments and maintained until the end of experimentation. Food was provided immediately after the daily training session to sufficiently maintain the animals' growth and motivation. Water was available *ad libitum* at all times. Colony rooms had a controlled room temperature (21°C) and a 12 h light/dark cycle (lights on at 8:00 am), and all experiments were conducted during the day. All animal use procedures were conducted according to an approved Institutional Animal Care and Use Committee protocol of Yonsei University College of Medicine.

Drugs

Cocaine hydrochloride was purchased from Belgopia (Louvain-La-Neuve, Belgium). It was dissolved in sterile 0.9% saline to a final concentration of 15 mg/ml.

Apparatus

The rGT was conducted in a set of eight identical touchscreen-based automated operant chambers housed in dense sound- and light-attenuating boxes (68.6 cm high × 60.7 cm long × 53.5 cm wide; Campden Instruments Ltd., Leics, UK). Each chamber was equipped with a house light (light-emitting diode), touch-sensitive liquid crystal display monitor (touchscreen; 15.0 inch, screen resolution 1,024 × 768), pellet dispenser, and food magazine unit (with light and infrared beam to detect entries) facing the touchscreen. The chambers had a trapezoidal shape [30 cm high × 33 cm long (from screen to magazine)×25 cm wide for the screen and 13 cm wide for the magazine; **Figure 1A**], which was designed to help focus the animal's attention on the touchscreen and reward delivery area (i.e., the food magazine) (11). On top of the chamber, a transparent lid was secured to the trapezoidal walls with latches to retain the animals inside the chambers. The floor was constructed from perforated stainless steel, and a tray for collecting litter was located below the floor. The touchscreen used sensitive optical infrared sensors that allowed the screen to reliably detect an animal's touch without pressure. A black plastic mask (36 cm high × 28 cm wide) with five response windows (the size of each window was 3.0 cm high × 3.0 cm wide, positioned in a row with the windows spaced 1.0 cm apart, 3.5 cm from the grid floor) was fitted in front of the touchscreen, which helped reduce accidental screen touches and clearly distinguish the response locations from the

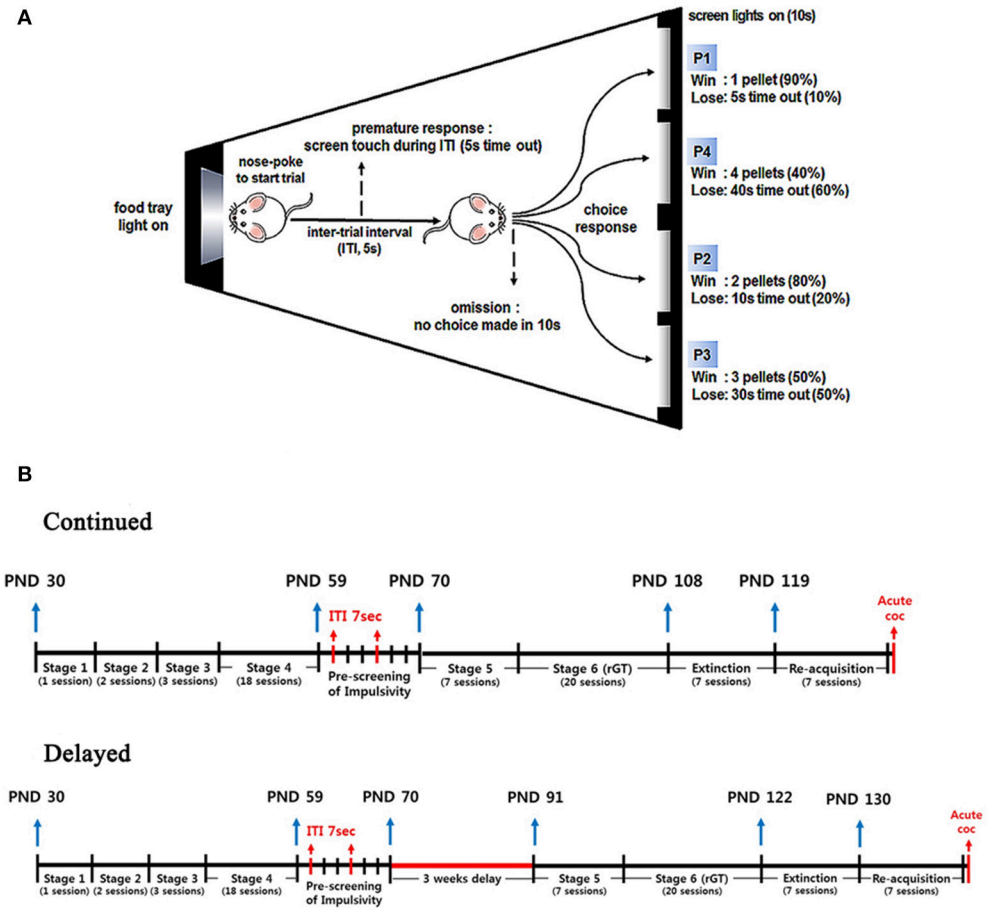

FIGURE 1 | Schematic diagram for the rGT chamber and time lines for the whole experimental procedures. **(A)** Schematic diagram of the rGT chamber, where a food magazine unit (left) and 4 response windows (right) are shown. Each window is represented as P1 through P4 with a different number of pellets, duration of time-out, and frequencies. **(B)** Time lines for the whole experimental procedures were illustrated with rat's age indicated. A single session can be added to the age as 1 day. Note that there were days with no experiments conducted during the weekends.

background. The visual stimulus, a solid white square, was shown only through the two left and two right response windows, the middle window was left black. We used the Whisker Standard Software (Campden Instruments, Ltd., Leics, UK) (21) as the controlling software, and the four chambers were controlled using two computers each.

rGT Pre-training

Pre-training methods have been described in detail in our previous study (12). In brief, animals were trained once daily in a 30 min session, 5 days per week. Sucrose pellets (45 mg) with chocolate flavor (Bio-Serve, Flemington, NJ, USA) were used as a reward. In stage 1, the animals were first habituated to the touchscreen chamber for one session. In stages 2 and 3, which lasted over five daily sessions, animals were trained to learn the relationship between the light stimulus on the screen and the reward pellet, and to touch the screen to receive a pellet as a reward. In this stage, the inter-trial interval (ITI) of the 5 sec rule was first applied such that animals had to wait for 5 sec after pushing their noses into the food magazine to start a new trial. In stage 4, which lasted over 16 to 18 daily sessions, animals serially learned to touch one of the four windows which were randomly lit, within different stimulus durations (starting from 60 sec, then serially reduced to 30, 20, and finally, 10 sec), to receive one pellet. Animals completed the task either within 100 trials or 30 min, whichever came first. In this stage, they learned for the first time that they were punished with a time-out (i.e., the white house-light was lit for 5 sec) if they touched the screen without waiting during ITI (premature) or if they did not touch the screen within the stimulus duration (omission). They were also punished if they touched other windows which were not lit. When the accuracy was >80% and omissions were fewer than 20%, the animals were considered to have acquired the task (i.e., with an ITI of 5 sec and a stimulus duration of 10 sec).

rGT Training

Essentially, during rGT training, the animals were confronted with four choices differing in their probability and magnitude of

reward (food) and punishment (time-out), and they had to learn an optimal strategy to determine the choice that provided the most reward per session (10). In stage 5, which lasted over 7 daily sessions, the animals learned for the first time the relationship between each window and the reward/punishment ratio assigned to that window, which was as follows: window (P1), 1 pellet (90%) or 5 sec time-out (10%); window (P2), 2 pellets (80%) or 10 sec time-out (20%); window (P3), 3 pellets (50%) or 30 sec time-out (50%); and window (P4), 4 pellets (40%) or 40 sec time-out (60%). In this stage, one of the four windows was randomly lit for 10-sec and animals were punished (i.e., the white house light was lit for 5 sec) for a premature response. Additionally, for the first time in this stage, animals were punished (time-out; i.e., the white house light was lit, and all the windows on the screen simultaneously flashed for 5 to 40 sec) even on correctly touching the screen according to the pre-designated schedule for each window. So far, from stages 1 to 5, only one of the four windows on the screen was randomly lit. However, in stage 6, all four windows were simultaneously lit when each new trial started, and animals were allowed to wait for an ITI of 5 sec of and then choose one of the four windows, which were lit for 10 sec. The reward and punishment settings designated for each window were the same as those introduced in stage 5. Depending on which window the animals chose, they would receive either reward (pellet) or punishment (time-out) with differently programmed probabilities. Once a trial was finished, regardless of the outcome, they again encountered four different choices in the next trial, and this process was repeated for 30 min. Hypothetically, if one window was chosen exclusively, the amount of reward pellets per session that an animal could obtain was as follows: P1, 295; P2, 411; P3, 135; and P4, 99 pellets (22). The percentage of choices [(number of choices for a specific window divided by the total number of choices made) $\times$ 100] was used to measure the animals' preferences for the different windows. After 20 daily sessions were completed, the average of the last three daily sessions' choice percentages was considered a basal score for the animals' risk-preference. Animals were categorized as risk-averse when their basal score for P2 (the most optimal choice) was equal to or higher than 60%, whereas they were categorized as risk-seeking when it was lower than 60%. To avoid any location bias, windows were allocated in a counterbalanced way as follows: for half of the animals, the windows were 1 (P1), 2 (P4), 3 (P2), and 4 (P3); for the other half of the animals, the windows were 1 (P4), 2 (P1), 3 (P3), and 4 (P2). In addition to premature response and omission (both were expressed as a percentage of the total number of trials initiated), choice-related behavioral parameters, such as choice response [(number of times the window was correctly touched divided by the total number of trials initiated) $\times$ 100], perseverative response (repeatedly touching the screen during punishment, calculated as the total number of screen touches divided by the total duration of punishment), feed-tray entry [repeatedly entering the food magazine, calculated as the number of feed-tray entries divided by the number of trials (including omissions) $\times$ 100], reward collection latency (the time required for animals to obtain the reward after a correct screen touch), and correct response latency (the time required for animals to correctly touch the screen, after the end of the ITI, while the screen was lit) were analyzed.

Pre-screening of Impulsivity

Following successful acquisition of the stage 4 task, with an ITI of 5 sec, rats were further tested to examine their trait impulsivity (impulsive action) in a modification of stage 4, consisting of two daily sessions with an ITI of 5-sec, followed by a session with an ITI of 7 sec, repeated twice consecutively to amplify the appearance of premature response (23). With the mean score of premature responses obtained from the measurements for the two sessions with ITI of 7 sec, rats were categorized as high impulsive (HI) if they scored above the standard error of the total group mean, and as low impulsive (LI) if they scored below. Rats which scored within the standard error were excluded from the subsequent experiments.

Design and Procedures

A schematic illustration showing time lines for the whole experimental design was depicted in **Figure 1B**.

Two days after starting the food restriction, all rats ($n = 64$) were serially trained in stages 1 to 4. Once they were categorized as HI ($n = 30$) and LI ($n = 28$), they were sub-divided into continued or delayed groups, resulting in four groups, i.e., HI-continued ($n = 15$), LI-continued ($n = 13$), HI-delayed ($n = 15$), and LI-delayed ($n = 15$). Rats in the continued group were continued undergoing training into stages 5 and 6 without delay after stage 4, while those in the delayed group were not trained for 3 weeks, after which their training into stages 5 and 6 was resumed. Thus, rats were exposed to rGT at different times. By the time they reached stage 5, rats in the continued group were $\sim$10 weeks old, while those in the delayed group were 13 weeks old.

Once the rats had completed all the sessions in stage 6, they were further sub-divided into risk-averse or risk-seeking groups according to the average score for P2 for the last 3 days of stage 6 training, resulting in eight different sub-groups, i.e., HI-continued-averse ($n = 7$), HI-continued-seeking ($n = 7$), LI-continued-averse ($n = 5$), LI-continued-seeking ($n = 7$), HI-delayed-averse ($n = 7$), HI-delayed-seeking ($n = 7$), LI-delayed-averse ($n = 5$), and LI-delayed-seeking ($n = 8$). A total of 5 rats (1 each from HI-continued, LI-continued, and HI-delayed, and 2 from LI-delayed) which had undergone fewer than five trials were excluded from all further analyses, and finally, results from 53 rats were used for analyzing the data presented herein.

After completion of stage 6, rats underwent extinction, comprising a total of seven daily sessions, in which they performed the same task as stage 6, but did not receive reward pellets. All other parameters were unchanged. Choice responses and omission (%) were used to assess whether extinction had occurred. After completion of extinction, the rats underwent re-acquisition comprising of seven daily sessions, in which they were re-exposed to the stage 6 task, with the reward pellets made available again. Finally, after completion of re-acquisition, the rats performed a single session of the stage 6 task following acute intraperitoneal administration of cocaine (15 mg/kg) 30 min before performing.

Statistical Analysis

Data are shown as mean + standard error of the mean, and they were analyzed using Sigma Plot, version 12.5 (Systat Software, Inc., Chicago, IL, USA). An arcsine transformation was performed for the data obtained as percentages before the analysis. The data were analyzed using two-way analysis of variance (ANOVA), with or without repeated measures, followed by *post-hoc* Bonferroni comparisons. ANOVA was validated by both normality and equal variance tests. Differences between experimental conditions were considered statistically significant when $p < 0.05$.

RESULTS

Pre-screening of Impulsivity

When allowed to wait for 7 sec, rather than the normal 5 sec, before touching the lit window on the screen, rats could be clearly categorized into LI and HI groups, according to their mean premature response scores of the duplicate measurements. Out of the total 64 rats, the mean ± standard error of the premature response score as a percentage was 27.53 ± 1.19%. Rats were categorized as HI if their mean scores were higher than the boundary of standard error of the total group mean (i.e., 28.72%), and as LI if their mean scores were lower than the boundary of standard error (i.e., 26.34%). After categorization, the mean values for the LI and HI groups were 18.25 and 36.25, respectively. **Figure 2** shows the mean values of the premature response scores during daily sessions.

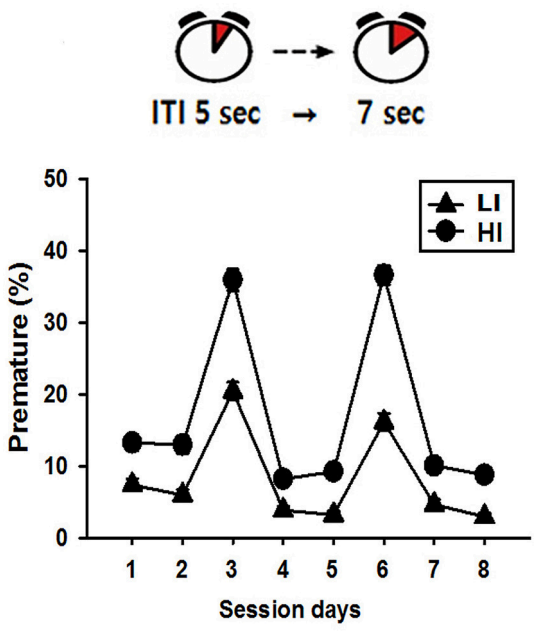

FIGURE 2 | Pre-screening of impulsivity scores. The mean values of premature response scores during daily sessions indicate that there were clear difference between LI and HI, especially when ITI was changed from 5 to 7 sec on session day 3 and 6.

Effect of Difference in Age at Exposure to rGT on Basal Scores for Risk-Preference

After completion of stage 6, rats were separated into risk-averse and risk-seeking groups, depending on their stabilized preference for P2 being above or below 60%, respectively (**Figure 3A).** There were no differences in the preferences toward risk choice between the LI and HI groups. Further, the continued and delayed groups did not exhibit differences in preferences. When we analyzed premature responses, it was found, as expected, that the HI group had higher scores than the LI group, regardless of their preferences. This was also the case when the risk-seeking group was compared with the risk-averse group (**Figure 3B**). The results of the two-way ANOVA conducted on these data showed a significant effect of risk preference [risk-averse vs. risk-seeking; $F_{(1, 24)} = 7.76$, $p < 0.011$]. Interestingly, within the risk-seeking group in the pre-selected HI group, the continued group showed significantly higher scores than the delayed group for premature response revealed by *post hoc* Bonferroni comparisons ($p = 0.033$; bottom panel in **Figure 3B**).

Re-acquisition After Extinction and Acute Cocaine Administration Differentially Modifies Premature Responses and Risk Preference Depending on the Age at Exposure to rGT

Next, we examined how extinction, re-acquisition, and acute cocaine administration affect both premature responses and preference scores during rGT. During the extinction period, premature response scores rapidly decreased to nearly zero in both continued and delayed groups. Interestingly, however, during the re-acquisition period, rats in the continued group showed significant increase in premature responses compared with the delayed group, regardless of pre-selected types of impulsivity or preference (**Figure 4**). For the LI-averse group, results of the two-way repeated-measures ANOVA showed significant effects of age at exposure to rGT [continued vs. delayed; $F_{(1, 8)} = 9.07$, $p = 0.017$] and different experimental periods [basal vs. acute cocaine administration; $F_{(7, 8)} = 6.76$, $p < 0.001$]. *Post hoc* Bonferroni comparisons revealed that the rats in the continued group showed premature response significantly more often ($p < 0.05$–0.01) than those in delayed group on re-acquisition days 1, 4, and 7. For the HI-averse group, results of the two-way repeated-measures ANOVA showed significant effects of different experimental period [$F_{(7, 12)} = 26.08$, $p < 0.001$] and age at exposure to rGT × different experimental period interaction [$F_{(7, 84)} = 3.01$, $p = 0.007$]. *Post hoc* Bonferroni comparisons revealed that the rats in the continued group had significantly higher ($p < 0.01$–0.05) premature response scores than those in the delayed group; the continued group also had higher scores than their basal scores ($p < 0.001$–0.05), on re-acquisition days 1 and 7. For the LI-seeking group, results of the two-way repeated-measures ANOVA showed significant effects of different experimental period [$F_{(7, 13)} = 12.80$, $p < 0.001$]. *Post hoc* Bonferroni comparisons revealed that the rats in the continued group had

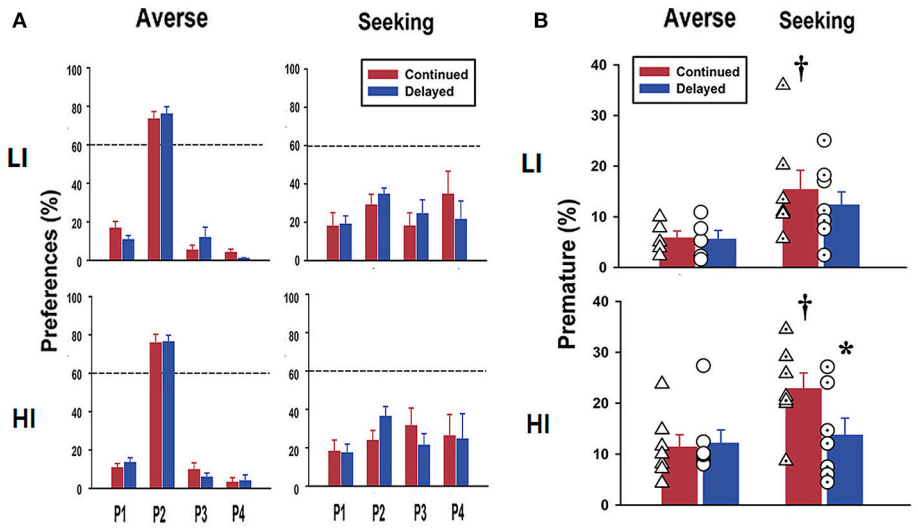

FIGURE 3 | Basal scores for risk preference and premature response scores after rGT. **(A)** Data obtained after rGT training clearly show different risk preferences between the groups. The risk-averse group overwhelmingly chose P2 over the other windows more than 60% of the choices, whereas the risk-seeking group chose P2 <60% of the choices. There were no significant differences between LI and HI groups. The continued group also made no differences when compared to the delayed group. **(B)** Premature response scores obtained after rGT show that the HI group had higher scores than the LI group, and it was the same for the risk-seeking group compared to the risk-averse group. Within the same risk-seeking group, the continued group had significantly higher increased scores for premature response than those in the delayed group, only in pre-categorized as the HI group. Values are expressed as a mean+standard error of mean. $^{*}p < 0.05$; compared to continued group within risk-seeking. $^{\dagger}p < 0.05$; compared to risk-averse within the continued group. Individual scores are shown as symbols (triangles and circles for continued and delayed group, respectively) overlaid on top of the bar graph.

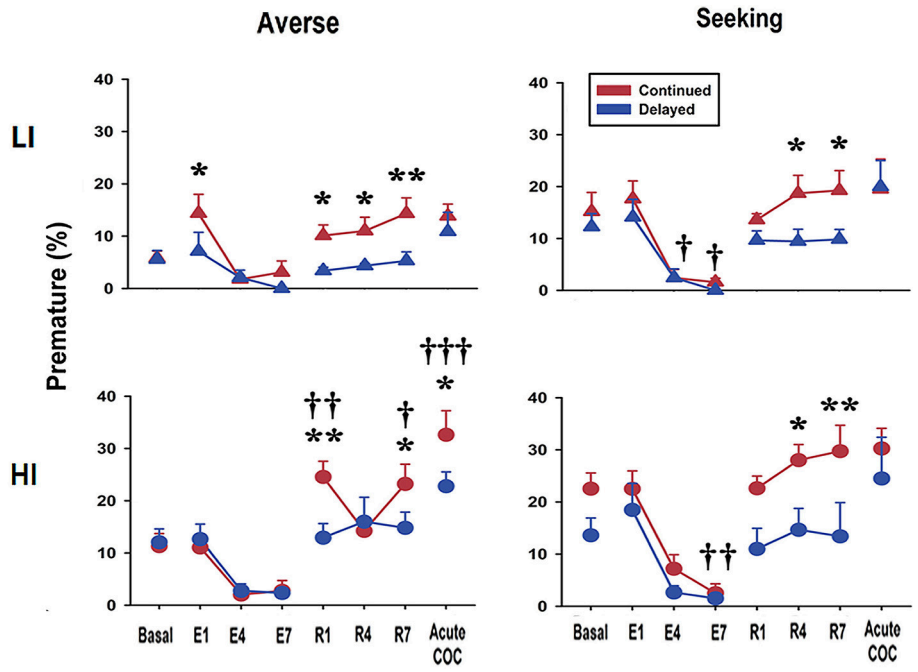

FIGURE 4 | Premature response scores during extinction, re-acquisition, and after acute cocaine injection. Premature response scores obtained during re-acquisition period show that the continued group had higher scores than the delayed group, regardless of sub-groups. Only in HI-averse group, the continued group compared to the delayed group significantly increased scores for premature response after acute cocaine injection. E and R represent extinction and re-acquisition, respectively. Values are expressed as a mean + standard error of mean. $^{*}p < 0.05$, $^{**}p < 0.01$; compared to the delayed group at each developmental period. $^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.01$, $^{\dagger\dagger\dagger}p < 0.001$; compared to the basal score within either the continued or the delayed group.

significantly higher premature response scores ($p < 0.05$) than those in the delayed group on re-acquisition days 4 and 7. For the HI-seeking group, results of the two-way repeated-measures ANOVA showed significant effects of age at exposure to rGT [$F_{(1, 12)} = 5.39$, $p = 0.039$] and different experimental period [$F_{(7, 12)} = 12.44$, $p < 0.001$]. *Post hoc* Bonferroni comparisons revealed that the rats in the continued group showed premature response significantly more often ($p < 0.01$–0.05) than those in the delayed group on both re-acquisition days 4 and 7. Finally, after acute cocaine administration, rats in the continued group showed significant increase of premature responses than those in the delayed group; however, this effect appeared only in the HI-averse group (**Figure 4**). *Post hoc* Bonferroni comparisons revealed that the rats in the continued group showed significantly higher premature response scores than those in the delayed group ($p < 0.05$); the continued group also showed higher scores than their basal scores ($p < 0.001$) after acute cocaine administration.

In contrast to the premature responses, the change of preference toward risk-seeking behavior was observed only when rats were acutely administered cocaine (**Figure 5**). Interestingly, among all the different combinations of groups, only in the HI-averse-delayed group, there were significant effects of drug [basal and acute cocaine; $F_{(1, 6)} = 8.93$, $p = 0.024$], window (P1, P2, P3, and P4; $F_{(3, 6)} = 42.51$, $p < 0.001$), and drug×window interaction [$F_{(3,18)} = 10.93$, $p < 0.001$]. *Post hoc* Bonferroni comparisons revealed that the rats acutely administered cocaine chose P2 significantly less often ($p < 0.001$), but chose P4 significantly more often ($p = 0.002$) than their basal preferences.

Analysis of Behavioral Parameters

We further analyzed several choice-related behavioral parameters (10, 24) from the data obtained for the different experimental period. Overall, acute cocaine injection decreased choice response ratios compared with basal score in the following sub-groups; HI-averse-continued, HI-averse-delayed, LI-seeking-continued, LI-seeking-delayed, and HI-seeking-delayed (**Tables 1A, B**). Remarkably, both omission and reward collection latency were significantly increased, compared with the basal score, after acute cocaine administration only in the HI-averse-delayed sub-group (**Table 1A**). Two-way repeated-measures of ANOVA in these data showed significant effects of age at exposure to rGT [$F_{(1, 12)} = 4.79$, $p = 0.049$] and different experimental period [$F_{(3, 12)} = 4.56$, $p = 0.008$] for omission, and showed significant effect of different experimental period [$F_{(3, 12)} = 3.31$, $p = 0.031$] for reward latency. *Post hoc* Bonferroni comparisons of these data revealed that the rats in the delayed group exhibited significantly higher omission and reward latency ($p < 0.01$–0.05) than those in the continued group.

DISCUSSION

The present results clearly show that impulsive action was strongly increased in rats exposed early to rGT, as young adults (continued), compared with those exposed late to rGT, as mature adults (delayed), during re-acquisition after extinction in all sub-groups. Further, our results reveal that, although rats in the continued group have no difference in the preference scores in

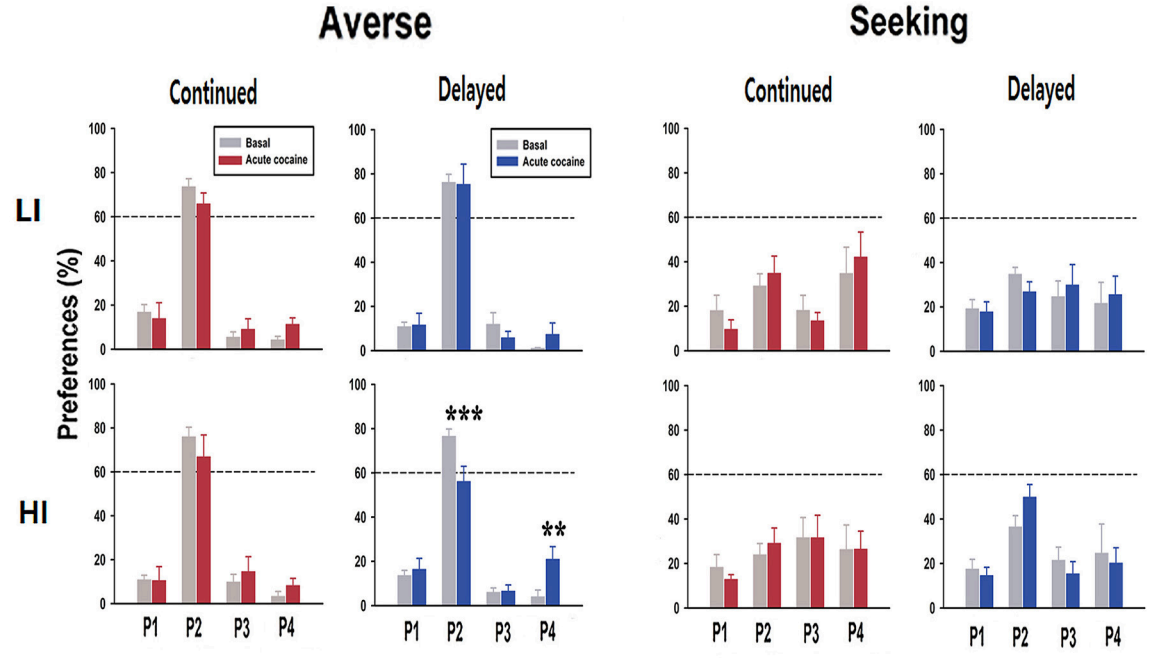

FIGURE 5 | Preference scores after acute cocaine injection. In response to acute cocaine injection, rats only in the HI-averse-delayed group showed more risk-seeking choice preference (i.e., they chose P2 less and P4 more). Values are expressed as a mean + standard error of mean. $^{**}p < 0.01$, $^{***}p < 0.001$; compared to the basal score within either P2 or P4.

TABLE 1A | Analysis of behavioral parameters in the risk-averse groups.

	Group	Period	Choice response	Omission (%)	Perseverative response	Correct response latency (sec)	Reward collection latency (sec)	Feed-tray entry
LI	**Continued**	Basal	60.40 ± 3.04	7.80 ± 1.64	1.40 ± 0.16	2.66 ± 0.16	2.59 ± 0.33	0.63 ± 0.13
		R1	53.80 ± 4.86	13.65 ± 4.23	1.51 ± 0.16	2.69 ± 0.41	3.32 ± 0.83	0.76 ± 0.07
		R7	59.80 ± 7.57	7.01 ± 1.73	1.65 ± 0.28	2.36 ± 0.19	2.88 ± 0.63	0.64 ± 0.07
		Acute coc	34.20 ± 9.26	20.38 ± 9.02	1.07 ± 0.22	2.78 ± 0.13	3.02 ± 0.51	0.35 ± 0.05
	Delayed	Basal	63.80 ± 8.33	7.39 ± 1.83	1.25 ± 0.18	2.81 ± 0.29	1.74 ± 0.17	1.19 ± 0.15
		R1	59.00 ± 3.70	13.18 ± 1.76	1.35 ± 0.23	3.45 ± 0.18	1.47 ± 0.07	0.99 ± 0.21
		R7	41.20 ± 5.03	11.19 ± 2.11	1.34 ± 0.35	2.98 ± 0.26	1.49 ± 0.08	1.26 ± 0.24
		Acute coc	40.20 ± 12.25	28.45 ± 10.56	1.50 ± 0.35	2.84 ± 0.57	3.49 ± 1.88	0.89 ± 0.18
HI	**Continued**	Basal	86.14 ± 3.16	2.39 ± 0.31	1.22 ± 0.13	1.81 ± 0.17	2.46 ± 0.81	1.07 ± 0.41
		R1	83.14 ± 6.95	2.61 ± 0.70	1.20 ± 0.22	1.86 ± 0.17	2.61 ± 1.11	1.66 ± 0.53
		R7	90.57 ± 5.43	0.78 ± 0.42	1.23 ± 0.17	1.58 ± 0.14	1.89 ± 0.18	1.49 ± 0.70
		Acute coc	55.29 ± 9.69***	7.42 ± 3.31	1.39 ± 0.19	2.01 ± 0.38	2.84 ± 0.51	0.73 ± 0.10
	Delayed	Basal	71.10 ± 6.10	3.64 ± 1.10	1.32 ± 0.22	2.15 ± 0.25	2.39 ± 0.53	0.77 ± 0.09
		R1	67.14 ± 10.07	8.81 ± 4.11	1.50 ± 0.35	2.57 ± 0.37	2.35 ± 0.54	1.21 ± 0.22
		R7	60.14 ± 5.73††	5.13 ± 1.50	0.93 ± 0.14	2.31 ± 0.26	2.88 ± 1.35	0.99 ± 0.23
		Acute coc	31.00 ± 4.15***,†	19.56 ± 7.74**,†	1.72 ± 0.35	2.63 ± 0.29	9.00 ± 3.26**,††	0.48 ± 0.10

*Each parameter's units of measurement are as follows: choice response (%), omission (%), perseverative response (actual number of touch), correct response latency (sec), reward collection latency (sec), feed tray entry (the number of feed-tray entries during ITI divided by the total number of trials initiated). **$p < 0.01$, ***$p < 0.001$; compared to the basal score within either continued or delayed group. †$p < 0.05$, ††$p < 0.01$; compared to the continued group after acute cocaine injection.*

TABLE 1B | Analysis of behavioral parameters in the risk-seeking groups.

	Group	Period	Choice response	Omission (%)	Perseverative response	Correct response latency (sec)	Reward collection latency (sec)	Feed-tray entry
LI	**Continued**	Basal	50.86 ± 5.21	5.36 ± 1.70	1.75 ± 0.17	2.06 ± 0.22	23.59 ± 8.14	0.89 ± 0.16
		R1	53.71 ± 4.06	9.09 ± 2.53	1.81 ± 0.41	2.45 ± 0.20	18.82 ± 8.92	1.03 ± 0.26
		R7	50.43 ± 4.70	6.37 ± 3.52	1.94 ± 0.27	1.98 ± 0.29	21.58 ± 9.31	0.94 ± 0.15
		Acute coc	34.71 ± 3.85*	19.08 ± 10.49	1.74 ± 0.28	2.07 ± 0.33	31.34 ± 11.39	0.65 ± 0.10
	Delayed	Basal	60.54 ± 6.04	4.49 ± 1.55	1.65 ± 0.16	1.96 ± 0.15	12.47 ± 4.56	1.25 ± 0.12
		R1	54.25 ± 6.89	13.91 ± 3.74	1.76 ± 0.33	2.68 ± 0.29	10.20 ± 3.51	1.58 ± 0.23
		R7	48.13 ± 6.98	6.26 ± 2.23	1.84 ± 0.29	2.58 ± 0.24	12.46 ± 4.36	1.37 ± 0.19
		Acute coc	33.75 ± 4.06***	13.53 ± 4.47	1.72 ± 0.45	2.49 ± 0.39	13.57 ± 4.21	0.83 ± 0.11
HI	**Continued**	Basal	54.05 ± 4.85	1.39 ± 0.47	2.21 ± 0.23	1.49 ± 0.15	20.96 ± 7.47	1.18 ± 0.41
		R1	54.43 ± 6.51	5.90 ± 2.05	1.77 ± 0.24	1.90 ± 0.24	20.80 ± 8.89	2.19 ± 0.69
		R7	59.14 ± 6.49	1.26 ± 0.81	2.32 ± 0.40	1.54 ± 0.21	20.73 ± 10.13	1.81 ± 0.84
		Acute coc	39.86 ± 4.78	5.42 ± 1.37	2.26 ± 0.25	1.56 ± 0.14	9.62 ± 2.18	0.63 ± 0.11
	Delayed	Basal	66.33 ± 7.62	2.34 ± 0.62	1.82 ± 0.24	1.80 ± 0.14	15.26 ± 8.26	0.66 ± 0.13
		R1	52.43 ± 8.45	11.29 ± 3.92	2.20 ± 0.59	2.52 ± 0.28	9.59 ± 5.87	0.73 ± 0.07
		R7	52.00 ± 7.92	2.76 ± 1.07	1.78 ± 0.27	2.09 ± 0.30	17.05 ± 8.66	0.76 ± 0.11
		Acute coc	44.00 ± 7.80*	16.55 ± 10.86	1.63 ± 0.43	2.36 ± 0.53	7.69 ± 2.85	0.62 ± 0.06

*Each parameter's units of measurement are as follows: choice response (%), omission (%), perseverative response (actual number of touch), correct response latency (sec), reward collection latency (sec), feed tray entry (the number of feed-tray entries during ITI divided by the total number of trials initiated). *$p < 0.05$, ***$p < 0.001$; compared to the basal within either continued or delayed group.*

rGT after acute cocaine administration compared with their basal scores, those in the delayed group with HI-averse characteristics exhibit altered preferences, resulting in decreased preference for P2 and a simultaneously increased preference for P4. This is the first direct demonstration, to our knowledge, that two distinct subtypes of impulsivity can be differentially manifested depending on the developmental period at which the animals were first exposed to rGT.

In the present study, we adopted the methods previously introduced (23), with the slight modification of pre-selecting rats showing high and low impulsive action. Similar to the previous study, when we applied a rule of 7 sec for ITI, rats showed premature responses, with higher overall scores, and the differences between the HI and LI groups were amplified. These results indicate that there are inherent individual differences in rats for responding prematurely, consequently revealing their traits as HI or LI.

Although detailed studies on the relationship between impulsive action and impulsive choice are still scarce, it has previously been shown, using a within-subjects approach in rats, that they are not correlated; in this study, 5-CSRTT and a delayed reward task were used to measure impulsive action and impulsive choice, respectively (25). Consistent with these results, we found that rats pre-selected as HI and LI both showed similar level of preference toward dis-advantageous choice in rGT, regardless of the age at which they were exposed to rGT (**Figure 3A**). This is interesting because there is a similarity between the experimental scheme of the previous study and ours, in that both studies were conducted with a within-subjects approach using two different behavioral measurements continuously within the same subjects. In our study, stage 4 during pre-training, which is equivalent to 5-CSRTT in terms of basic concept and procedure, measures impulsive action, while stage 6, which is the main training for rGT, measures impulsive choice. These results indicate that difference at the level of impulsive action does not affect the appearance of impulsive choice later, at least in absence of external disturbances (e.g., stressful environment), supporting the notion that they are separable and distinct forms of impulsivity.

Nonetheless, it is often considered that one form of impulsivity (impulsive action) contributes to the development of disorders related to decision-making, mostly by enhancing the other form of impulsivity (impulsive choice) (26). Notably, it has been demonstrated that pre-selected HI rats are more prone to the development of compulsive drug taking even in the face of aversive outcomes (23, 27). Moreover, behavioral addiction, for example, gambling disorder, which is a typical manifestation of disorder with high impulsivity choice, is known to be associated with impulsive action (28). These results suggest that impulsive action somehow contributes to the appearance of impulsive choice, especially in an environmental setting with drugs of abuse (the former) and an unknown stressful situation (e.g., financial difficulty; the latter). Similarly, in the present study, when HI rats in the delayed group, previously categorized as risk-averse, were administered a single dose of cocaine after experiencing extinction and re-acquisition, they showed increased preference toward risk-seeking, which was not observed in LI rats (**Figure 5**). These results support the hypothesis that high impulsive action potentially contributes to the increased chance of making an impulsive choice when subjects are under the influence of drugs of abuse or/and stressful situation.

Further analysis of several choice-related behavioral parameters (10, 24) from the data obtained after acute cocaine injection revealed an interesting finding. Remarkably, only in the sub-group which showed preference change toward risk-seeking, i.e., HI-averse-delayed group, the reward collection latency was significantly higher, when either compared with the continued group after acute cocaine administration or the basal score of the same sub-group (**Table 1**). The higher reward collection latency may indicate that rats were more interested in an object, for example, the screen (or light on the screen) in this case, other than the pellet reward itself, consequently resulting in increased latency in collecting the reward. As shown in our previous study, there is a positive correlation between reward collection latency and disadvantageous choice in rGT (12); the higher reward collection latency observed in the HI-averse-delayed group may further indicate that this sub-group is more likely to be in the process of moving toward risk-seeking behavior, consistent with their actual decreased and increased preference scores for P2 and P4, respectively (**Figure 5**).

In contrast with the delayed group, the HI-averse-continued group did not exhibit significant change in the preference toward risk-seeking behavior even after acute cocaine administration (**Figure 5**). Instead, they showed conspicuous increase in premature responses compared with their basal scores, during re-acquisition as well as after acute cocaine administration (**Figure 4**). Although there were differences in the strength of the data, a similar trend, i.e., higher premature responses in continued than in delayed groups, also appeared throughout the other sub-groups (LI-averse, LI-seeking, and HI-seeking). These results show that rats in the continued group remained strongly consistent with their inherent trait rather than altering their behavior toward that of another subtype, i.e., impulsivity choice, as opposed to the delayed group.

Interestingly, a previous study showed that adolescent rats exposed to stress hormone exhibited reduced impulsive action but increased impulsive choice (15), which vaguely hints at the factors that differentially influence impulsive action and impulsive choice depending on the situation. However, our experimental schemes differ from those employed in the aforementioned study, with the rats in the continued group being exposed to rGT at ∼10 weeks of age, which is equivalent to the late adolescent/young adult stage, while those in the delayed group were exposed to rGT at ∼13 weeks, which is equivalent to the mature adult stage (13, 16). In order to see if there is any potential impact on the results by such interruption in performance, rats in delayed group performed stage 4 briefly again for 3 days just before entering into stage 5. Interestingly, it was verified that they all successfully passed the criterion for more than 80% of accuracy and <20% of omission scores, except two, which showed more than 20% in omission at this stage, but later back to <20% of omission score stably during stage 5 and thereafter. These results show

that rats in delayed group still remember and are able to perform with no difficulty even with 3 weeks of interruption in performance. Thus, we can speculate that it is the difference in the age, a developmentally sensitive period, at first exposure to rGT that may somehow contribute to differential expression of the two subtypes of impulsivity. At present, we have no satisfactory explanation as to how all the differences in our results manifested.

In conclusion, our data clearly indicate that impulsive action and choice are distinct aspects of impulsivity, which are differentially influenced in rats by the age at the first exposed to gambling task. Our data also demonstrate that the differences may not be evident, and in order to resolve the two components, rats must be exposed to a stressful situation (e.g., extinction and subsequent re-acquisition) and/or drugs of abuse (e.g., acute cocaine injection). Finally, the mechanism through which the brain affects this process of differential influence of developmental periods on impulsivity remains largely unknown. More studies will certainly be conducted on these interesting phenomena in the future.

AUTHOR CONTRIBUTIONS

BC, WK, and J-HK designed the experimental strategy and analyzed the data. BC, MK, and WK performed all the experiments. All author prepared the figures and tables in the manuscript. J-HK wrote the manuscript. All authors commented on and approved the final version of the manuscript.

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Increased Insular Cortical Thickness Associated With Symptom Severity in Male Youths With Internet Gaming Disorder: A Surface-Based Morphometric Study

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With the rising increase in Internet-usage, Internet gaming disorder (IGD) has gained massive attention worldwide. However, detailed cerebral morphological changes remain unclear in youths with IGD. In the current study, our aim was to investigate cortical morphology and further explore the relationship between the cortical morphology and symptom severity in male youths with IGD. Forty-eight male youths with IGD and 32 age- and education-matched normal controls received magnetic resonance imaging scans. We employed a recently proposed surface-based morphometric approach for the measurement of cortical thickness (CT). We found that youths with IGD showed increased CT in the bilateral insulae and the right inferior temporal gyrus. Moreover, significantly decreased CT were found in several brain areas in youths with IGD, including the bilateral banks of the superior temporal sulci, the right inferior parietal cortex, the right precuneus, the right precentral gyrus, and the left middle temporal gyrus. Additionally, youths with IGD demonstrated a significantly positive correlation between the left insular CT and symptom severity. Our data provide evidence for the finding of abnormal CT in distributed cerebral areas and support the notion that altered structural abnormalities observed in substance addiction are also manifested in IGD. Such information extends current knowledge about IGD-related brain reorganization and could help future efforts in identifying the role of insula in the disorder.

Keywords: cortical thickness, insula, Internet gaming disorder, surface-based morphometry, symptom severity

INTRODUCTION

According to the authoritative announcement of China Internet Network Information Center, till December 2017, the population of netizens in China has reached 772 million, accounting for about one-fifth of the total population of Internet users worldwide.[1] With the rapid popularity of the Internet, the phenomenon of clinical impairments or distress caused by maladaptive use

[1]http://www.cnnic.net.cn (Accessed: March 17, 2018).

of the Internet has grasped the attention of medical and public health professionals (1–7). Research on maladaptive use of the Internet has become a rapidly evolving field of study (8, 9). In acknowledgment of the studies that have already been published in this field, the Section III of DSM-5 classified "Internet gaming disorder" (IGD) as a condition in need of further research before being officially recognized as an independent clinical disorder (10). As a probable candidate for behavioral addiction, IGD was defined in particular as "persistent and recurrent use of the Internet to engage in games" (11) and has gained massive attention worldwide. Scholars within the field have been motivated to provide empirical evidence for this potential clinical category by applying different study approaches such as epidemiology, psychosociology, and neuroimaging. For example, epidemiological studies have shown that the overall prevalence of IGD ranged from 0.7 to 15.6% in studies of naturalistic populations, with an average percentage of 4.7% over the years (12). In addition, several theoretical models have been proposed for inspiring clear hypotheses on the mechanisms underlying the clinical phenomenon of IGD, which can be useful for the theory-driven development of assessment tools and treatments (12–15).

The technological advancement of neuroimaging, especially non-invasive magnetic resonance imaging (MRI), has made it possible to assess both anatomical and functional brain characteristics of IGD (9). Convergent evidence has indicated that brain structural alterations were associated with individuals with IGD, which suggested an underpinning neuroscientific basis for IGD (8). For example, Han et al. (16) reported increased gray matter volume of the left thalamus in individuals with IGD, and Zhou et al. reported decreased gray matter density of the left cingulate cortex and left insula in individuals with IGD (17). With regard to those structural alterations, there was an influential explanation that the neural mechanisms underlying IGD resemble those of substance addiction (14, 18). Although such behavioral addictions do not involve a chemical intoxicant or substance, study evidence revealed that many aspects of behavioral addiction are similar to those of substance addiction (19, 20). For example, a common neurobiological feature during the resting state (21) and similar impulsivity and executive dysfunctions have been reported between IGD and alcohol use disorder (20). An open question thus is whether these altered structural abnormalities observed in substance addiction also manifest in IGD.

In the past decades, tremendous progress has been made in the techniques and applications of cortical surface morphometry based on structural MRI (22). Previous studies have indicated that surface-based brain mapping may offer advantages over volume-based brain mapping to capture the fine structure of cortical anatomy, since it provides a series of cortical measures that possess anatomical meanings, such as cortical thickness (CT) (22, 23). To the best of our knowledge, so far, very few studies have conducted surface-based brain mapping in the individuals with IGD. Reassuringly, as comparable references, one study has demonstrated the reduction of orbitofrontal CT in male adolescents with Internet addiction (24), and the other revealed a changed CT pattern in late adolescence with online gaming addiction (25). However, both studies were conducted before the publishing of DSM-5, and different criteria were applied throughout those studies. It is our belief that the features of cortical anatomy in IGD are not well known; neither is its association with symptoms of IGD. Therefore, it is necessary to assess the morphological features of IGD using the new DSM-5 approach. In the present study, we used surface-based morphometry (SBM) approaches to examine CT changes of the whole brain in male youths with IGD. According to previous findings derived from studies on IGD (8, 24, 25) and substance addiction (26), we hypothesized that male youths with IGD may have increased CT in the insula. Considering that the insula has been proposed to be crucial for the formation and maintenance of IGD (15), we further speculated that increased insular CT may be associated with symptom severity in male youths with IGD.

MATERIALS AND METHODS

Participants

All participants were recruited from local universities and the surrounding community *via* advertisements and word of mouth. Participants were then pre-selected through an online questionnaire and telephone screening. Given the higher prevalence of Internet addiction in males versus females in China (27, 28), only male participants were included. Forty-eight youths who reported Internet gaming as their primary online activity met at least five of the nine DSM-5 criteria for IGD (10). Participant's Internet addictive behavior was assessed with a Chinese version of Internet Addiction Test (IAT) (29). IAT includes 20 items on a 5-point Likert scale (scored from 1 to 5) indicating the level of Internet usage, with good internal consistency and concurrent validity (30, 31). The higher the score, the greater the problems caused by Internet usage. All IGD subjects satisfied with their score on the IAT more than the proposed cutoff score (i.e., ≥50) (32, 33). Male youths who dissatisfied the proposed criteria for IGD were pre-selected as normal controls (NCs). Among them, 32 participants were determined as NCs based on their score of less than 30 on the IAT. NCs satisfied with fewer than four of the nine criteria for IGD proposed by DSM-5. All participants were right-handed as assessed with the Edinburgh Handedness Inventory (34). A brief structured clinical interview tool, the Mini International Neuropsychiatric Interview (35), was used to screen for several psychiatric disorders. Exclusion criteria for the participants included intracranial pathology, brain injury, neurological disorder, several psychiatric disorders, substance abuse, contraindications for MRI examinations, and excessive head motion. The demographic characteristics of youths with IGD and NCs are summarized in **Table 1**.

MRI Data Acquisition

Magnetic resonance imaging scans were obtained by using a 3.0 Tesla Magnetom Trio Tim (Siemens Medical System, Erlangen, Germany) at the Department of Medical Imaging, The Affiliated Wuxi People's Hospital of Nanjing Medical University. Foam pads were used to reduce head motion and scanner noise. Three-dimensional T1-weighted images were acquired by employing a 3D-MPRAGE sequence with the following parameters: time

repetition = 2,300 ms, time echo = 2.98 ms, flip angle = 9°, matrix size = 256 × 256, field of view = 256 mm × 256 mm, 160 sagittal slices, slice thickness = 1.2 mm, acquisition voxel size = 1 mm × 1 mm × 1.2 mm, and total acquisition time = 303 s.

MRI Data Processing

To identify cortical alternations in youths with IGD, an SBM was performed using the CAT toolbox[2] with the SPM12 software.[3] A detailed description of the processing procedure of the CAT toolbox can be found elsewhere.[4] In brief, this toolbox uses a fully automated method that allows for measurement of CT and reconstructions of the central surface in one step. It uses a tissue segmentation to estimate the white matter (WM) distance, then projects the local maxima (which is equal to the CT) to other gray matter voxels by using a neighbor relationship described by the WM distance. This projection-based thickness allows the handling of partial volume information, sulcal blurring, and sulcal asymmetries with no need of explicit sulcus reconstruction (36). For statistical analysis of surface measure, the CT images were smoothed with a 15 mm full width-half maximum Gaussian kernel.

[2]http://dbm.neuro.uni-jena.de/cat/ (Accessed: March 17, 2018).
[3]http://www.fil.ion.ucl.ac.uk/spm/software/spm12/ (Accessed: March 17, 2018).
[4]http://dbm.neuro.uni-jena.de/cat12/CAT12-Manual.pdf (Accessed: March 17, 2018).

TABLE 1 | Demographic characteristics of youths with IGD and NCs.

Variable	Youths with IGD (*N* = 48)	NCs (*N* = 32)	Statistics	*P* value
Age (years)	20.58 ± 0.96[a]	21.06 ± 2.18	$t = -1.17$	0.25
Education (years)	14.54 ± 0.92	15.00 ± 2.14	$t = -1.14$	0.26
IAT total scores	68.90 ± 8.22	22.72 ± 3.79	$t = 29.71$	<0.01
Reported game playing time (h/week)	23.17 ± 3.64	7.44 ± 3.37	$t = 19.50$	<0.01
Scores of DSM-5 criteria	5.96 ± 1.01	1.88 ± 0.79	$t = 19.25$	<0.01

[a]*Mean ± SD.*
IAT, Internet addiction test; IGD, Internet gaming disorder; NC, normal control.

Statistical Analysis

To detect statistical significance of group differences in demographic variables between youths with IGD and NCs, the Student's *t*-test was used. To determine the cortical changes in youths with IGD, we used an analysis of covariance model with diagnostic group as fixed variable, including age as the confounding covariate. Whole-brain peak-level family wise error corrections with $P < 0.05$ (two-tailed) were used in all comparisons to ensure the statistical significance. Then, to further delineate the association between the cortical morphology and symptom severity (reflected by total scores of IAT) in youths with IGD and NCs, respectively, a multiple regression model with IAT total scores as the independent variable was used. Since education level and age were significantly correlated within youths with IGD ($P < 0.001$) and NCs ($P < 0.001$), the multiple regression model included only age as a confounding covariate. For exploratory analysis, we relaxed the peak-level significance threshold to 0.001 (two-tailed, uncorrected) and the cluster-level significance threshold with cluster-size >100. The scatter plot of the relationship between IAT total scores and the mean values of CT was created using GraphPad Prism.[5] Identification of brain regions was determined with the Desikan–Killiany brain atlas (37).

RESULTS

Forty-eight youths with IGD and 32 NCs were analyzed in the present study. No significant differences were detected between youths with IGD and NCs in age and education. Compared with NCs, youths with IGD showed a significant increase in IAT total scores and reported game playing time and scores of DSM-5 criteria (**Table 1**).

In comparison with NCs, brain areas with significantly increased CT were found in youths with IGD, including the bilateral insulae and the right inferior temporal gyrus (**Table 2**). Moreover, significantly decreased CTs were found in several brain areas in youths with IGD, including the bilateral banks of the superior temporal sulci (STS), the right inferior parietal cortex,

[5]https://www.graphpad.com (Accessed: March 17, 2018).

TABLE 2 | Brain regions showing group differences in CT.

Index	Cluster size	Peak MNI coordinate			Peak *t* value	Side	Overlap of DK atlas[a] (%)	Region
		x	*y*	*z*				
Youths with IGD > NCs								
1	1,474	38	−17	1	6.02	Right	100	Insula
2	531	−40	−10	2	5.57	Left	100	Insula
3	33	57	−47	−22	4.68	Right	100	Inferior temporal gyrus
Youths with IGD < NCs								
4	136	46	−45	12	−4.93	Right	61	Banks of the superior temporal sulcus
							39	Inferior parietal cortex
5	159	19	−70	31	−4.85	Right	100	Precuneus
6	14	−48	−35	−4	−4.55	Left	54	Banks of the superior temporal sulcus
							46	Middle temporal gyrus
7	7	49	−8	32	−4.53	Right	100	Precentral gyrus

[a]*Desikan–Killiany brain atlas.*
CT, cortical thickness; IGD, Internet gaming disorder; NCs, normal controls.

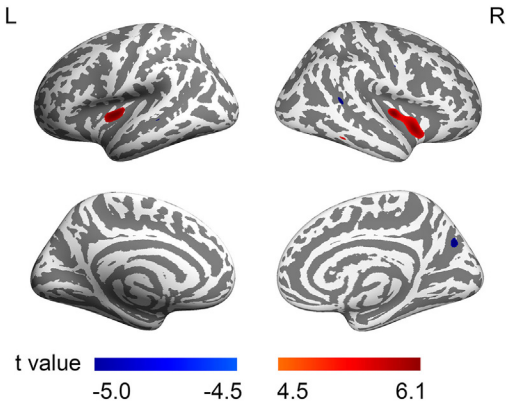

FIGURE 1 | Brain regions with abnormal cortical thickness (CT) in male youths with Internet gaming disorder (IGD). The warm color denotes the brain regions having increased CT, and the cold color denotes the brain regions having decreased CT in youths with IGD. The colored bars show *t* values. L, left; R, right.

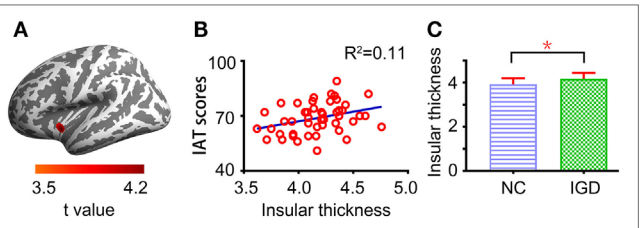

FIGURE 2 | **(A)** The panel shows the left lateral brain image depicting a correlation between the left insular cortical thickness (CT) and Internet Addiction Test (IAT) total scores in male youths with Internet gaming disorder (IGD). The image was peak-level thresholded at $P < 0.001$ (two-tailed, uncorrected) and cluster-level thresholded at cluster size > 100 for exploratory analysis. The warm color denotes the positive correlation, and the colored bar shows *t* values. **(B)** The scatter plot shows the relationship between means of the left insular CT and IAT total scores in youths with IGD. R^2, the coefficient of determination. **(C)** The histogram illustrates group means of the left insular CT for youths with IGD and normal controls (NCs).*$P < 0.05$. Error bars reflect the SD.

the right precuneus, the right precentral gyrus, and the left middle temporal gyrus (**Table 2**). In youths with IGD, the regression analysis revealed that the CT values in the left insula were positively correlated with IAT total scores (cluster size = 285, peak coordinate $MNI_{xyz} = [-38, -1, -6]$, $t = 4.19$, see **Figures 2A,B**). Compared with NCs, youths with IGD showed significantly increased means of the left insular CT (**Figure 2C**). No significantly negative correlations were observed between the CT and IAT total scores in youths with IGD. In addition, no significant correlations were observed between the CT and IAT total scores in NCs.

DISCUSSION

The present study used the SBM approach to characterize cortical morphological features in youths with IGD. The primary finding was that youths with IGD had significant CT alterations in distributed cerebral areas, including the insular, parietal, temporal, and frontal cortices. Particularly, youths with IGD showed a significant association between increased insular CT and IGD symptom severity (reflected by IAT total scores). These findings provide new evidence of cortical morphological abnormalities in IGD and highlight a key role played by the insula in the symptom manifestation of this disorder.

Previous studies have demonstrated several specific brain regions associated with IGD, such as the amygdala (38), the insula (39, 40), the precuneus (41), and the middle temporal gyrus (42). In line with the literature, the present study revealed a distributed pattern of CT abnormality in youths with IGD, including the insula, the superior temporal sulcus, the precuneus, the precentral gyrus, and the middle temporal gyrus (**Figure 1**). Previous studies have shown that Internet game playing was associated with the brain regions responsible for attention and control, impulse control, motor function, emotional regulation, and sensory-motor coordination (14). It is thus conceivable that multiple brain regions have been reported to be probable neural substrates in Internet addictive behavior (38, 39, 43).

Among our findings, the abnormality of the insular CT and its association with IGD symptom severity were especially interesting. This finding was in line with the previous structural MRI studies (17, 25, 44), which convergently demonstrated structural changes of the insula in individuals with IGD. Our data were also in line with recent functional MRI studies, one of which reported enhanced activity of the bilateral insulae in individuals with problematic Internet use during a monetary incentive learning task (45). Zhang et al. (39) observed an impaired functional connectivity pattern of the insula in subjects with IGD, and their finding was supported by another research which reported an association between IGD severity and insula-based functional connectivity (40). In terms of function, the insula is believed to play a major role in diverse functions such as multimodal sensory processing (46), social decision making (47), emotional experience (48), and motor control (49). Furthermore, the insula is proposed to integrate internal and external information to raise an awareness of the "global emotional moment" experiences that aid in maintaining a context relevant homeostatic state (50, 51). Neuroimaging and lesion studies have suggested that the insula plays an important role in cigarette smoking behavior (52, 53). Moreover, Tanabe et al. reported that the insula cortex was thicker in substance dependent men (26). According to the proposed tripartite neurocognitive model of IGD (15), the insula should be one of the key components underlying IGD, which maintains the craving for an Internet game. The activity of the insula may enhance the drive to play the Internet game and weaken the inhibitive abilities regarding this action. Thus, our study provided new supporting evidence for this model of IGD and highlighted that involvement of the insula in IGD is similar to those of substance addiction. Such information may help to develop effective intervention strategies. For example, psychopharmacological treatments and psychotherapy targeting the circuits including the insula may be effective in weakening craving in individuals with IGD. On the other hand,

our results were comparable with the findings derived from a previous independent SBM study, which reported reduced CT of the left insula in individuals (12 males and 6 females) with online gaming addiction (25). Inconsistent with their hemilateral change pattern of CT in the insula (25), the present study showed increased CT of the bilateral insulae in individuals with IGD. One possible reason for the inconsistent results was the differences in sex composition of the samples. Previous studies have revealed that sex is an important modulator of Internet-related behavior (54). Although the effect of sex on the insular CT in individuals with IGD is still unclear, a recent SBM study demonstrated a diagnosis-by-sex interaction on insular CT in substance-dependent individuals (26). Other possible reasons may be related to the methodology, the sample size, and the heterogeneity of participants. The specific roles of insula in IGD require further investigation in future studies by employing a more comprehensive design. Altogether anatomical and functional abnormalities in the insula were widely implicated in IGD. Our findings extend current knowledge about IGD-related insular cortical morphological characteristics and their associations with clinical symptoms.

Another interesting finding of the current study was the significantly decreased CT in the bilateral banks of STS. The banks of STS, defined as the posterior aspect of STS (37), are involved in the processing of various activities such as recognition of motion and faces and understanding of social cues (55). A recent functional MRI study provided evidence that the posterior STS serves as the hub for the distributed brain network for social perception (56). This suggests that the posterior STS is functionally tightly coupled with other brain circuitries and likely integrates social signals processed by more specialized subsystems (56). Furthermore, experimental studies have indicated the role of STS in both real-life situations and games (57, 58). On the one hand, the gray matter density of the STS was specifically associated with online social network size in healthy participants (58). On the other hand, swear words induced more activation in the STS when compared with negative words in young adolescents with IGD (59). A recent meta-analysis also confirmed that STS has been implicated in "the theory of mind" during human–human interactions (60). Therefore, we believe that our finding of involvement of the STS in IGD is a conceivable consequence, which sheds light on the underlying brain structure in IGD. However, the specific roles of the STS in IGD require additional investigation in future studies by employing a more comprehensive design model considering both the structural and functional requirements.

Several issues need to be further considered. First, we employed a recently proposed projection-based thickness approach (36) for measurement of CT in the present study. Such projection-based thickness approach enables the processing of partial volume information, sulcal blurring, and sulcal asymmetries with no need for explicit sulcus reconstruction either *via* skeleton or thinning method and may be superior in certain respects to previous approaches (22, 36). Second, whether these abnormalities observed in our data were a consequence or precondition of IGD remains a question yet to be answered. The answer requires further investigation in future studies by employing a more comprehensive design. Third, the Desikan–Killiany brain atlas handles the insula as a whole region. However, functional MRI and histological studies have shown that the insula is not a homogenous cortical region, which could be functionally subdivided into several distinct subregions (61, 62). Future SBM studies are encouraged to employ an atlas with fine subregional structures of insula. In addition, previous studies have demonstrated that behavioral and neural mechanisms of IGD mostly overlap with those of substance use disorders (18). Thus, more cognitive measurements such as rewards, cravings, and memory-related tasks are needed to explain the findings of the present study.

CONCLUSION

Taken together, our data demonstrated that youths with IGD had significant CT alterations in distributed cerebral areas, including the insular, parietal, temporal, and frontal cortices. Particularly, youths with IGD showed a significantly positive correlation between symptom severity and the left insular CT. This work extends current knowledge about IGD-related cortical morphological features and their associations with clinical symptoms. Such information could help with future efforts to identify the role of the insula in the disorder.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Medical Ethics Committee of The Affiliated Wuxi Mental Health Center of Nanjing Medical University with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Medical Ethics Committee of The Affiliated Wuxi Mental Health Center of Nanjing Medical University.

AUTHOR CONTRIBUTIONS

ZZ and LT designed the study. FZ, JL, QT, JW, and LC contributed to the acquisition of the data. LT, SW, and JL analyzed the data, interpreted the results, and drafted the manuscript. All the authors critically reviewed content and approved the final version for publication.

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Subregions of the Anterior Cingulate Cortex Form Distinct Functional Connectivity Patterns in Young Males With Internet Gaming Disorder With Comorbid Depression

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Depression is one of the most common comorbid conditions in Internet Gaming Disorder (IGD). Although there have been many studies on the pathophysiology of IGD, the neurobiological basis underlying the close association between depression and IGD has not been fully clarified. Previous neuroimaging studies have demonstrated functional and structural abnormalities in the anterior cingulate cortex (ACC) in IGD patients. In this study, we explored functional connectivity (FC) abnormalities involving subregions of the ACC in IGD subjects with comorbid depression. We performed a resting state seed-based FC analysis of 21 male young adults with IGD with comorbid depression (IGDdep+ group, 23.6 ± 2.4 years), 22 male young adults without IGD with comorbid depression (IGDdep− group, 24.0 ± 1.6 years), and 20 male age-matched healthy controls (24.0 ± 2.2 years). ACC-seeded FC was evaluated using the CONN-fMRI FC toolbox. The dorsal ACC (dACC), the pregenual ACC (pgACC), and the subgenual ACC (sgACC) were selected as seed regions. Both IGD groups had stronger pgACC FC with the right precuneus, the posterior cingulate cortex, and the left inferior frontal gyrus/insula than the control group. The IGDdep+ group had stronger dACC FC with the left precuneus and the right cerebellar lobule IX than the control and IGDdep- groups. The IGDdep+ group also had weaker pgACC FC with the right dorsomedial prefrontal cortex and the right supplementary motor area and had weaker sgACC FC with the left precuneus, the left lingual gyrus, and the left postcentral gyrus than the other groups. The strength of the connectivity between the sgACC and the left precuneus correlated positively with a higher omission error rate in the continuous performance test in the IGDdep+ group. In addition, the IGDdep− group had stronger sgACC FC with the left dorsolateral prefrontal cortex than the other groups. Our findings suggest that young males with IGD comorbid with depression have FC alterations of the default mode network and diminished FC with the prefrontal cortex. This altered FC pattern may be involved in the close association of IGD and depression.

Keywords: anterior cingulate cortex, default mode network, depression, functional connectivity, Internet Gaming Disorder

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INTRODUCTION

During the past decade, much research has been conducted on Internet Gaming Disorder (IGD), which is characterized by a difficulty in controlling Internet game use despite psychosocial disturbance (1). The high rate of comorbidity and the causal relationship between IGD and other psychiatric diseases have attracted much attention (2). Depression is a common comorbid psychiatric condition in IGD, and the comorbidity of IGD and depression has been related to more serious psychosocial burdens (3). A maladaptive emotional regulation strategy that suppresses rather than uses cognitive reappraisal of emotion has been presented as a contributing factor to the comorbidity of IGD and depression (4). Several neurobiological factors, such as decreased inter-hemispheric connectivity of the frontal regions and structural alterations in the dorsolateral prefrontal cortex, have been suggested to mediate the relationship between IGD and depressed mood (5, 6). Although these previous studies have improved our understanding of the associations between IGD and depression, research on the relationship between IGD and depression remains scarce despite its high clinical significance. Because a consensus on therapeutic tools for IGD is still lacking (7), further understanding of the associations between IGD and depression could provide new targets for IGD intervention. For instance, a recent study reported that bupropion was more effective than escitalopram as a treatment for IGD patients with comorbid depression (8).

Evidence has indicated that structural and functional dysfunctions of the anterior cingulate cortex (ACC) underlie the development and maintenance of IGD (9). Altered interactions between the ACC and other regions of the brain may contribute to the development of IGD and its related clinical characteristics. The linkages between the ACC and other regions of the brain are complex; each of the subregions of the ACC connect to different regions of the brain with different and specific functions (10). It has been suggested that the dorsal ACC (dACC) is involved in attentional and executive control via connections with the dorsolateral prefrontal cortex (DLPFC) (11, 12) and that the rostral ACC (rACC) is involved in emotional processing via connections with the amygdala, hippocampus, and the orbitofrontal cortex (OFC) (13). The rACC is divided into the pregenual ACC (pgACC) and the subgenual ACC (sgACC) (14). The pgACC has been shown to have dense connectivity with the lateral prefrontal cortex and plays an important role in top-down regulation of emotional stimuli (15). The sgACC has been found to have strong connectivity with the amygdala and the ventral striatum and contributes to autonomic control and conditioning learning for emotional processing (16).

Resting state functional connectivity (FC) between the ACC and other regions of the brain can be used to evaluate the interactions of the ACC with the other regions of the brain. Previous resting state functional magnetic resonance imaging (fMRI) studies showed that individuals with IGD had reduced FC between the dACC and some of the subcortical regions of the brain, including the dorsal striatum, the pallidum, and the thalamus, and increased FC between the rACC and the anterior insula (17, 18). These findings are consistent with the view that diminished executive control and enhanced reward seeking may underlie IGD (19). In IGD patients with comorbid depression, comorbidity with depression associated with reduced suppression of the default mode network (DMN), which may contribute to the attentional problems (20). The DMN and its interactions with other brain networks were found to play important roles in depression (21). It has been suggested that the DMN during the depressed state includes the rACC, especially the sgACC (22, 23). Individuals with depression have been shown to have increased FC between the sgACC and areas of the anterior DMN (24) and the salience network (SN) (25). Thus, both IGD and depression alter the FC of the subregions of the ACC. These FC alterations may contribute to the comorbidity of IGD and depression and its related clinical characteristics, but more research is needed on the relationships between IGD and depression and FC alterations.

The executive function is the higher order cognitive processes that is essential for proper control over behavior, and previous studies have demonstrated that executive functions are impaired in IGD (26), for instance, subjects with IGD showed high impulsivity, which is an example of diminished executive control (27, 28). Executive deficits have also been associated with depression (29), for example, depressed patients have demonstrated altered attentional control (30), thus attentional control has been a therapeutic target for depression (31). Executive deficit is an important component of the pathophysiology and clinical manifestations of IGD and depression. However, the exact role of the executive function in the relationship between IGD and depression has not yet been fully elucidated.

The aim of this study was to investigate the ACC-seeded FC of IGD subjects with depression. Three subregions of the ACC, the dACC, the pgACC, and the sgACC, were analyzed. We hypothesized that IGD subjects would show different patterns of ACC-based FC depending on whether comorbid depression was present or not. Based on previous studies, we expected that subjects with IGD would have reduced FC between the dACC and the subcortical regions and increased FC between the rACC (pgACC or sgACC) and seeds of the SN regardless of the presence of comorbidity with depression. We also expected that FC between the sgACC and other DMN- or SN-related seed regions would be higher in IGD subjects with comorbid depression reflecting their DMN abnormalities. We tested these expectations through resting state seed-based FC analysis, and we examined correlations between FC alterations and executive functions in IGD patients with comorbid depression. Impulsivity and attentional processes, which are clinical variables of executive functions, were assessed with self-reporting questionnaires for impulsivity and a continuous performance test (CPT) for attentional processes.

METHODS

Subjects

This study was conducted from February 2015–April 2017, and the protocols for this study were approved by the Institutional Review Board at Severance Hospital, Yonsei University. Subjects

were recruited via online advertisements, flyers, and word of mouth. All of the subjects were informed of the entire procedure and signed an informed consent before participating in the study.

We screened 101 young male adults for this study. According to previous epidemiological studies, IGD is more common in males (32). Because there are gender differences in the behavioral characteristics and motives for online gaming (33), this study was conducted only for men to reduce confounding effect. Subjects were examined for their Internet usage patterns and they completed Young's Internet Addiction Test (IAT) (34). Subjects who used the Internet primarily for gaming and whose IAT scores (34) exceeded 50 were interviewed according to the IGD diagnostic criteria of the DSM Fifth Edition to determine whether IGD was present (35). Subsequently, subjects with IGD were assessed for depression using the Beck Depression Inventory (BDI) (36). Among the subjects with IGD, those with a BDI score of 20 or higher were classified as IGD subjects with comorbid depression, whereas those with a BDI score of 13 or lower were classified as IGD subjects without comorbid depression. All of the subjects were assessed for their intelligence quotient (IQ) using the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV) (37). All of the subjects were also assessed for the presence of major psychiatric disorders using the Structured Clinical Interview from the DSM Fourth Edition (SCID-IV) (38). All subjects with a BDI score of 20 or higher were confirmed to have current depression (satisfying the criteria of mild depressive episode or major depressive episode). Subjects with the following were excluded: a neurological disorder or medical illness, major psychiatric illness other than IGD or depression (i.e., bipolar disorder, psychotic disorder, substance use disorder, attention deficit/hyperactivity disorder), mental retardation, or radiological contra-indications on the MRI scan.

After the screening process, 63 young male adults 20–27 years of age (mean: 23.8 ± 2.0 years) participated in the study, and all of them were right-handed. Subjects with IGD were subdivided into two groups according to their comorbid depression: IGD subjects with comorbid depression (IGDdep+ group, $n = 21$; 23.6 ± 2.4 years) and IGD subjects without comorbid depression (IGDdep- group, $n = 22$; 24.0 ± 1.6 years). Subjects who spent less than 2 h per day on gaming and scored below 50 points on the IAT were classified as healthy controls ($n = 20$; 24.0 ± 2.2 years). In addition to the IAT and BDI used in the screening process, subjects completed the Alcohol Use Disorders Identification Test (AUDIT) (39), the Beck Anxiety Inventory (BAI) (40), and the Barratt Impulsiveness Scale-version 11 (BIS-11) self-reporting questionnaires (41).

Continuous Performance Test (CPT)

We applied the computerized Comprehensive Attention Test to assess the abilities of sustained attention and divided attention (42). In the sustained attention task, various shapes are presented on the computer screen every 2 s as a visual stimulus, and the task is performed for 10 min. Subjects were instructed to press the space bar as quickly as possible whenever visual stimuli were displayed, but not when an "X" shape was presented. The sustained attention task assesses the ability to exert consistent behavioral responses while sustaining attention to continuous and repetitive stimuli. This task also estimates impulsivity by assessing whether a subject could suppress behavioral responses to specific stimuli. In the divided attention task, visual and auditory stimuli are presented at the same time every 2 s, and the task takes a total of 3 min and 20 s. Subjects were instructed to press the spacebar as quickly as possible in the event that the immediately preceding visual stimulus or auditory stimulus is presented again. The divided attention task assesses whether subjects can process two or more stimuli simultaneously by properly dividing their attention. Two behavioral variables were measured for performance on the CPT. The omission error is the failure to perform a required behavioral response and it reflects inattention. The commission error is the presence of behavioral responses that should have been suppressed and it reflects impulsivity.

MRI Image Acquisition and Pre-processing

MRI images were acquired using a 3T Siemens Magnetom MRI scanner equipped with an eight-channel head coil. The fMRI data were collected using a single-shot T2-weighted gradient echo planar pulse sequence (echo time = 30 ms, repetition time = 2,200 ms, flip angle = 90°, field of view = 240 mm, matrix = 64 × 64, slice thickness = 4 mm) for 6 min. Subjects were instructed to gaze at the white crosshair in the center of the black background without any cognitive, lingual, or motor activity. An anatomical template for the fMRI data was acquired using a T1-weighted spoiled gradient echo sequence (TE = 2.19 ms, TR = 1,780 ms, flip angle = 9°, field of view =256 mm, matrix = 256 × 256, slice thickness = 1 mm). Pre-processing and statistical analysis of the data were performed using SPM8 (Welcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm). For each subject, the initial seven points in the time series were discarded to eliminate signal decay. To adjust for motor artifacts for each subject, we checked that the maximal head movement in each axis was <2 mm and that there was no unexpected head motion by visually inspecting realignment parameter estimates. For each subject, functional brain images were realigned and co-registered to structural images. The co-registered images were spatially normalized to the Montreal Neurological Institute (MNI) template (provided by SPM8) using a 12-parameter affine transformation and non-linear iterations. Parameters of normalization were applied to unwrapped functional images, which were then re-sampled to a voxel size of 2 × 2 × 2 mm. Data were smoothed using an 8 mm full-width at half-maximum kernel.

FC Analysis

Seed-to-voxel FC maps for each subject were constructed using the CONN-fMRI FC toolbox (http://www.nitrc.org/projects/conn). Seed regions for subregions of the ACC were defined as 5 mm radius sphere-centered coordinates derived from previous FC studies (dACC: 4 14 36; pgACC: −2 44 20; sgACC: 2 20−10) (43, 44). The waveform of each brain voxel was temporally filtered by means of a bandpass filter (0.008 Hz < f < 0.09 Hz) to adjust for low-frequency drift and high-frequency noise effects. A linear regression analysis was conducted to remove signals from the ventricular area and the white matter (45).

To minimize the effects of head movement, motion parameters were entered into the linear regression analysis. To estimate the strength of an FC, correlation coefficients were computed and converted to z-values using Fisher's r-to-z transformation. Then, FC strength estimates were compared between groups using analysis of variance (ANOVA) at each voxel. As statistical inferences for the exploratory whole-brain analysis, a cluster forming threshold using a height threshold of uncorrected p-value < 0.001 and an extent threshold of 100 contiguous voxels was applied. After clusters with significant group differences were evaluated, Bonferroni *post hoc* tests were performed to examine which groups were different from the others.

Statistical Analysis

One-way ANOVA tests were used to compare demographic and clinical variables, including age, IQ, IAT, AUDIT, BDI, BAI, and BIS scores, among the three groups. Because the assumptions for normality were not met, comparisons of behavioral performance on the CPT between the groups were analyzed using the Kruskal Wallis test. The Bonferroni correction was applied for *post hoc* analysis. Partial correlation analysis of connectivity strength, BIS subscales, and behavioral performance of the CPT was performed after controlling for BDI and BAI. Statistical analyses were performed with SPSS (Chicago, IL) with significance set at $p < 0.05$ (two-tailed).

RESULTS

Demographic and Clinical Variables of Subjects

Controls and IGD subjects did not differ significantly in age, IQ, and AUDIT score (**Table 1**). Psychometric self-report scales showed differences in IAT [$F_{(2, 60)} = 111.949$, $p < 0.001$], BDI [$F_{(2, 60)} = 185.146$, $p < 0.001$], and BAI [$F_{(2, 60)} = 30.498$, $p < 0.001$] scores. BIS subscales differed between groups [non-planning: $F_{(2, 60)} = 11.229$, $p < 0.001$; motor: $F_{(2, 60)} = 11.246$, $p < 0.001$; cognitive: $F_{(2, 60)} = 11.019$, $p < 0.001$]. *Post hoc* testing showed that both IGD groups had significantly higher IAT and BIS scores than the control group. The IGDdep+ group showed higher BDI and BAI scores than the other groups. Comparison of behavioral performance on the CPT showed differences only in the omission error rate in the divided attention task ($\chi^2 = 6.130$, $p = 0.047$). *Post hoc* testing showed that the IGDdep+ group had a higher omission error rate than the other groups.

FC Analysis

In the whole-brain analysis, multiple clusters with significant differences in FC were found between the groups (**Table 2**). The dACC-based FC analysis showed that the IGDdep+ group had stronger dACC FC with the left precuneus and the right cerebellar lobule IX than the other groups (**Figure 1**). The pgACC-based FC analysis showed that the IGDdep+ group had weaker pgACC FC with the right dorsomedial prefrontal cortex (dmPFC) and the right supplementary motor area (SMA) than the other groups (**Figure 2**). Both IGD groups had stronger pgACC FC with the right precuneus, the left posterior cingulate cortex (PCC), and the left inferior frontal gyrus/anterior insula (IFG/AI) than the controls. The sgACC-based FC analysis showed that the IGDdep+ group had weaker sgACC FC with the left precuneus, the left lingual gyrus, and the left postcentral gyrus than the other groups (**Figure 3**). The IGDdep- group had stronger sgACC FC with the left dorsolateral prefrontal cortex (dlPFC) than the other groups.

The correlation analysis showed a correlation between pgACC-IFG/AI connectivity strength and cognitive impulsivity in the IGDdep- group ($r = 0.482$, $p = 0.031$; **Figure 4A**) and a correlation between sgACC-precuneus connectivity strength and omission error in the sustained attention task in the IGDdep+ group ($r = -0.499$, $p = 0.030$; **Figure 4B**). The other correlation tests showed no statistical significance.

DISCUSSION

In this study, ACC-based FC in IGD subjects with and without depression was analyzed. Both IGD groups had stronger pgACC FC with the right precuneus, the PCC, and the left IFG/AI than the control subjects, but there were differences in FC patterns between IGD subjects with and without depression. IGD subjects with comorbid depression had stronger dACC FC with the precuneus and right cerebellar lobule IX than the other subjects. IGD subjects with comorbid depression also had weaker pgACC FC with the right dmPFC and the right SMA and weaker sgACC FC with the left precuneus, the left lingual gyrus, and the left postcentral gyrus than the other subjects. These FC alterations, which differ partially based on the presence or absence of comorbid depression, are consistent with our hypothesis that IGD patients with comorbid depression may have a characteristic neurobiological basis that contributes to their distinctive clinical features.

In comparison with other groups, IGD subjects with comorbid depression showed stronger dACC FC with the precuneus and the right cerebellar lobule IX, which have been associated with the DMN (46, 47). These findings are consistent with previous evidence that IGD subjects with comorbid depression may have hyperconnectivity between the ACC and the DMN-related brain regions, which reflects their difficulty in suppressing the DMN (20). However, the sgACC-based FC analysis showed that FC between the sgACC and the left precuneus was significantly weaker in IGD subjects with comorbid depression than in the other groups. Previous studies have indicated that the anterior and posterior DMN has asynchronous activity patterns in the depressive state (48). Our finding of weak sgACC-precuneus FC support a previous study that demonstrated changes in FC between the anterior and posterior DMN in depression (49). In addition, weak sgACC-precuneus connectivity correlated with a high omission error rate in the sustained attention task in IGD subjects with comorbid depression. A higher frequency of omission errors in IGD subjects with comorbid depression suggests that attentional problems are more pronounced in subjects with IGD when depression is involved. The significant correlation between sgACC-precuneus connectivity and omission error rate supports

TABLE 1 | Demographic and clinical variables of subjects.

	Controls ($n = 20$)	IGD_{dep-} ($n = 22$)	IGD_{dep+} ($n = 21$)	Test	*p*-value	*Post hoc* test
Age, year	24.0 ± 2.2	24.0 ± 1.6	23.6 ± 2.4	$F_{(2, 60)} = 0.267$	0.767	
Full Scale IQ	107.9 ± 10.7	109.9 ± 11.9	102.2 ± 12.5	$F_{(2, 60)} = 2.452$	0.095	
IAT	26.4 ± 9.8	69.4 ± 12.5	71.7 ± 10.1	$F_{(2, 60)} = 111.949$	<0.001	IGD_{dep-}, IGD_{dep+} > HC
BDI	5.0 ± 3.5	7.6 ± 3.4	25.6 ± 4.3	$F_{(2, 60)} = 185.146$	<0.001	IGDdep+ > HC, IGDdep-
BAI	4.8 ± 4.4	6.7 ± 5.1	19.9 ± 9.7	$F_{(2, 60)} = 30.498$	<0.001	IGDdep+ > HC, IGDdep-
AUDIT	9.8 ± 7.1	14.1 ± 7.5	11.5 ± 7.8	$F_{(2, 60)} = 1.768$	0.179	
BIS SCALES						
Non-planning impulsivity	16.5 ± 5.6	25.6 ± 7.7	22.9 ± 5.4	$F_{(2, 60)} = 11.229$	<0.001	IGD_{dep-}, IGD_{dep+} > HC
Motor impulsivity	12.9 ± 3.3	18.5 ± 4.4	17.7 ± 4.4	$F_{(2, 60)} = 11.246$	<0.001	IGD_{dep-}, IGD_{dep+} > HC
Cognitive impulsivity	11.2 ± 4.0	15.0 ± 2.7	16.1 ± 3.7	$F_{(2, 60)} = 11.019$	<0.001	IGD_{dep-}, IGD_{dep+} > HC
SUSTAINED ATTENTION TASK, NUMBER						
Omission error	1.4 ± 2.6	1.1 ± 1.6	1.6 ± 3.6	$\chi^2 = 0.114$	0.944	
Commission error	5.4 ± 3.0	8.3 ± 7.0	9.2 ± 9.2	$\chi^2 = 1.163$	0.559	
DIVIDED ATTENTION TASK, NUMBER						
Omission error	4.7 ± 6.1	5.4 ± 8.1	10.3 ± 10.4	$\chi^2 = 6.130$	0.047	IGDdep+ > HC, IGDdep-
Commission error	3.5 ± 2.2	3.4 ± 5.2	4.3 ± 7.8	$\chi^2 = 1.786$	0.409	

Group comparisons were conducted by one-way analysis of variance (ANOVA) tests. Because assumptions for normality were not met for the behavioral variables for the attention tasks, the Kruskal Wallis test was used for comparison.
IGD_{dep-}, Internet Gaming Disorder subjects without comorbid depression; IGD_{dep+}, Internet Gaming Disorder subjects with comorbid depression; IQ, intelligence quotient; IAT, Internet Addiction Test; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; AUDIT, Alcohol Use Disorders Identification Test; BIS, Barratt Impulsiveness Scale.

TABLE 2 | Whole-brain seed-based functional connectivity (FC) analysis.

Region	Side	k_E	Z	X	y	z	*Post hoc* test
SEED: DORSAL ACC							
Precuneus	Left	256	4.50	−2	−46	48	IGD_{de+} > IGD_{de-} > Controls
Cerebellar lobule IX	Right	129	4.12	10	−42	−40	IGD_{de+} > IGD_{de-}, Controls
SEED: PREGENUAL ACC							
Supplementary motor area	Right	352	5.11	32	6	64	IGD_{de-}, Controls > IGD_{de+}
Dorsomedial prefrontal cortex	Right	111	4.71	10	52	34	IGD_{de-}, Controls > IGD_{de+}
Precuneus	Right	184	4.46	16	−42	54	IGD_{de+}, IGD_{de-} > Controls
Posterior cingulate cortex	Left	359	4.02	−12	−22	42	IGD_{de+}, IGD_{de-} > Controls
Inferior frontal gyrus	Left	135	4.29	−42	2	16	IGD_{de-} > IGD_{de+} > Controls
SEED: SUBGENUAL ACC							
Dorsolateral prefrontal cortex	Left	254	4.34	−36	34	38	IGD_{de-} > IGD_{de+}, Controls
Lingual gyrus	Left	145	4.21	−18	−86	−12	IGD_{de-}, Controls > IGD_{de+}
Precuneus	Left	100	3.75	−8	−62	46	Controls > IGD_{de+}
Postcentral gyrus	Left	186	3.75	−42	−12	38	IGD_{de-} > IGD_{de+}

Brain regions in which FC showed significant differences between groups [height threshold of uncorrected p-value < 0.001, extent threshold of contiguous k_e > 100 voxels (18)].
IGD_{dep}, Internet Gaming disorder subjects without comorbid depression; IGD_{dep+}, Internet Gaming Disorder subjects with comorbid depression; ACC, anterior cingulate cortex.

the hypothesis that FC alterations of the DMN contribute to impairments in attentional processes.

In comparison with the other groups, IGD subjects with comorbid depression showed weaker pgACC FC with the right dmPFC and the right SMA. It has been shown that the dmPFC is innervated by dopamine and associated with modulation of the salient and motivational values of stimuli (50). The dmPFC has been associated with reappraisal of emotional stimuli (51), and alteration of FC of the dmPFC with other brain regions has been reported in depressed patients (52, 53). The dmPFC has also been suggested to play an important role in the neurocircuitry of addiction (54). Taken together, altered FC of the dmPFC may be a crucial link between addictive Internet game use and depression. Furthermore, previous studies have shown that FC between the pgACC and the dmPFC associates closely with responses to transcranial magnetic stimulation (TMS) treatment (55) and that bupropion increases resting state FC in the dmPFC (56). Altered FC of the dmPFC has

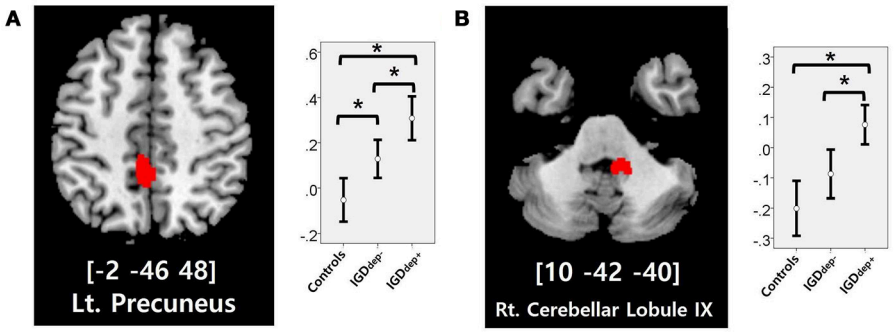

FIGURE 1 | Brain regions showing significant differences in dACC-based FC between groups. **(A)** Left precuneus and **(B)** right cerebellar lobule IX. Height threshold of uncorrected *p*-value < 0.001 and extent threshold of 100 contiguous voxels. The peak coordinates of each cluster are indicated by the Montreal Neurological Institute (MNI) system. *Post hoc* tests were conducted to detect differences across groups using the Bonferroni correction. *$p < 0.05$.

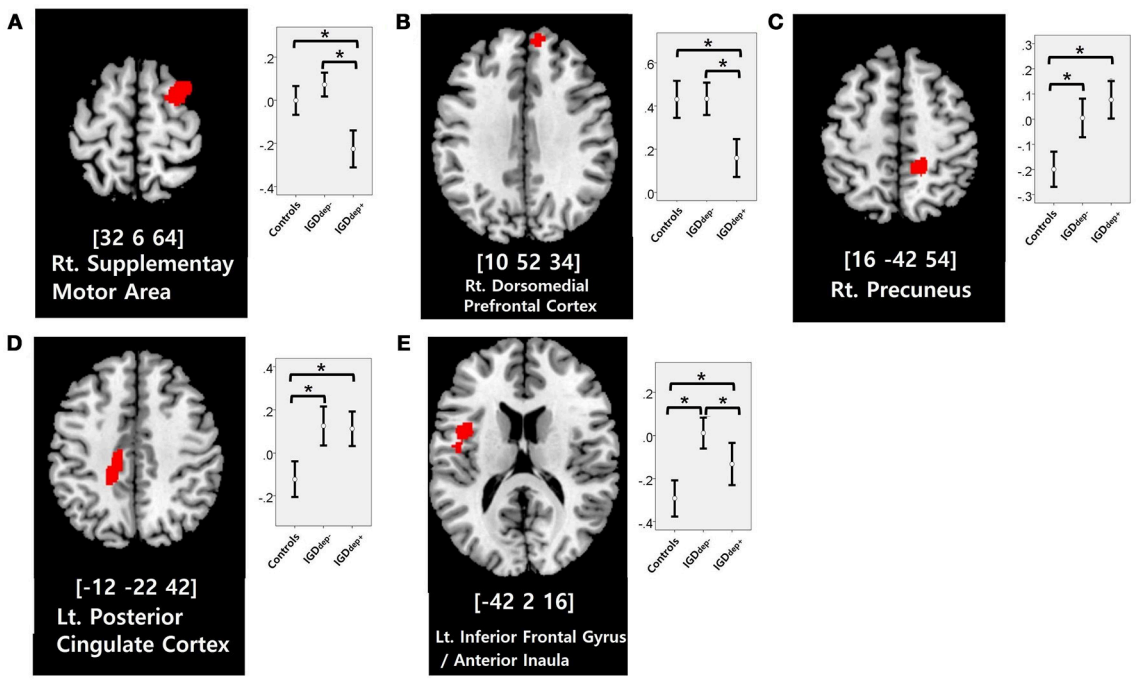

FIGURE 2 | Brain regions showing significant differences in pgACC-based FC between groups. **(A)** Right supplementary motor area, **(B)** right dorsomedial prefrontal cortex, **(C)** right precuneus, **(D)** left posterior cingulate cortex, and **(E)** left inferior frontal gyrus/anterior insula. Height threshold of uncorrected *p*-value < 0.001 and extent threshold of 100 contiguous voxels. The peak coordinates of each cluster are indicated by the Montreal Neurological Institute (MNI) system. *Post hoc* tests were conducted to detect differences across groups using the Bonferroni correction. *$p < 0.05$.

significant potential as a target of therapeutic intervention for IGD patients with comorbid depression. In addition, the SMA has been associated with cognitive control of behavior (57), and structural or functional alteration of the SMA in IGD has been reported (58, 59). Our finding of altered FC in the SMA may relate to diminished behavioral control over excessive gaming.

In comparison with controls, IGD subjects showed stronger FC between the pgACC and the left IFG/AI. Furthermore, IGD subjects without comorbid depression showed stronger pgACC-IFG/AI connectivity, which correlated significantly with higher cognitive impulsivity reflecting decision-making tendencies based on short-term satisfaction (60). Because the left IFG/AI is a seed region of the SN (61), these findings are consistent with our expectation that subjects with IGD would have increased FC of the rACC with seeds of the SN. Altered interaction between the SN and other brain networks has been suggested to contribute to the motivational, affective, and cognitive characteristics observed in addiction (62). Our current results and previous evidence (63) indicate that FC alterations in the SN, especially hyperconnectivity between the DMN and the SN, play pivotal roles in the pathophysiology of IGD. IGD subjects without comorbid depression also showed stronger sgACC FC with the left dlPFC than the other groups. Aberrant functional

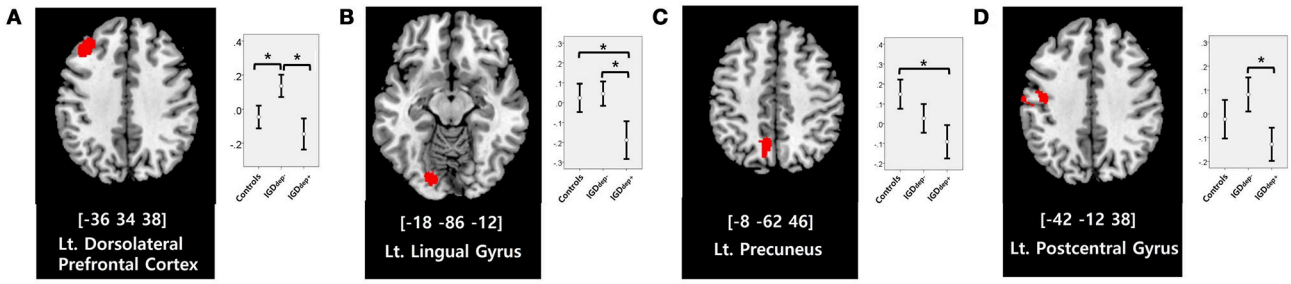

FIGURE 3 | Brain regions showing significant differences in sgACC-based FC between groups. **(A)** Left dorsolateral prefrontal cortex, **(B)** left lingual gyrus, **(C)** left precuneus, and **(D)** left postcentral gyrus. Height threshold of uncorrected p-value < 0.001 and extent threshold of 100 contiguous voxels. The peak coordinates of each cluster are indicated by the Montreal Neurological Institute (MNI) system. *Post hoc* tests were conducted to detect differences across groups using the Bonferroni correction. $^{*}p < 0.05$.

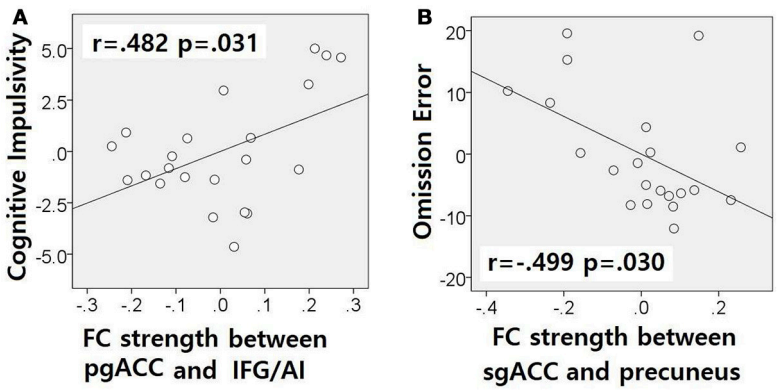

FIGURE 4 | Partial correlation analyses after controlling for BDI and BAI. Non-standardized residuals were used to make scatter plots. **(A)** IGD subjects without comorbid depression exhibited a positive correlation between pgACC-IFG/AI connectivity and the BIS-cognitive impulsivity subscale score ($r = 0.482$, $p = 0.031$). **(B)** IGD subjects with comorbid depression exhibited a negative correlation between sgACC-precuneus connectivity and omission error rate in the divided attention task ($r = -0.499$, $p = 0.030$).

interactions between brain networks have been proposed as part of the pathophysiology of IGD (64, 65). Hyperconnectivity between the DMN and the central executive network may also be a neurobiological factor underlying IGD.

There were several limitations in this study. First, this study was cross-sectional, and although this study investigated the comorbidity of depression and IGD, there is currently no information about the causal relationship between the two diseases. Further longitudinal studies are needed to properly interpret the current imaging findings. Second, this study involved a small number of subjects and only focused on some of the regions of the brain even though the relationship between IGD and depression likely involves complex neurobiological mechanisms. It would be helpful to explore brain connectivity in a large number of subjects without focusing on specific seed regions of interest. Third, the study was carried out with only male subjects. Previous studies have shown that IGD is becoming more common in females (66). For the results of this study to become more generalized, further studies should include female and male gaming addicts. Finally, the study did not sufficiently control for variables that may affect the relationship between depression and IGD, and this study did not fully elucidate the brain-behavior relationship in IGD. Further studies would require broader consideration of the subjects' clinical characteristics, which may relate to their uncontrolled Internet gaming.

In conclusion, depressed and non-depressed IGD patients differed in their ACC-based FC patterns. IGD subjects with comorbid depression showed specific FC alterations in the DMN. Altered FC between the anterior and posterior DMN may associate with impaired attentional processes in IGD subjects with comorbid depression. IGD subjects with comorbid depression also had weak FC between the ACC and the dmPFC reflecting impaired regulation of emotional stimuli. Our resting fMRI results suggest that there is a neurobiological basis for the strong association between IGD and depression, which may be an important therapeutic target in the future.

ETHICS STATEMENT

All of the procedures involving human participants were performed in accordance with the ethical standards of the institutional and national research committees and with the 1964

Helsinki declaration and its later amendments. The experimental protocol was approved by the Institutional Review Board at Severance Hospital, Yonsei University, Seoul, Korea.

AUTHOR CONTRIBUTIONS

DL and Y-CJ conceived and designed the study. JL recruited participants and acquired the imaging data. DL drafted the manuscript. KN and Y-CJ critically reviewed the manuscript and provided important intellectual content. All of the authors critically reviewed and approved the final version of this manuscript for publication.

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Impulsive Internet Game Play Is Associated With Increased Functional Connectivity Between the Default Mode and Salience Networks in Depressed Patients With Short Allele of Serotonin Transporter Gene

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Hong JS, Kim SM, Bae S and Han DH (2018) Impulsive Internet Game Play Is Associated With Increased Functional Connectivity Between the Default Mode and Salience Networks in Depressed Patients With Short Allele of Serotonin Transporter Gene. Front. Psychiatry 9:125. doi: 10.3389/fpsyt.2018.00125

Problematic Internet game play is often accompanied by major depressive disorder (MDD). Depression seems to be closely related to altered functional connectivity (FC) within (and between) the default mode network (DMN) and salience network. In addition, serotonergic neurotransmission may regulate the symptoms of depression, including impulsivity, potentially by modulating the DMN. We hypothesized that altered connectivity between the DMN and salience network could mediate an association between the 5HTTLPR genotype and impulsivity in patients with depression. A total of 54 participants with problematic Internet game play and MDD completed the research protocol. We genotyped for 5HTTLPR and assessed the DMN FC using resting-state functional magnetic resonance imaging. The severity of Internet game play, depressive symptoms, anxiety, attention and impulsivity, and behavioral inhibition and activation were assessed using the Young Internet Addiction Scale (YIAS), Beck Depressive Inventory, Beck Anxiety Inventory (BAI), Korean Attention Deficit Hyperactivity Disorder scale, and the Behavioral Inhibition and Activation Scales (BIS-BAS), respectively. The SS allele was associated with increased FC within the DMN, including the middle prefrontal cortex (MPFC) to the posterior cingulate cortex, and within the salience network, including the right supramarginal gyrus (SMG) to the right rostral prefrontal cortex (RPFC), right anterior insular (AInsular) to right SMG, anterior cingulate cortex (ACC) to left RPFC, and left AInsular to right RPFC, and between the DMN and salience network, including the MPFC to the ACC. In addition, the FC from the MPFC to ACC positively correlated with the BIS and YIAS scores in the SS allele group. The SS allele of 5HTTLPR might modulate the FC within and between the DMN and salience network, which may ultimately be a risk factor for impulsive Internet game play in patients with MDD.

Keywords: serotonin transporter gene, Internet gaming disorder, default mode network, salience network, major depressive disorder

INTRODUCTION

Several national studies have demonstrated the relationship between impulsive Internet game play and major depressive disorder (MDD) (1–3). The severity of Internet use was associated with the risk of major depression in a group of 3,449 Korean middle school students (2). In a Hong Kong community (aged 18–60 years), the severity of Internet gaming disorder (IGD) was moderately strong correlation with the severity of depressive symptoms (3). A cross-sectional study of an Australian teenage community demonstrated that excessive Internet game play was associated with depression, anxiety, and poor health status (1). In studies on the treatment of patients with MDD and IGD, an improvement in depressive symptoms was associated with a reduction in the severity of IGD (4, 5). A comparison between the effects of bupropion and escitalopram on impulsive Internet game play in patients with MDD reported that decreased depressive symptoms were associated with an improvement of IGD in both groups (4). Furthermore, 12 weeks of bupropion treatment of 50 Patients with MDD and IGD also improved the symptoms of depression and IGD (5).

Recent studies suggested that IGD is caused by system level alterations between networks, rather than by the functional deficit within isolated regions (4–6). Many functional brain studies have demonstrated that human cognitive processes are orchestrated by a set of coherent spatiotemporal Independent Component networks (topographically organized human brain areas) (7). Our previous two studies demonstrated that the DMN and salience network were frequently associated in patients with MDD and IGD (4, 5). Sixty patients with MDD and IGD showed a failure to suppress DMN during an attentionally demanding task (the Wisconsin card sorting test) (5). In addition, decreased functional connectivity (FC) between the salience network and the DMN was associated with improved IGD symptoms and impulsivity in patients with MDD and IGD after 12 weeks of bupropion treatment (4). The FC in patients with MDD is thought to decrease between anterior DMN and posterior DMN, and increase between the salience network and anterior DMN (8). The salience network, which consists of the frontoinsular cortex, anterior cingulate, amygdala, and temporal pole, has been implicated in switching between the DMN and executive network (9). Grodin et al. reported that decreased volume within the salience network, including in the anterior insular (AInsular) and anterior cingulate, was negatively correlated with self-report impulsivity, decisional impulsivity, and compulsive measures (10).

Several neuroimaging studies have suggested that the serotonin transporter polymorphic region (5HTTLPR) plays an important neuromodulatory role on the DMN. In a positron emission tomography study, Hahn et al. (11) demonstrated that the density of the serotonin 1A (5-HT_{1A}) receptor was associated with the FC within DMN. David et al. (12) suggested that the 5-HT_{1A} receptor density could be modulated by genetic variants of 5HTTLPR. In a study of the effects of 5HTTLPR variants on impulsivity in patients with MDD, Cha et al. suggested that the short allele of 5HTTLPR increases impulsivity by decreasing the FC between the DMN and superior frontal gyrus (SFG) (13). The 5HTTLPR in SLC6A4 was reported to lower the transcription of the gene encoding serotonin (14). Due to the regulation of serotonergic neurotransmission, the short allele of 5HTTLPR is thought to play a role in the symptoms including depressive mood, impulsivity, and neuroticism of patients with MDD (15). Furthermore, escitalopram and venlafaxine was reportedly less effective on patients with MDD, who had the short allele of 5HTTLPR, than on those with the long allele. In a study of venlafaxine treatment study, short allele of 5HTTLPR was less effective than long allele of 5HTTLPR in patients with MDD (16) In our previous study, Internet use in 166 high school students was more excessive in students who were homozygous for the short allelic variant of the serotonin transporter gene (ss-5HTTLPR), compared to healthy participants (17).

Therefore, we hypothesized that the 5HTLPR short allele was associated with increased FC within the DMN and salience network, as well as increased FC between the two networks, which may lead to impulsive Internet game play in patients with MDD.

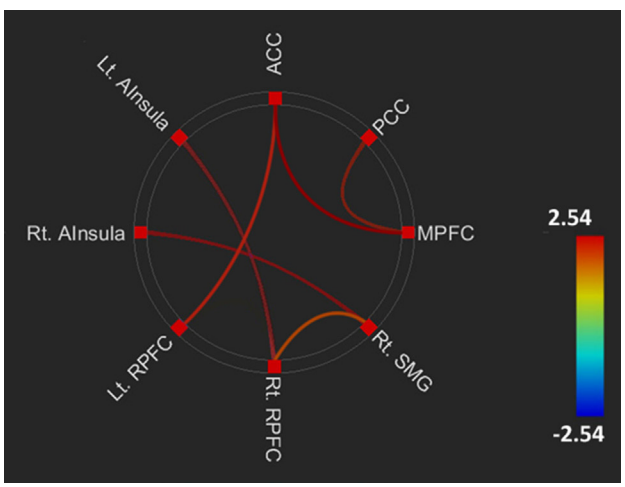

FIGURE 1 | Comparing brain functional connectivity of brain areas between the SS and SL + LL allele groups. Default mode network.middle prefrontal cortex (DMN.MPFC) to posterior cingulate cortex (DMN.PCC): $t = 2.42$, FDRq = 0.02; left salience network.anterior insular (SAL.AInsula) to right rostral prefrontal cortex (SAL.RPFC): $t = 2.42$, FDRq = 0.02; right SAL. AInsula (SAL.AInsula) to right SAL supramarginal gyrus (SAL.SMG): $t = 2.40$, FDRq = 0.02; right SAL.SMG to right SAL.RPFC: $t = 2.02$, FDRq < 0.05; SAL.ACC to left SAL.RPFC: $t = 2.15$, $p = 0.04$; DMN.MPFC to anterior cingulate cortex (SAL.ACC): $t = 2.61$, FDRq = 0.01.

MATERIALS AND METHODS

Participants

A total of 60 patients with problematic Internet game play and MDD agreed to participate in the current research. All patients were diagnosed as MDD based on the Diagnostic Statistical Manual of Mental Disorder-V (DSM-V) (18). The criterion used to define IGD in the present study was the same as that used in our prior study (19). The criteria was as follows: (1) Internet game play time more than 4 h per day or 30 h per week, (2) Young Internet Addiction Scale (YIAS) score >50, (3) irritable, anxious,

and aggressive behaviors upon request to stop Internet game play, (4) impaired behavior or distress, economic problems, and maladaptive life pattern as a result of problematic Internet game play, (5) disruptive diurnal rhythms (difficulty waking up during daytime hours due to reduced sleep at night related to Internet game play), and (6) loss of job or school truancy. The inclusion criteria were as follows: (1) diagnosed as MDD, (2) problematic Internet game play, (3) drug-naive, (4) over 18 years old, and (5) right-handed. The exclusion criteria included the following: (1) history or current episode of other psychiatric disorders, (2) IQ <80, (3) substance abuse history (except for alcohol and tobacco), (4) neurological or medical disorder, and (5) contraindication for magnetic resonance imaging (MRI) scanning. Of the 60 patients with MDD and IGD, 2 patients had low IQ (<80), 3 patients had a history of psychiatric medication, and 1 patient had a history of bipolar disorder. A total of 54 patients with MDD and IGD completed the final research protocol. The research protocol was approved by the Institutional Review Board of Chung Ang University Hospital. Written informed consent was provided by patients.

Clinical Scale

The severity of Internet game play was assessed using the YIAS. The YIAS is a self-reporting scale for the severity of Internet use, with an internal consistency ranging from 0.90 to 0.91 (20). Depressive symptoms and anxiety were assessed using the Beck Depressive Inventory (BDI), with an internal consistency from 0.75 to 0.85 (21), and the Beck Anxiety Inventory (BAI), with Cronbach's $\alpha = 0.93$ (22), respectively. Attention and impulsiveness were assessed with the Korean Attention Deficit Hyperactivity Disorder scale (K-ARS) and Behavioral Inhibition and Activation Scales (BIS-BAS), respectively, which had an internal consistency from 0.77 to 0.89 (23) and 0.78 to 0.79 (24), respectively.

MRI Acquisition and Preprocessing

Resting-state brain activity was assessed using 3T blood-oxygen-level dependent functional MRI (Philips Achieva 3.0 Tesla TX MRI scanner, TR = 3 s, 12-min scan, 240 volumes, 128 × 128 matrix, 40 slices at a 4.0-mm slice thickness). Preprocessing included despiking (AFNI: 3dDespike), motion correction (SPM 12b), coregistration to Magnetization Prepared RApid Gradient Echo image (SPM 12b), normalization, smoothing, temporal detrend (Matlab: detrend.m), bandpass filtering (Matlab: idealfilter.m), and voxelwise regression of identically bandpass filtered time series of six head motion parameters (realignment steps with six rigid-body parameters characterizing the estimated subject motion for each subject), degraded CSF, degraded white matter, and facial soft tissues (MATLAB), as previously described (25–27). All images were spatially normalized to the standard Montreal Neurological Institute space (SPM 12b), spatially smoothed with a 4-mm FWHM 3D Gaussian kernel to reduce spatial noise, linearly de-trended, and temporally filtered with a bandwidth of 0.01–0.08 Hz to reduce the effects of low-frequency drift and high-frequency noise, respectively. To address the possibility of micro-head movements affecting connectivity results (28, 29), time points with head motion >0.2 mm were censored, but no regression of the global signal was performed (30, 31). To assess the susceptibility of head motion, independent *t*-tests were performed to ensure that groups did not differ on rotation or translation parameter [translation: SS group = 0.039 ± 0.018, SL + LL group = 0.042 ± 0.016, $p = 0.172$; rotation: SS group = 0.0007 ± 0.00004, SL + LL group = 0.0008 ± 0.00003, $p = 0.165$]; average frame wise displacements were included as co-variates. The initial volumes (240 volumes) of each participant were used in the current study.

In group independent component analysis of the 54 participants in the current research, five brain circuits including the DMN, salience network, visual, dorsal attention network (DAT), and cerebellar network were best matched. Of the five regions, we selected two networks (DMN and salience). We extracted 11 regions of two brain networks [4 DMNs: middle prefrontal cortex (MPFC), right/left lateral parietal cortex, and posterior cingulate cortex (PCC); 7 salience networks: right/left AInsular, right/left supramarginal gyrus (SMG), right/left rostral prefrontal cortex (RPFC), and anterior cingulate cortex (ACC)] from rois toolbox folder (ver.15; www.Nitrc.org/projects/conn/rois). Fisher-transformed correlation coefficients were measured for each pair of regions of interest (ROI) in each participant. The FC was calculated between ROIs using the CONN-fMRI FC toolbox (ver.15; www.Nitrc.org/projects/conn). Between-group effects were considered significant with a cluster level false discovery rate (FDR; $q < 0.05$), considering the multiple comparison correction of 55 pairs of 11 regions.

Genotyping

Genotyping was performed at Labgenomics, Korea. Genomic DNA was extracted from blood (stored frozen) using a G-DEX™ II Genomic DNA Extraction Kit (Intron Biotechnology, Korea), according to the manufacturer's protocol. The region encompassing 5HTTLPR polymorphisms was amplified with the primers FORWARD: 5′-GGCGTTGCCGCTCTGAATGC-3′ and REVERSE: 5′- GAGGGGACTGAGCTGGACAACCAC-3′ *via* a polymerase chain reaction in 2.5 mM 7-deaza dNTP mix (Roche, Germany). Amplicons were resolved on a 2% agarose gel (Solgent, Korea) and visualized under a UV transilluminator. Herein the 528- and 484-bp bands will be called the L and S alleles of 5HTTLPR, respectively.

Statistical Analyses

An independent *t*-test was performed to compare the mean differences of age, school years, BDI, BAI, K-ARS, YIAS, BAS, and BIS scores between the SS allele group and SL + LL allele group. Controlling for age, an ANCOVA was applied to measure differences in FC between the SS allele and SL + LL allele groups. Controlling for age, YIAS score, and BAS score, partial correlation was performed to assess the association between clinical scales, as well as between clinical scales and brain connectivity.

RESULTS

Demographic and Clinical Characteristics

There were no significant differences in demographic data between SS allele group and SL + LL allele group, but

impulsivity and severity of IGD were higher in SS allele group than those observed in SL + LL allele group. The sample in the current study consisted of 54 patients with MDD (all men) with a mean age of 21.7 ± 3.6 years (range: 18–28 years). The distribution of the current sample was as follows: SS allele ($n = 28$), SL allele ($n = 21$), and LL allele ($n = 5$). The current sample satisfied the Hardy–Weinberg equilibrium ($\chi^2 = 0.13$, df = 1, $p = 0.71$). There were no significant differences in age, school years, BDI, BAI, K-ARS, and BIS scores between the SS allele group and SL + LL allele group. However, the SS allele group had higher YIAS and BAS scores than SL + LL allele group (**Table 1**).

Comparing Brain FC of the DMN and Salience Network Between the SS and SL + LL Allele Groups

The FC within DMN and salience network, and between the networks, in the SS allele group (serotonin deficit) was higher than that in the SL + LL allele group. Compared to the SL + LL allele group, the SS allele group had greater FC within the DMN, including MPFC to PCC ($t = 2.42$, $p = 0.02$), and the salience network, including the right SMG to right RPFC ($t = 2.02$, $p < 0.05$), right AInsular to right SMG ($t = 2.40$, $p = 0.02$), ACC to left RPFC ($t = 2.15$, $p = 0.04$), and left AInsular to right RPFC ($t = 2.42$, $p = 0.02$), and between the DMN and salience network, including the MPFC to ACC ($t = 2.61$, $p = 0.01$) (**Figure 1**).

Correlation Between Clinical Scales and Brain Connectivity

Impulsivity and severity of IGD were associated with the FC between DMN and salience network in patients with MDD and IGD in the SS allele group alone.

In all patients with MDD and IGD, there was positive correlation between the BAS score and YIAS score ($r = 0.63$, $p < 0.01$). The BDI scores had no significant correlations with YIAS scores ($r = 0.03$, $p = 0.79$) and BAS scores ($r = 0.07$, $p = 0.61$). The YIAS scores ($r = 0.58$, $p < 0.01$) and BAS scores ($r = 0.42$, $p < 0.01$) were positively correlated with FC from the ACC to MPFC. Furthermore, the BDI score was positively correlated with the FC from the PCC to the MPFC ($r = 0.71$ $p < 0.01$) (**Figure 2**). The BDI scores were not correlated with the FC from the ACC to the MPFC ($r = 0.11$, $p = 0.49$). The YIAS scores ($r = 0.28$, $p = 0.06$) and BAS scores ($r = 0.25$, $p = 0.08$) were not correlated with the FC from the PCC to the MPFC.

In the SS allele group, there was a positive correlation between the BAS score and YIAS score ($r = 0.68$, $p < 0.01$). Even after controlling for each of the two measures, the BAS score ($r = 0.48$, $p = 0.01$) and YIAS score ($r = 0.64$, $p < 0.01$) were positively correlated with the FC from the ACC to the MPFC (**Figure 3**). In the SL + LL allele group, there was no correlation between BAS score and YIAS score ($r = 0.34$, $p = 0.09$). After controlling for each of the two measures, the BAS scores ($r = 0.21$, $p = 0.32$) and YIAS score ($r = 0.29$, $p = 0.06$) were not correlated with the FC from the ACC to the MPFC.

TABLE 1 | Demographic and clinical characteristics.

	SS-allele group (28)	SL + LL allele group (26)	Statistics
Age	22.3 ± 7.6	20.0 ± 4.6	$t = 1.56$, $p = 0.12$
School years	11.7 ± 1.8	11.8 ± 1.6	$t = 0.11$, $p = 0.91$
BDI	22.3 ± 7.6	20.8 ± 4.5	$t = 1.41$, $p = 0.16$
BAI	12.2 ± 6.1	11.5 ± 7.0	$t = 0.40$, $p = 0.69$
K-ARS	12.1 ± 6.2	11.6 ± 5.3	$t = 0.31$, $p = 0.75$
YIAS*	65.8 ± 11.1	60.0 ± 7.7	$t = 2.31$, $p = 0.03$
BAS*	23.0 ± 3.2	19.8 ± 3.2	$t = 3.01$, $p < 0.01$
BIS	28.3 ± 8.5	26.2 ± 8.5	$t = 0.87$, $p = 0.38$

BDI, Beck Depressive Inventory; BAI, Beck Anxiety Inventory; K-ARS, Korea Attention Deficit Hyperactivity Disorder Scale; YIAS, Young Internet Addiction Scale; BIS-BAS, Behavioral Inhibition and Activation Scales.
**Statistically significant.*

DISCUSSION

Comparison of Clinical Characteristics Between the SS and SL + LL Allele Groups

In the current study, there were no significant differences in depressive symptoms between the SS and SL + LL allele groups. The effects of the 5HTTLPR polymorphism on depressive symptoms in patients with MDD are controversial. In pharmacological studies, the S allele is thought to predict a bad response to medication in diseases associated with serotonergic system dysfunction (32, 33). A meta-analysis demonstrated that the 5HTTLPR polymorphism did not play a major role in predicting the progress of mood symptoms in Asian patients with MDD (34).

However, we found that the SS allele group had higher YIAS and BAS scores than the SL + LL allele group. In our previous study of 166 adolescent, adolescents with excessive Internet use had higher frequencies of the SS allele of 5HTTLPR and harm avoidance, compared to those in the SL + LL allele group (17). In addition, there was a positive correlation between BAS scores and YIAS scores. An association between impulsiveness and the 5HTTLP polymorphism has also been reported in other studies. When the effect of fluoxetine on reducing impulsiveness and irritability was assessed using the Modified Overt Aggression Scale, patients with L carrier (SL + LL alleles) borderline personality disorder showed a better response than S carriers (35). Taken together, we cautiously suggest that short allele of 5HTTLPR is associated with impulsive Internet game play in patients with MDD and IGD.

Comparing Brain Functional Connectivity of the DMN and Salience Network Between the SS and SL + LL Allele Groups

All patients with MDD and IGD in the present study showed a positive correlation between the BDI scores and FC within the DMN. Mulders et al. reported the increase in the FC within DMN and within salience network in patients with MDD, compared to healthy control participants (8). In addition, the FC between DMN and salience network was higher in patients with MDD than in healthy participants (8). Moreover, IGD symptoms in patients with MDD were reportedly associated with increased FC between the DMN and salience network (4, 5).

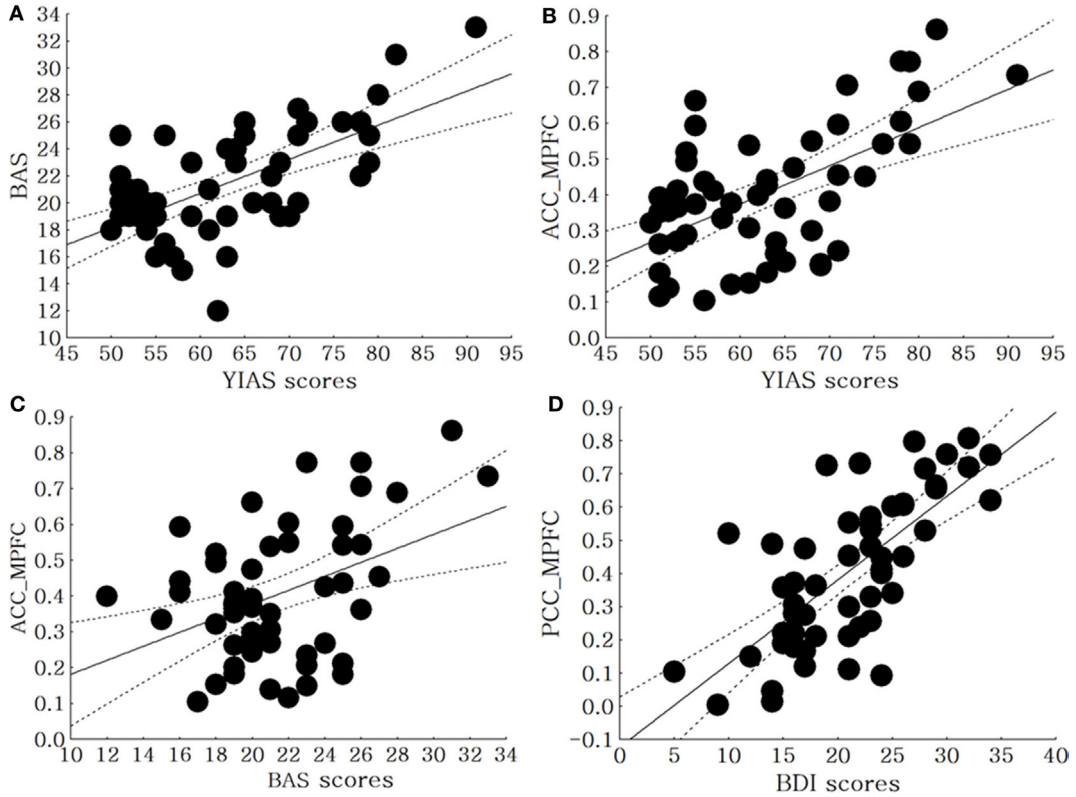

FIGURE 2 | Correlation between clinical scales and brain connectivity in all patients with major depressive disorder (MDD) and Internet gaming disorder (IGD). **(A)** Correlation between the BAS scores and the Young Internet Addiction Scale (YIAS) scores in all patients with MDD with IGD ($r = 0.63$, $p < 0.01$), **(B)** correlation between the YIAS scores and FC between anterior cingulate cortex (ACC) to middle prefrontal cortex (MPFC) in all Patients with MDD with IGD ($r = 0.58$, $p < 0.01$), **(C)** correlation between the BAS scores and FC between ACC to MPFC in all patients with MDD with IGD ($r = 0.42$, $p < 0.01$), **(D)** correlation between the Beck Depressive Inventory (BDI) scores and FC between PCC to MPFC in all patients with MDD with IGD ($r = 0.51$, $p < 0.01$).

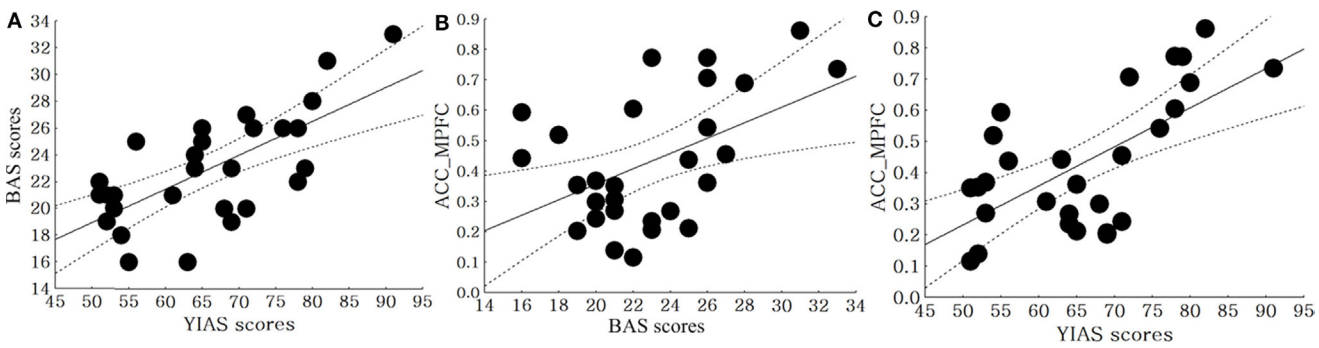

FIGURE 3 | Correlation between clinical scales and brain connectivity in the SS allele and SL + LL allele groups. **(A)** Correlation between the BAS and Young Internet Addiction Scale (YIAS) scores in the SS allele group ($r = 0.68$, $p < 0.01$), **(B)** correlation between the BIS scores and FC from anterior cingulate cortex (ACC) to middle prefrontal cortex (MPFC) in SS allele group ($r = 0.48$, $p = 0.01$), **(C)** correlation between the YIAS scores and FC from ACC to MPFC in SS allele group ($r = 0.64$, $p < 0.01$).

Considering the increased FC within (and between) the DMN and salience network in the SS allele group, our genetic neuroimaging findings suggest that the serotonergic system may play a role in impulsive Internet game play in patients with MDD. Previous reports already demonstrated that the deficit of serotonin neurotransmission in the DMN and salience network were associated with the severity of mood symptoms, chemical addictive symptoms, and impulsive Internet gaming symptoms (13, 36). Patients with MDD, who have the S allele, show microstructural white matter abnormalities within the frontolimbic

networks and a lower remission rate, compared to patients with MDD who have the LL allele (36). Furthermore, Cha et al. reported that the S allele genotypes of 5HTTLPR (SS and SL) were associated with lower FC between the posterior DMN and SFG (13). In that study, path modeling analysis demonstrated that increased FC between the DMN and SFG would mediate impulsivity in patients with MDD (13). Increased FC within the DMN and salience network was also found in codeine-dependent patients; the FC within those areas was associated with impulsivity (37). Increased FC between the DMN and salience network was also reported in patients with IGD who had a childhood history of ADHD (38).

In our results, the SS allele group showed greater FC within the DMN and salience network, and between these networks, compared to the SL + LL allele group. In addition, BAS scores and YIAS scores were positively correlated with the FC between the DMN and salience network in SS allele group alone. Taken together, our results suggest that the short allele of 5HTTLPR may increase FC within the DMN and salience network, which may subsequently aggravate impulsive Internet game play in patients with MDD.

Limitations

A couple of limitations in the current study must be noted. First, the relatively small number of participants prevented the generalization of the current results. Second, there were no neurocognitive tests for assessing the function of the DMN or salience network. Thus, future studies should consider assessing a larger cohort of participants and applying a neurocognitive test.

CONCLUSION

The current results suggested that the SS allele of 5HTTLPR can be a risk factor for impulsiveness and excessive Internet game play in patients with MDD and IGD. In addition, the SS allele of 5HTTLPR may modulate FC, not only within the DMN and salience network but also between the networks.

ETHICS STATEMENT

The research protocol was approved by the Institutional Review Board of Chung Ang University Hospital. The study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1964 and subsequent amendments or similar ethical standards. Written informed consent was obtained from all participants.

AUTHOR CONTRIBUTIONS

JH, SK, and DH contributed to patient recruitment, and data collection and processing. JH, SB, and DH analyzed the data. All authors participated to drawing up the manuscript and were involved in the intellectual workup for the article. All authors read and approved the final manuscript.

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Internet Game Overuse Is Associated With an Alteration of Fronto-Striatal Functional Connectivity During Reward Feedback Processing

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Internet gaming disorder is associated with abnormal reward processing in the reward circuit, which is known to interact with other brain regions during feedback learning. Kim et al. (1) observed that individuals with internet game overuse (IGO) exhibit altered behavior and neural activity for non-monetary reward, but not for monetary reward. Here, we extend our analysis of IGO to the functional connectivity of the reward network. Functional MRI data were obtained during a stimulus-response association learning task from 18 young males with IGO and 20 age-matched controls, where either monetary or non-monetary rewards were given as positive feedback for a correct response. Group differences in task-dependent functional connectivity were examined for the ventromedial prefrontal cortex (vmPFC) and ventral striatum (VS), which are known for reward evaluation and hedonic response processing, respectively, using a generalized form of the psychophysiological interaction approach. For non-monetary reward processing, no differences in functional connectivity were found. In contrast, for monetary reward, connectivity of the vmPFC with the left caudate nucleus was weaker for the IGO group relative to controls, while vmPFC connectivity with the right nucleus accumbens (NAcc) was elevated. The strength of vmPFC-NAcc functional connectivity appeared to be behaviorally relevant, because individuals with stronger vmPFC-NAcc connectivity showed lower learning rates for monetary reward. In addition, the IGO group showed weaker ventral striatum functional connectivity with various brain regions, including the right ventrolateral prefrontal cortex, dorsal anterior cingulate regions, and left pallidum. Thus, for monetary reward, the IGO group exhibited stronger functional connectivity within the brain regions involved in motivational salience, whereas they showed reduced functional connectivity the widely distributed brain areas involved in learning or attention. These differences in functional connectivity of reward networks, along with related behavioral impairments of reward learning, suggest that internet gaming disorder is associated with the increased incentive salience or "wanting" of addiction disorders, and may serve as the neurobiological mechanisms underlying the impaired goal-directed behavior.

Keywords: internet gaming disorder, monetary reward, task-based functional connectivity, ventromedial prefrontal cortex, ventral striatum

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INTRODUCTION

Feedback learning is a typical goal-directed behavior in that it involves using information about outcomes from past behavior to guide future behaviors in order to obtain desirable outcomes. Feedback-guided learning is known to be mediated by dopaminergic mesolimbic neurons projecting to the striatum and prefrontal cortex (2–5). This neural system has been shown to be involved in hedonic feelings (6), predicting rewards (7), and evaluating incentives (8, 9). Dysfunction of this system has been proposed to have a role in the development and maintenance of addiction (10, 11). Given that addiction involves the compulsive pursuit of rewards (e.g., drug, alcohol, or gambling) despite negative consequences, it has been suggested that a dysfunctional dopaminergic reward system enhances the motivational value of recurring addiction-related stimuli, and impairs inhibition of the actions associated with negative consequences (12).

A dysfunctional dopaminergic system has also been reported for the behavioral addiction that is the object of this study, internet gaming disorder (IGD) [for reviews, see (13, 14)]. IGD is characterized as excessive internet gaming, despite negative psychological and social consequences, and is listed as a putative non-substance addiction in the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) (15). Recent studies have linked IGD to disrupted function in brain reward circuitry (16), associated with abnormal sensitivity to reinforcement values (17) and impaired use of negative feedback to adjust ongoing behavior (18, 19). Addiction-related alterations in the interconnections between different brain systems have been observed, not only for those involved in reward processing, but also for those associated with emotional and executive control (10, 20, 21). Using a resting-state functional connectivity approach that measures inter-regional correlations of spontaneous low-frequency fluctuations of blood oxygenation-level-dependent (BOLD) signals during rest, previous studies have reported that individuals with IGD have alterations in intrinsic functional connectivity of the same reward circuits that are involved in addiction disorders. For example, Zhang et al. (22) found reduced functional connectivity between the ventral tegmental area and the nucleus accumbens (NAcc) within reward circuits in IGD individuals. Notably, the strength of this connectivity was negatively associated with craving for internet gaming. Reduced functional connectivity between the striatum (i.e., caudate nucleus and pallidum) and prefrontal cortical regions was also found in individuals with IGD, and this reduction in the connectivity of the cortico-striatal reward circuit was associated with severity of the internet addiction (23) and habitual internet use (24). In addition, Yuan et al. (25) reported that for IGD, this reduced connectivity is associated with cognitive control deficits, in particular, more response errors in the Stroop task. These results indicate that IGD is associated with alterations in resting-state functional connectivity patterns in the cortico-straital circuits responsible for reward and cognitive control.

In addition to functional connectivity at rest, examinations of functional connectivity during performance of tasks have reveal effects of IGD. For example, reduced functional connectivity between insular cortex and the lingual gyrus (which is associated with visual processing and attention bias) was observed during cue processing in an internet gaming cue-reactivity task (26). Furthermore, during a Go-Stop inhibition task, adolescents with internet addiction, unlike the control group, did not show effective connections between the striatum and inferior frontal gyrus, and aberrant connectivity of this network was associated with failures of behavioral inhibition (27). Given that learning from feedback is involved in the dynamic functional coupling of striatal and frontal regions (28), determining how the functional connectivity patterns of this reward network during reward feedback processing is affected by IGD would be informative.

Here we present a further analysis of a previously published functional MRI (fMRI) activation study (1) that examined brain activation patterns, but not functional connectivity. In that study, we found IGD-related differences in activation for symbolic reward, but not for monetary reward. The goal of the current study is to determine if functional connectivity in the reward network is altered by IGD. In contrast to our previous study, we observed alterations in connectivity related to monetary, but not symbolic reward. We also asked if the degree of alteration of functional connectivity was related to feedback learning performance: the only connectivity change related to behavior was correlated with poorer performance for monetary reward.

For connectivity analyses, two regions of the reward network were chosen for seeds: the ventromedial prefrontal cortex (vmPFC), known for evaluating the subjective value of objects and events (29); and the ventral striatum (VS), known for encoding hedonic experiences (30). The generalized psychophysiological interactions (gPPI) toolbox (31) was used to map group differences in functional connectivity during reward processing.

MATERIALS AND METHODS

Participants

The data for this study are those obtained by Kim et al. (1) from 18 young males with internet game overuse (IGO) and 20 control males. All were right-handed, and none reported a history of neurological or psychiatric disorders. The detail recruitment procedures are explained in a previous report (1). Those individuals with high IGADS (Internet Game Addiction Diagnostic Scale, higher than the upper 20% of the distribution, i.e., 67) (32) and IAT (50 or higher on the modified Korean version of Young's Internet Addiction Test) scores (33, 34) were assigned to the IGO group. Those showing low IGADS (lower than the mean, i.e., 47) and IAT (<50) scores, and reporting no internet game activity, were assigned to the control group. The scores from the Beck Depression Inventory (BDI) (35) and the Barratt Impulsiveness Scale-11-Revised (BIS-11) (36) were also obtained.

Approval of the protocol was obtained from the Institutional Review Board of Kangwon National University. The study was carried out in accordance with the recommendations of the principles of Declaration of Helsinki, and written consent was obtained from all participants after the study objectives and experimental methods were fully explained. Participants received the incentives earned during the learning task after finishing the experiment.

Feedback-Based Learning Paradigm

fMRI data were obtained during a four-run scanning session, in which participants were asked to learn stimulus-response associations in a trial-and-error fashion. For each trial, one English letter was presented for 2.5 s as a learning stimulus, during which time one of four alternative keys (two keys for the index and middle finger of each hand) was to be chosen (**Figure 1A**). For a correct response, defined by a fixed relationship between a finger and a given learning stimulus, either a monetary reward (+500 KRW) or a non-monetary reward (the Chinese symbol for right [正]) was provided as positive feedback. For an incorrect response, a monetary penalty (−500 KRW) or non-monetary penalty (the Chinese symbol for incorrect [不]) was given as negative feedback. Feedback was presented for 1 s, following a 1.5 s inter-stimulus interval (ISI) during which a "+" was displayed. Jittered inter-trial intervals (ITI) with a display of "+" (mean = 4 s, range = 2.5–6.5 s) were used to optimize statistical efficiency (37). Participants were informed that the association contingency between letter and target response was fixed for all stimuli. For each run, six association pairs were presented eight times (a total of 48 trials per run). We manipulated three learning conditions (i.e., *gain*, *loss*, and *neutral* conditions), each of which differently assigned to the type of positive and negative feedback (**Figure 1B**). For the association assigned to the *gain* condition, monetary reward followed a correct response, whereas symbolic penalty followed an incorrect response. For the *loss* condition, a symbolic reward was used for positive feedback, whereas a monetary penalty served as negative feedback. For the *neutral* condition, only the symbolic reward or penalty followed correct and incorrect responses, respectively.

In order to examine the relationship between functional connectivity and individual efficiency in reward feedback processing, the rate of correct-stay responses (correct-stay rate is the rate of choosing the same response for the same learning stimulus after a trial with a reward, that is, a correct response) was used as the only behavioral variable. The average correct-stay rate is listed in **Table 1**.

MRI Acquisition and Preprocessing

MRI data were collected while participants performed the learning task on a 3-Tesla SIEMENS TRIO scanner with a 12-channel radio frequency coil, T2*-weighted echo planar images (TR = 2,000 ms, TE =30 ms, flip angle = 90°, field of

TABLE 1 | Demographic, clinical, and behavioral characteristics of participants.

	IGO	Controls	*T*	*p*
N	18	20		
Age (years)	22.17 ± 2.0	21.20 ± 2.2	1.40	$p = 0.169$
IAT	62.78 ± 10.3	29.75 ± 5.9	12.30	$p < 0.001$**
Time being spent for game (h)	24.06 ± 11.5	0.91 ± 3.3	7.66	$p < 0.001$**
Depression (BDI)	14.17 ± 8.8	6.45 ± 4.9	3.39	$p = 0.001$*
Impulsivity (BIS-11)	72.56 ± 9.6	59.20 ± 7.8	4.70	$p < 0.001$**
Correct-stay rate				
Monetary reward	0.94 ± 0.09	0.95 ± 0.04	−0.57	$p = 0.169$
Symbolic reward	0.82 ± 0.18	0.91 ± 0.07	−2.17	$p = 0.036$*

*Mean values are displayed with standard deviations. IGO, Internet game overuse; IAT, Internet Addiction Test; BDI, Beck depression inventory; BIS-11, Barret Impulsivity Scale-11. *Statistical significant at $p < 0.05$ (two-tailed), **$p < 0.001$ (two-tailed). Adapted from Kim et al. (1).*

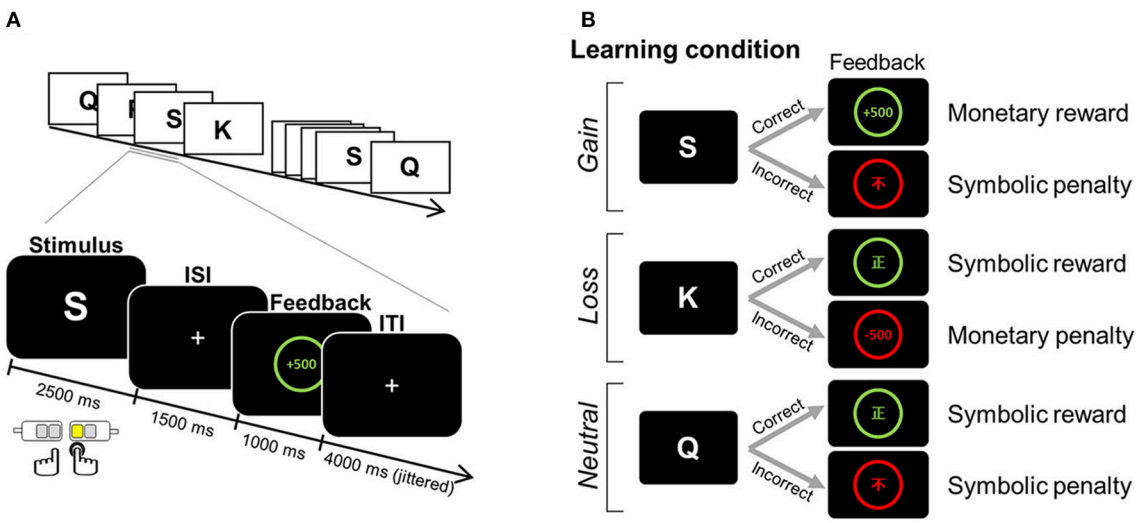

FIGURE 1 | Example of an experimental task. **(A)** Paradigm of the feedback learning task. One English letter was presented as a learning stimulus for which a response was selected from one of four alternatives. Based on the feedback that followed, the association between a given learning stimulus and a target response was to be learned in a trial-and-error fashion. **(B)** The positive and negative feedbacks for correct and incorrect choices differed, depending on three learning conditions assigned to the association: monetary reward and symbolic penalty for the *gain* condition; symbolic reward and monetary penalty for the *loss* condition; and symbolic reward and symbolic penalty for the *neutral* condition. ISI, inter-stimulus interval; ITI, inter-trial interval. Adapted from Kim et al. (1).

view = 240 mm^2, matrix size = 80 × 80, voxel size= 3.0 × 3.0 × 3.0 mm, slice thickness = 3 with 1mm gap, 36 slices, descending sequential, 223 volumes per runs). High resolution T1-weighted data were acquired for anatomical localization using a 3D fast-field echo sequence (TR = 1,900 ms, TE = 2.52 ms, flip angle = 9°, field of view = 256 × 256 mm, matrix size = 256 × 256 × 192, voxel size = 1.0 × 1.0 × 1.0 mm).

The preprocessing of fMRI data was performed using Statistical Parametric Mapping software (SPM12; Wellcome Trust Centre for Neuroimaging, London, UK; www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB R2013b (The MathWorks, Inc., Natick, MA). First, the origin of the coordinates (i.e., x, y, z = 0, 0, 0) was set to the midpoint of the anterior commissure for an individual structural image. Functional data were realigned to the first volume to correct for subject movements. Realigned images were then slice-time corrected to the middle of the image acquisition. The functional images were spatially transformed to Montreal Neurologic Institute (MNI) space (resampled at 2 × 2 × 2 mm voxel sizes) by applying the deformation field generated from the segmentation procedures using the Tissue Probability Map template. To increase the signal-to-noise ratio, normalized functional images were spatially smoothed with a 6-mm Gaussian kernel. Individual fMRI data were high-pass filtered with a 120-s cutoff period. Spike and head motion in the functional images were detected using the artifact detection toolbox (ART; www.nitrc.org/projects/artifactdetect). A volume was considered as an outlier if the global mean signal was greater than 5 z-scores, and the head movement was larger than 2 mm. The outliers were subjected to an individual-level functional connectivity analysis as nuisance regressors to remove the potential influence of head movements and spiking artifacts. The number of outliers across the four runs did not differ between groups (IGO: mean [M] = 18.2, *SD* = 17.9; controls: M = 10.7, *SD* = 11.9, $t = 1.53$, $p = 0.13$). We further evaluated micro-head movements by measuring the mean framewise displacement (38). No significant differences between the IGO and control group were found on this mean framewise displacement (IGO: M = 0.145, *SD* = 0.04; controls: M = 0.143, *SD* = 0.06, $t = 0.12$, $p = 0.90$).

Defining of Two Seed Regions: vmPFC and VS

Two seed regions known for reward processing were selected: VS for its involvement in hedonic processing and vmPFC for its association with value processing (**Figure 2**). In order to define the VS seed, an anatomical template was created by combining the caudate head of the Wake Forest University (WFU) Pick Atlas (human-atlas TD Brodmann's areas +) and the nucleus accumbens of the Harvard-Oxford subcortical structural atlas, resulting in a total volume of 4920 mm^3 ($k = 615$). For the vmPFC, the coordinates (MNI coordinates: $x, y, z = -2, 40, -4$) from a previous meta-analysis study (39) were used. The Marsbar toolbox (version 0.41; http://marsbar.sourceforge.net) (40) was used to define a region of the vmPFC ROI centered at those coordinates (box mask, $x = 20$, $y = 10$, $z = 10$ mm, $k = 275$, volumes = 2,200 mm^3). We then applied a functional brain mask to these seed regions to confine them to the areas involved in reward processing. The functional mask was the region where the activations for all positive feedback (monetary reward + symbolic reward) were greater than for all negative feedback (monetary penalty + symbolic penalty), based on the results of the second-level analysis across participants (uncorrected $p < 0.001$). The size of the final seed region for VS was 3,072 mm^3 ($k = 384$), and that for vmPFC was 2,080 mm^3 ($k = 260$).

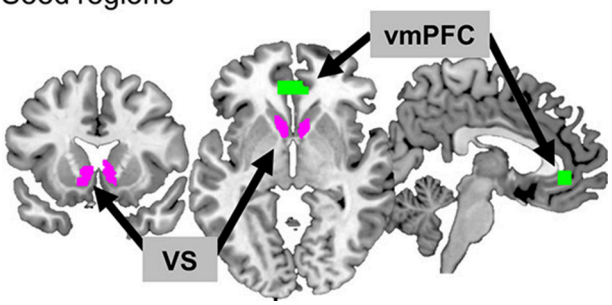

FIGURE 2 | Two seed regions. The ventromedial prefrontal cortex (vmPFC) and ventral striatum (VS) are depicted in green and purple, respectively.

Connectivity Analysis Using gPPI

The group difference was examined for task-specific functional connectivity using gPPI (https://www.nitrc.org/projects/gppi), where functional connectivity was analyzed using the interaction between a psychological factor (i.e., monetary reward) and a physiological factor (i.e., an activity of a seed region). This analysis was performed for each of the two seed regions, vmPFC and VS.

At the individual subject-level, a whole-brain analysis was performed using the general linear model with three types of repressor: (1) psychological regressors, time-locked to the onsets of the feedback presentation, and convolved by the canonical hemodynamic response function; (2) physiological activity of the seed region; and (3) PPI regressors. For the psychological regressors, we modeled six psychological events based on combinations of two feedbacks with opposite valences (reward and penalty) and three types of learning condition (*gain*, *loss*, or *neutral*) associated with a given trial. These events were monetary reward and symbolic penalty for the *gain* condition, symbolic reward and monetary penalty for the *loss* condition, and symbolic reward, and symbolic penalty for the *neutral* condition. For the physiological activity, an eigen-variate of the time-series was estimated from all voxels of a seed region where the underlying neuronal activity was calculated by deconvolving the BOLD signal. The PPI regressors were obtained by multiplying a given reward event (monetary reward in the *gain* condition and symbolic reward in the *neutral* condition) by the estimated physiological activation of the seed region. For monetary reward, the positive feedback of the *gain* condition was modeled. For symbolic reward, however, only symbolic reward events in the *neutral* condition, where the symbolic penalty was used as negative feedback as the *gain* condition,

were included. We did not model PPI regressors for symbolic reward events in the *loss* condition, where monetary penalty was used as negative feedback. The average number of monetary and symbolic rewards included in the PPI analysis was 43.8 ($SD = 4.6$) and 38.7 trials ($SD = 8.6$), respectively, and there was no group difference in the number of events for each reward type (for monetary reward, $t = -1.208$, $p = 0.235$; for symbolic reward, $t = -1.525$, $p = 0.150$). In addition, regressors of no interest (i.e., the six realignment parameters and the outlier volumes) were modeled to control for head movements and spike signals. For each seed region, the PPI connectivity contrast was obtained for monetary reward, symbolic reward (compared with the baseline), and the comparison between two reward types (monetary—symbolic reward). Each contrast was subjected to a whole brain analysis, where a group difference was tested between the IGO and control group with a two-sample *t*-test.

In the group-level analysis, the resulting statistical parametric maps were corrected for multiple comparisons by using a cluster-level family-wise error (FWE) corrected $p = 0.05$, where the primary threshold was set at a voxel-level $p = 0.001$, and a cluster extent threshold of $k > 23$ (184 mm^3) was used. The cluster extent was calculated with a Monte Carlo simulation using the Matlab script (41). For each significant brain region, the beta-value (β) was extracted from the individual-level PPI contrast image using the MarsBar toolbox in order to plot the strength of functional connectivity.

Connectivity-Behavior Correlation Analysis

We also examined the relationship between individual differences in strength of functional connectivity and behavior. For behavior, we used the internet gaming related measurements (i.e., IAT), personality measurements (i.e., depression and impulsivity scale), and learning efficiency for reward (i.e., correct-stay rate), as shown in **Table 1**. Pearson correlation analysis was performed with a threshold for statistical significance of $p < 0.05$, using IBM SPSS statistics 20.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Ventromedial Prefrontal Cortex (vmPFC) Connectivity

In a whole-brain PPI analysis of the vmPFC (**Table 2** and **Figure 3**), the IGO group showed stronger coupling with the right NAcc, but weaker functional coupling with the left caudate nucleus, relative to the control group. None of the group comparisons revealed functional coupling with the vmPFC for the symbolic reward itself, or for the monetary reward—symbolic reward PPI contrast (**Table 2**).

Ventral Striatum (VS) Connectivity

The IGO group showed no stronger functional coupling of VS relative to the control group (**Table 3**). Instead, the functional connectivity of VS was weaker relative to the control group for various brain regions, such as couplings with the right splenium of corpus, left pallidum, right lingual gyrus, right dorsal anterior cingulate cortex (dACC), right precuneus, and right ventrolateral prefrontal cortex (vlPFC) (**Table 3** and **Figure 4**).

No significant group difference in functional coupling of VS was observed for symbolic reward (**Table 3**). For the monetary reward vs. symbolic reward PPI contrast, we assessed whether changes of functional coupling patterns during processing of the monetary reward vs. symbolic reward differed between the groups. The group comparison revealed a significant interaction effect for the left fusiform gyrus and midbrain, including part of the tectum and ventral tegmental area (**Table 3**).

Connectivity-Behavior Relationship

In a further correlation analysis examining the behavioral relevance of functional connectivity strength showing group differences, we found that the strength of vmPFC-NAcc functional connectivity during monetary reward was negatively correlated with the correct-stay rate for monetary reward [$r_{(16)} = -0.516$, $p = 0.028$; $r_{(15)} = -0.233$, $p = 0.369$ after removing the outlier shown in **Figure 5**]. As shown in **Figure 5**, IGO individuals with stronger vmPFC-NAcc connectivity for monetary reward exhibited a reduced tendency to choose the same response on the next occasion when monetary reward was given as positive feedback, relative to those showing weaker connectivity. A similar, but weaker trend for a negative association was observed in the control group [$r_{(18)} = -0.440$, $p = 0.052$]. There were no significant relationships between vmPFC-NAcc functional connectivity strength and the severity of internet addiction, or between vmPFC-NAcc functional connectivity strength and other personality assessments (including depression and impulsivity).

None of the individual differences in internet gaming related measurements, personality assessments or behavioral performance were associated with vmPFC-caudate nucleus functional connectivity or any identified VS functional connectivity (e.g., VS-pallidum, VS-dACC, VS-precuneus) for monetary reward.

DISCUSSION

Given that there were no IGO related differences in brain activation for monetary, unlike symbolic reward (1), the current task-based functional connectivity analysis for monetary reward is unlikely to be biased by pre-existing group differences in activation levels. Consequently, monetary reward is the main focus of the discussion that follows. It is worth noting that the IGO-associated functional network changes to be described could not have been observed in a conventional fMRI activation study, including that of Kim et al. (1).

Weaker vmPFC Connectivity With the Caudate Nucleus

The vmPFC is known to be involved in translating rewards to representations of subjective value (39, 42). It has reciprocal connections with the striatum for cognitive and affective/emotional functions (43, 44). Our findings reveal a dissociated functional coupling of the vmPFC with sub-regions of the striatum associated with IGO: weaker functional

TABLE 2 | Regions showing significant group differences in task-dependent connectivity with the ventromedial prefrontal cortex (vmPFC).

Region	R/L	BA	MNI coordinates			Stats	
			x	*y*	*z*	*T*	Size*
MONETARY REWARD FEEDBACK							
IGO group > Control group							
NAcc	R	-	4	12	−8	5.30	31
IGO group < Control group							
caudate nucleus	L	-	−10	10	16	4.76	26
SYMBOLIC REWARD FEEDBACK							
IGO group > Control group							
NS							
IGO group < Control group							
NS							
REWARD-TYPE INTERACTION (MONETARY > SYMBOLIC REWARD FEEDBACK)							
IGO group > Control group							
NS							
IGO group < Control group							
NS							

*MNI coordinates for the local maxima of clusters with significant voxels (cluster-level corrected $p < 0.05$). *Size refers to volume of cluster, stated in number of voxels (2mm × 2mm × 2mm).*

NS, not significant; R, right; L, left; BA, Brodmann areas; NAcc, nucleus accumbens.

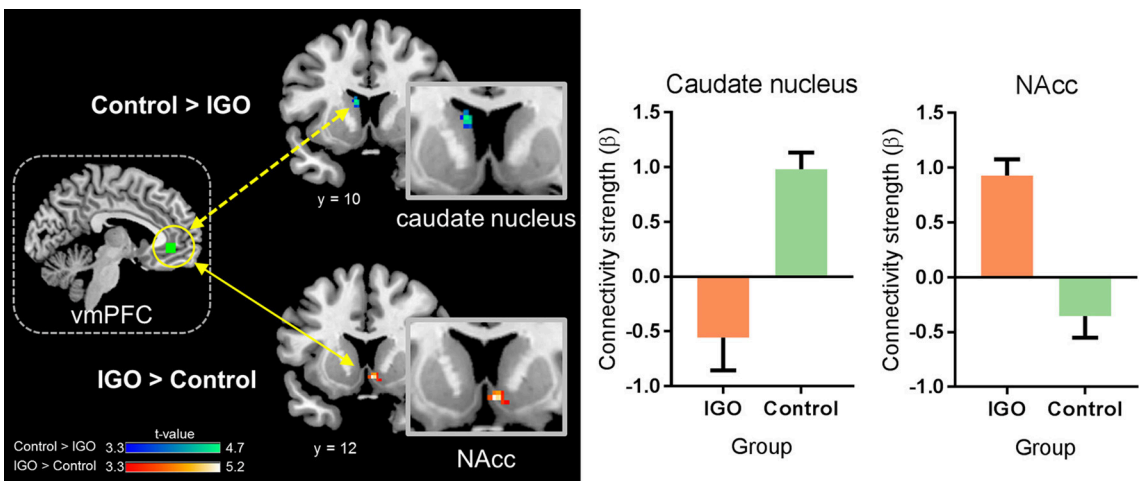

FIGURE 3 | Group differences in functional connectivity of the ventromedial prefrontal cortex (vmPFC) during monetary reward processing. The IGO group showed significantly greater functional connectivity between the vmPFC and nucleus accumbens (NAcc) during monetary reward, whereas the control group showed greater connectivity between the vmPFC and caudate nucleus. Mean ± SEM; cluster-level corrected $p < 0.05$.

connectivity with the dorsal striatum (i.e., the caudate nucleus), and stronger connectivity with the ventral striatum (i.e., the NAcc).

The caudate nucleus is the target region of dopamine projection neurons in the substantia nigra, and is known to be involved in encoding action-outcome associations during reward learning (45). It is one of the brain regions where IGD-associated abnormalities have been widely reported in molecular (46), structural (47, 48), and functional studies (17). For example, young adults with internet addiction exhibit reduced dopamine D2 receptor availability in the bilateral dorsal caudate, and the severity of internet addiction measured by IAT scales is negatively associated with dopamine D2 receptor availability in the left caudate (46). Also, IGD individuals appear to have increased gray matter volume in the caudate, along with impaired cognitive control performance (47). Dong et al. (17) have reported reduced caudate activation in individuals with internet addiction during decision making in the context of "continuous" wins, suggesting insufficient attention to previous behavior selections and their outcomes.

Brain activations in response to positive feedback have been reported in both the caudate nucleus and vmPFC, especially

TABLE 3 | Regions showing significant group differences in task-dependent connectivity with the ventral striatum (VS).

Region	R/L	BA	MNI coordinates			Stats	
			x	*y*	*z*	*T*	Size*
MONETARY REWARD FEEDBACK							
IGO group > Control group							
NS							
IGO group < Control group							
splenium†	R	–	6	−28	32	5.58	60
pallidum	L	–	−14	0	−2	4.99	26
lingual gyrus	R	17	2	−68	8	4.96	23
dACC	R	32	4	32	30	4.60	27
precuneus	R	23	4	−44	40	4.56	65
vlPFC	R	44	32	12	32	4.00	28
SYMBOLIC REWARD FEEDBACK							
IGO group > Control group							
NS							
IGO group < Control group							
NS							
REWARD-TYPE INTERACTION (MONETARY > SYMBOLIC REWARD FEEDBACK)							
IGO group > Control group							
NS							
IGO group < Control group							
fusiform gyrus	L	19	−30	−70	−6	4.51	35
midbrain tectum	L	–	−12	−24	−14	4.07	36
ventral tegmental area	M	–	0	−36	−14	3.84	55

*MNI coordinates for the local maxima of clusters with significant voxels (cluster-level corrected $p < 0.05$). *Size refers to volume of cluster, stated in number of voxels (2mm × 2mm ×2mm). †The splenium of the corpus callosum was merged with the adjacent precuneus at an uncorrected $p < 0.005$. NS, not significant; R, right; L, left; M, medial; BA, Brodmann areas; dACC, dorsal anterior cingulate cortex; vlPFG, ventrolateral prefrontal cortex.*

when feedback contains information for future behavior (49). The anatomical strength of the caudate-vmPFC connection has been shown to predict the flexibility of goal-directed action (50). The impaired functional communication between the dorsal striatum and vmPFC found in the IGO group of this study implies that there should be abnormal decision making or failure of behavioral adjustment for monetary reward, particularly since similar findings have been reported for other types of addiction. For example, Lee et al. (51) reported reduced functional coupling between the dorsal striatum and orbitofrontal region surrounding the vmPFC during an Odd-Even-Pass task in individuals with alcohol dependence, in association with their persistent selection of maladaptive choices. However, we did not find a link between the weak vmPFC-dorsal striatum connectivity of IGO and learning performance for monetary reward.

Stronger vmPFC Connectivity With the Nucleus Accumbens

In contrast to vmPFC-caudate nucleus connectivity, vmPFC-NAcc connectivity was enhanced in the IGO group. The NAcc, as one of the main components of the ventral striatum, has been suggested to be involved in assigning incentive salience to a rewarding stimulus. The vmPFC-NAcc circuit has been proposed to be a neuropathological mechanism of addiction (52). For example, there is increased functional connectivity between the ventral striatum and the vmPFC in heroin-dependent individuals during the resting state (53). An increased vmPFC-NAcc connectivity was also reported in alcohol-dependent young adults during reward processing, and individual differences in this connectivity were associated with the frequency of alcohol usage (54).

Our findings are in line with the conclusions of Volkow et al. (55), who proposed that addiction is related to "NOW" circuits, wherein elevated vmPFC/NAcc circuit favors choosing an immediate reward. The current finding of vmPFC-NAcc coupling in the IGO group is consistent with pathological changes in the neuronal mechanisms involved in reward value processing in substance addiction, particularly within the "wanting" circuits.

Although there was a negative correlation between vmPFC-NAcc functional connectivity and the correct-stay rate for monetary reward, caution should be exercised in interpreting this finding. Note that two individuals of the IGO group whose strengths of vmPFC-NAcc functional connectivity were highly enhanced during monetary reward delivery showed the lowest correct-stay rate. In particular, one participant in the IGO group could be identified as a statistical outlier [Cook's Distance method; (56)]. The negative correlation originally found in the IGO group [$r_{(16)} = -0.516$, $p = 0.028$] is

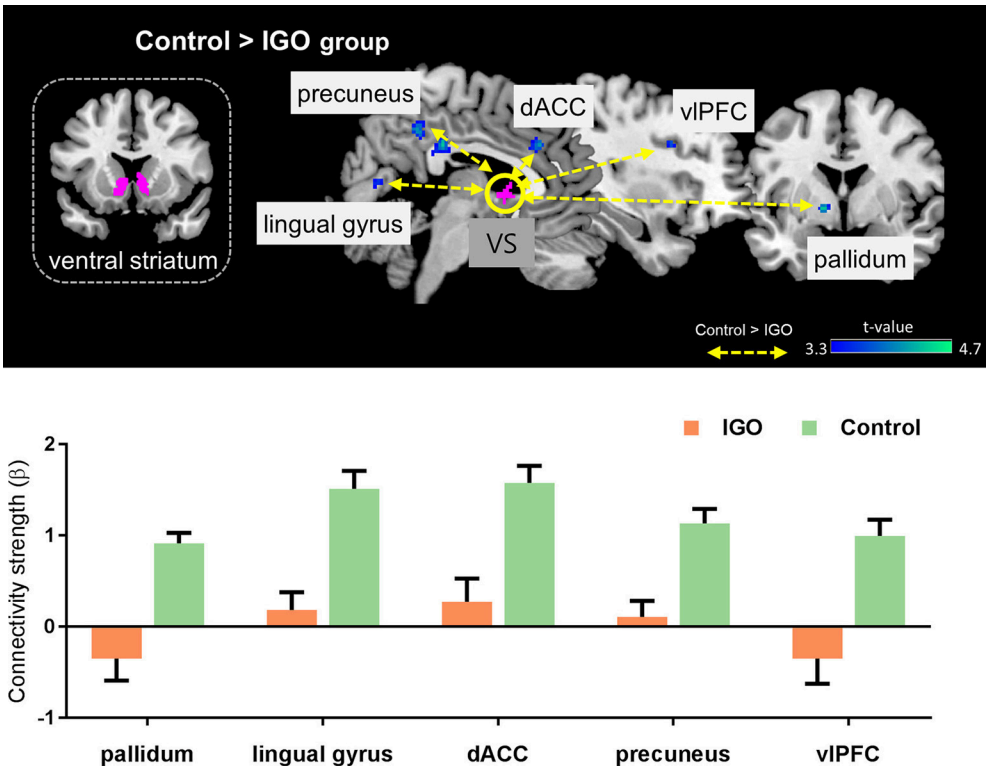

FIGURE 4 | Top: Group differences in functional connectivity with the ventral striatum (VS) during monetary reward feedback. **Bottom:** Beta estimates for connectivity of the VS seed. Mean ± SEM; cluster-level corrected $p < 0.05$.

no longer significant if this outlier is removed from the analysis [$r_{(15)}$=−0.233, $p = 0.369$]. Alternatively, we think this outlier is just the extreme example of this negative relationship, in which the participant with the most enhanced vmPFC-NAcc functional coupling for monetary reward would experience the greatest cognitive interference in reward feedback processing. This participant's low performance was specific only to monetary reward (0.65: averaged correct-stay rate of IGO group = 0.941; $SD = 0.094$), not to symbolic reward (0.77: averaged correct-stay rate of IGO group = 0.822; $SD = 0.179$). This suggests that the outlier's poor behavioral performance was not associated with a misunderstanding of task instructions or poor learning ability in general. Moreover, a similar trend of a negative relationship existed even in the normal control group [$r_{(18)} = -0.440$, $p = 0.052$], indicating that the increased vmPFC-NAcc functional coupling was associated with poor learning performance for monetary reward, regardless of IGO problems. This interpretation is supported by a previous report that among healthy participants individuals with increased ventral striatum-vmPFC connectivity showed greater impulsive behavioral tendency during a delay discount task (57). The current finding of strengthened vmPFC-NAcc functional connectivity in the IGO group can be understood as a similar pathological mechanism of an increased salience within "wanting" circuits (58). In other words, the enhanced vmPFC-NAcc coupling for the reward incentive in IGO individuals may be related to a greater saliency response for reward, which may be a possible underlying mechanism of problematic internet overuse behavior for salient incentives.

Weaker VS Connectivity With the Dorsal Anterior Cingulate Cortex

Our examination of task-based VS functional connectivity revealed that IGO individuals have weaker VS-dACC coupling relative to the control group. This reduced functional coupling between the ventral striatum and dACC is consistent with previous findings. Intrinsic connectivity of the ventral striatum-dACC has been shown to be associated with greater severity of nicotine (59) and cocaine addiction (60). Also, Crane et al. (61) have reported that the high-risk group in alcohol-use disorder (i.e., binge drinkers) have difficulty engaging this network during reward processing.

In the context of learning, the dACC has an important role in coding action-outcome associations, including integrating reward history to guide decisions for potential rewards (62, 63). It has also been suggested to be involved in signaling the need for attention during learning (64). Abnormalities in dACC function for feedback processing in IGD individuals have been reported. Yau et al. (65) noted that adolescents with problematic internet use have blunted feedback-related negativity and P300 amplitudes during risk-taking, suggesting abnormal ACC function in early and late feedback processing. Given that VS is also a critical brain region for reward-associated learning (66) as well as for reward processing (67),

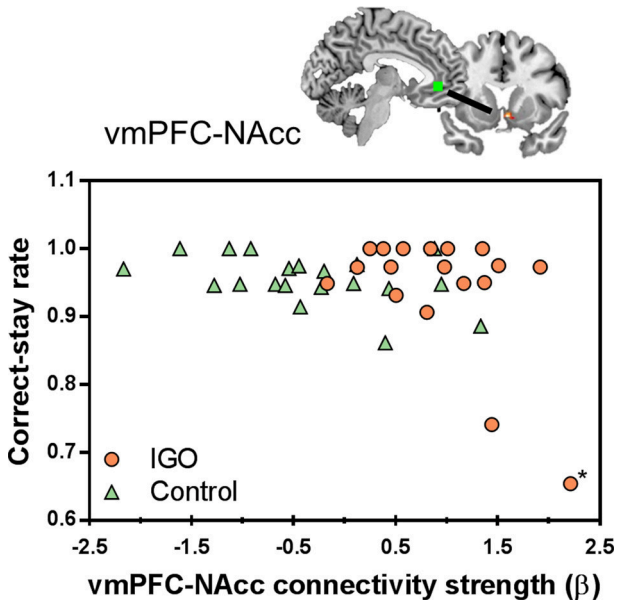

FIGURE 5 | Individual differences in the vmPFC-NAcc functional connectivity for monetary reward and learning performance. Individuals with higher functional connectivity strength between the vmPFC and NAcc in response to monetary reward showed lower correct-stay rate for the monetary reward, particularly in the IGO group. The asterisk marks an outlier in the IGO group.

the functional coupling between VS and dACC must have a critical role in feedback learning, in which the outcome values for selected responses are updated. Therefore, altered VS-dACC functional coupling in the IGO group could indicate a difficulty in representing value signals attached to action-outcome relationships, which in turn could lead to learning problems, even though impaired learning performance was not observed for monetary reward.

Weaker VS Connectivity With Other Cortical and Subcortical Regions

We found widespread abnormal functional couplings in the vlPFC, precuneus, and lingual gyrus in association with IGO. These regions are involved in various cognitive controls during feedback learning. For example, the vlPFC is known for guiding flexible goal-directed behavior by integrating motivation information from subcortical areas (68, 69). The precuneus and lingual gyrus are activated in response to monetary reward during reversal learning when a reward is given as a signal to reverse the roles (70). According to Dong et al. (71), there is reduced inferior frontal cortex activation in IGD individuals when making risky choices. The reduced functional connectivity between VS and the various cortical regions in the IGO group of the current study suggest impaired cognitive controls of feedback processing when a monetary reward is given as positive feedback.

We also found that the IGO group exhibited weaker VS functional connectivity with the pallidum during monetary reward processing. The pallidum receives efferent connections from the ventral striatum, especially from the NAcc, and sends a signal to the cortex via relays through the thalamus (72). The pallidum is mainly known to be associated with motor functions, but a role in reward processing has also been widely discussed (73). Zhai et al. (74) reported that IGD is associated with reduced white matter efficiency in the pallidum. The VS and pallidum are both implicated in the hedonic impact of addiction, which is thought to be mediated by opioid systems (75), we speculate that reduced VS-Pallidum functional connectivity in IGO individuals may reflect reduced hedonic pleasure for monetary reward. This interpretation is in line with a theoretical model of addiction that incorporates decreased hedonic set points (76).

Why Are Effects on Functional Connectivity Only for Monetary Reward?

For monetary reward only, the IGO group showed altered functional connectivity's, with either weaker stronger or stronger patterns. During feedback learning, participants were aware that a correct response could result in either a monetary or a symbolic reward. Because they had not been informed about which learning stimulus was to be followed by a monetary, as opposed to symbolic reward, the delivery of a monetary reward would have had greater motivational saliency relative to a symbolic reward. That these effects were confined to the IGO group suggests that this saliency had more impact on IGO individuals than controls.

In spite of the functional connectivity effects observed in IGO individuals for monetary reward, we did not detect a learning impairment for monetary reward in the IGO group relative to controls. One possible reason for this could be a ceiling effect. In this feedback learning paradigm, where each feedback was given based on a deterministic stimulus-outcome contingency, the average correct-stay rate for monetary reward was very high in both groups (IGO group: $M = 0.94$, $SD = 0.09$; control group: $M = 0.95$, $SD = 0.04$). Consequently, it would be difficult to resolve any learning impairment for learning from monetary reward, even in the IGO group. Another possibility is that IGO individuals might rely on other compensatory cognitive resources to learn the S-R associations, resulting in performance similar to the controls. However, we found no evidence to support the compensatory hypothesis, because most of the functional networks investigated were weaker in the IGO group than in controls. For the only instance of increased functional connectivity in the IGO group (i.e., vmPFC-NAcc coupling), the relationship with the behavioral performance was the opposite of expectation: individuals with stronger vmPFC-NAcc coupling for monetary reward exhibited a reduced tendency to choose the same response in subsequent occasions. Thus, if there is a compensatory mechanism for overcoming learning impairment for reward feedback in IGO, it must exist outside of the vmPFC or VS coupling networks. Finally, we should consider the possibility that compensatory mechanisms of IGO occur not during the time of feedback processing, as investigated in the current study, but during the inter-trial interval (working memory strategy) or during stimulus presentation/response selection. Consistent with this idea, a previous report (1) suggests that IGO individuals recruited a working memory strategy specifically for monetary

reward in order to compensate for their reward learning impairment.

Caveats and Limitations

Although we observed different functional connectivity patterns of VS and vmPFC in the IGO group, the degree of these abnormalities was not associated with the severity of symptoms of internet gaming addiction. The abnormalities found in the functional networks involved in reward information processing could result from the heavy use of internet gaming of the IGO individuals. However, this possibility has not been supported by our data, since we couldn't find any correlation between the time being spent on gaming and the connectivity strengths. An alternative possibility is that the severity of addiction may not show a linear relationship with the degree of abnormalities in reward processing. Another is that individuals with certain inherent, pre-existing functional network features may be more likely to fall into gaming overuse problems. For example, casual gaming activity may become problematic for those who are relatively inefficient in processing cognitive/attentional demands to control the environment when experiencing pleasure for highly salient rewards, putting such otherwise normal individuals at risk for IGD. Longitudinal studies will be needed to address the long-term effects of internet gaming usage or risk factors in information processing.

Depression and attention-deficit/hyperactivity disorder (ADHD) have been implicated in reward processing (77, 78), both of which are also well-known psychiatric comorbidities of IGD (79). The changes in functional connectivity patterns we observed in the IGO group were not associated with any of the comorbidities of IGD, such as depression or impulsivity. Since group differences for monetary reward were observed in functional brain networks known to be involved in saliency and cognitive control of reward, it is reasonable to assume that these differences are related to reward information processing. Therefore, the differences in information processing for monetary reward are likely critical IGD features that can occur independently from personality traits or emotional disorders.

It is important to discuss a couple of limitations of this report. Our IGO group consisted of young males who were considered "at risk" of IGD. One must use caution in generalizing our findings to IGO females, or to males or females clinically diagnosed with IGD (80). Another issue is our use of a fixed inter-stimulus interval between the learning stimuli and feedback display, as is typical of S-R association learning paradigms. This fixed interval could have caused the imaging data for feedback-related activation to be affected by residual activity from the feedback anticipation period (i.e., cue presentation or response initiation). Indeed, a previous study examining the reward prediction error in IGD revealed blunted VS activation during cue processing (81). Finally, one should keep in mind that the functional connectivity approach does not reveal direct or causal relationships between two regions, even though some of our interpretations have been informed by specific anatomical interconnections found in animal studies.

CONCLUSIONS

In conclusion, the IGO group exhibited stronger functional connectivity within brain regions of the reward network involved in motivational salience, whereas the controls showed greater connectivity with widely distributed brain areas associated with learning or attention during feedback learning from a salient incentive. The enhanced functional connectivity of the vmPFC-NAcc network, and the related learning impairment, suggest that IGD is associated with the increased incentive salience or "wanting" related to addiction disorders, which may provide a neurobiological explanation for the impaired goal-directed behavior. In addition, the weaker functional connectivity between the reward circuit and other brain regions related to cognitive control (dACC or vlPFC) or learning (dorsal striatum) suggests there may be additional learning impairments. Despite the differences in functional connectivity for processing monetary reward, the greater motivational saliency of this feedback apparently obscured any learning impairment, possibly because of a compensatory strategy that was not investigated in this paradigm, such as working memory.

AUTHOR CONTRIBUTIONS

JK and EK conceived of and designed the study. JK collected and analyzed the fMRI data. JK and EK interpreted the data and drafted the manuscript. Both authors approved the final version of the manuscript.

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Increased Attentional Bias Toward Visual Cues in Internet Gaming Disorder and Obsessive-Compulsive Disorder: An Event-Related Potential Study

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Internet gaming disorder (IGD) is a newly identified potential addiction disorder associated with compulsive internet-game playing behavior and attentional bias toward online gaming- related cues. Attentional bias toward addiction-related cues is the core feature of addiction that is associated with craving, but the pathophysiology of attentional bias in IGD is not well-understood, such as its relationship to compulsivity. In this study, we used the electrophysiological marker of late positive potential (LPP) to compare attentional bias in IGD and obsessive compulsive disorder (OCD). Twenty patients with IGD, 20 patients with OCD, and 23 healthy control (HC) subjects viewed a series of game-related, OCD-related, and neutral pictures while their event-related potentials (ERPs) were recorded. The game-related cues included in-game screen captures of popular internet games. The OCD-related cues included pictures which provokes obsessive and compulsive symptoms of contamination/washing or checking. LPPs were calculated as the mean value of amplitudes between 350 and 750 ms at the centro-parietal (CP1, CPz, CP2) and parietal (P1, Pz, P2) electrode sites. Higher LPP amplitudes were found for game-related cues in the IGD group than in the HCs, and higher LPP amplitudes were observed in the OCD group for OCD-related cues. The IGD group did not exhibit LPP changes in response to OCD-related cues. Subjective scales demonstrated increased arousal to game-related cues and OCD-related cues in both the IGD and OCD groups compared with the HC group. Increased LPPs in response to disorder-specific cues (game-related and OCD-related) were found in both IGD and OCD groups respectively, although the groups showed overlapping arousal on subjective scales. Our results indicate that LPP is a candidate neurophysiological marker for cue-related craving in IGD.

Keywords: event-related potential, late positive potential, craving, attentional bias, internet gaming disorder, obsessive compulsive disorder, cue reactivity

INTRODUCTION

Internet gaming disorder (IGD) was newly included as a putative addiction disorder in section Results, or "a condition for further study" of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (1). The DSM-5 defines the condition as "excessive and prolonged pattern of internet gaming leading to clinically significant impairment or distress." The symptoms of IGD are similar to those of addiction-related phenomenon, including "continued excessive use of internet games despite adverse consequences," "loss of control (compulsive playing)," and "craving" (2, 3). Accordingly, many researchers proposed that IGD be regarded as one of behavioral addictions. However, there are concerns of other researchers that current operationalization of IGD criteria needs more specificity, because the problematic behaviors of pathologic gaming may be different from those of substance use disorders (4). Therefore integrative understanding of neurobiological substrate and clinical phenomenon of IGD is important to clarify the condition from other disorders with similar clinical features.

One of core phenomenology of addiction is repeated behavior involving continued excessive use of substance or behavior. Obsessive-compulsive disorder (OCD) is also related to repetitive compulsive behavior, so there is some phenomenological overlap between IGD and OCD in terms of repetitive behaviors (5). Traditionally, repetitive behaviors can be seen in terms of the domain of impulsivity and compulsivity, where impulsivity and compulsivity have been proposed as opposite constructs. Impulsivity is described as a predisposition toward unplanned reactions to stimuli, meanwhile compulsivity involves repetitive behavior often motivated by the need to reduce or prevent anxiety (6). Previous conceptualizations of IGD have focused on the behavioral feature of impulsivity (7). However in a recent study, directly comparing impulsivity and compulsivity in IGD, OCD, and alcohol use disorder patients using neurocognitive measurements, IGD seemed to share neurocognitive dysfunctions of impulsivity and compulsivity (5). In addition, neurobiological studies have demonstrated the dysfunction of frontal areas within inhibitory brain circuitry or reward circuitry in addiction, which may be related to both impulsivity and compulsivity (8, 9). A recent review proposed IGD lie between behavioral addiction and impulse-control disorders as initial impulsivity followed by compulsivity in behavioral addiction can be differentiated from impulse-control disorder (10). Taken together, direct comparison of IGD and OCD with neurobiological substrate may provide more specific conceptualization between impulsivity and compulsivity.

Craving is another of the core characteristics of addiction (11). Conditioning to drug-related cues underlies the change in salience, and the change in mesolimbic dopamine transmission is regarded as the mechanism. Attentional bias is enhanced attention being afforded to drugs and drug-related cues due to increased incentive salience (12), is often used to examine craving (13, 14). Attentional bias is associated with cue-elicited craving. In IGD, the brain regions activated in response to the visual presentation of gaming cues correspond to the key regions associated with drug-related addiction (15). A previous study demonstrated that the efficacy of treatment for IGD is associated with changes in functional connectivity in the cortical-ventral striatum circuitry, which mediates gaming craving and attentional bias (16). Several previous studies have employed the late positive potential (LPP) and event-related potential (ERP) components in the study of attentional bias, which represent motivated attention to emotionally salient stimuli (17, 18). The LPP is a midline ERP that becomes evident approximately from 350 to 750 ms following arousing emotional stimulus (17, 19). Increased LPP amplitude in response to drug-related cues has consistently been observed in various substance use disorders, such as cocaine use, alcohol use disorder and smoking (20–22). Recently, a few studies involving individuals with OCD have reported abnormalities in LPP in response to OCD-related pictures; however, only one study showed a stronger late positive complex, which is similar to LPP, in excessive computer game players compared to casual players using parietal electrodes (23).

The aim of this study was to examine and compare cue-related reactivity in individuals with IGD and OCD using LPP. We hypothesized that individuals with IGD would exhibit increased LPPs in response to game-related images. In addition, we aimed to compare the cue reactivity in IGD patients as well as the OCD patients.

METHODS

Participants and Clinical Assessments

Twenty patients with IGD, 20 patients with OCD, and 23 healthy control (HC) subjects participated in this study. The participants in the IGD and HC groups were recruited from the addiction outpatient clinic at the SMG-SNU Boramae Medical Center and via an internet advertisement. The participants in the OCD group were recruited from the OCD outpatient clinic at Seoul National University Hospital (SNUH). An experienced psychiatrist conducted interviews to confirm the diagnoses of IGD and OCD using the DSM-5 criteria. OCD patients with comorbid IGD were excluded from this study. All subjects with IGD were drug-naïve and participated in one of three popular internet games (League of Legend, FIFA, Sudden Attack), which were selected as game-related cues, for >4 h/day. Only patients with OCD who had compulsive symptoms of the washing or checking type were included, as pictures provoking washing or checking compulsions were selected as OCD-related cues. Six of the OCD patients were medication-naïve, 8 were medication-free for >1 month before entering the study, and 6 were medicated at the time of testing. The six medicated OCD patients were taking selective serotonin reuptake inhibitors, and one patient was prescribed a small dose of olanzapine (2.5 mg) as an adjuvant. The HC subjects played internet games for <2 h/day and were confirmed to have no past or current psychiatric illness using the Mini-International Neuropsychiatric Interview (24). For all the participants, Young's Internet Addiction Test (IAT) (25) was used to measure the severity of internet gaming addiction, and the severity of OCD was assessed using the Yale-Brown obsessive compulsive scale (Y-BOCS) (26). The Hamilton rating scale for depression (HAM-D) (27) and the Hamilton rating scale for anxiety (HAM-A) (28) were used to assess depressive and anxiety

symptoms. The participants' intelligence quotient (IQ) was measured using the abbreviated version of the Korean-Wechsler Adult Intelligence Scale. The exclusion criteria included a lifetime diagnosis of substance abuse or dependence, neurological disease, significant head injury accompanied by loss of consciousness, any medical illness with documented cognitive sequelae, sensory impairments, and intellectual disability (IQ < 70).

All the participants fully understood the study procedure and provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki, and the institutional review boards of SMG-SNU Boramae Medical Center and SNUH approved the study.

Cue Reactivity Task and EEG Recordings

The cue reactivity task consisted of three types of picture sets: (1) the game-related cues included in-game screen captures of three popular internet games (i.e., *League of Legends*, *FIFA*, and *Sudden Attack*); (2) the OCD-related cues included pictures from the contamination/washing and checking categories in the Berlin Obsessive Compulsive Disorder Picture Set (BOCD-PS), which were validated for provocation of anxiety and compulsive behavior (29); and (3) the neutral pictures were adopted from the neutral category of the International Affective Picture System (IAPS) (30). Each individual visual stimulus was matched for size (resolution of 1,024 × 768 pixels, 361 × 271 mm, 72 dpi), luminance, brightness, and color. Each category (League of Legends, FIFA, Sudden Attack, Washing, Checking, Neutral) consisted of 7 different pictures, and a pseudo-random series of pictures was repeated 6 times during the task run. The stimulus duration was 3,000 ms, and the inter-stimulus interval was 2,000 ms. The six categories of picture stimuli and sample task sequences are presented in **Figure 1.**

The participants were seated comfortably in a dimly lit, electrically shielded room ∼60 cm from a monitor and instructed to watch the screen carefully. Continuous electroencephalogram (EEG) recordings were made using a Neuroscan 128-channel Synamps system with a 128-channel Quick-Cap based on the modified 10–20 international system (Compumedics, Charlotte, NC). The electrodes at the mastoid sites served as reference electrodes, and the ground electrode was placed between the FPz and Fz electrode sites. The EEG was digitized at a 1,000-Hz sampling rate with an online filter of 0.05–100 Hz. Eye-movement artifacts were monitored by recording the vertical and horizontal electro-oculogram using electrodes below and on the outer canthus of the left eye. The resistance at all the electrode sites was below 5 kΩ. After completing the EEG recording during the cue reactivity task, the participants were asked to rate their arousal and valence for all stimuli, their craving in response to the game-related cues, and their desire to engage in compulsive behavior (compulsion) for the OCD-related cues using a visual analog scale ranging from 0 to 10.

ERP Analysis

The ERP data were pre-processed using Curry 7.0 software (Compumedics, Charlotte, NC). The EEG recordings were re-referenced to a common average reference, and eye-movement artifacts were reduced using the artifact-reduction algorithm in the Curry software (31). The continuous EEG data were bandpass filtered between 0.1 and 30 Hz, epoched to 200 ms pre-stimulus and 3,000 ms post-stimulus, and baseline-corrected using the averaged pre-stimulus interval voltage. Epochs containing EEG amplitudes that exceeded ± 100 μV were rejected automatically. The epochs were then averaged separately for each class (Game vs. OCD vs. Neutral). The LPPs were calculated as the mean values of amplitudes between 350 and 750 ms at the centro-parietal (CP1, CPz, CP2) and parietal (P1, Pz, P2) electrode sites. Electrode sites were selected as reported in a previous study (23).

Statistical Analysis

Demographics, clinical characteristics, and rating scores were compared among the groups using one-way analysis of variance (ANOVA), independent sample *t*-tests, or Welch's test if the variances were not equal. A χ^2 analysis or Fisher's exact test was used for categorical data analysis. The cue effects on the mean LPP amplitudes were analyzed using repeated-measures ANOVAs with the electrode sites (CP1, CPz, CP2, P1, Pz, P2) and the 3 stimuli (Game, OCD, Neutral) as within-subject factors and group (HC, IGD, OCD) as a between-subjects factor. Group comparisons of the mean LPP amplitudes were performed using repeated-measures ANOVAs with the 6 centro-parietal electrode sites as the within-subject factors and group (HC, IGD, OCD) as a between-subjects factor. A *post-hoc* Tukey's honestly significant difference (HSD) test was used to identify specific group differences. SPSS software (ver. 22.0; IBM Corp., Armonk, NY) was used for the statistical analyses. Statistical significance was set at $P < 0.05$.

RESULTS

Demographics, Clinical Characteristics, and Ratings for Each Stimulus

We did not find significant differences with regard to sex, handedness, IQ, or education (**Table 1**). However, all clinical characteristics (i.e., scores on the IAT, Y-BOCS, HAM-D, and HAM-A) exhibited significant group differences. The participants with IGD had the highest scores on the IAT, the patients with OCD had intermediate scores, and the HCs had the lowest scores on the IAT (IGD vs. HC, $P < 0.001$; IGD vs. OCD, $P < 0.001$; OCD vs. HC, $P = 0.425$). The patients with OCD had higher Y-BOCS, HAM-D, and HAM-A scores than the subjects with IGD ($P < 0.001$) and the HCs ($P < 0.001$). **Table 2** summarizes the results of the ratings for arousal, valence, craving, and compulsion elicited by each stimulus category. The game-related cues elicited higher arousal in the patients with IGD and the patients with OCD than in the HC subjects (IGD vs. HC, $P < 0.001$; OCD vs. HC, $P = 0.020$). The OCD-related cues also provoked increased arousal among the patients with IGD and those with OCD compared with the level of arousal reported by HC subjects (IGD vs. HC, $P = 0.012$; OCD vs. HC, $P < 0.001$). The patients with OCD exhibited significantly higher arousal levels to the neutral IAPS pictures than did the HC group ($P < 0.001$). Valence

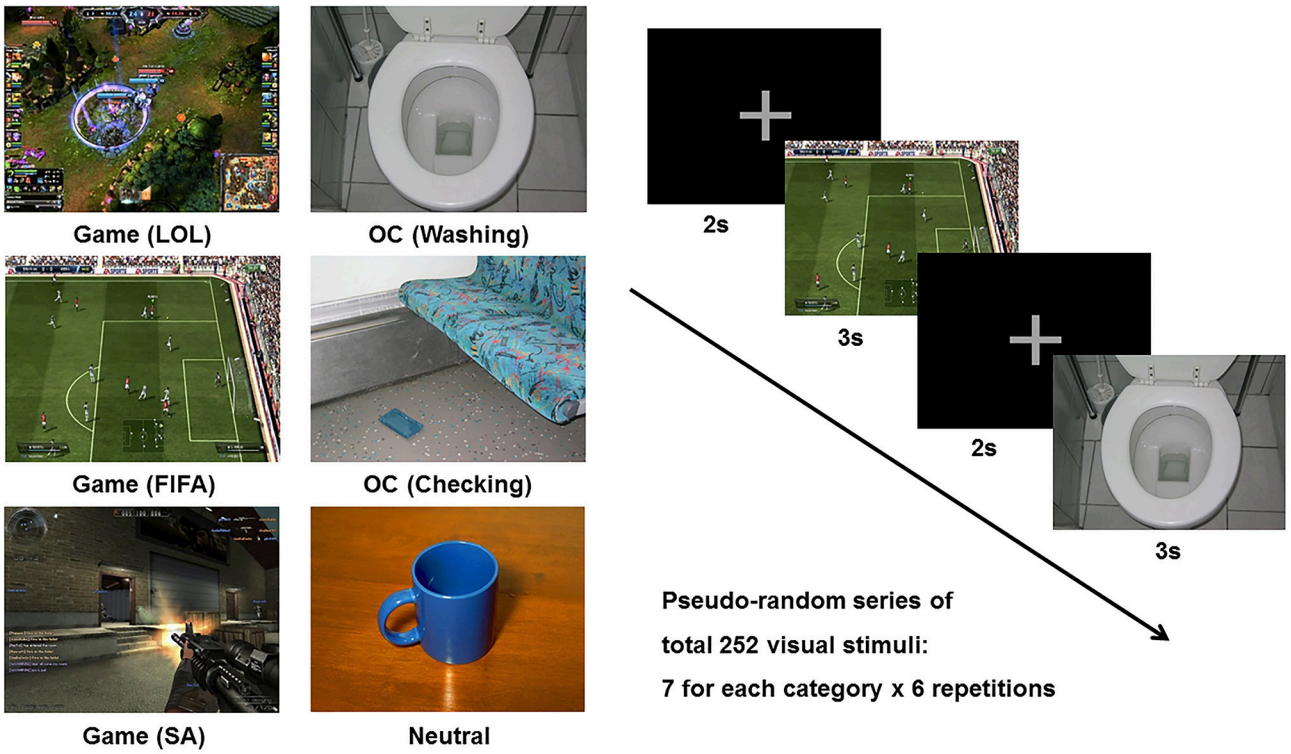

FIGURE 1 | Example of the six categories of stimuli (League of Legend, FIFA, Sudden Attack, Washing, Checking, Neutral) and a sample task sequence. Game, game-related cue; LOL, League of Legend; SA, Sudden Attack; OCD, obsessive-compulsive disorder-related cue.

did not differ across the groups for any of the three stimulus categories.

LPP Amplitudes

Figure 2 displays the grand-averaged LPP waveforms at CPz across the three participant groups and the three cue categories. A significant main effect of cue (Game, OCD, Neutral) on mean LPP amplitude [$F_{(1,60)} = 11.298$, $P < 0.001$] and group by cue interaction [$F_{(1,60)} = 3.957$, $P = 0.005$] was found. Repeated-measures ANOVAs with the electrode sites (6 centro-parietal electrode sites) as within-subject factors and group (HC, IGD, OCD) as a between-subjects factor revealed a significant main effect of group on mean LPP amplitude for game-related cues [$F_{(2,60)} = 3.732$, $P = 0.022$] and OCD-related cues [$F_{(2,60)} = 3.739$, $P = 0.029$]. Group effect was not significant for the mean LPP amplitude elicited by the neutral IAPS pictures [$F_{(2,60)} = 0.574$, $P = 0.566$]. A *post-hoc* Tukey's HSD test demonstrated that the mean LPP amplitude for game-related cues was enhanced in the subjects with IGD ($P = 0.022$) compared with that in the HCs. In addition, the mean LPP amplitude for the OCD-related cues was higher in the patients with OCD ($P = 0.029$) than in the HC subjects. **Table 3** presents the means (standard deviations) and the group comparison results for LPP amplitude at each electrode site. The game-related cues elicited higher LPP amplitudes in the patients with IGD than in the HC subjects at the CP1, CPz, and P2 electrode sites. At the CP2 electrode site, the patients with OCD exhibited increased LPP amplitude compared with the patients with IGD. The subjects with OCD exhibited higher LPP amplitudes than the HC subjects at the P2 electrode site.

Correlations

We could not find any significant correlation between LPPs and clinical scales, such as severity of addiction in the IGD group and YBOCS scores among OCD patients.

DISCUSSION

To our knowledge, this is the first study to directly compare the neurophysiological markers of cue-related attentional bias in IGD and OCD patients. The study participants with IGD exhibited increased LPP amplitudes in response to game-related pictures, indicating the enhanced salience of game-related cues. Interestingly, higher LPPs were observed in the IGD group, irrespective of specific game differences (i.e., League of Legends, FIFA, Sudden Attack). In addition, the patients with IGD did not exhibit LPP changes in response to OCD-related cues. Our results indicate that LPP would be a neurophysiological candidate marker for the diagnosis of IGD and craving of IGD.

TABLE 1 | Demographic and clinical characteristics of participants.

	HC	IGD	OCD	Statistical analysis[a]	
	(*N* = 23)	(*N* = 20)	(*N* = 20)	χ^2 or *F*	*P*
Sex (Male/Female)	15/8	19/1	15/5	5.621	0.060
Handedness (Right/Left)	22/1	18/2	20/0	2.219	0.330
Age (years)	24.8 (4.7)	24.5 (4.2)	25.3 (6.1)	0.145	0.865
IQ	116.2 (8.0)	108.1 (15.2)	109.3 (15.6)	2.451	0.098
Education (years)	13.7 (1.3)	14.5 (1.7)	13.7 (2.0)	1.503	0.231
IAT[b]	32.7 (11.4)	61.5 (11.8)	37.2 (10.8)	38.319	<0.001**
Hours of game playing	0.4 (0.6)	4.4 (3.4)	1.0 (1.5)	20.663	<0.001**
Y-BOCS Total	0.0 (0.2)	1.1 (2.3)	21.4 (6.7)	183.801	<0.001**
Obsession	0.0 (0.0)	0.5 (1.5)	10.7 (4.1)	124.357	<0.001**
Compulsion	0.0 (0.2)	1.0 (2.1)	10.7 (3.1)	164.675	<0.001**
HAM-D	2.2 (3.0)	5.2 (4.1)	12.0 (6.5)	23.626	<0.001**
HAM-A	1.2 (1.4)	3.5 (2.9)	11.9 (7.0)	34.427	<0.001**

HC, healthy control; IGD, internet gaming disorder; OCD, obsessive-compulsive disorder; IQ, intelligence quotient; IAT, Korean version of Young's Internet Addiction Test; Y-BOCS, Yale-Brown obsessive-compulsive scale; HAM-D, Hamilton rating scale for depression; HAM-A, Hamilton rating scale for anxiety.
*Data are presented as means (standard deviation). **P < 0.005.*
[a]*Analysis of variance, χ^2 analysis or Fisher's exact test for categorical data.*
[b]*With 2 missing values in OCD group.*

TABLE 2 | Ratings for arousal, valence, craving, and compulsion elicited by each stimulus category.

	HC	IGD	OCD	Statistical analysis[a]		*Post-hoc* analysis		
	(*N* = 22)	(*N* = 20)	(*N* = 20)	*F*	*P*	IGD vs. HC	OCD vs. HC	IGD vs. OCD
GAME STIMULI (LOL, FIFA, SA)								
Arousal[b]	2.7 (1.7)	4.7 (1.6)	4.1 (1.3)	8.934	<0.001**	<0.001**	0.020*	0.385
Valence[c]	4.7 (0.8)	5.3 (0.9)	4.9 (1.3)	1.655	0.200	0.183	0.851	0.449
Craving[d]	2.6 (1.9)	4.6 (1.8)	3.7 (1.5)	6.967	0.002**	0.001**	0.107	0.246
OCD-RELATED STIMULI (WASHING, CHECKING)								
Arousal[b]	2.8 (1.3)	4.1 (1.4)	4.8 (1.5)	10.855	<0.001**	0.012*	<0.001**	0.272
Valence[c]	3.8 (0.5)	3.7 (0.6)	3.5 (1.1)	0.978	0.382	0.885	0.357	0.649
Compulsion[e]	3.3 (1.5)	4.4 (1.6)	5.1 (1.8)	6.398	0.003**	0.067	0.002**	0.456
NEUTRAL STIMULI (IAPS NEUTRAL)								
Arousal[b]	2.0 (0.8)	2.7 (1.4)	3.5 (1.3)	8.591	0.001**	0.164	<0.001**	0.072
Valence[c]	5.8 (0.9)	5.6 (0.7)	5.5 (0.9)	0.932	0.399	0.612	0.392	0.931

HC, healthy control; IGD, internet gaming disorder; OCD, obsessive-compulsive disorder; LOL, League of Legend; SA, Sudden Attack; IAPS, International Affective Picture System.
*Data are presented as means (standard deviation). *P < 0.05. **P < 0.005.*
[a]*Analysis of variance.*
[b]*Arousal: extreme calmness (0) ∼ extreme excitement (10).*
[c]*Valence: extremely negative (0) ∼ extremely positive (10).*
[d]*Craving: no desire to play game (0) ∼ extreme desire to play game (10).*
[e]*Compulsion: no desire to engage in compulsive behavior (0) ∼ extreme desire to engage in compulsive behavior (10).*

The present study extends the findings of previous studies of addicted patients regarding attentional bias toward addiction-related cues to individuals with IGD, as evidenced by the increased LPP amplitudes in response to the visual presentation of online game-related pictures. Previously, for most substance use disorders, increased LPPs were consistently reported in relation to craving (20–22). Craving influences drug-seeking behavior (18) and has been associated with relapse in substance use disorders (14, 32). In a recent study of craving using LPP, increased LPP amplitudes for drug-related cues relative to non-drug-related cues were found in individuals with cocaine use disorder; however, the LPP changes were reversed from baseline to 6–month follow-up with treatment, wherein the extent of LPP reversal was correlated with decreased craving at follow-up (18). The ERP results obtained in the present study demonstrate an increased LPP amplitude in individuals with IGD compared with the amplitude measured in normal controls, in accord with a previous study of excessive computer gaming players (23) and studies of substance use disorder. However, our results failed to identify significant correlations

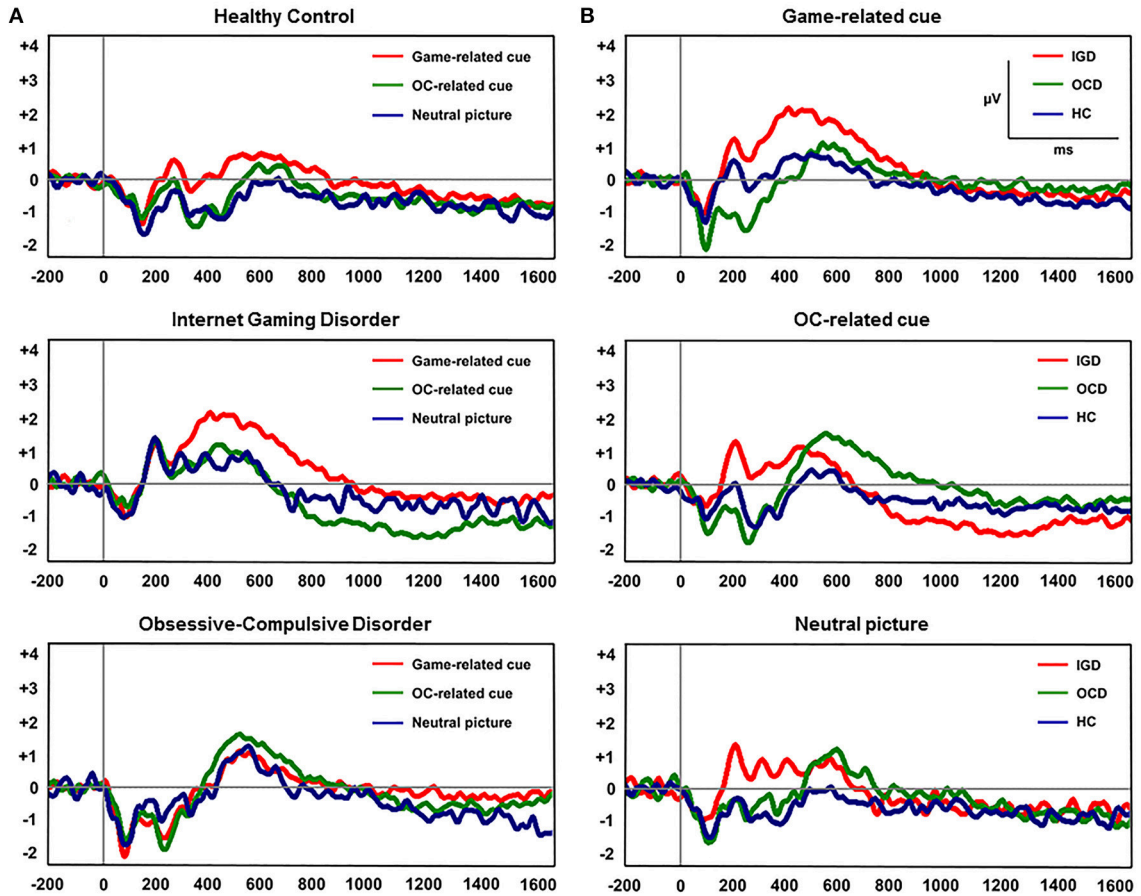

FIGURE 2 | (A) Grand-averaged late positive potential (LPP) waveforms elicited by the three classes of cue-related pictures at the CPz electrode site. **(B)** Grand-averaged LPP waveforms across the three participant groups at the CPz electrode site.

with severity of craving in individuals with IGD. One aspect that could obscure the correlation with craving is that our subjects with IGD were not abstaining from gaming. Another aspect to consider is that for individuals with IGD, exposure to real-life cues often occurs multi-modally rather than only through a visual modality. A recent review noted that correlations between neural cue reactivity and clinical covariates are significantly more powerful for multisensory cues than for unisensory cues (8). However, previous EEG studies of individuals with IGD observed a pattern for resting-state EEG that was distinct from the pattern observed for individuals with substance use disorder. A previous study by our group found that lower absolute beta power may be a trait market of IGD, whereas higher absolute delta power has been observed for alcohol use disorder (33). Taken together, the results confirm attentional bias is present in IGD in response to game-related cues using the ERP paradigm. However, further studies are required to directly compare LPPs between individuals with IGD and those with substance use disorder.

Our results revealed no difference in LPPs according to differences in the cues of specific games (League of Legends, FIFA, Sudden Attack). Whether the pathophysiologies of IGD patients are heterogeneous in terms of, for example, the type of preferred internet game remains relatively unexplored. This study observed no differences among internet game types, which suggests that there are common underpinnings of the neurobiology of craving in IGD, regardless of subtle differences in game type. Several functional MRI studies have investigated the change in brain activation among individuals with IGD in response to the presentation of game-related cues, and abnormalities in the prefrontal cortex (PFC) have been consistently reported. In one of the first fMRI studies, game-related cues enhanced activation of the orbitofrontal cortex (OFC), nucleus accumbens, dorsolateral prefrontal cortex (DLPFC), and the caudate nucleus among individuals with IDG compared with the activation measured for a control group (15). Another study affirmed the activation of the DLPFC, parahippocampus and precuneus and found that the DLPFC and precuneus were correlated with subjective gaming urge under cue exposure (15). Meanwhile, a recent study that combined ERP and fMRI methods reported that enhanced source activity for emotional compared to neutral conditions in temporal,

TABLE 3 | Comparison of late positive potentials (LPPs) that averaged between 350 and 750 ms post-stimulus onset across the three groups.

Late positive potential (μV)	HC	IGD	OCD	Statistical analysis[a]		*Post-hoc* analysis		
	(*N* = 23)	(*N* = 20)	(*N* = 20)	*F*	*P*	IGD vs. HC	OCD vs. HC	IGD vs. OCD
GAME STIMULI (LOL, FIFA, SA)								
CP1 electrode site	0.3 (1.3)	1.6 (1.6)	1.1 (1.7)	4.253	0.019*	0.015*	0.193	0.527
CPz electrode site	−0.2 (1.4)	1.2 (2.1)	0.3 (1.6)	3.370	0.041*	0.034*	0.671	0.230
CP2 electrode site	0.4 (1.2)	0.6 (2.1)	1.0 (1.9)	0.668	0.516	0.932	0.494	0.731
P1 electrode site	2.5 (1.8)	3.6 (2.5)	2.7 (1.2)	1.857	0.165	0.164	0.930	0.331
Pz electrode site	2.4 (1.8)	3.4 (1.9)	2.8 (2.0)	1.485	0.235	0.205	0.730	0.622
P2 electrode site	2.3 (1.6)	3.8 (1.8)	3.1 (2.2)	3.525	0.036*	0.027*	0.347	0.455
OCD-RELATED STIMULI (WASHING, CHECKING)								
CP1 electrode site	0.2 (1.4)	0.5 (1.6)	1.3 (1.5)	2.742	0.073	0.857	0.069	0.222
CPz electrode site	−0.3 (1.1)	0.1 (2.3)	0.6 (2.3)	1.290	0.283	0.820	0.254	0.602
CP2 electrode site	0.5 (1.5)	−0.5 (1.4)	1.3 (2.1)	5.744	0.005*	0.149	0.251	0.004**
P1 electrode site	2.5 (2.2)	2.7 (2.3)	3.1 (1.3)	0.509	0.603	0.942	0.581	0.795
Pz electrode site	2.2 (1.8)	2.6 (1.8)	3.4 (1.5)	2.444	0.095	0.716	0.080	0.365
P2 electrode site	2.2 (1.7)	3.2 (2.0)	3.6 (1.9)	3.528	0.036*	0.190	0.033*	0.713
NEUTRAL STIMULI (IAPS NEUTRAL)								
CP1 electrode site	0.0 (1.4)	0.3 (1.4)	0.5 (1.9)	0.578	0.564	0.776	0.546	0.931
CPz electrode site	−0.5 (1.5)	0.1 (2.0)	−0.1 (1.7)	0.673	0.514	0.500	0.728	0.933
CP2 electrode site	0.1 (1.5)	−1.0 (1.6)	0.4 (1.7)	2.595	0.083	0.230	0.814	0.080
P1 electrode site	2.2 (2.1)	2.3 (2.2)	1.3 (0.3)	0.169	0.845	0.956	0.947	0.831
Pz electrode site	1.9 (2.0)	2.3 (1.6)	2.4 (1.6)	0.536	0.588	0.759	0.581	0.958
P2 electrode site	2.0 (1.9)	2.7 (2.0)	2.8 (2.0)	1.313	0.277	0.410	0.311	0.982

HC, healthy control; IGD, internet gaming disorder; OCD, obsessive-compulsive disorder; LOL, League of Legend; SA, Sudden Attack; IAPS, International Affective Picture System. Data are presented as means (standard deviation). $^{*}P < 0.05$. $^{**}P < 0.005$.

[a] *Analysis of variance.*

and frontal regions including ventromedial prefrontal cortex (34). The PFC processes emotion-related information (15) and is necessary for proper control, planning, and flexibility of behaviors (9). Hence, dysfunction in the PFC leads to the loss of flexibility to adjust the salience value of reward as a function of context and contributes to the bias of increased salience toward addiction-related cues, which may associate with craving. In this regard, the absence of game-specific differences in LPP in our results may suggest that a common mechanism, such as dysfunction of the PFC, is present in individuals with IGD.

Compulsive behaviors and unwanted, repetitive thoughts are characteristics of OCD (35), and converging neurobiological evidence demonstrates that dysfunction in the cortico-striato-thalamo-cortical circuit, particularly the OFC, underlies the pathophysiology of the disorder (36). Dysfunction of the OFC has been indicated in meta-analyses of both task-based and resting-state functional imaging studies (37), and structural changes in the OFC have also been consistently reported in previous MRI studies (37). Moreover, abnormalities in the OFC have been observed in unaffected relatives of patients with OCD (37, 38), suggesting a genetic influence on the circuitry of the OFC in the pathophysiology of OCD. The OFC subserves in the representation of reward and punishment and in inhibitory control; therefore, dysfunction of the OFC is associated with deficits in the function of response inhibition, set shifting and decision making in patients with OCD (37). It has thus been repeatedly proposed that dysfunction of the OFC related to the salience attribution system and inhibitory function also underlies the pathophysiology of addiction and OCD (39, 40). Volkow and Morales (9) proposed that the ventromedial PFC (including the OFC) becomes hyperactive in addiction when an individual is exposed to drugs or cues, increasing reward salience. In a previous study with cocaine abusers, activation of the OFC was associated with craving (39). However, prior studies of changes in cue-related ERP in OCD have been limited, although one study recently investigated the alteration of LPP in individuals with OCD (41). Paul et al. (41) reported enhanced LPPs in response to OCD-relevant pictures compared with LPPs measured in response to neutral pictures among OCD patients, and the LPP abnormalities persisted when cognitive distraction successfully reduced self-reported arousal. Accordingly, our results revealed higher LPPs in response to OCD-related cues than to game-related cues among patients with OCD. In our study, the subjective results suggested that individuals with IGD exhibited increased arousal to both game-related and OCD-related cues, and patients with OCD also presented concurrent arousal to both cues. The discrepancy between subjective concurrent arousal and group-specific LPPs response suggest that the LPPs appear to reflect the sustained increase in attention toward, and processing of salient stimuli instead of arousal *per se* (19, 41). In consistence with the previous LPP study, we could not find significant correlation between OCD symptom severity and

LPP (41). It is partly because OCD could be better understood at a system or network level (42). Previous studies in OCD presented interconnected dysfunctions of error detection system as well as inhibitory control, and the former is associated with abnormalities of earlier ERP component such as error-related negativity (ERN) than LPP (43). Integrative approach using various ERP markers is needed in future studies to understand the pathophysiology of OCD.

A few studies have investigated compulsivity in individuals with IGD and reported inconsistent findings due to the use of different study methods. Our group previously reported no deficits in 15 patients with IGD using the Cambridge Neuropsychological Test Automated Battery (CANTAB) (7), but a study with 86 patients of IGD revealed dysfunction of cognitive flexibility (5). Moreover, other studies have reported deficits in cognitive flexibility using a cue-related go/no-go task (44). Fauth-Buhler and Mann (45) insisted that the inconsistency among findings related to compulsivity may be explained by whether game-related stimuli were employed and suggests that patients with IGD may have more reward-related problems than general problems with cognitive flexibility. Otherwise, impulsivity and compulsivity may contribute to the phenomenology of IGD in concerted manner as initial impulsivity followed by compulsivity in behavioral addiction (5). Further studies are needed to examine the effect of cognitive aberrance in IGD.

The limitations of the present study include the following. First, we did not observe a significant correlation between LPP changes and the clinical variables. Further investigation using multimodal cues or more real-life cues appears necessary. Another limitation of the study is that we only investigated cross-sectional differences between the groups. A longitudinal follow-up of LPP could reveal changes in cue-related attentional bias according to clinical prognosis. In addition, our samples were not gender-matched across 3 groups and HCs had high IQ with a standard deviation above the population mean. However, the strength of this study is that it is the first to directly investigate neurophysiological markers of cue reactivity in IGD and OCD.

To conclude, our study showed that LPP increased in response to disorder-specific cues in IGD and OCD (game-related cues and OCD-related cues), while subjective arousals were overlapped in response to both cues. Our findings indicate that LPP could be a neurophysiological marker for cue-related craving in IGD. These results provide additional neurophysiological evidence for understanding the mechanism of craving in IGD, further demonstrating the potential clinical utility of LPP in providing a marker for efficacy of IGD- related treatment, such as cue-exposure therapy.

AUTHOR CONTRIBUTIONS

SK, MK, and J-SC were responsible for the study concept and design. SK, MK, and TL contributed to the acquisition of ERP data. MK and MP performed the ERP analysis. MK, SP, and TL contributed to the acquisition and analysis of clinical data. SK, J-SC, D-JK, and JK assisted with data analysis and interpretation of findings. SK drafted the manuscript. SK, SP, and J-SC provided critical revision of the manuscript for important intellectual content. All authors critically reviewed the manuscript content and approved the final version for publication.

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Neural Correlates of Distorted Self-concept in Individuals With Internet Gaming Disorder: A Functional MRI Study

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Background and aims: Discrepancy between ideal self-guide and actual self-concept evoke dejection-related feeling, and often individuals with internet gaming disorder (IGD) use games as the tool to escape those negative emotions. The aim of this study was to evaluate the pattern of self-discrepancy based on actual and ideal self-images and elucidate the neural correlates underlying the distorted self in individuals with IGD.

Methods: Nineteen male individuals with IGD and 20 healthy controls (HCs) underwent functional magnetic resonance imaging where they decided on whether they agreed with the adjectives describing their actual or ideal self on a four-point Likert Scale. Two-sample *t*-test on the self-discrepancy contrast was conducted for neuroimaging analysis and correlation analysis was performed between the behavioral data and regional activities.

Results: The IGD group evaluated both their ideal self and actual self more negatively than the HC group. Actual self-concept was associated with satisfaction with psychological needs as opposed to ideal self-guide. Brain activity in the inferior parietal lobule was significantly decreased in individuals with IGD relative to HCs in the self-discrepancy contrast. In addition, neural activity during evaluating actual self-concept showed a significant group difference.

Conclusion: These results provide novel evidence for distorted self-concept of people with IGD. Individuals with IGD had a negative ideal and actual self-image. Neurobiologically, dysfunction in the inferior parietal lobule associated with emotional regulation and negative self-evaluation was found in IGD. Considering the characteristics of IGD that often develop in adolescence, this self-concept problem should be noted and applied with appropriate therapy.

Keywords: internet gaming disorder, self-discrepancy, actual self-concept, ideal self-guide, inferior parietal lobule

INTRODUCTION

Internet gaming disorder (IGD) is characterized by functional impairment in personal or social life from excessive internet game use. It is an emerging disorder due to the spread of the Internet (1). This condition has a significant symptomatic similarity to substance use disorders and behavior addiction (2, 3). However, the difference between other addictive mediators and Internet games is that games are relatively easy to access even at a younger age (4). Thus, it is no surprise that IGD mainly occurs in teenagers (5). One of the developmental tasks to be accomplished in adolescence is the formation of identity (6). Because games reduce other interests in daily life, adolescents preoccupied with games might be thwarted in achieving the formation of identity and other developmental tasks (7).

Self-discrepancy theory (SDT) explains that distorted self-images can cause various emotional discomfort (8). This theory assumes three domains of self: actual self, ideal self, and ought self. Actual self-concept is the perception of one's own attributes, ideal self-guide is the representation of the attributes that the person wants to possess, and ought self-guide is the representation of the properties that someone else believes the person should possess. Negative emotions arise when there is high discrepancy between the domains. Specifically, a significant mismatch between actual self-concept and ideal self-guide is related to dejection such as low self-esteem or frustration (8–11). Because Internet games can be used as a means of escaping these negative emotions, it is important to understand the relationship between IGD and self-discrepancy (12–14).

SDT has been used to explain several psychiatric disorders including addictive disorders. Studies show that substance abusers show a high level of self-discrepancy (15) and that distress associated with self-discrepancy predicts alcohol consumption (16). Among addictive disorders, distorted self-image or self-discrepancy in IGD may be clinically more important as IGD-related symptoms occur at a young age. Game users could become confused about their identity as they are constantly exposed to avatars similar to their ideal fantasy (17–19). Despite concerns about identity confusion, little is known about which specific domains of self-images are associated with self-discrepancy.

Impairment of self-regulation is one of the major psychopathologies of addiction (20). Self-regulation ability is related to how well basic psychological needs are satisfied (21, 22). These basic psychological needs, consisting of autonomy, competence, and relatedness, are important factors affecting individual growth and integration (22–24). If these are not satisfied from a young age, individuals may struggle to form a stable self-image. It is known that people who are dissatisfied with basic psychological needs use social media networks (25), as well as Internet games (26). Despite the connection between basic psychological needs and self-image, the relationship between the two has not been elucidated.

The concept of self-discrepancy is mostly studied observationally using self-report to support the theory, and little is known about the neural correlates of self-discrepancy. A single study suggests that self-discrepancy was associated with activation in the reward system including the striatum, which might be linked to the desire for one's ideal self (27). In terms of self-referential processing, which is the basis of self-discrepancy, the medial prefrontal cortex (MPFC) is involved (28, 29). Also, a meta-analysis showed that individuals with IGD have the prefrontal dysfunction related to their self-regulation problem (30). Given the importance of self-image in adolescence, investigating the neurobiological underpinnings of self-discrepancy in IGD would play an important role in understanding the psychopathology and establishing treatment strategies of the disorder.

The aim of this study was to investigate the neural correlates underlying the distorted self of individuals with IGD in relation to their satisfaction with basic psychological needs. We developed a self-concept task for fMRI to evaluate the attitudes of self-discrepancy based on actual and ideal self-images. Considering previous research that games are used to avoid negative emotions caused by self-discrepancy, we hypothesized that individuals with IGD would show higher self-discrepancy. Also, individuals with IGD who were frequently exposed to game avatars that were close to their ideal fantasy would have impairment in both actual self-concept and ideal self-guide. Neurobiologically, we hypothesized that individuals with IGD would show dysfunction in the striatum and MPFC, which are associated with self-discrepancy.

METHODS

Participants

In total, 19 individuals with IGD (mean age ± standard deviation: 23.3 ± 2.4) and 20 age-matched healthy controls (HCs) (mean age ± standard deviation: 23.4 ± 1.2) participated in this study. Considering the epidemiology of IGD (31–33), male participants in their 20 s playing internet games more than 30 h a week were recruited through internet advertisement. Then, participants who met the DSM-5 proposed criteria for IGD (1) in a psychiatric interview were enrolled. Participants with IGD who had a history of depressive disorder or attention deficit hyperactivity disorder were included in consideration of various comorbid conditions (1). Considering that the features of IGD have not yet been fully studied, however, participants who were suffering from on-going psychiatric illness except IGD or those who suffered from other addictive disorders were excluded. All participants were right-handed (34) and did not have medical and neurological illness. This study was approved by the Institutional Review Board of Yonsei University Gangnam Severance Hospital and carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants before the study began.

Assessment Scale

To measure the presence and the severity of Internet dependency, the internet addiction test (IAT) was used (35). The IAT is a 20-item scale with a 5-point score, ranging from 1 (very rarely) to 5 (very frequently). Scores higher than 50 indicate problematic internet use. Participants were instructed to evaluate their internet use, especially on the basis of internet game use.

Degree of psychological needs satisfaction was assessed by the Basic Psychological Needs Scale (BPNS) (36, 37). This consisted of 21 items with 7-point Likert scale (1: not at all true to 7: very true). Higher scores meant a higher level of psychological needs satisfaction.

Behavioral Task

Participants performed the self-concept task during fMRI scanning. The task asked the participants' view of actual and ideal self. A sentence describing actual self (e.g., I am a modest person) and ideal self (e.g., I want to be a modest person) was presented on the screen and participants answered how well the sentence described themselves by clicking one of four buttons (1: strongly disagree to 4: strongly agree). A total of 48 trait adjectives (24 positive and 24 negative) were used in these sentences. The task comprised 8 blocks for each condition (actual self and ideal self). A block lasted for 32 s and a 16 s rest period was placed between the blocks. In each block, 6 different sentences (3 sentences with a positive adjective and 3 sentences with a negative adjective) were presented for 3 s each with an inter-stimulus interval jittered between 0.5 and 3.5 s. The sequence of experimental blocks and sentences was pseudo-randomized.

Image Acquisition

MRI data were acquired on a 3 Tesla scanner (Magnetom Verio, Siemens Medical Solutions, Erlangen, Germany). Functional images were collected using a gradient echo planar imaging sequence (echo time = 30 ms, repetition time = 2,000 ms, flip angle = 90°, slice thickness = 3 mm, number of slices = 30, and matrix size 64 × 64). Three scans were discarded before image acquisition started. Structural images were also collected using a 3D spoiled-gradient-recall sequence (echo time = 2.46 ms, repetition time = 1,900 ms, flip angle = 9°, slice thickness = 1 mm, number of slices = 176, and matrix size = 256 × 256).

Behavioral Data Analysis

A "positivity score" was calculated as the average of 48 responses per condition indicating the positive level of the actual and the ideal self. Higher scores indicated that the participants had a more positive representation of themselves. Also, a "self-discrepancy score" was constructed by subtracting the positivity score of the ideal self from that of the actual self. Analysis of variance (ANOVA) was performed to evaluate the main and interaction effect of group (HC vs. IGD) and condition (actual self vs. ideal self) on the positivity scores. In addition, independent *t*-test was used for group comparison of the self-related scores (positivity scores and self-discrepancy scores), and Pearson's correlation analysis was performed between these scores and BPNS scores in each group. SPSS (ver. 23; SPSS Inc., Chicago, IL, USA) was used and a p-value < 0.05 was considered significant.

Neuroimaging Data Analysis

Preprocessing and analysis of fMRI data were performed with Statistical Parametric Mapping, version 12 (Wellcome Department of Cognitive Neurology, University College London). fMRI images were corrected for the differences of slice acquisition time. Then, individual head motions were corrected based on realignment on the first image. Functional images were co-registered on the structural images. The structural images were normalized to the standard template spatially, and transformation matrices were applied to the functional images. These images were smoothed with a Gaussian kernel of 6 mm full-width at half-maximum.

For the individual analysis, the actual self and ideal self conditions convolving the canonical hemodynamic response function were used as regressors of interest and 6 movement parameters were included as regressors of non-interest in general linear model. Three main contrast images were created: actual self, ideal self, and self-discrepancy (ideal self—actual self). One sample *t*-test for the comparison between the actual self and ideal self was performed in each group. Full factorial analysis of variance was applied to investigate the interaction effect between group and condition, and additional two sample *t*-test was performed on self-discrepancy contrast images. Results were considered significant at a threshold of corrected $p < 0.05$, which corresponded to the family-wise error corrected significance at the cluster level with a cluster-defining threshold of $p < 0.005$. For a *post-hoc* analysis, whole clusters identified in two-sample *t*-test were defined as the regions of interest (ROIs) and their regional activity was extracted with MarsBaR version 0.44. Using SPSS, Pearson's correlation analysis was performed between neural activities in each contrast and behavioral data (BPNS scores and self-discrepancy score). Also, regional activities for the actual self and ideal self conditions were compared using independent *t*-tests. Results were considered significant at $p < 0.05$.

TABLE 1 | Demographic and clinical characteristics of individuals with internet gaming disorder (IGD) and healthy control (HC).

	IGD ($n = 19$)	HC ($n = 20$)	*t*	*p*
Age (years)	23.3 (2.4)	23.4 (1.2)	−0.2	0.6
Education years	15.0 (2.5)	15.4 (1.5).	−0.6	0.5
Intelligence quotient	113.3 (15.6)	108.7 (8.5)	1.1	0.3
Internet addiction test	73.0 (9.7)	24.9 (6.1)	18.4	<0.01
Basic psychological needs scale	78.4 (13.1)	89.4 (12.3)	−2.7	0.01

Data are given as mean (standard deviation).

RESULTS

Clinical Characteristics and Behavioral Response to the Self-concept Task

Demographic and clinical characteristics are presented in **Table 1**. Scores of IAT (IGD: 73.0 ± 9.7, HC: 24.9 ± 6.1, $t = 18.4$, $p < 0.01$) and BPNS (IGD: 78.4 ± 13.1, HC: 89.4 ± 12.3, $t = -2.7$, $p = 0.01$) were significantly different between individuals with IGD and HCs.

Figure 1 displays the results of the self-concept task. The main effects of group ($F = 16.7$, $p < 0.001$) and condition ($F = 69.4$, $p < 0.001$) were observed, but no significant group-by-condition

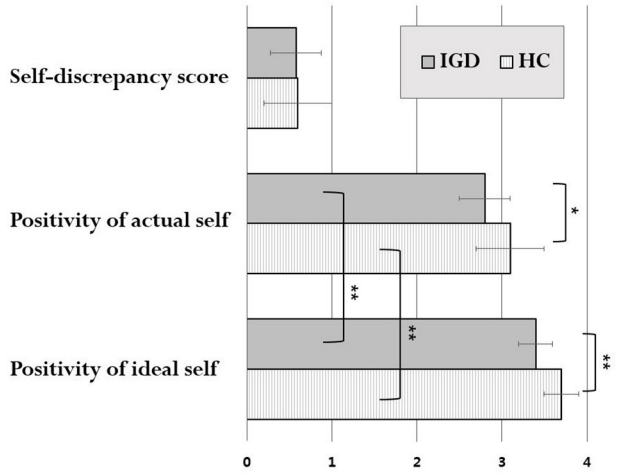

FIGURE 1 | Behavioral responses to the self-concept task. Positivity scores of the ideal self and actual self were significantly lower in individuals with internet gaming disorder (IGD) than in healthy controls (HC). Degree of self-discrepancy (positivity scores of the ideal self−positivity scores of the actual self) was not significantly different between the two groups. *$p < 0.05$, **$p < 0.01$.

interaction effect was found. The positivity scores of the ideal ($t = -4.6$ $p < 0.01$) and actual self ($t = -2.2$, $p = 0.03$) were significantly lower in the IGD group than in the HC group. However, there was no group difference in the self-discrepancy scores ($t = -0.18$, $p = 0.9$). Also, the positivity scores of the ideal self were higher than those of the actual self in both groups (IGD: $t = 7.9$, $p < 0.01$; HC: $t = 6.4$, $p < 0.01$).

The IAT scores were negatively associated with the BPNS scores in individuals with IGD ($r = -0.52$, $p = 0.02$). The self-discrepancy scores were negatively correlated with the BPNS scores (IGD: $r = -0.8$, $p < 0.01$; HC: $r = -0.5$, $p = 0.01$), and these BPNS scores were also correlated with the positivity scores of the actual self in both groups (IGD: $r = 0.7$, $p < 0.01$; HC: $r = 0.6$, $p < 0.01$). There were no statistically significant correlations between the BPNS scores and the positivity scores of the ideal self (IGD: $r = -0.1$, $p = 0.5$; HC: $r = 0.4$, $p = 0.1$).

Neural Response to the Self-concept Task

Figure 2 presents the brain regions related to self-concept in each group. Significantly higher activity in the actual self condition compared to the ideal self condition was observed in the bilateral MPFC (MNI coordinates: 6, 54, 14, voxel number 1,000, $z = 4.5$, $p_{FWE} < 0.01$) in HCs and in the right MPFC (MNI coordinates: 4, 12, 60, voxel number 492, $z = 4.0$, $p_{FWE} < 0.01$) in individuals with IGD. In the ideal self condition compared to the actual self condition, HCs showed significantly higher activity in the left calcarine cortex (MNI coordinates: −10, −86, 2, voxel number 457, $z = 3.9$, $p_{FWE} = 0.01$), whereas individuals with IGD showed no significant result.

Full factorial analysis showed that the main effect of group was observed in the right MPFC (MNI coordinates: 4, 14, 58, voxel number 386, $z = 4.5$, $p_{FWE} < 0.01$) and right caudate (MNI coordinates: 10, 8, 16 voxel number 301, $z = 3.4$, $p_{FWE} = 0.03$), whereas there was no significant main effect of condition and group-by-condition interaction effect. Using two-sample t-test on the self-discrepancy contrasts, the right inferior parietal lobule (IPL) showed significantly lower activity in individuals with IGD than in HCs (MNI coordinates 40, −50, 44, voxel number 459, $z = 4.1$, $p_{FWE} = 0.01$) (**Figure 3A**). IPL activity in the self-discrepancy contrast was positively correlated with the self-discrepancy scores ($r = 0.6$, $p < 0.01$) in HCs, but not in individuals with IGD (**Figure 3B**). There was no significant correlation between this regional activity and the BPNS scores in both groups (IGD: $r = -0.2$, $p = 0.3$; HC: $r = -0.1$, $p = 0.7$). Meanwhile, IPL activity in the actual self contrast was significantly higher in individuals with IGD than in HCs ($t = 2.7$, $p < 0.01$), whereas no significant group difference was found in the ideal self contrast (**Figure 3C**).

DISCUSSION

The purpose of this study was to elucidate the neural correlates of distorted self-concept based on self-discrepancy in individuals with IGD. In individuals with IGD, it was confirmed that they were negatively biased toward their actual self-concept and ideal self-guide rather than HCs. It is a conventional hypothesis that individuals engage in specific actions to reduce self-discrepancy, and similarly individuals with IGD use games as a way to escape negative feelings caused by self-discrepancy (12–14). Self-discrepancy in our patient sample was similar to that in HCs, though self-discrepancy was greater in individuals with IGD vs. HCs in several other studies (12, 14). There are two possibilities for this discrepancy. First, the previous studies involved younger participants than our study. It is important to consider the possibility that self-discrepancy is less likely in older adolescents who have had some degree of self-development than those who had internet addiction since a younger adolescent age. Second, the method of measuring self-discrepancy used in our study might not have been delicate enough to assess the difference. If participants were asked to assess the difference between actual and ideal self-concept directly (12), or if the Likert scale had been expanded as in previous studies (14), a group difference of self-discrepancy might have materialized. In both cases, it does not mean that there was no problem with self-concept in IGD. It should be noted that both actual self-concept and ideal self-guide were negatively biased in individuals with IGD.

Neurobiologically, a meaningful difference was found between individuals with IGD and HCs. For example, the calcarine cortex was more activated when HCs evaluated ideal self-concept compared to actual self-concept. The calcarine cortex is activated in mental imagery processing as well as when actively watching something (38). In the implicit inference process, this area serves as a bridge that enables explicit access when activated. Imagining ideal self-concept would be a more implicit process than speculating actual self-concept and the result could be understood in that sense. On the other hand, the MPFC was more activated in both groups when participants evaluated actual

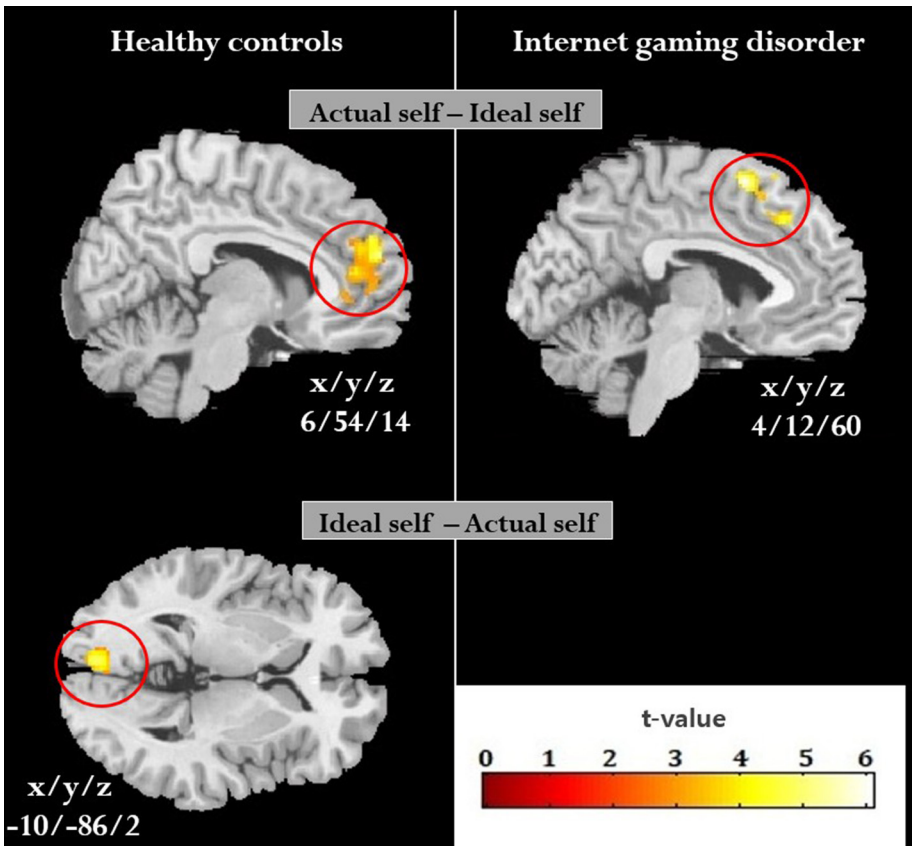

FIGURE 2 | Brain regions showing a significant difference in the comparison between the actual self and ideal self in each group. Increased activity in the actual self compared to the ideal self was found in the bilateral medial prefrontal cortex in healthy controls and the right medial prefrontal cortex in individuals with internet gaming disorder, whereas increased activity in the ideal self compared to the actual self was observed only in the left calcarine cortex in healthy controls.

self-concept than when they evaluated ideal self-guide. Given the role of the MPFC in self-referential processing (28, 29), it can be inferred that our task was appropriate for evaluating self-image. In addition, there was a group difference in activity of the MPFC and caudate regardless of the two self conditions. These regions have been known to constitute the reward system and be functionally changed in individuals with IGD (39). Aberrant activation in the MPFC has been understood from the perspective of self-regulation, impulse control, and reward mechanism which are problematic in IGD (30). Hyperactivation in the caudate has been related to habitual craving response in IGD (40).

The main finding of our study is that individuals with IGD showed dysfunctional IPL activity in relation to self-discrepancy. Although the group-by-condition interaction effect was not found, individuals with IGD showed decreased activity in the IPL in the self-discrepancy contrast. As IPL activity was increased in HCs, the self-discrepancy score was also increased. Considering the role of this region as a regulator of negative emotion (41), feeling emotional discomfort might be related to IPL activity in HCs. For individuals with IGD, this kind of protection process might not be operating. Another possibility of the neural difference in self-discrepancy may be due to aberrantly increased activity when evaluating actual self-concept in individuals with IGD. The IPL has been associated with negative valence or arousal (42, 43). In addition, IPL activity is particularly decreased, when dealing with self-related negative words (44). In our study, however, this normal response to reducing IPL activity when dealing with negative words did not occur in individuals with IGD. In this context, the problems of actual self-concept rather than ideal self-guide should be considered more important in individuals with IGD.

A previous longitudinal study has shown a reciprocal relationship; individuals who had low BPNS scores were more likely to become individuals with IGD, and the BPNS scores became lower in individuals with IGD (26). We also confirmed that individuals with IGD were less satisfied with their psychological needs, and the degree of dissatisfaction was associated with the severity of the gaming addiction. In addition, we found that participants with low BPNS scores had problems with their self-image. Participants with lower BPNS scores rated their own discrepancy higher and rated actual self-concept more negatively. It is important to note that the lack of satisfaction with psychological needs was more related to negative actual self-concepts than to ideal self-guide. Because gaming leads to

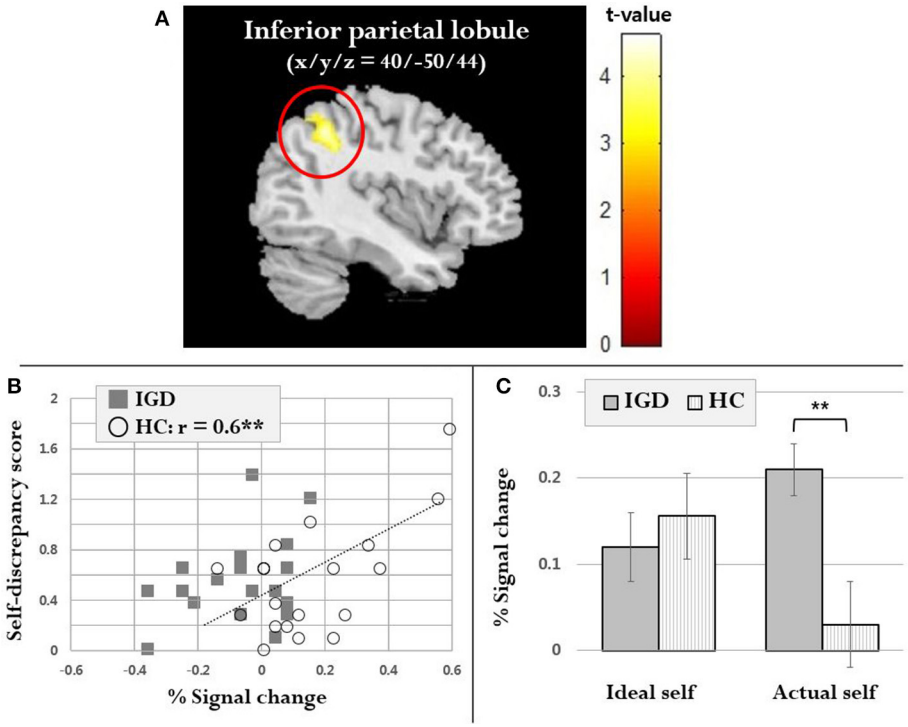

FIGURE 3 | Neural responses during the self-concept task. As shown in **(A)**, individuals with internet gaming disorder (IGD) showed significantly lower inferior parietal lobule (IPL) activity in the self-discrepancy contrast than healthy controls (HC). The correlation between IPL activity in the self-discrepancy contrast and behavioral data is displayed in **(B)**. IPL activity in the ideal self and actual self conditions in each group is displayed in panel **(C)**. $^{**}p < 0.01$.

distorted self-concept, individuals with IGD should avoid the positive view that games will enable them to achieve competence, autonomy, and relationships that are not achieved in real life.

Unlike previous tasks that were designed to assess the distance between the actual self and the ideal self in terms of a personality trait, this task was designed to examine the actual self and the ideal self separately. Due to the difference in study design, no activation might be observed in the striatum with regard to self-discrepancy. In addition, a previous study suggested that self-discrepancy primed the desire of good outcome and activated the reward system (27). However, individuals with IGD had negative attitudes of their self-image and dysfunction in processing actual self-concept. Therefore, negative self-related regions might be observed rather than the reward system.

Several limitations should be considered in this study. The major problem was that this study had some recruitment bias for the following reasons. First, to identify IGD-specific neural correlates, we excluded patients who currently had other comorbidities. Second, only male participants in their 20 s were included in this study, and thus it is limited to generalize the result to individuals with IGD in early adolescence or late adulthood. Third, it is difficult to distinguish whether the distorted self was the cause of excessive gaming or the consequences of playing games too much, because of the nature of the cross-sectional study. Fourth, it should be noted that the fMRI task did not evaluate self-discrepancy itself but evaluated it by considering the difference between the actual self and ideal self.

Despite the limitations, our study is meaningful in that the results identify dysfunction in the brain associated with the distorted self in IGD. Individuals with IGD may have problems with emotional regulation or self-evaluation as can be inferred from dysfunction in the IPL. Behaviorally, individuals with IGD had both negative attitude toward actual self-concept and ideal self-guide, though their self-discrepancy was not so great. Negative ideal self-guide in IGD might discourage them from having any goals or motivations to achieve in the future. Special attention should be paid to distorted actual self-concept that has been detected not only behaviorally but also neurobiologically, when understanding the disorder or setting the treatment strategies. Considering the characteristics of the internet gaming environment where users can experience new roles and identities (45), individuals with IGD should pay attention to having distorted self-image.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Circulating MicroRNA Expression Levels Associated With Internet Gaming Disorder

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Background: Addictive use of the Internet and online games is a potential psychiatric disorder termed Internet gaming disorder (IGD). Altered microRNA (miRNA) expression profiles have been reported in blood and brain tissue of patients with certain psychiatric disorders and suggested as biomarkers. However, there have been no reports on blood miRNA profiles in IGD.

Methods: To discover IGD-associated miRNAs, we analyzed the miRNA expression profiles of 51 samples (25 IGD and 26 controls) using the TaqMan Low Density miRNA Array. For validation, we performed quantitative reverse transcription PCR with 36 independent samples (20 IGD and 16 controls).

Results: Through discovery and independent validation, we identified three miRNAs (hsa-miR-200c-3p, hsa-miR-26b-5p, hsa-miR-652-3p) that were significantly downregulated in the IGD group. Individuals with all three miRNA alterations had a much higher risk of IGD than those with no alteration [odds ratio (OR) 22, 95% CI 2.29–211.11], and the ORs increased dose dependently with number of altered miRNAs. The predicted target genes of the three miRNAs were associated with neural pathways. We explored the protein expression of the three downstream target genes by western blot and confirmed that expression of GABRB2 and DPYSL2 was significantly higher in the IGD group.

Conclusion: We observed that expressions of hsa-miR-200c-3p, hsa-miR-26b-5p, and hsa-miR-652-3p were downregulated in the IGD patients. Our results will be helpful to understand the pathophysiology of IGD.

Keywords: Internet gaming disorder, microRNA, biomarker, addiction, western blot

INTRODUCTION

Addictive use of the Internet and Internet-based games is not just a social phenomenon in countries with extensive Internet access infrastructure, but a potential psychiatric disorder termed Internet gaming disorder (IGD) (1–3). According to epidemiological reports, prevalence rates of IGD in adolescents vary across countries, ranging from 0.8 to 26.7% (4). Particularly, studies show prevalence rates above 10% in adolescents in many Asian countries such as South Korea, China, Taiwan, Hong Kong, and Singapore (4). IGD is associated with impairment in cognition, psycho-social relationships, and daily life; for example, declining academic or occupational performance (4–7). IGD is now included in Section III (Conditions for Further Study) of the fifth revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (8). However, in spite of its clinico-social importance, little is known about the molecular genetic mechanism behind IGD.

Recent large-scale twin studies have suggested a genetic background to IGD (9, 10). Vink et al. investigated individual differences in compulsive Internet use with 5,247 monozygotic and dizygotic adolescent twins in the Netherlands Twin Register and reported that 48% of the differences were explained by genetic factors (9). Li et al. observed 825 pairs of Chinese adolescent twins and reported that genetic factors explained 58–66% of the differences (10). Accordingly, polymorphisms of the genes involved in neurotransmission, cognition, and attention such as dopamine receptor D2 gene (*DRD2*), catecholamine-O-methyltransferase gene (*COMT*), serotonin transporter gene (*5HTTLPR*), and cholinergic receptor nicotinic alpha 4 gene (*CHRNA4*) have been reported to be significantly associated with Internet addiction (11–13). Recently, Kim et al. screened variants of more than 100 candidate genes related to production, action, and metabolism of neurotransmitters by next generation sequencing analysis and reported that rs2229910 of *NTRK3* gene is associated with IGD (14).

In addition to the genetic factors, it is also well known that neurobehavioral phenotypes are epigenetically controlled by non-coding RNAs including microRNAs (miRNAs) (15, 16). miRNAs are small non-coding single-stranded RNA molecules (approximately 20–23 nucleotides in length), that negatively regulate expression of protein-coding genes by degrading mRNAs and play a critical role in the pathophysiological process of diverse diseases (17). Lines of evidence have demonstrated that miRNAs are abundant in the human central nervous system (CNS) and act to fine tune the expression levels of their target genes, which are involved in the development and maturation of CNS system (15). Indeed, recent studies have revealed that miRNA expression profiles are altered in brain tissue of patients with psychiatric disorders, suggesting that their expression profiles could be biomarkers for psychiatric disorders (15, 16, 18). For example, through postmortem analysis, Lopez et al. reported that expression of miR-1202, which regulates the expression of metabotropic glutamate receptor-4 gene and predicts the response to antidepressant, was downregulated in prefrontal cortex tissues of major depression disorder patients (19). In terms of biomarker screening, this approach has a clear limitation because performing a biopsy of CNS tissue for screening is impossible. Since miRNAs can be detected in blood (plasma or serum), circulating miRNAs have a definite advantage as non-invasive biomarkers in neuropsychiatric disorders. However, to date, there have been no studies about circulating miRNA profiles in IGD. Better understanding of circulating miRNA expression profiles could help to clarify the mechanism of IGD development and facilitate clinical translation.

In this study, we aimed to identify IGD-associated miRNA markers by observing differentially expressed plasma miRNAs between the IGD and control groups and explored their biological implications.

MATERIALS AND METHODS

Study Subjects

We surveyed 3,166 teenagers (aged 12–18 years) using DSM-V IGD scoring. Among them, 251 (168 males and 83 females) were diagnosed as IGD according to the DSM-V criteria (8). A total of 91 individuals (49 IGDs and 42 controls) provided the informed consent for this study. Among them, four individuals were excluded according to the exclusion criteria. Finally, 87 individuals (45 IGD subjects and 42 healthy control individuals) were enrolled for this study. Among them, 51 participants (25 IGD patients and 26 controls) were recruited as the discovery set from 2014 to 2016. The other 36 participants (20 IGD patients and 16 controls) were recruited as the independent validation set from 2016. All participants were Korean individuals, enrolled from Seoul St. Mary's Hospital (Seoul, South Korea) and Seoul National University Boramae Hospital (Seoul, South Korea). All participants underwent a structured interview by a psychiatrist based on the Korean Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS-PL) (20). All participants completed the Block Design and Vocabulary subtests of the Korean-Wechsler Intelligence Scale for Children, 4th edition (K-WISC-IV) (21). Impulsiveness were assessed by Barratt Impulsiveness Scale (BIS) (22). Behavioral Inhibition System (BInS) and Behavioral Activation System (BAS) scales were measured to assess personality dimension (23). Exclusion criteria included past or current major medical disorders (e.g., diabetes mellitus), neurological disorder (e.g., seizure disorders, head injury), psychiatric disorders (e.g., major depressive disorder, anxiety disorders), mental retardation, or any substance abuse (e.g., tobacco, cannabis, alcohol). The general characteristics of the study subjects are summarized in **Table 1**. This study was approved by the Institutional Review Board of the Catholic University Medical College of Korea (MC16SISI0120). All participants and their parents gave written informed consent.

TaqMan Low Density miRNA Array (TLDA) Experiments

Peripheral blood was collected from each participant and transferred to the laboratory within 4 h to minimize the blood cell lysis. The specimen was centrifuged at 3,000 rpm for 10 min at room temperature. Then, supernatant (plasma layer) was

TABLE 1 | General characteristics of the study subjects.

	Discovery			Validation			Combined		
	Control	**IGD**	***P*-value**	**Control**	**IGD**	***P*-value**	**Control**	**IGD**	***P*-value**
N	26	25		16	20		42	45	
Age (years)									
Median (min–max)	13 (12–17)	13 (12–15)	0.759	15 (13–18)	14.5 (12–18)	0.628	14 (12–18)	14 (12–18)	0.509
Weekly Internet gaming hours (h)									
Median (min–max)	5.25 (2–17)	18 (6–46)	1.27E–6[a]	5.5 (2–23)	8 (1–112)	0.374	5.5 (2–23)	14 (1–112)	1.63E–5[a]
Monthly household income (million KRW)									
Median (min–max)	5 (1–9)	3 (1–9)	0.588	4 (4–4)	2 (2–2)	1.000	5 (1–9)	3 (1–9)	0.460
Education (years)									
Median (min–max)	8 (7–9)	8 (7–9)	0.584	12 (12–12)	6 (6–13)	0.305	8 (7–12)	8 (6–13)	0.269
K-WISC: block design									
Median (min–max)	10.5 (4–17)	10 (4–16)	0.544	10 (3–16)	12.5 (4–15)	0.125	10 (3–17)	11 (4–16)	0.598
K-WISC: vocabulary									
Median (min–max)	9 (5–17)	7 (5–13)	0.174	9.5 (8–15)	11.5 (5–15)	0.595	9 (5–17)	9 (5–15)	0.527
KS									
Median (min–max)	24 (17–36)	37 (22–51)	3.81E–6[a]	29 (17–34)	59 (22–108)	1.2E–5[a]	25 (17–36)	40 (22–108)	2.05E–10[a]
BIS									
Median (min–max)	63 (35–75)	67.5 (45–81)	0.080	61 (45–79)	63 (32–82)	0.835	62 (35–79)	65 (32–82)	0.240
BAS									
Median (min–max)	31 (15–40)	31 (13–51)	0.558	36.5 (22–48)	34 (27–52)	1.000	32 (15–48)	34 (13–52)	0.637
BInS									
Median (min–max)	18 (10–26)	17.5 (13–27)	0.642	18.5 (12–25)	20 (13–21)	0.138	18 (10–26)	19 (13–27)	0.302

IGD, Internet gaming disorder patients; KS, Korean Internet Addiction Proneness Scale; BIS, Barratt Impulsivity Scale; BAS, Behavioral Activation System; BInS, Behavioral Inhibition System; KRW, Korean Won.

[a]*P < 0.05 (Mann–Whitney–Wilcoxon test).*

collected without contaminating the blood cells. Circulating miRNAs were extracted using TaqMan miRNA ABC Purification Kit (Human Panel A; Thermo Fisher Scientific, Waltham, MA, USA) according to the manufacturer's instruction. In brief, 50 μL of plasma sample and 100 μL of ABC buffer were mixed. After hybridization with target-specific anti-miRNA magnetic beads, bounded circulating miRNAs were eluted from the beads with 100 μL of elution buffer. In the discovery phase, 381 miRNAs were examined from 51 plasma samples (25 IGDs and 26 controls) using the TaqMan miRNA ABC Purification Kit (Human Panel A; Thermo Fisher Scientific, Waltham, MA, USA) according to the manufacturer's instructions. Megaplex reverse transcription and pre-amplification reactions were performed to increase the quantity of cDNA for miRNA expression analysis using MegaplexPreAmp Primers Human Pool A and TaqManPreAmp Master Mix (Thermo Fisher Scientific). The TLDA panel A v2.0 (Thermo Fisher Scientific) was run on the ViiA7 real-time PCR system (Thermo Fisher Scientific) to evaluate expression of the miRNAs. Raw data were processed using ExpressionSuite Software v1.0.4 (Thermo Fisher Scientific) to determine Ct values for each miRNA.

Data Analysis for TLDA

We first measured threshold cycles (Ct value) of each miRNA. miRNAs with a Ct value >35 were considered as undetectable and excluded from subsequent analysis. All Ct values were normalized to the Ct value of miR-374b (ΔCt value), one of the most stably expressed miRNAs circulating in human plasma (24). A log2 fold-change ratio (ΔΔCt value) of expression was calculated using mean values of control samples as a calibrator in the HTqPCR package in Bioconductor (25). The relative quantification (RQ) of each miRNA target was defined as $2^{-\Delta\Delta Ct}$. For hypothetical testing of the difference in expression between two groups, we applied surrogate variable analysis (SVA) to capture heterogeneities such as batch effects in the experiments using the *sva* package in Bioconductor (26). miRNAs with a *P*-value <0.05 were considered to be significantly different between two groups.

Gene Set Enrichment Analysis

For gene set enrichment analysis, we used ToppFun in ToppGene Suite (27) to infer significantly enriched Gene Ontology (GO) (28) terms, pathway, and disease terms. As the input for this approach, we used 1,230 predicted target genes of the candidate miRNAs. Pathway analysis was used to find significant pathways of the predicted target genes according to KEGG, BioCarta, Reactome, GeneMAPP, and MSigDBin the ToppGene pathways. The significance of functional enrichment terms was determined based on the Bonferroni-adjusted *P*-value.

Quantitative Reverse Transcription PCR (qRT-PCR) Validation and Replication

To validate the 10 miRNAs that were differentially expressed in the discovery stage, qRT-PCR was performed using the TaqMan MicroRNA Assay (miR-15b-5p, #000390; miR-26b-5p, #000407; miR-29b-3p, #000413; miR-125b-5p, #000449; miR-200c-3p, #002300; miR-337-5p, #002156; miR-411-5p, #001610;

miR-423-5p, #002340; miR-483-5p, #002338; and miR-652-3p, #002352) and the ViiA7 system (Life Technologies) according to the manufacturer's protocol. Ten nanograms of total RNA was converted to first-strand cDNA with miRNA-specific primers using the TaqMan MicroRNA Reverse Transcription Kit (#4366596, Life Technologies), followed by real-time PCR with TaqMan Probes. The RQ of each miRNA was defined as $2^{-\Delta Ct}$, where ΔCt is the difference in threshold cycles for the sample in question, normalized against the endogenous miRNA (miR-374b-5p, #001319). All PCR reactions were carried out in triplicate, and their Ct values were averaged. We calculated a log2 fold-change ratio (ΔΔCt) of each miRNA in the same way as in the array-based analysis. A non-parametric Mann–Whitney–Wilcoxon test was performed to test the differences in expression levels of miRNAs in two groups with a threshold *P*-value of 0.05.

Western Blot Analysis

Each serum sample was first depleted of the top 14 high-abundance proteins (albumin, immunoglobulin G, immunoglobulin A, serotransferrin, haptoglobin, alpha-1 antitrypsin, fibrinogen, alpha-2 macroglobulin, alpha-1 acid glycoprotein, immunoglobulin M, apolipoprotein A-I, apolipoprotein A-II, complement C3, and transthyretin) using the MARS-14 column (4.6 × 50 mm, Agilent Technology, Santa Clara, CA, USA) prior to western blot analysis. The unbound fraction obtained from the MARS-14 column was concentrated using an Amicon Ultracel-3 centrifugal filter (3 kDa cutoff), and then the protein concentration was determined using the bicinchoninic acid method. The same amounts (from 10 to 30 μg) of control and IGD serum samples were separated on a 4–20% Mini-PROTEAN TGX precast gel (Bio-Rad, CA, USA) and transferred to a polyvinylidene difluoride membrane. Next, the membrane was blocked in TBS-T (190 mM NaCl, 25 mM Tris–HCl, pH 7.5, and 0.05% Tween 20) with 5% non-fat dry milk at room temperature for 30 min. The membranes were then incubated with primary antibodies against DPYSL2 (1:500, Novus Biologicals, Littleton, CO, USA), GABRB2 (1:1000, Abcam, Cambridge, MA, USA), and CNR1 (1:100, Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA), DUSP4 (1:500, MybioSource, San Diego, CA, USA), and PI15 (1:500, MybioSource, San Diego, CA, USA) in TBS-T with 5% non-fat dry milk at 4°C overnight, and then with appropriate secondary antibodies either bovine anti-mouse (1:1,000, Santa Cruz Biotechnology) or goat anti-rabbit (1:1,000, Cell Signaling, Beverly, MA, USA) conjugated to horseradish peroxidase at room temperature for 1 h. Signal detection was performed using chemiluminescence with ECL reagent (GE healthcare, Piscataway, NJ, USA). We quantified the western blot results using the TotalLab 1D analysis software (Non-linear Dynamics, Newcastle upon Tyne, UK). Then, the densitometry ratio value was calculated by dividing the densitometry value of each sample as described elsewhere (29). As a control for normalization, a serum sample pooled from 46 IGD and control samples was used for every experiment. Statistical significance was determined using a non-parametric Mann–Whitney–Wilcoxon test with a threshold *P*-value of 0.05.

RESULTS

Characteristics of the Study Subjects

The demographic and clinical features of the study subjects are shown in **Table 1**. When we compared the IGD and control groups according to the Korean Internet Addiction Proneness Scale (*K*-Scale) as described elsewhere (20, 30), the IGD group showed a significantly higher median K-Scale value than the control group (37 vs. 24, $P = 3.81 \times 10^{-6}$) (**Table 1**). Median weekly time spent on Internet gaming in the IGD group was significantly longer than that of controls (18 vs. 5.25 h, $P = 1.27 \times 10^{-6}$). Whereas there was no significant difference between two groups in age, monthly household income, duration of education, block design, and vocabulary subtest results of the K-WISC, BIS, BInS, and BAS.

Differentially Expressed miRNAs Between IGD and Controls

To discover IGD-associated miRNAs, we adopted a two-step (discovery and independent validation) approach. The study design and overall strategy are illustrated in Figure S1 in Supplementary Material. In the discovery stage, we analyzed miRNA expression profiles of 51 samples (25 IGDs and 26 controls) using the miRNA array containing 384 miRNAs. Expression levels of 10 miRNAs were found to be significantly different between the IGD and control groups (**Table 2**). Relative expression levels of these 10 miRNAs are shown in **Figure 1**. Among them, two (hsa-miR-423-5p and hsa-miR-483-5p) were upregulated and eight (hsa-miR-15b-5p, hsa-miR-26b-5p, hsa-miR-29b-3p, hsa-miR-125b-5p, hsa-miR-200c-3p, hsa-miR-337c-5p, hsa-miR-411-5p, and hsa-miR-652-3p) were downregulated in the IGD group.

qRT-PCR Validation of the Candidate miRNAs

To validate the 10 candidate miRNAs, we performed qRT-PCR with an independent validation set (20 IGDs and 16 controls) (Table S1 in Supplementary Material). Three of these miRNAs (hsa-miR-200c-3p, hsa-miR-26b-5p, and hsa-miR-652-3p) were significantly downregulated in the IGD group of the validation set (**Table 2**). Three other miRNAs (hsa-miR-337c-5p, hsa-miR-125b, and hsa-miR-423-5p) were also downregulated in the IGD group but not significantly. Remaining four miRNAs (hsa-miR-15b-5p, hsa-miR-29b-3p, hsa-miR-411-5p, and hsa-miR-423-5p) were expressed oppositely in the validation set. When we combined the discovery and validation sets (a total of 45 IGD subjects and 42 controls), the three validated miRNAs were consistently significant (**Table 2**). Detailed information, chromosomal locations, mature sequences, and expression levels in the CNS of these three miRNAs are available in Table S2 in Supplementary Material.

Synergistic Effect of Simultaneous Alteration of the Three miRNAs on IGD Risk

To evaluate the combined effect of the three miRNAs, we observed the odds ratios (ORs) of the four subgroups (with 0, 1, 2, or 3 miRNA alterations). miRNA alteration was defined by the RQ

TABLE 2 | Differentially expressed microRNAs (miRNAs) and fold changes.

miRNA	Discovery		Validation		Combined	
	P-value	Fold change	*P*-value	Fold change	*P*-value	Fold change
hsa-miR-15b-5p	0.033	0.829	0.694	1.119	0.381	0.947
hsa-miR-26b-5p[a]	0.008	0.871	0.049	0.841	0.013	0.857
hsa-miR-29b-3p	0.005	0.400	0.560	1.187	0.089	0.647
hsa-miR-125b-5p	0.021	0.582	0.290	0.950	0.069	0.723
hsa-miR-200c-3p[a]	0.011	0.336	0.003	0.542	2.93×10^{-5}	0.415
hsa-miR-337c-5p	0.009	0.385	0.582	0.872	0.020	0.553
hsa-miR-411-5p	0.004	0.322	0.336	1.282	0.158	0.595
hsa-miR-423-5p	0.026	1.387	0.189	0.955	0.518	1.175
hsa-miR-483-5p	0.018	1.861	0.765	1.413	0.211	1.647
hsa-miR-652-3p[a]	0.019	0.715	0.049	0.877	0.011	0.782

[a]*miRNAs significantly altered in both discovery and validation sets in a consistent manner.*

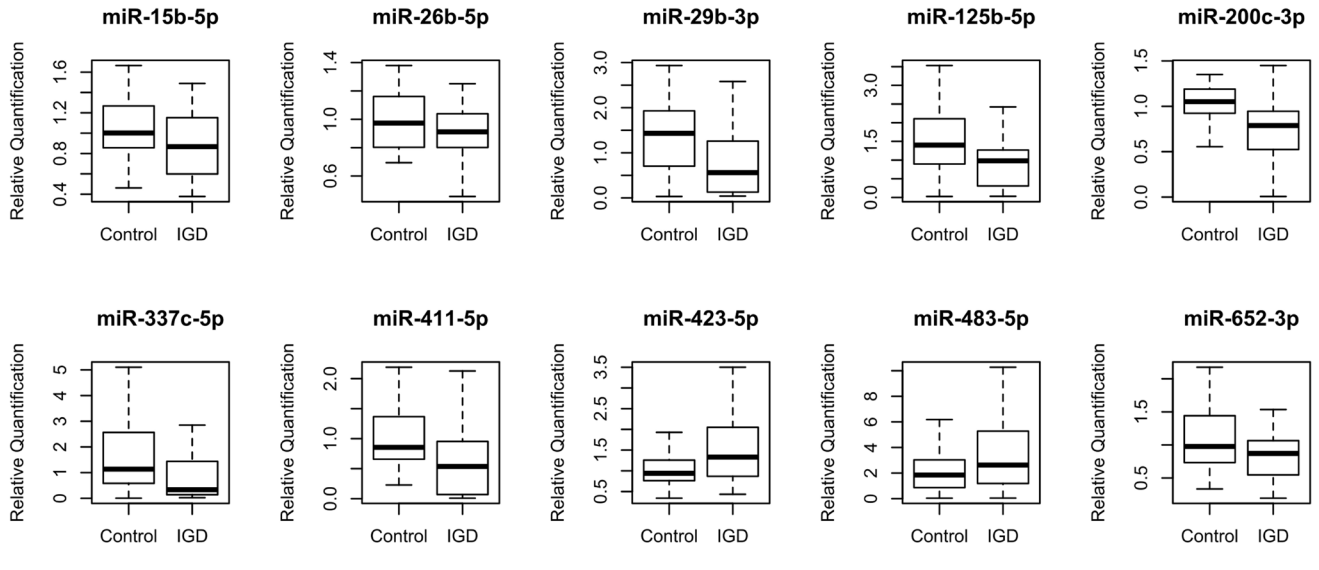

FIGURE 1 | Relative expression levels of 10 differentially expressed miRNAs. Relative quantification (RQ) was normalized to miR-374b-5p.

value as described in Section "Materials and Methods." Because all three miRNAs markers were downregulated in the IGD group, a miRNA whose RQ value was below one was defied as altered one. Detailed information of each study subject's RQ value for the three miRNAs is available in Table S3 in Supplementary Material. For each subgroup, odds were calculated as the ratio of number of controls to that of IGDs, then each OR was calculated by dividing odds of each subgroup by odds of the subgroup without any miRNA alterations. Individuals with three miRNA alterations showed a risk 22 times higher than those without any miRNA alteration (OR 22, 95% CI 2.29–211.11). ORs showed an increasing trend with the number of altered miRNAs from 0 to 3 ($r^2 = 0.996$) (**Figure 2**).

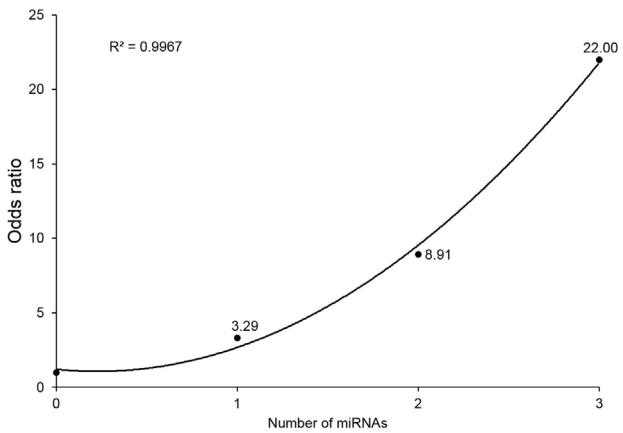

FIGURE 2 | Odds ratios (ORs) by number of downregulated microRNA (miRNA) markers. Values above point estimates are the ORs (95% confidence interval).

GO and Pathway Analysis of Target Genes of the Candidate miRNAs

To gain insight into the functions of the three miRNA markers significantly downregulated in the IGD group, their target genes

were predicted using the miRWalk 2.0 database (31). A total of 1,230 genes were consistently predicted as downstream targets by four algorithms (miRWalk, miRanda, RNA22, and Targetscan) using the miRWalk database (32–34) (Table S4 in Supplementary Material). Gene set enrichment analysis using ToppFun in ToppGene Suite showed that the target genes of those miRNAs were significantly associated with neural development pathways such as "Axon guidance" and GO terms such as "neurogenesis" (Table S5 in Supplementary Material).

Expression of the Predicted Target Genes

Among the downstream target genes of the three miRNAs, 140 were predicted simultaneously for two or more miRNAs (Table S4 in Supplementary Material). To explore whether their protein expressions levels of the downstream target genes are different between the IGD and control groups, we selected 2 genes (*DUSP4* and *PI15*), which are predicted as downstream targets of all 3 miRNAs and additional 3 genes (*GABRB2*, *DPYSL2*, and *CNR1*) from those predicted for 2 miRNAs and performed western blot analysis with the plasma samples from 28 IGDs and 28 controls available for the experiment. We compared the expressions of the five targets between the IGD and control groups by measuring the band intensity and area as described elsewhere (29). Among them, the expression levels of DPYSL2 (28 IGDs and 28 controls, $P = 0.0037$) and GABBR2 (27 IGDs and 28 controls, $P = 0.0052$) were significantly higher in the IGD group (**Figure 3**). However, we could not observe differential expressions of CNR1 ($P = 0.0853$), DUSP4 ($P = 0.5443$), and PI15 ($P = 0.6346$).

DISCUSSION

It has been reported that miRNAs are involved in neuronal development (35, 36), and differential expression of brain miRNAs

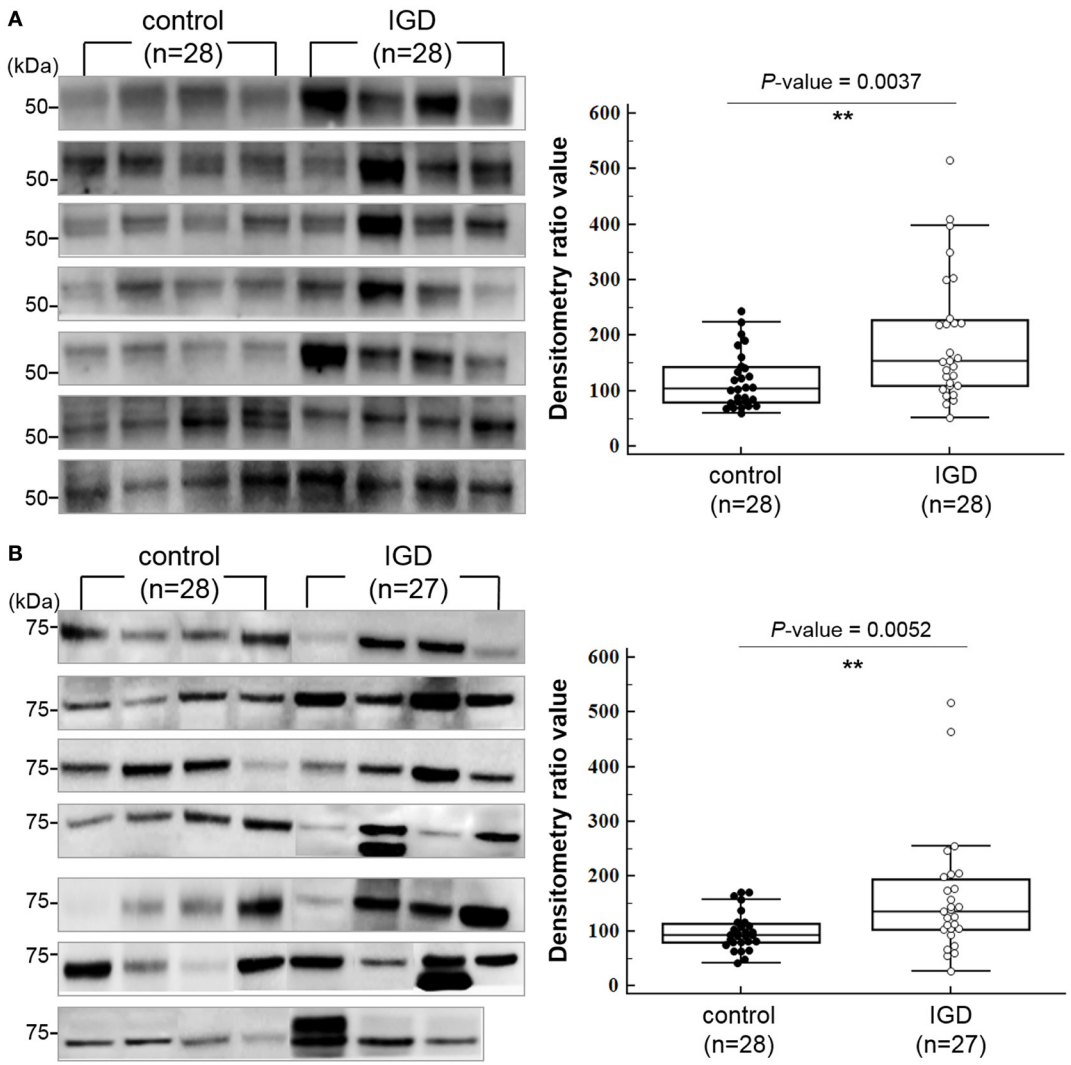

FIGURE 3 | Western blot images and box-dot-plots showing expression of **(A)** DPYSL2 and **(B)** GABRB2. Both DPYSL2 and GABRB2 proteins exhibited significant differences in their expression levels between the Internet gaming disorder (IGD) and control samples (*P*-value <0.05). The two proteins were expressed at higher levels in the IGD samples.

are observed in psychiatric diseases such as schizophrenia (37). Therefore, it is plausible that circulating miRNA profiles could be useful biomarkers for IGD. Circulating miRNAs have been suggested as biomarkers for diverse neuropsychiatric disorders (38–40); however, the molecular mechanisms behind IGD development are still largely unknown despite its clinical and social importance. Specifically, there have been no studies on IGD-associated miRNAs. The aim of this study was twofold. First, we attempted to discover plasma miRNAs associated with IGD. Second, we evaluated the biological implication of the miRNA candidates by exploring protein expression and GO of downstream target genes. Through genome-wide screening of miRNA expression profiles and downstream validation of the candidates, we discovered that expression of three miRNAs (hsa-miR-200c-3p, hsa-miR-26b-5p, and hsa-miR-652-3p) was significantly lower in IGD patients than controls. Although the expression patterns of other seven miRNA candidates were not replicated in the validation, it can be false negative due to small sample size in this study. To our knowledge, this is the first report on the possibility that blood miRNA expression profiles could be useful biomarkers for IGD. Combination of the three miRNA markers could serve as a minimally invasive tool for early identification of people at risk of IGD.

The miRNAs identified in this study have been reported to be involved in diverse neuropsychiatric disorders. Expression of hsa-miR-200c in blood has been reported to be downregulated in several psychiatric disorders such as schizophrenia (41) and major depressive episodes (42). miR-200c was reported to be more highly expressed in synaptic fractions than in total forebrain (43) and also to be associated with neuronal cell death (44). Based on these previous reports, miR-200c is involved in neurodevelopment and can be associated with neuropsychiatric disorders if its expression is perturbed. Several studies have suggested association between miR-652 and risk of neuropsychiatric disorders. Similar to our approach, to identify blood biomarkers for schizophrenia, Lai et al. carried out TLDA analysis with schizophrenia patients and normal controls, and found that seven miRNAs including hsa-miR-652 were differentially expressed in schizophrenia patients (45). In the subsequent study, they designed a prediction model using the miRNA expression data and successfully distinguished schizophrenia from normal control (46). Altered expression of hsa-miR-652 was also observed in alcoholics (47). Hsa-miR-26b was found to be activated during neuronal cell differentiation (48). Perkins et al. reported that hsa-miR-26b was downregulated in the prefrontal cortex of schizophrenia patients (49).

Although there is no direct evidence to support the relationship between the perturbed expression of these miRNAs and the pathophysiology of IGD, we can infer that dysregulation of these miRNAs may be associated with the pathophysiology of IGD based on various previous reports on the downstream genes we predicted. Some of the downstream genes of the three miRNAs such as *GABRB2*, *CNR1*, *NRXN1*, and *DPYSL2* are reported to be associated with neuropsychiatric disorders. Gamma-aminobutyric acid (GABA) is a major inhibitory neurotransmitter in the CNS. Dysregulation of the GABA receptor, is implicated in neuropsychiatric disorders including addiction, anxiety, and depression (50), which are also the main features of IGD (8). Genetic polymorphisms in GABA receptor genes are reported to be associated with alcohol addiction and schizophrenia (51, 52). Dihydropyrimidinase-like 2 (DPYSL2) is a member of the collapsin response mediator protein family, which plays a role in microtubule assembly, synaptic signaling, and regulation of axonal growth. Consequently, this molecule has been suggested as a biomarker for psychiatric disorders (53, 54). Polymorphism in the *DPYSL2* gene was also reported to be associated with alcohol use disorder (55). Previous reports and our data suggest that overexpression of GABRB2 and DPYSL2, downstream targets of the downregulated miRNAs, has implications for the pathogenesis of neuropsychiatric disorders including IGD. Cannabinoid receptor type 1 (CNR1) is a presynaptic heteroreceptor that modulates neurotransmitter release and disturbances in cannabinoid signaling are associated with various neuropsychiatric disorders (56). Genetic polymorphism of *CNR1* gene is known to be associated with substance dependence in Caucasians (57). In a rat model, activation of ventral hippocampus CNR1 disrupts normal social behavior and cognition (58). Genetic alteration in the NRXN family is known to be involved in diverse neuropsychiatric disorders including addiction (59).

To examine the biological implication of the three miRNA candidates in a more direct way, we explored protein expression of their downstream target genes. Due to the limited availability of plasma samples, of the 140 common candidates (predicted as downstream of 2 or more miRNAs), we examined 5 targets (GABRB2, DPYSL2, CNR1, DUSP4, and PI15) by western blot and confirmed that expression of GABRB2 and DPYSL2 was significantly higher in the IGD group. Previous reports and our data suggest that overexpression of GABRB2 and DPYSL2, downstream targets of the downregulated miRNAs, may have implications for the pathogenesis of neuropsychiatric disorders including IGD. The results of GO and pathway analysis of neural development pathways also support the neurobiological implication of the miRNA markers. Another interesting finding was the synergistic effect of simultaneous alteration of the miRNAs. Individuals with downregulation of all 3 miRNAs showed 22 times higher risk than those with no downregulation, and the ORs increased in a dose-dependent manner. Although CI for these three alterations were wide due to limited sample size, the clear positive correlation ($r^2 = 0.996$) supports the synergistic effect of the three miRNAs.

Although we did discover the IGD-associated miRNA markers and individuals with all three miRNA alterations had a risk 22 times higher than those without any miRNA alterations, there are several limitations in this study. First, the small sample size increased the likelihood of missing other significant miRNA markers. Second, since our data were not enough to clarify whether the plasma miRNA profiles are either cause or effect, we cannot confirm the biological roles of these non-invasive markers in a clinical setting. Further miRNA profiling and their downstream gene analysis using human brain tissue from brain tissue bank can give a more direct answer. Brain tissue analysis with a gaming disorder animal model also would be helpful. Third, due to the limited availability of plasma samples, we examined only five downstream candidate molecules. Exploring more

downstream targets with a larger sample set will be helpful to further understand the molecular mechanism of IGD.

In summary, through genome-wide screening of miRNA expression profiles and independent validation, we discovered three IGD-associated miRNAs (hsa-miR-200c-3p, hsa-miR-26b-5p, and hsa-miR-652-3p). Many of their downstream genes are reported to be involved in diverse neuropsychiatric disorders, and experimental validation of altered expression of these downstream genes support the implication of the miRNAs identified in this study. We found that individuals with downregulation of all three miRNA are at high risk of IGD. Together with the known clinical or environmental risk factors and diagnostic criteria, our findings can facilitate early intervention to help people at higher risk of IGD.

ETHICS STATEMENT

This study was approved by the Institutional Review Board of the Catholic University Medical College of Korea (MC16SISI0120). All participants and their parents gave written informed consent.

AUTHOR CONTRIBUTIONS

ML and HC contributed equally to this paper. ML, D-JK, and Y-JC designed the study. SJ, S-MC, YP, DC, and JL performed experiments and data generation. J-WC, S-HP, J-SC, and D-JK collected blood samples and clinical information. ML, HC, S-HY, and Y-JC analyzed data. ML, HC, S-HY, and Y-JC described the manuscript. Y-JC supervised the project.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://www.frontiersin.org/articles/10.3389/fpsyt.2018.00081/full#supplementary-material.

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Altered Heart Rate Variability During Gameplay in Internet Gaming Disorder: The Impact of Situations During the Game

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Internet gaming disorder (IGD) is characterized by a loss of control over gaming and a decline in psychosocial functioning derived from excessive gameplay. We hypothesized that individuals with IGD would show different autonomic nervous system (ANS) responses to the games than those without IGD. In this study, heart rate variability (HRV) was assessed in 21 young males with IGD and 27 healthy controls while playing their favorite Internet game. The subjects could examine the game logs to identify the most and least concentrated periods of the game. The changes in HRV during specific 5-min periods of the game (first, last, and high- and low-attention) were compared between groups via a repeated measures analysis of variance. Significant predictors of HRV patterns during gameplay were determined from stepwise multiple linear regression analyses. Subjects with IGD showed a significant difference from controls in the patterns of vagally mediated HRV, such that they showed significant reductions in high-frequency HRV, particularly during the periods of high attention and the last 5 min, compared with baseline values. A regression analysis showed that the IGD symptom scale score was a significant predictor of this reduction. These results suggest that an altered HRV response to specific gaming situations is related to addictive patterns of gaming and may reflect the diminished executive control of individuals with IGD while playing Internet games.

Keywords: autonomic nervous system, heart rate variability, internet gaming disorder, gameplay, addiction

INTRODUCTION

Internet gaming disorder (IGD), one of the most studied forms of Internet addiction, is characterized by a difficulty in controlling excessive Internet game use despite negative psychosocial consequences (1). Although it has not yet been fully clarified, much effort has been devoted to elucidating the neurobiological background underlying IGD (2). Some researchers are interested in the physiological features of IGD, particularly in autonomic nervous system (ANS) dysfunction. ANS dysfunction has been associated with psychiatric disorders (3), including substance abuse and behavioral addiction (4, 5). As the ANS responds to internal and external stimuli to maintain homeostasis, its function is closely related to adaptive adjustments in behavior strategies (6). ANS dysfunction likely contributes to the development and maintenance of loss of control over gaming, as individuals with IGD are unable to adjust their behavior strategies despite negative outcomes.

ANS function can be assessed non-invasively by measuring heart rate variability (HRV). A study by Lin et al. found that school-aged children with Internet addictions had lower levels of total-power HRV than non-addicted children (7). The authors also indicated that children with Internet addiction had lower high-frequency (HF) percentages and higher low-frequency (LF) percentages than non-addicted children. Data from Kim et al. similarly showed that adolescents with IGD had lower total-power HRV, but both HF and LF values were significantly lower and their ratios did not differ between those with IGD and controls (8). However, there is not sufficient evidence, with mixed results reported in previous studies, to clarify the role of ANS function in IGD.

To more accurately assess ANS function, it may be useful to measure HRV responses to particular stimuli as well as during the resting state, as this better reflects the ability of the ANS to respond appropriately and adaptively to environmental change (9). A previous study on Internet addiction showed that individuals with problematic Internet use had a lower standard deviation of the R-R interval (SDNN, reflects overall HRV levels) than non-problematic users during rest but not during and after the Trier social stress test (TSST) (10). This measure could be applied to assess HRV responses to gaming-related stimuli rather than general stress stimuli. Our previous work suggested that individuals with IGD have HRV suppression during gameplay (11). As HRV suppression may represent inefficient executive control (12), we speculated that HRV suppression in response to gaming in individuals with IGD reflects an imbalance between enhanced reward-seeking and diminished executive control (13). However, our previous study only analyzed HRV data for the first 5 min of the game. These data do not encompass the full range of responses to the variety of situations that gaming comprises, such as those requiring high levels of attention with many points to consider and those with repetitive actions or that have little influence on the final outcome of the game, which require less attention. Our previous study also did not include the subjects' perceptions of these various situations in the game. Thus, further data are needed assessing the alterations of HRV throughout the duration of the game to determine the role of the ANS in IGD pathophysiology.

Numerous studies on addiction suggest that addictive behaviors begin from a voluntary and goal-directed pattern that gradually becomes habitual and compulsive (14, 15). This progression accompanies several neurobiological changes, including weakened prefrontal cortical control and strengthened dorsal striatal control (16, 17). With this in mind, addictive gaming may also be associated with habitual and compulsive behavioral patterns. Individuals with IGD may thus be less influenced by prefrontal control, even when playing games at a high level of attention, and consequently play games in a habitual or compulsive manner rather than a goal-directed manner. To appropriately interpret these behavioral patterns, the situational factors of game should be considered.

We hypothesized that the difference in gaming behaviors between individuals with and without IGD become apparent during situations demanding a high level of attention, reflecting an addictive pattern of habitual gameplay with weakened prefrontal cortical control. We also hypothesized that HRV response during periods of high attention would be significantly related to the severity of IGD rather than to other psychological problems (e.g., depression and anxiety). Unlike the previous studies of HRV in IGD, the current study analyzed the changes in HRV during the game in which gaming addicts were actually addicted, and included consideration of the situational factors of game. Thus, in this study, we analyzed HRV of young males with and without IGD while playing an Internet game at specific time periods, including the initial and final periods, as well as during periods when the gamer was and was not particularly focused. We examined how HRV values change during these different situations, whether they differ between individuals with and without IGD, and if they are associated with the severity of IGD.

MATERIALS AND METHODS

Participants

The Institutional Review Board approved the protocol for this study (HYI-16-044), and all subjects provided signed informed consent before participating. This study included 48 subjects, all right handed and aged between 16 and 27 years (mean age: 22.0 $\pm$ 2.8 years), who were recruited through online bulletin boards, flyers, and word of mouth. All subjects were assessed for their Internet-use patterns. All subjects in this study frequently played "League of Legends" (Riot Games, 2009), the most popular multiplayer online battle arena game in Korea. To control for the difference of hedonic sensation or familiarity of each subject for the game, only those who were in the same rank in the game were recruited. Participants who primarily used the Internet for gaming and scored above 50 on the Young's Internet-addiction test (Y-IAT) (18) were classified as subjects with IGD ($n = 21$; age, 22.3 $\pm$ 2.9 years). They were reassessed for IGD via a psychiatric interview based on the criteria in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (1). Subjects who scored below 50 on the Y-IAT were classified as controls ($n = 27$; age, 21.8 $\pm$ 2.8 years).

All subjects were screened via a four-item brief screening tool (19) (feeling nervous, anxious, or on edge; not being able to stop or control worrying; feeling down, depressed, or hopeless; little interest or pleasure in doing things) to ensure they had no clinically significant depression or anxiety symptoms during more than half of the last 2 weeks. The Korean version of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, was also used to assess the presence of major mental disorders other than IGD (20) and the Wechsler adult intelligence scale IV was used to assess intelligence quotients (21). All subjects completed the following respective self-report questionnaires regarding depression, anxiety, alcohol-related problems, childhood symptoms of attention-deficit/hyperactivity disorder, and impulsivity: the Beck depression inventory (22), the Beck anxiety inventory (23), the alcohol-use disorders identification test (24), the Wender Utah rating scale (25), and the Barratt impulsiveness scale, version 11 (26).

Subjects with a substantial psychiatric comorbid condition other than IGD (e.g., depression, psychotic disorder, or substance

dependence), neurological or medical disorder that affected the HRV (e.g., cardiac disease or endocrine disease), low intelligence, or were taking drugs that affected the HRV (e.g., beta blockers or anticholinergics) were excluded from the study. All subjects were psychiatric medication naïve at the time of assessment.

Experimental Protocol

The experimental protocol for this study is presented in **Figure 1**. After a rest period of at least 10 min, resting-state electrocardiograms (ECGs) were recorded for 5 min while subjects were in a relaxed sitting position for the baseline HRV. The subjects then played the online game League of Legends three times, with a 5-min rest after each game. Each game lasted for at least 20 min. After each game ended, subjects checked the game log to identify 5-min periods of high attention and low attention. For each game, initial HRV (during the first 5 min), high- and low-attention HRV (during the 5-min periods of high and low attention, respectively), and last-time HRV (during the final 5 min of the game) signals were analyzed. HRV values for each period were averaged from 3 games. After all the games were over, HRV signals were measured in the resting state for 5 min for the post-game HRV.

HRV Analysis

Three ECG channels were connected to each of the subjects' chests to obtain ECG signals via an MP150 (BIOPAC Systems Inc., Santa Barbara, CA, USA). To eliminate noise from the subjects' movement, breathing, and muscle electrical activity, the data were preprocessed using third-order Butterworth high-pass filtering with a 0.1-Hz cutoff frequency, a sixth-order Butterworth notch filter, and third-order Butterworth low-pass filtering with a 15-Hz cutoff frequency (27, 28). All ECG signals were acquired at 200 Hz, and the Pan and Tomkins method was used to automatically detect R-R intervals (29).

HRV parameters were extracted from time and frequency-domains, using a HRV analysis software (30). The time-domain method measures the time between R-R intervals or the instantaneous heart rate at a specific time. The time-domain parameters used in this study were the SDNN and the root mean squared differences of successive N-N intervals (RMSSD). SDNN indicates overall HRV, whereas RMSSD indicates short-term changes in heart rate and is used to predict parasympathetic activity (31). For the frequency-domain analyses, we used a 20% filter to remove ectopic beats, and data were interpolated at 4 Hz (32). The frequency-domain parameters were transformed with an autoregressive model. The LF domain of HRV (0.04–0.15 Hz) reflects parasympathetic and sympathetic nerve activity, whereas the HF domain (0.15–0.4 Hz) mainly represents parasympathetic activity (33). The frequency-domain HRV parameters with skewed distributions were logarithmically transformed (34). The LF/HF ratio was used as an index of sympathovagal balance (35).

Statistical Analysis

Statistical analyses were performed with Statistical Package for the Social Sciences (SPSS), version 24.0 K (SPSS Inc., Chicago, IL, USA). A p-value of <0.05 was considered statistically significant. Independent t-tests were used to compare demographic and psychometric characteristics or absolute values of HRV parameters between subjects with IGD and controls. Repeated measures analyses of variance (ANOVAs) were used to group differences in longitudinal changes of HRV, using the period (baseline, initial, high-attention, low-attention, last-time, and post-game) as the within-subjects factor and group (IGD subjects or controls) as the between-subjects factor. Among the various parameters of HRV (lnLF, lnHF, SDNN, RMSSD, and LF/HF), we tested which parameter was statistically significant in the interaction between group and period, and *post-hoc* comparisons were applied to test whether the

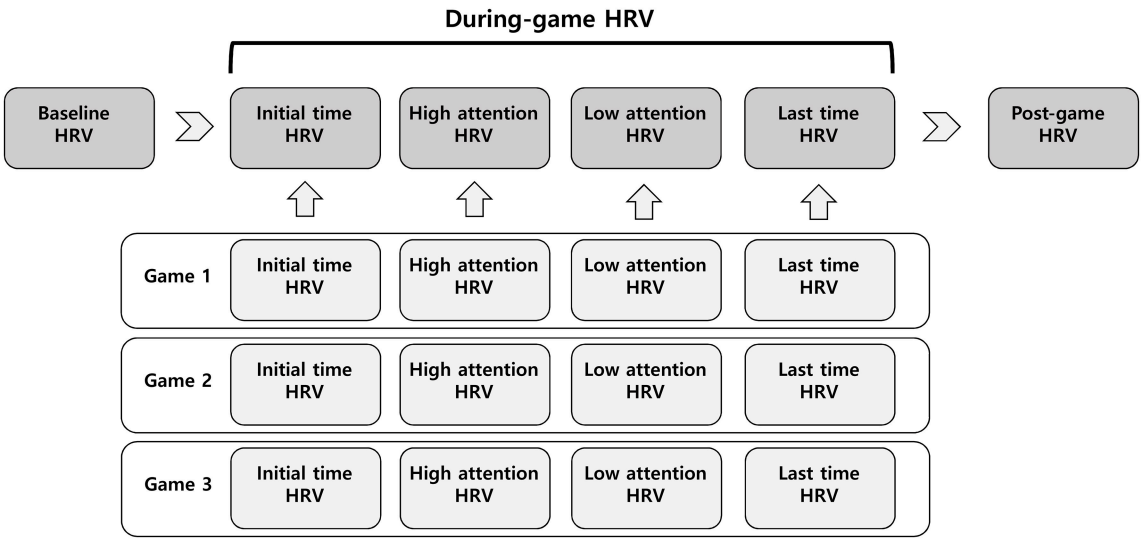

FIGURE 1 | Experimental protocol of measurements for heart rate variability (HRV). Each period was 5 min.

TABLE 1 | Demographics and clinical variables of subjects.

Variable	Control ($n = 27$)	IGD ($n = 21$)	p-value
DEMOGRAPHICS			
Age, years	21.8 (2.8)	22.3 (2.9)	0.494
Education level, years	12.1 (0.4)	11.8 (0.8)	0.103
Full-scale intelligence quotient	110.1 (10.5)	110.7 (12.0)	0.953
PSYCHOLOGICAL FACTORS			
Young Internet-addiction test	30.8 (11.6)	63.1 (8.8)	**<0.001**
Beck depression inventory	7.0 (4.9)	9.5 (7.9)	0.285
Beck anxiety inventory	5.6 (4.5)	5.7 (4.4)	0.944
Barratt impulsiveness scale	49.9 (5.5)	56.4 (7.8)	**0.003**
Alcohol-use disorder identification test	10.6 (5.6)	10.8 (7.4)	0.953
Wender Utah rating scale	28.5 (12.5)	24.3 (14.6)	0.232

Data are presented as means (standard deviations).
IGD, Internet gaming disorder.
Bold value means that p-value is less than 0.05.

differences between certain periods were statistically significant. Bonferroni's corrections ($p < 0.05/15$) were conducted to adjust for multiple comparisons (15 paired comparisons of six periods). These analyses were used to characterize the patterns of HRV during gameplay (changes of specific HRV parameters between specific periods in the game) in subjects with IGD. Stepwise multiple linear regression analyses were then conducted to identify significant predictors of these patterns. For these analyses, demographic or psychometric characteristics (Y-IAT, age, intelligence quotient, scores from self-report questionnaires) of all subjects were entered as independent variables.

RESULTS

Clinical Characteristics of the Subjects

Subjects with IGD had Y-IAT scores that were significantly higher than the controls ($p < 0.001$; **Table 1**). Subjects with IGD and controls did not differ significantly in self-reported scale scores for depression, anxiety, alcohol-related problems, and childhood attention-deficit/hyperactivity symptoms. However, subjects with IGD scored significantly higher on tests of impulsivity than did controls ($p = 0.003$).

HRV Changes

For all periods, there were no statistically significant differences between subjects with IGD and controls in any of the HRV parameters (**Table 2**). However, interaction effects between period and group were statistically significant for lnHF ($p = 0.043$) and RMSSD ($p = 0.028$) via repeated measures ANOVAs (**Table 3**).

Post-hoc comparisons showed that subjects with IGD had significant reductions in lnHF for high-attention HRV ($p = 0.001$) and last-time HRV ($p = 0.003$) compared with that for baseline HRV. Although not statistically significant after correction for multiple comparisons, subjects with IGD also had trends toward reductions in RMSSD for high-attention HRV ($p = 0.007$) compared with that for baseline HRV. Unlike

TABLE 2 | Absolute values of HRV parameters in subjects.

Parameter	Baseline HRV			Initial-time HRV			High-attention HRV			Low-attention HRV			Last-time HRV			Post-game HRV		
	Control	IGD	p-value	Control	IGD	p-value	Control	IGD	p-value	Control	IGD	p-value	Control	IGD	p-value	Control	IGD	p-value
LnHF	4.3 (0.9)	4.7 (0.7)	0.079	4.4 (0.7)	4.3 (0.7)	0.764	4.3 (0.8)	4.2 (0.7)	0.535	4.4 (0.8)	4.3 (0.6)	0.899	4.3 (0.8)	4.3 (0.6)	0.977	4.2 (0.8)	4.5 (0.7)	0.182
LnLF	5.7 (0.8)	6.0 (0.6)	0.164	5.8 (0.7)	5.6 (0.5)	0.269	5.8 (0.6)	5.6 (0.6)	0.267	5.8 (0.7)	5.6 (0.5)	0.345	5.7 (0.7)	5.7 (0.5)	0.697	5.7 (0.9)	5.8 (0.5)	0.564
SDNN	45.3 (22.8)	50.3 (14.5)	0.386	48.4 (16.0)	46.5 (14.2)	0.677	47.7 (16.6)	44.6 (13.3)	0.493	49.3 (17.4)	45.9 (13.3)	0.463	48.2 (19.0)	45.3 (14.7)	0.571	45.0 (20.0)	50.1 (13.9)	0.326
RMSSD	35.3 (22.2)	40.7 (19.5)	0.387	36.3 (16.1)	32.5 (11.4)	0.371	35.7 (16.7)	31.2 (12.7)	0.311	35.7 (17.3)	32.3 (11.6)	0.448	35.3 (18.4)	31.4 (13.1)	0.424	32.3 (18.3)	38.1 (17.0)	0.262
LF/HF	4.6 (2.7)	4.6 (3.7)	0.967	4.6 (1.9)	4.0 (1.6)	0.253	4.9 (2.5)	4.7 (2.6)	0.859	4.8 (2.3)	4.2 (2.0)	0.336	4.7 (2.0)	4.5 (1.8)	0.681	5.5 (3.5)	4.9 (4.8)	0.656

Data are presented as means (standard deviations). HRV, heart rate variability; 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.

TABLE 3 | Repeated measures ANOVA for HRV parameters.

Parameter	Source	η_p^2	*F*	*p*-value
LnHF	Group	0.004	0.163	0.689
	Period	0.303	3.651	**0.008**
	Period × Group	0.232	2.541	**0.043**
LnLF	Group	0.001	0.046	0.831
	Period	0.113	1.074	0.389
	Period × Group	0.192	1.999	0.099
SDNN	Group	<0.001	0.002	0.967
	Period	0.109	1.031	0.412
	Period × Group	0.183	1.884	0.118
RMSSD	Group	0.001	0.025	0.875
	Period	0.215	2.306	0.061
	Period × Group	0.251	2.814	**0.028**
LF/HF	Group	0.008	0.392	0.534
	Period	0.114	1.078	0.387
	Period × Group	0.083	0.759	0.584

η_p^2, effect size as partial eta-squared. HRV, heart rate variability; 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.
Bold value means that p-value is less than 0.05.

TABLE 4 | Stepwise multiple linear regression analysis with HRV features.

Independent variables	β	*t*	*p*-value
With difference in lnHF between high-attention and baseline HRVs as dependent variables			
Age	−0.510	−0.368	0.714
Full-scale intelligence quotient	−0.226	−1.684	0.099
Young Internet-addiction test	−0.378	−2.766	**0.008**
Beck depression inventory	0.256	1.848	0.071
Beck anxiety inventory	0.032	0.234	0.816
Barratt impulsiveness scale	0.059	0.374	0.710
Alcohol-use disorder identification test	0.110	0.803	0.426
Wender Utah rating scale	−0.090	−0.653	0.517
$R^2 = 0.143$; adjusted $R^2 = 0.124$; SEE = 13.6			
With difference in lnHF between last-time and baseline HRVs as dependent variables			
Age	−0.145	−1.046	0.301
Full-scale intelligence quotient	−0.179	−1.306	0.198
Young Internet-addiction test	−0.369	−2.611	**0.012**
Beck depression inventory	0.308	2.178	**0.035**
Beck anxiety inventory	−0.087	−0.533	0.596
Barratt impulsiveness scale	0.030	0.187	0.853
Alcohol-use disorder identification test	0.069	0.490	0.627
Wender Utah rating scale	0.082	0.584	0.562
$R^2 = 0.169$; adjusted $R^2 = 0.132$; SEE = 0.5			

β, standardized regression coefficient. HRV, heart rate variability; lnHF, natural logarithm of high frequency.
Bold value means that p-value is less than 0.05.

subjects with IGD, subjects without IGD did not show significant differences in any of the HRV parameter between specific periods ($p > 0.05$).

Stepwise multiple linear regression analyses were performed with the differences of lnHF for high-attention HRV and last-time HRV relative to baseline HRV as the dependent variables (**Table 4**). Of the independent variables, only the Y-IAT score was a significant predictor of the difference of lnHF between high-attention HRV and baseline HRV. However, the Y-IAT score and Beck depression inventory score were significant predictors of the difference in lnHF between last-time HRV and baseline HRV. All the variables used for multiple linear regression had a variance inflation factor of <5.

DISCUSSION

In this study, we measured the changes in HRV in young males with IGD while they played an Internet game. Although the absolute values for HRVs did not differ between young males with IGD and controls, those with IGD had significant differences with respect to longitudinal changes of lnHF and RMSSD during gaming. Specifically, lnHF was reduced from baseline during periods of high attention and during the last 5 min of the game, supporting our hypothesis that a characteristic HRV response would become apparent during game periods requiring a high level of attention. Further analyses supported our second hypothesis, showing that the severity of the IGD, assessed by the Y-IAT score, predicted this characteristic reduction in lnHF.

The group differences in patterns of change in lnHF and RMSSD we observed during gameplay are consistent with a previous study, suggesting that HRV responses in subjects with IGD differ from those of controls while playing the game (11). HF and RMSSD are closely correlated and reflect vagal activity (35). The neurovisceral model suggests that vagally mediated HRV is an index that reflects executive control over affective and cognitive processes (36). According to this model, these differences are related to the difficulty in exerting executive control over excessive gaming in subjects with IGD.

Subjects with IGD showed significant reductions in lnHF for high-attention HRV and last-time HRV compared with that for baseline HRV. Although statistical significance was not high enough, they also showed trends toward reductions in RMSSD for high-attention HRV compared with that for baseline HRV. A large reduction of vagally mediated HRV is suggested to be a specialized HRV feature that reliably reflects weakened prefrontal neural function responsible for top-down executive control (37). In the present study, the subjects determined what period required high attention, and the gameplay during the final 5 min was a determinant of whether the game was won or lost. Thus, during these important periods, the reduction in HF-HRV suggests that top-down executive control was diminished when the demand for concentration on the game was increased. We infer that these characteristics of gameplay in young males with IGD are related to their habitual/compulsive game use.

Interestingly, the only predictor of the reduced lnHF during periods of high attention was the severity of the IGD, suggesting

that an altered HRV response to gaming in individuals with IGD reflects the addictive features of gaming. Therefore, the current findings support a putative role of altered ANS response to gaming in the status of IGD. On the other hand, the severity of both IGD and depression predicted the reduction in lnHF during last 5 min of the game, when some of the gamers may have given up. We speculate that psychological characteristics of depression affect the extent to which subjects concentrate at the end of the game, which is associated with their HRV responses.

As psychological conditions (e.g., depression and anxiety) were assessed prior to participation, we ensured that the subjects with IGD and controls did not differ in this regard. This may explain why no significant differences in the resting-state HRVs were observed. However, subjects with IGD self-reported higher impulsiveness than controls, in agreement with previous studies in which high impulsivity is the prominent psychobehavioral feature in IGD (38, 39). Moreover, high impulsivity is related to diminished executive function (40). Nevertheless, impulsivity and executive function each contain various components, and the relationship between them is complex (41). Further research is needed to clarify the association between the high impulsivity of individuals with IGD and their HRV responses to gaming.

There are some limitations to this study. First, the sample size of this study is small, thus not all variables affecting HRV could be controlled. Second, the inclusion of indexes besides HRV is needed to fully reflect the subjects' physiological and autonomic responses to gaming. Third, the design of this study was cross-sectional; therefore, the changes in HRV responses observed during gameplay should be followed up in longitudinal studies of subjects with IGD. Such studies would validate the use of HRV as an important index reflecting the progress of treatments for IGD.

Despite its limitations, our current study is the first to analyze HRV data during the game, encompassing responses to the specific gaming situations. Young males with IGD showed vagally mediated HRV responses to gaming that were significantly different from those of healthy controls, particularly during periods requiring high attention. They showed a reduction in HF-HRV that was also related to the severity of their IGD. This alteration in their autonomic responses suggests that individuals with IGD are less influenced by executive control, even when playing games at a high level of attention. Our results suggest that the habitual gaming behaviors of individuals with loss of control over gaming reflects diminished prefrontal control.

ETHICS STATEMENT

All of the procedures involving human participants were performed in accordance with the ethical standards of the institutional and national research committees and with the 1964 Helsinki declaration and its later amendments. The experimental protocol was approved by the Institutional Review Board at Hanyang University (HYI-16-044).

AUTHOR CONTRIBUTIONS

Y-CJ and IK contributed to the study design. JP and JEL collected the clinical and bio-signal data. SH and DL performed statistical analysis and wrote the first draft of the manuscript. KN, JL and DJ provided critical revision of the manuscript and important intellectual content. All authors contributed to manuscript revision, read, and approved the submitted version.

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Role of Frontostriatal Connectivity in Adolescents With Excessive Smartphone Use

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As smartphone use has grown rapidly over recent decade, it has been a growing interest in the potential negative impact of excessive smartphone use. In this study, we aim to identify altered brain connectivity associated with excessive smartphone use, and to investigate correlations between withdrawal symptoms, cortisol concentrations, and frontostriatal connectivity. We focused on investigating functional connectivity in frontostriatal regions, including the orbitofrontal cortex (OFC), midcingulate cortex (MCC), and nucleus accumbens (NAcc), which is related to reward processing and cognitive control. We analyzed data from 38 adolescents with excessive smartphone use (SP) and 42 healthy controls (HC). In the SP group compared with HC, we observed lower functional connectivity between the right OFC and NAcc, and between the left OFC and MCC. Moreover, functional connectivity between the MCC and NAcc was greater in SP compared with HC. Subsequently, we examined the relationship between Internet use withdrawal symptoms, cortisol concentrations, and functional connectivity between the OFC and NAcc in SP and HC. We observed that more severe withdrawal symptoms were associated with higher cortisol concentrations in adolescents with excessive smartphone use. The most interesting finding was that we observed a negative correlation between OFC connectivity with the NAcc and both withdrawal symptoms and cortisol concentrations. The functional connectivity between the OFC and NAcc, and between the OFC and MCC are related to cognitive control of emotional stimuli including reward. The current study suggests that adolescents with SP had reduced functional connectivity in these regions related to cognitive control. Furthermore, Internet use withdrawal symptoms appear to elicit cortisol secretion, and this psychophysiological change may affect frontostriatal connectivity. Our findings provide important clues to understanding the effects of excessive use of smartphones on brain functional connectivity in adolescence.

Keywords: excessive smartphone use, frontostriatal connectivity, cortisol, problematic internet use, withdrawal

INTRODUCTION

Following recent developments in mobile communication technology, smartphones have become a necessity of everyday life beyond simple interpersonal communication. We use smartphone for various activities, such as information searching, online gaming, and social networking. Despite many benefits resulting from these developments, it has been reported that excessive mobile phone use could induce potentially risky behaviors, such as uncontrolled use and disturbance of adaptive behavior, which can have a negative impact on various aspects of daily life (1).

Nowadays, all kinds of media content are continuously available via portable mobile devices such as smartphones (2). It is possible that emotional sensitivity and protracted development of cognitive control during adolescence may make those at this stage of life more reactive to emotion-arousing media (3). A previous study reported that adolescents tend to use smartphones more often for Internet use than do adults, and they are more likely to be exposed to problematic smartphone use (4). Recently, cognitive neuroscience studies have used structural and functional magnetic resonance imaging (fMRI) to examine how the adolescent brain changes over course of adolescence (3). Given that brain regions involved in many social and cognitive functions are undergoing such broad changes during adolescence, it might be supposed that adolescents are greatly influenced by social interaction that occurs via the Internet.

It has been reported that negative aspects of excessive smartphone use are similar to Internet addiction, including Internet gaming disorder (5). In the previous study, Internet addiction and pathological Internet use have been revealed to induce negative outcomes such as uncontrolled Internet use, tolerance, withdrawal, social isolation, and poor academic or professional achievement (6). Previous research has suggested that individuals Internet addiction disorder (IAD) showed excessive use, tolerance, and withdrawal symptoms similar to substance use disorder (7). A study of the diagnostic criteria has revealed that 96% of individuals with IAD reported withdrawal symptoms (8). Moreover, a factor analysis of Internet addiction suggested that withdrawal symptoms are highest in Korean adolescents aged between 10 and 19 years (9). Withdrawal symptoms include anxiety about situations in which the Internet is not available and craving Internet use (9). In the previous case study of mobile phone dependence (MPD), individual with MPD might feel uncomfortable and annoyed in the absence of their mobile phone, including feeling a physical and psychological emptiness associated with withdrawal (10). Altogether, withdrawal symptoms are important factor in the pathological use of Internet. As a portable media for Internet use, the excessive use of the smartphone may be closely associated with the symptoms of the IAD.

To explore whether brain functional connectivity in the PFC is associated with withdrawal and cortisol concentrations might be helpful in understanding dysfunctional behavior associated with excessive smartphone use. Several previous studies have shown that anxiety experienced during real life stressful situations, as well as that induced by experimental situations, is related to increased cortisol levels (11–13). In previous studies of substance addiction, cortisol levels were positively correlated with withdrawal symptoms (13, 14). It is known that the hippocampus, amygdala, and prefrontal cortex (PFC) were associated with cortisol regulation in response to stress (15). The previous human studies related to the role of the PFC in cortisol regulation could find in functional neuroimaging studies investigating neural correlates of psychological stress processing (16–18). Previous neuroimaging studies of addictive behaviors have suggested a crucial role for the PFC in regulation of limbic regions and engagement of executive function, such as self-control, salience attribution, and awareness (19). In chronic drug use, it has been reported that corticolimbic areas such as the OFC and dorsal ACC located in midcingulate cortex (MCC) mediate processing of reward salience, motivation, and inhibitory control (20, 21). Previous studies have identified the OFC and ventral striatum (VS), including the nucleus accumbens (NAcc), as a set of reward-related brain structures (22), Another imaging study reported that compared with healthy controls, chronic cocaine abusers had lower metabolism in the right OFC and NAcc, which was related to cognitive inhibition (23). Previous structural neuroimaging studies have suggested the potential role of the NAcc in the excessive smartphone use. A diffusion tensor imaging (DTI) study has recently reported that individuals with smartphone dependence showed deficits in white matter structure such as internal capsule around NAcc, which was correlated with the severity of smartphone dependence (24). Moreover, another study revealed that high frequency of checking Facebook on the smartphone was associated with smaller gray matter volumes of the NAcc (25). Given the role of the OFC, MCC, and NAcc in reward processing and cognitive control, investigations of the functional connectivity among these regions has become key to understanding addictive behavior in excessive smartphone use.

Intrinsic functional connectivity acquired in resting-state fMRI can be defined as the temporal correlation of a neurophysiological marker measured in spatially different brain areas (26). Here, we focus on altered brain connectivity related to reward processing and cognitive control in the resting state in adolescents with excessive smartphone use compared with healthy controls. Additionally, we investigated correlations of functional connectivity of frontostriatal regions with Internet use withdrawal symptoms and increased cortisol concentrations.

METHODS

Participants

In this study, we enrolled adolescent boys and girls aged 12–18 years by using online recruiting. A total of 801 adolescents responded to the online survey of smartphone use, and 127 adolescents and their parents expressed willingness to participate in the fMRI study. Subsequently, participants were divided into two groups (adolescents with excessive smartphone use, SP, and healthy controls, HC) according to an assessment by a clinician on the basis of the Korean Smartphone Addiction Proneness Scale (SAPS) (27) for Youth (for full details see section Clinical

Assessments). Lastly, 80 adolescents passed MRI safety screening questionnaire.

The purpose and procedures of the study were explained to the participants and their parents prior to participation. Exclusion criteria involved past or current major medical disorders (e.g., diabetes mellitus), neurological disorders (e.g., seizure disorders, head injury) or psychiatric disorders (e.g., major mood disorders). All participants had normal or corrected-to-normal vision and were right-handed as evaluated by the Edinburgh Handedness Inventory (28).

For the fMRI study, 40 adolescents with SP (32 male and 8 female) and 40 HC (32 male and 8 female) were included. In order to screen out adolescents with current psychiatric diagnoses, all participants received the structured interview with the Korean Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS-PL) (29) through a clinician. Of the adolescents with SP, one participant was excluded because of depressive disorder. Moreover, data from three participants were excluded because of severe head motion during acquisition. Therefore, data from 38 adolescents with SP (32 male and 6 females, mean age: 14.90 ± 1.49 years) and 38 HC (30 male and 8 females, mean age: 14.12 ± 1.34 years) were included in the analysis (**Table 1**). Each participant 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 relevant guidelines and regulations.

Clinical Assessments

Excessive smartphone use was estimated with the Korean SAPS for Youth (27). Investigation of the reliability of the scale yielded a Cronbach's alpha of 0.88. The SAPS is a self-report scale that includes 15 items, and responses are scored on a four-point Likert scale (1: Not at all to 4: Always). The SAPS has four subscales: disturbance of adaptive functions, virtual life orientation, withdrawal, and tolerance. Participants were classified as SP if their total score exceeded 42, or if their subscale scores exceeded 14, 12, and 13 for disturbance of adaptive function, withdrawal, and tolerance, respectively. Otherwise, participants were classified as HC.

Additionally, severity of problematic Internet use was estimated with the Korean Internet Addiction Proneness Scale (the K-scale) developed by the South Korean government in 2002 (30). The K-scale includes 15 items and responses are scored on a four-point Likert scale (1: Not at all to 4: Always). The K-scale has seven subscales: daily life disturbance, disturbance of reality testing, automatic addictive thoughts, virtual interpersonal relationships, deviant behavior, and tolerance. The reliability and validity of the K-scale have been established for elementary school, and middle and high school students (31).

Finally, severity of depressive symptoms was assessed with the Beck's Depression Inventory (32) and severity of anxiety symptoms was assessed with the Beck's Anxiety Inventory (33). A brief assessment of Intellectual functioning was conducted using the Vocabulary and Block Design subtests of the Korean-Wechsler Intelligence Scale for Children, 4th edition (K-WISC- IV) (34). These two subtests have good reliability and high correlation with the full-scale scores of WISC (35). All participants completed the vocabulary and block design which were the subtests for the verbal comprehension index and perceptual reasoning index, respectively.

Physiological Assessments

Blood samples from all participants were collected in the afternoon (between 13:00 and 15:00) and kept at room temperature for 2 h before being centrifuged at 1,000x g for 15 min. The upper phase (serum) was transferred into a fresh tube. Serum was stored at −80°C until immunoassay was performed. Cortisol levels were analyzed with the Human Circadian/Stress Magnetic Bead Panel (HNCSMAG-35 K, EMD Millipore, Billerica, MA, USA) according to the manufacturer's instructions. In brief, 25 μL antibody-immobilized beads were added to each well containing standard and serum samples, and the plate was incubated overnight at 4°C. After washing with 200 μL wash buffer, 50 μL detection antibody was added to each well and the plate was incubated at room temperature for 1 h. Fifty microliters streptavidin-phycoerythrin was added to each well and the plate was incubated at room temperature for 30 min. After washing with 200 μL wash buffer, 150 μL sheath fluid was added to each well and the plate was read on the Luminex 200TM (EMD Millipore, Billerica, MA, USA).

MRI Data Acquisition

Functional and structural MRI data were acquired with a 3-Tesla MAGNETOM Verio system (Siemens, Erlangen, Germany) equipped with a 16-channel head coil. Participants' heads were cushioned with attached earmuffs. Functional images were obtained with a T2*-weighted gradient echo echo-planar imaging sequence: repetition time (TR) = 2,000 ms, echo time (TE) = 30 ms, voxel size = 3.59 × 3.59 × 3.60 mm, matrix size = 64 × 64, and slice number = 31. During scanning, participants were instructed to fixate their eyes on a crosshair and to remain as motionless as possible at rest. Structural images with a resolution of 1 × 1 × 1 mm were acquired with a 3D T1-weighted gradient echo sequence (176 slices, TR = 1,780 ms, TE = 2.22 ms, and image matrix = 256 × 256).

Functional Connectivity Analysis

Resting-state fMRI data were preprocessed with SPM12 (http://www.fil.ion.ucl.ac.uk/spm/). Functional images were corrected for slice-timing and head motion, and spatially normalized to the same coordinate frame as the Montreal Neurological Institute template brain. They were subsequently, spatially smoothed with a Gaussian kernel of 6 mm full width at half maximum. A nonlinear deformation field for spatial normalization was derived from the segmentation of the structural MRI volume coregistered to the mean of the realigned resting state fMRI volumes. Additionally, nuisance covariates, including six head movement parameters estimated during realignment of the functional images.

Region of interest (ROI)-to-ROI functional connectivity network analyses were performed with in-house software (the Intuitive Resting-state Functional Connectivity toolbox, iRSFC, https://github.com/skyeong/iRSFC) running on MATLAB

TABLE 1 | Demographic characteristics of the SP and HC.

	SP ($n = 38$)		NC ($n = 38$)		*t*-score
	Mean	**SD**	**Mean**	**SD**	
Age	14.95	1.45	14.08	1.28	2.77*
K- WISC: block design	8.87	2.36	10.84	2.50	−3.54*
K- WISC: vocabulary	10.32	2.90	11.18	2.98	−0.20
Gender					
Male	84.2% ($n = 32$)		78.9% ($n = 30$)		$x^2 = 0.35$
Female	15.8% ($n = 6$)		21.1% ($n = 8$)		
Time for smartphone using per week(h)	32.55	28.83	15.18	8.70	3.56**
SAPS	36.71	8.27	22.08	3.15	10.19**
Disturbance of adaptive function	13.42	3.09	8.13	1.65	9.31**
Withdrawal	8.45	3.78	5.32	1.40	4.79**
Tolerance	11.55	2.69	6.45	1.45	10.31**
K-scale	31.89	7.48	22.24	3.74	7.12**
Disturbance of adaptive function	9.82	3.19	7.05	1.77	4.67**
Withdrawal	8.87	2.45	6.37	1.85	4.96**
Tolerance	9.32	3.11	6.37	1.85	5.02**
BDI	12.26	9.61	6.34	4.80	3.40*
BAI	8.03	9.69	4.82	7.35	1.63

*SP, excessive smartphone use group; HC, Healthy control group; SAPS, Smartphone Addiction Proneness Scale; K-scale, Korean Internet Addiction Proneness Scale; BDI, Beck's Depression Inventory; BAI, Beck's Anxiety Inventory. *p< 0.01, **p< 0.001.*

R2011b (The MathWorks Inc., Natick, MA). First, linear trends of the time courses were removed and temporally band-pass filtered (0.009–0.08 Hz) to denoise the signals, removing physiological noise and low frequency signal drifts. Nuisance covariates, including six head movement parameters estimated during realignment of the functional images, as well as global, cerebrospinal fluid, and white matter signals were regressed out.

To construct each participant's ROI-to-ROI functional connectivity networks, we selected five ROIs as follows: the left OFC, right OFC, and midcingulate cortex (MCC) (**Figure 1**), extracted from the automated anatomical labeling (AAL) brain atlas (36), and the left and right NAcc (**Figure 1C**), extracted from the probabilistic Harvard-Oxford subcortical atlas (thresholded at 50%). We focused on the OFC because of its role in cognitive regulation (37) and decision making (38). Moreover, it has been reported that the MCC in AAL brain atlas, a key region comprising the salience network (39), is implicated in conflict monitoring (40). We generated specifically the MCC ROI, based on the AAL brain atlas, which is combined the left and right hemispheres because the MCC is located to medial section in the brain. Given reward and stimuli sensitivity observed in excessive smartphone users, we focused on the role of the NAcc related to reward processing (41, 42) or reward expectation (43). We calculated correlation coefficients between the time series of these five regions, which were then transformed to z-values by using Fisher r-to-z transformation. The outputs of the ROI-to-ROI functional connectivity network analyses represent the matrix of the connection strength between the five ROIs.

A two-sample *t*-test was conducted on each participant's functional connectivity network for group comparisons. We analyzed functional connectivity between ROIs within hemispheres because of probability of functional lateralization that have been reported in previous studies (44, 45). The significance level was determined at a *p*-value of 0.05 with the false discovery rate procedure for correcting multiple comparisons over the ROIs in each hemisphere. Furthermore, we examined the relationship between Internet use withdrawal, cortisol levels, and functional connectivity strength in each group. Results of the correlation analyses were transformed to z scores using Fisher's r-to-z for group comparisons.

RESULTS

Clinical and Physiological Data

Table 1 present the demographic and clinical characteristics of the two groups. The two groups did not show significant differences in scores for the vocabulary subtest of the K-WISC, the distribution of gender, the BAI scores and cortisol concentrations. Compared to HC, the SP was significantly greater in age [$t_{(74)} = 2.77$, $p < 0.01$], time spent using a smartphone per week [$t_{(74)} = 3.56$, $p < 0.005$], SAPS scores [$t_{(74)} = 10.19$, $p < 0.001$], K-Scale scores [$t_{(74)} = 7.12$, $p < 0.001$], and BDI scores [$t_{(74)} = 3.40$, $p < 0.005$] and lower in scores for block design subtest of the K-WISC [$t_{(74)} = -3.54$, $p < 0.005$]. In particular, adolescents with SP, compared to HC, had greater scores for disturbance of adaptive functions [$t_{(74)} = 9.31$, $p < 0.001$], withdrawal [$t_{(74)} = 4.79$, $p < 0.001$], and tolerance [$t_{(74)} = 10.31$, $p < 0.001$] subscales of the SAPS. Similarly, adolescents with SP, compared to HC, had greater scores for disturbance of adaptive functions [$t_{(74)} = 4.67$, $p < 0.001$], withdrawal [$t_{(74)} = 4.96$, $p < 0.001$], and tolerance [$t_{(74)} = 5.02$, $p < 0.001$] subscales of the K-Scale.

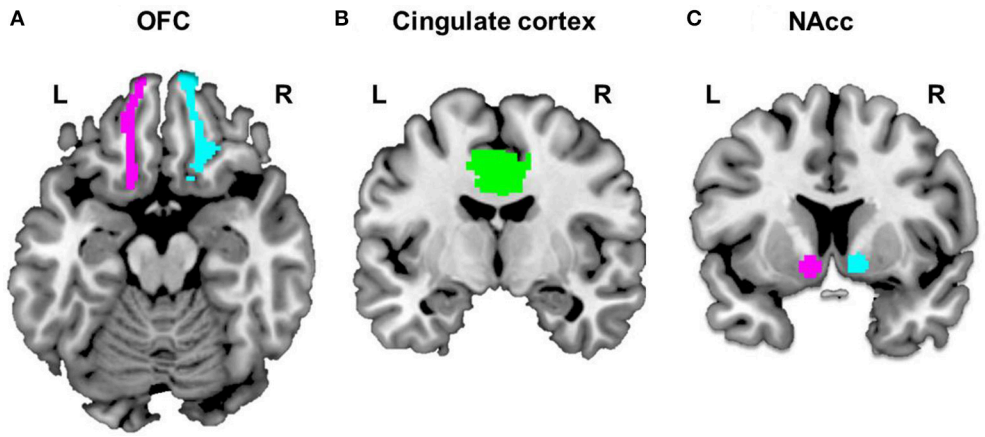

FIGURE 1 | Selected ROIs. Five regions of Interest (ROIs) were selected to construct each subject's ROI-to-ROI as follows: the bilateral OFC **(A)** and cingulate cortex **(B)**, extracted from the automated anatomical labeling (AAL) brain atlas and bilateral NAcc **(C)**, extracted from the probabilistic Harvard-Oxford subcortical atlas (thresholded at 50%).

Functional Connectivity

Figure 2 present group differences in ROI-to-ROI functional connectivity. To explore brain imaging markers underlying excessive smartphone use, we examined functional connectivity between the left and right OFC, MCC, and left and right NAcc in each hemisphere in adolescents with SP and HC. In the right hemisphere, we observed weaker the right OFC connectivity with the right NAcc in adolescents with SP compared with HC [$t_{(74)} = -2.25$, corrected $p < 0.05$], whereas there was stronger connectivity between the right NAcc and MCC in adolescents with SP compared with HC [$t_{(74)} = 2.42$, corrected $p < 0.05$]. There was no significant difference in the right OFC and MCC connectivity between the two groups. In the left hemisphere, adolescents with SP had lower connectivity between the left OFC and MCC compared with HC [$t_{(74)} = -2.47$, corrected $p < 0.05$]. There were no other significant differences observed in the left hemisphere.

To consider the effect of potential confounds in group comparisons, we performed ANCOVA with age, the scores of the block design and BDI as covariate of no interest to adjust for the effects of the clinical variables when comparing the functional connectivity between the two groups. The functional connectivity between the right OFC and right NAcc [$F_{(1,73)} = 5.79$, $p < 0.05$], the right NAcc and MCC [$F_{(1,73)} = 5.61$, $p < 0.05$], and the left OFC and MCC [$F_{(1,73)} = 4.87$, $p < 0.05$] were still significantly different between the two groups, after adjusting for age. When adjusting for the BDI scores, between-group differences in functional connectivity between the right NAcc and MCC [$F_{(1,73)} = 4.93$, $p < 0.05$], and the left OFC and MCC [$F_{(1,73)} = 5.47$, $p < 0.05$] remained significant, but the right OFC-NAcc functional connectivity showed a trend toward significance [$F_{(1,73)} = 3.49$, $p = 0.066$]. Lastly, after adjusting for the scores of the block design, between-group differences in functional connectivity between the right OFC and NAcc [$F_{(1,73)} = 4.17$, $p < 0.05$] and the right NAcc and MCC [$F_{(1,73)} = 5.42$, $p < 0.05$] presented significance, whereas the left OFC-MCC functional connectivity was not significantly different between the groups [$F_{(1,73)} = 2.39$, $p = 0.126$].

Correlations

Figure 3 presents the results of the correlation analyses between withdrawal symptoms, cortisol concentrations, and the left frontostriatal connectivity. The relationship between Internet use withdrawal symptoms and cortisol concentrations was significantly correlated in adolescents with SP ($r = 0.33$, $p < 0.05$), but not in HC did not ($r = -0.07$, $p = 0.68$), and the correlation coefficients were statistically different between the two groups ($z = 1.73$, $p < 0.05$). Internet use withdrawal symptoms was negatively correlated with the left frontostriatal connectivity in the adolescents with SP ($r = -0.40$, $p < 0.05$), but not in HC ($r = -0.04$, $p = 0.80$), whose correlation coefficients was significantly different between the groups ($z = 1.6$, $p < 0.05$). Lastly, the left frontostriatal connectivity was negatively correlated with cortisol concentrations in adolescents with SP ($r = -0.43$, $p < 0.01$), not in HC ($r = -0.18$, $p = 0.48$). However, these correlation coefficients were not significantly different between the groups ($z = -1.43$, $p = 0.07$).

DISCUSSION

In recent years, the use of smartphones has increased rapidly, and the negative phenomenon of excessive use of smartphones, including dependency, problematic use, and addictive behaviors (46), have been reported. Excessive Internet and smartphone use has become problematic for adolescents who may experience negative emotional, cognitive, and physical states during and after use (46). Resting-state connectivity analysis allows us to identify altered intrinsic functional connectivity in brain regions associated with cognitive control and affective-motivational processes in adolescents with excessive smartphone use (47). In this study, we aimed to identify altered brain connectivity associated with excessive smartphone use, and

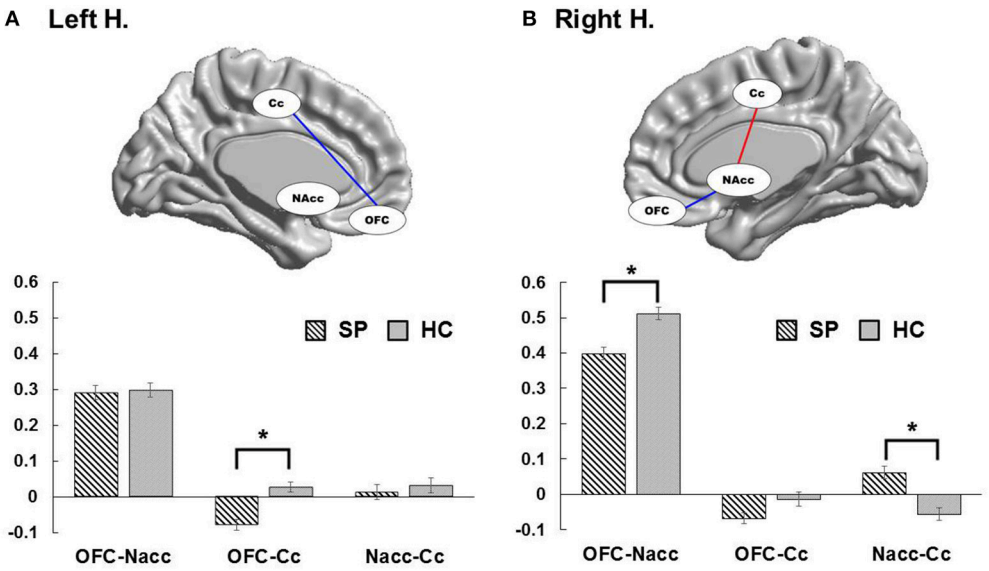

FIGURE 2 | Group differences of functional connectivity in each hemisphere. In the left hemisphere, adolescents with SP had decreased connectivity between the OFC and cingulate cortex compared with HC **(A)**. In the right hemisphere, adolescents with SP showed weaker OFC connectivity with the NAcc in compared with HC, whereas they revealed stronger connectivity between the NAcc and cingulate cortex in compared with HC **(B)**.

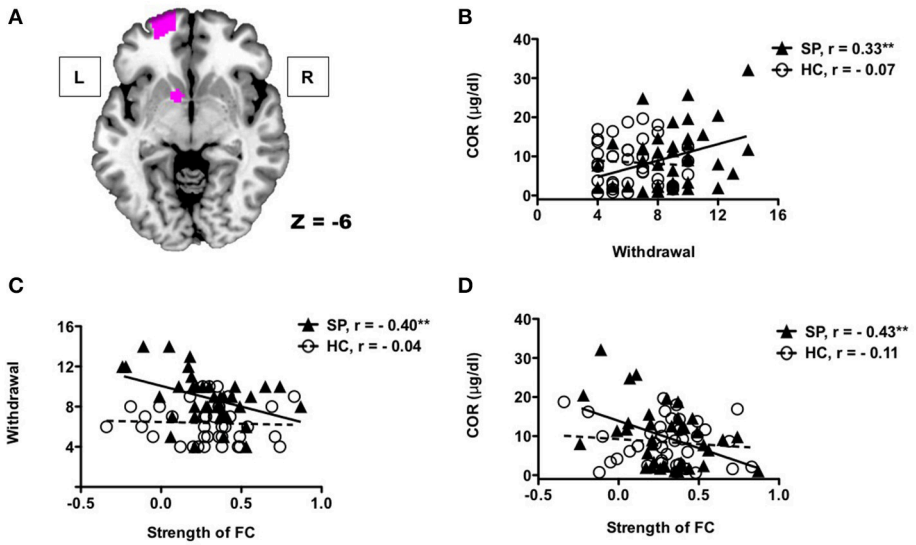

FIGURE 3 | Correlations between withdrawal symptoms, cortisol concentrations, and functional connectivity The left OFC and NAcc **(A)**. Adolescents with SP showed positive correlation between Internet use withdrawal symptoms and cortisol concentrations **(B)**. There were significant correlations between frontostriatal connectivity of the left hemisphere and Internet use withdrawal symptoms **(C)**, and between frontostriatal connectivity and cortisol concentrations **(D)** in adolescents with SP.

investigated correlations among withdrawal symptoms, cortisol concentrations, and frontostriatal connectivity.

The results of this study indicated that adolescents with SP had lower functional connectivity between the right OFC and NAcc, and between the left OFC and MCC. It is known that brain development in adolescence is associated with gradual improvements in cognitive control, which is related to PFC involvement. However, there is also heightened reward responsiveness to social and affective stimuli related to increased activity in the VS (47). Previous studies have reported that the NAcc is linked to reward anticipation and the OFC is related to decision making in reward processing (48–50). These previous findings highlight that the NAcc may be responsible for affective signals of reward and use these to modulate learning of reward associations (51, 52). In contrast, the OFC mostly monitors and evaluates reward outcomes (51, 52). Given the role of the PFC

and VS in reward processing, weakened connectivity between the PFC, including the OFC, and the VS might cause impaired top-down executive control of impulsiveness. Moreover, in the previous study using DTI, SP had significantly lower white matter integrity in internal capsule compared to HC, which was associated with the severity of smartphone dependence (24). These previous results are consistent with our findings related to functional abnormality in NAcc.

In a previous structural imaging study, participants with internet gaming disorder had reduced gray matter volumes in the ACC and orbitofrontal PFC, suggesting that internet gaming disorder is related to both functional and structural alterations in frontocingulate regions (53). Moreover, previous research has suggested that cocaine abusers have reduced OFC responsivity when controlling drug-taking behavior (54), and research using positron emission tomography identified decreased metabolism in the OFC induced by inhibition cues of craving (23). In previous studies of substance addiction, reduced regional activity in the OFC and cingulate gyrus were associated with decreased dopamine function (55). Previous findings also suggest that dopamine responses in individuals with substance abuse induced functional impairment of the OFC and ACC similar to those in patients with depression (56). Moreover, in a study using emotional faces, individuals with SP showed lower activity in frontocingulate regions compared with healthy individuals (57). Therefore, it could be supposed that intrinsic functional connectivity between the OFC and NAcc, and between the OFC and MCC are connected with cognitive control of emotional stimuli including reward. Our results indicated that adolescents with excessive smartphone use revealed lower functional connectivity in regions related to cognitive control compared to HC.

In the results of the group comparisons including covariates, we did not observe the functional connectivity between left OFC and MCC following adjustment for the scores of the block design. Block design is designed to assess problem solving, space perception, and visual processing. This finding, thus, could explain that intelligence domain related to perceptual reasoning might be associated with the frontocingulate connectivity implicated in cognitive control. In the further work, it would be important to investigate the effect of smartphone dependency on the association between perceptual reasoning and prefrontal functional connectivity. We also observed the marginal effect of the BDI on the group difference in the right frontostriatal connectivity. Given the previous results reporting the relationship between depression and IA (58, 59), the functional connectivity study related to depression in adolescents with smartphone dependency would seem to be worth.

In this study, functional connectivity between the MCC and NAcc was greater in adolescents with SP compared with HC. The role of dorsal ACC located in MCC includes monitoring for cognitive control (40) and guiding reward-based decision making (60). Moreover, the MCC, which is related to salience of stimuli, regulates responses by providing updated predictions of expected cognitive demands (61). In terms of functional connectivity with the NAcc, it could suggest that the MCC plays a role in monitoring signals related to reward. Therefore, greater functional connectivity between the MCC and NAcc in adolescents with SP compared with HC may reflect heightened monitoring based on reward processing in the resting state.

Adolescents are more likely to exhibit problematic smartphone use patterns after substituting a smartphone for the Internet (62). In this study, we identified that higher withdrawal symptoms were related to higher cortisol concentrations in adolescents with SP compared to HC. It was reported that withdrawal induced by drug involve the emergence of negative emotion state, characterized by an inability to experience pleasure from common non-drug related rewards. (56). Previous research suggests that the central pathology underlying IAD might be more similar to addiction than a disorder of impulse control (7). The Internet use withdrawal symptoms were correlated with both left frontostriatal connectivity and cortisol concentrations in adolescents with SP compared to HC. Cortisol plays a key role in the physical adaptation to increased energy demands during stress period (15). In a previous study, patients undergoing alcohol withdrawal showed increased cortisol concentrations (63). It was known that the OFC collect and integrate sensory information from the body and the environment, and participates in controlling one's emotional state (64). In the previous study, decreased OFC activity is connected with increased cortisol level in response to a stress task (65). It was reported that cortisol induced coordinated stress response in the PFC (66). Given the role of the OFC in cortisol secretion (67, 68), Internet use withdrawal symptom will likely lead to cortisol secretion, and this psychophysiological change might subsequently affect frontostriatal connectivity. In the frontostriatal connectivity, we focused on the role of NAcc in reward processing. Previous research using reward paradigms have reported enhanced neural activity in the VS of adolescents in response to monetary rewards (69), and it was suggested that this activity related to heightened sensitivity to social reward (3). Social reward sensitivity might be a strong motivation for social media use and could instigate Internet use via a smartphone in adolescents. Therefore, it could explain that the negative correlation between the frontostriatal connectivity and withdrawal symptoms in SP is related to cognitive deficits of reward responsiveness that accompany withdrawal from smartphone dependence.

A smartphone has included various applications that require Internet access (24). Thus, excessive smartphone use could cause physical, mental and psychosocial problems similar to Internet addiction (70). On the other hands, it has been reported that the specific sources of addictive content were difference between excessive smartphone use and Internet addiction (71). In this study, we investigated excessive smartphone use including Internet use. Smartphone is almost portable, have quick access to information, and communicate instantly. Therefore, it can be inferred that the results of this study reflect factors related to immediate and sustained response compared to widespread Internet addiction.

Finally, several important limitations need to be considered. First, although we controlled for comorbidities such as attention deficit hyperactivity, depression, and anxiety through

clinical interviews, various psychological and environmental variables of participants were not considered. Second, the main contents of the smartphone use were not considered in this study. A future study with a stronger focus on the effect of the specific content of smartphones, such as games or social network service, is therefore required. Lastly, we have to consider further work associated with a longitudinal study of the brain development in adolescents in other to validate the cause and effect of excessive smartphone use.

In summary, we used a functional connectivity analysis to identify regional connectivity related to cognitive control and reward prediction in adolescents with SP, and investigated functional connectivity in such adolescents compared with HC. In adolescents with SP, functional connectivity between the OFC and NAcc, and between the OFC and MCC was lower compared to HC. Furthermore, we observed less functional connectivity between the OFC and NAcc related to withdrawal symptoms and cortisol secretion. Our findings suggest that excessive smartphone use is related to altered functional connectivity between regions related to cognitive control and reward prediction. The understanding the brain regions that show altered functional connectivity might be helpful for developing effective interventions to control Internet use in adolescents.

AUTHOR CONTRIBUTIONS

D-JK and J-WC contributed to the conception and design of study. J-WC and JC contributed to the acquisition of imaging data. HC undertook the clinical assessments. J-WC and JC performed imaging data analysis. J-WC wrote the manuscript including the figures and tables. JC and M-RC assisted with the explanation of data and contributed to the final draft of the manuscript. HC, K-JA, J-SC, and D-JK contributed revising the manuscript logically for important theoretical content. All authors contributed to the manuscript and have approved the final manuscript.

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Altered Prefrontal and Inferior Parietal Activity During a Stroop Task in Individuals With Problematic Hypersexual Behavior

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Accumulating evidence suggests a relationship between problematic hypersexual behavior (PHB) and diminished executive control. Clinical studies have demonstrated that individuals with PHB exhibit high levels of impulsivity; however, relatively little is known regarding the neural mechanisms underlying impaired executive control in PHB. This study investigated the neural correlates of executive control in individuals with PHB and healthy controls using event-related functional magnetic resonance imaging (fMRI). Twenty-three individuals with PHB and 22 healthy control participants underwent fMRI while performing a Stroop task. Response time and error rates were measured as surrogate indicators of executive control. Individuals with PHB exhibited impaired task performance and lower activation in the right dorsolateral prefrontal cortex (DLPFC) and inferior parietal cortex relative to healthy controls during the Stroop task. In addition, blood oxygen level-dependent responses in these areas were negatively associated with PHB severity. The right DLPFC and inferior parietal cortex are associated with higher-order cognitive control and visual attention, respectively. Our findings suggest that individuals with PHB have diminished executive control and impaired functionality in the right DLPFC and inferior parietal cortex, providing a neural basis for PHB.

Keywords: problematic hypersexual behavior, executive control, Stroop task, functional magnetic resonance imaging, dorsolateral prefrontal cortex, inferior parietal cortex

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INTRODUCTION

Problematic hypersexual behavior (PHB) refers to the inability of an individual to control inappropriate or excessive sexual fantasies, urges, or behaviors that cause subjective distress or impairments in daily functioning (1–3). Individuals with PHB can contract sexually transmitted diseases or experience unwanted pregnancies from promiscuous sexual relations (4, 5). PHB typically begins in late adolescence or early adulthood, is thought to be chronic or episodic, and mainly affects men (4). The disorder has an estimated prevalence of 3–6% among the community and college students in the US (6–8). In Korea, about 2% of all college students have PHB (9).

The nosology and optimal diagnostic criteria for PHB remain controversial. Whether PHB can be conceptualized as a behavioral addiction, impulse control disorder, or another psychiatric disorder continues to be a topic of debate (10). Regardless of whether PHB is best described as one of those disorders, it shares similar psychological characteristics (i.e., craving, withdrawal, and

loss of control) with other forms of problematic excessive behavior, such as gambling disorder and internet gaming disorder (3, 11–14).

Addictive and compulsive behaviors including gambling disorder and internet gaming disorder have been speculated to be related to a loss of control. Specifically, loss or impairment of executive control is a critical characteristic of problematic excessive behavior. Indeed, previous studies have identified a significant correlation between the two (15, 16). A study on pathological gambling demonstrated that individuals with the disorder performed poorly on the reverse Stroop task (16), suggesting that pathological gambling behavior may be due to impaired executive control, which results in an inability to inhibit irrelevant information during such tasks. Similarly, another study revealed that relative to control participants, individuals with internet gaming disorder exhibited impaired executive control associated with diminished medial frontal activation (15).

Emerging evidence also suggests that executive control impairments occur in PHB (17, 18). One brain imaging study demonstrated that participants with PHB had difficulties with impulse control in a go/no-go task and exhibited a higher degree of mean diffusivity in the superior frontal region (17). In a pilot study, Reid et al. (18) used questionnaire responses to identify a specific relationship between executive control and PHB, observing an association between diminished executive control and PHB; however, contradictory results were obtained in a subsequent study (19) that utilized standardized neuropsychological tests to assess executive control.

Since executive function results among individuals with PHB are inconsistent, additional works need to be conducted to provide conclusive findings. Therefore, our aim was to resolve the aforementioned discrepancies among previous studies by using psychological tests and neuroimaging.

The color-word Stroop test was initially designed to assess executive control ability and has generally been used to identify individuals with brain damage that has affected interference-control processing (20). In the Stroop task, participants are instructed to name the font color of a series of color words, and the response time and error rate are used as outcome measures. Since word reading is a more dominant process than color naming in incongruent conditions (e.g., RED printed in blue font), participants exhibit longer reaction times and higher error rates than in congruent conditions (e.g., RED printed in red ink). Several neuroimaging studies have demonstrated that the Stroop task activates a distributed neural network of brain regions including the prefrontal cortex, parietal lobe, motor areas, and temporal lobe (21–23).

The most consistently supported finding is that the prefrontal cortex plays a key role in Stroop performance (24). This area is involved in executive functions and other higher-order cognitions, which are the main neural correlates of problematic excessive behavior (14). Several researchers have reported that individuals with problematic excessive behavior have anatomical and functional disruptions in the prefrontal cortex. This region is known to be implicated in impulse regulation, so disruptions in this area underlie problematic excessive behavior and account for the erosion of free will (25).

Since the Stroop task requires executive control ability and individuals with PHB have decreased control over their sexual behaviors, we hypothesized that the PHB group would show poorer Stroop task performance compared to the control group. Specifically, these differences would be larger in the incongruent condition. We also predicted that there would be larger differences in brain activations associated with executive control, such as in the prefrontal cortex.

MATERIALS AND METHODS

Participants

This study was approved by the Institutional Review Board of Chungnam National University (Approval number: 201309-SB-003-01; Daejeon, S. Korea), and all participants provided written informed consent prior to enrollment. Twenty-three men with PHB (mean age = 26.12, SD = 4.11) and 22 healthy men (mean age = 26.27, SD = 3.39) participated in the functional magnetic resonance imaging (fMRI) experiment. Some of the participants attended in another study, i.e., the sexual craving experiment conducted in our laboratory (26). Roivainen (27) reviewed recent large-scale studies and found gender differences in processing speed and cognitive factors. Specifically, females have advantages in processing speed tests involving alphabets and rapid naming tasks while males are faster with reaction time tasks and finger tapping. Given these known gender disparities, we chose to include a male-only group in our study.

All participants were right-handed, native Korean speakers, and had no past or present major neurological injury or illness as evaluated with a self-report questionnaire. Prior to inclusion in the study, an experienced psychiatrist administered structured psychiatric interviews to all participants using the proposed PHB diagnostic criteria utilized in previous studies (2, 28) and the DSM-5 criteria (Supplementary Materials, **Table S1**). Individuals with PHB met the proposed PHB diagnostic criteria and were free from any other axis I disorder based on the DSM-5 (29). All PHB participants were not involved in any treatment for their disorder.

Twenty-two healthy controls with similar demographics to those of the subjects were recruited from the community via advertisements and flyers.

The Sexual Addiction Screening Test-R (SAST) (28) and the Hypersexual Behavior Inventory (HBI) (30) were used to examine PHB severity in each participant and to identify any relationship between PHB severity and neural responses to the Stroop interference task. The reliability of the SAST-R and HBI have been previously calculated as Cronbach's $\alpha = 0.91$ and 0.96, respectively (28, 30). The SAST-R contains 20 questions designed to assess sexual addiction tendencies; total scores range from 0 to 20 points, with higher scores indicating more severe addiction. The HBI comprises 19 questions, and the total score ranges from 19 to 95 points. Reid et al. (30) suggested a total score $\geq$53 as the cutoff for hypersexual disorders. All PHB participants in this

Abbreviations: DLPFC, dorsolateral prefrontal cortex; EPI_BOLD, echo-planar imaging blood oxygen level-dependent; HBI, Hypersexual Behavior Inventory; PHB, problematic hypersexual behavior; SAST: Sexual Addiction Screening Test.

study scored above the cutoff for HBI. Individuals with PHB had an average SAST-R score of 11.3 (SD = 3.3) and an average HBI score of 54.4 (SD = 7.3).

Participant demographic characteristics and sexual activity information for the previous 6 months are presented in **Table 1**. The PHB group showed significantly earlier age of first sexual intercourse and more number sexual partners, frequent sexual intercourse, masturbation, and viewing pornography per week compared to the control group. Also, PHB group showed significantly higher score on SAST-R and HBI.

Task and Experimental Paradigm

The Stroop test is named after John Ridley Stroop (31), who is credited with the first English publication of the effects associated with incongruent stimuli. The present study used a modified version of the Stroop task developed by Peterson et al. (32) during fMRI scanning. Participants held one of two keypads, each equipped with two response buttons, in each hand. We tried to eliminate any effects (e.g., effect of handedness, Simon effect) that was induced during the experiment. To eliminate the effects, we had 24 different stimuli per one word that show the location of the color button on the keypad. The one example out of 24 stimuli is the **Figure 1** as the order of color button was Red, Yellow, Green, Blue. During the experiment, the order of color button was randomly presented out of 24 stimuli per each trial. By repeating the task, we were also able to collect more data to increase the reliability of the results. Participants practiced one run before the scanning session, and they all indicated that they had a clear understanding of the task. Stimuli were presented via an overhead mirror during fMRI scanning.

The Stroop task was divided into congruent and incongruent conditions. In the congruent condition, a word in a semantically matched color (e.g., the word "RED" in red color) was displayed on a screen, and participants were instructed to press the corresponding color button as quickly as possible. In the incongruent condition, a word with unmatched meaning and color (e.g., the word "RED" in yellow color) was displayed on the screen, and participants were instructed to press the color button that corresponded to the color of the word while ignoring the meaning of the word. The target stimulus was presented in the center of the display screen. Four possible answers (color words in white font) were presented above it (in the upper visual field) to minimize contextual memory demands, as shown in **Figure 1**.

The order of events and time for each condition were as follows: (1) first, an instruction alerting the participant to the start of the experiment was presented for 6 s; (2) second, an empty black screen was presented for a random interval of 400–1,000 ms as the inter-stimulus interval; (3) third, a stimulus (congruent trial or incongruent trial) was presented for 1,300 ms; and (4) lastly, an empty screen was presented again for 4,000 ms.

The Stroop task of the present study was designed as an event-related paradigm and comprised 130 congruent conditions plus 85 incongruent conditions presented in a randomized order. The task was repeated twice, and each task lasted 444 s. Examples of the Stroop stimuli and the fMRI paradigm are shown in **Figure 1**.

Imaging Acquisition

An echo-planar imaging blood oxygen level-dependent (EPI-BOLD) method was used to acquire brain images. The parameters for image acquisition were as follows: repetition time/echo time = 2,000/28 ms; field of view = 240 × 240 mm; matrix size = 64 × 64; slice thickness = 5 mm, no gap; and flip angle = 80°. The overall volume of each experimental session was 222 images, and included three dummy images acquired

TABLE 1 | Demographic characteristics.

	Control group (n = 22)	PHB group (n = 23)	t-values or chi-square values
Age (years)	26.3 (3.4)	26.1 (4.1)	
MARITAL STATUS[a]			
Single	50.0	47.8	0.30
In a relationship	41.0	43.5	
Engaged/Married	9.0	8.7	
Education (years)	16.3 (3.0)	15.6 (4.1)	0.65
WAIS-R total IQ[b]	108.2 (7.1)	110.3 (7.6)	0.95
Age of first sexual intercourse (years)	20.3 (3.7)	16.7 (5.9)	2.44*
SEXUAL RELATIONSHIP STATUS[a]			
Exclusive	50.0	30.4	2.06
Non-exclusive	13.6	56.5	
Not sexually active	36.4	13.1	
Number of sexual partners[b]	2.5 (3.5)	20.9 (27.5)	3.11**
Frequency of sexual intercourse per week[b]	0.5 (0.7)	3.7 (2.6)	5.58***
Frequency of masturbation per week[b]	1.7 (0.9)	5.1 (3.2)	4.80***
Frequency of viewing pornography per week[b]	2.3 (0.6)	5.5 (2.7)	5.42***
SAST–R[b]	0.5 (0.9)	11.3 (3.3)	14.82***
HBI[b]	26.9 (13.5)	54.4 (7.3)	8.55***

PHB, Problematic Hypersexual Behavior; WAIS-R, Wechsler Adult Intelligence Scale-Revised; SAST-R, Sexual Addiction Screening Test revised; HBI, Hypersexual Behavior Inventory.

[a]Data are presented as percentages of the total cohort and analyzed using a chi-square test.

[b]Data are represented as means with standard deviations and analyzed using an independent sample t-test. Data reflect information regarding behaviors in the previous 6 months.

**p < 0.05, **p < 0.01, and ***p < 0.001.*

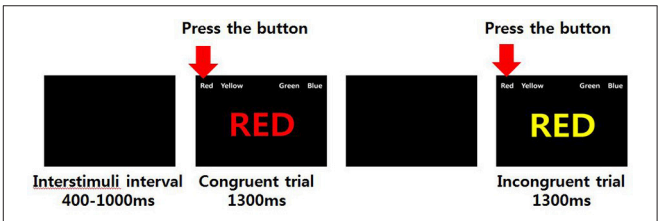

FIGURE 1 | Examples of congruent and incongruent conditions in the Stroop task.

across 6 s. T1-weighted images were collected as structural images with the following acquisition parameters: repetition time/echo time = 280/14 ms; FOV = 240 × 240 mm, matrix size = 256 × 256; slice thickness = 4 mm; and flip angle = 60°. The imaging plane was positioned parallel to the anterior commissure-posterior commissure line.

Statistical Analyses

Behavioral Data Analysis

The mean response times and percentages of correct responses were calculated in each condition. To normalize the distribution of response time data, we transformed the response time using the following equation: log (1/response time) (33). The log-transformed response time was used for the two-way analysis of variance (ANOVA) with group as the between-subjects factor (i.e., participants with PHB vs. healthy controls) and condition as the within-subjects factor (i.e., congruent vs. incongruent stimuli).

The percentages of correct responses (i.e., hit rates) between conditions in each group and between groups in each condition were analyzed non-parametrically using the Wilcoxon rank sum test or Mann-Whitney U test ($p < 0.05$). All analyses were conducted using SPSS version 20.0 (IBM Corp., Armonk, NY, USA).

Imaging Data Analysis

Statistical Parametric Mapping version 8 (SPM 8, Wellcome Department of Imaging Neuroscience, London, UK) was used to analyze brain imaging data. Functional data were realigned to the first scan of each session as a reference using three-dimensional rigid body registration with six degrees of freedom. Then, the realigned scans were coregistered to each participant's anatomical image and normalized to the MNI (Montreal Neurologic Institute) coordinate system. To decrease spatial noise, data were smoothed using an 8-mm isotropic Gaussian kernel.

After preprocessing, a design matrix was constructed for each condition in each participant. When constructing the design matrix, degrees of head movement/rotation during head movement compensation were added as regression variables to increase the signal-to-noise ratio. Then, z-maps were generated according to the stimulus condition (congruent and incongruent) for each individual. To identify specific brain regions exhibiting different patterns of activity between individuals with PHB and healthy controls, an ANOVA was conducted using condition (congruent vs. incongruent) as the within-group variable and group (individuals with PHB vs. controls) as the between-group variable [false discovery rate (FDR)-corrected, $p < 0.05$].

Based on previous neuroimaging studies on Stroop task and addicts and the results of the ANOVA, the dorsolateral prefrontal cortex (DLPFC) and inferior parietal cortex were selected as regions of interest (ROIs) (21–25).

To extract percent signal changes from ROIs, the MarsBaR 0.42 program (http://www.sourceforge.net/projects/marsbar) was used in an SPM toolbox (http://www.fil.ion.ucl.ac.uk/spm/ext). The ROIs were defined by centering spheres on the respective peak voxels with a radius of 5 mm for all activated areas in the interaction results (FDR-corrected, $p < 0.05$). To compare these values between groups with follow-up t-tests, the percent signal change was extracted for each subject, and a two-way ANOVA was performed using SPSS version 20. To evaluate the relationship between PHB severity and neural responses to the Stroop interference, correlation analyses were performed between percent signal changes from the ROIs during the incongruent condition and the scores of standardized measurements (i.e., SAST-R and HBI scores).

RESULTS

Behavioral Results

A two-way ANOVA revealed a significant main effect of condition [$F_{(1,43)} = 171.43$, $p < 0.001$, Cohen's $f = 3.99$], indicating that the response was generally slower in the incongruent condition compared to that in the congruent condition. There was no significant interaction effect between condition and group [$F_{(1,43)} = 0.34$] or main effect of group [$F_{(1,43)} = 1.98$, **Figure 2**].

The non-parametric Wilcoxon test indicated a significant accuracy difference between the congruent and incongruent conditions in both the PHB ($Z = -6.39$, $p < 0.05$) and control ($Z = 5.71$, $p < 0.05$) groups, indicating that there

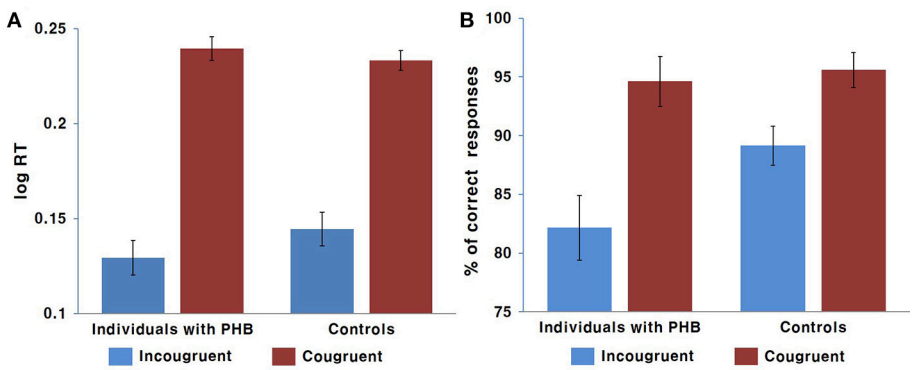

FIGURE 2 | Behavioral results. **(A)** Mean response time in ms. **(B)** Mean response accuracy as a percentage. Error bars indicate the standard error of the mean.

was generally a higher incidence of error responses in the incongruent condition. We also identified significant differences in performance accuracy between groups for the incongruent condition ($Z = -2.12$, $p < 0.05$), indicating that the healthy controls performed better than the PHB group; however, there were no significant between-group differences in response accuracy for the congruent condition ($Z = -1.48$, **Figure 2**). These data indicate that both groups responded accurately to congruent conditions, whereas participants with PHB were more likely to respond inaccurately in conditions that required inappropriate incongruent effects to be ignored.

Imaging Results

Main Effect of Condition

A main effect of condition (congruent vs. incongruent) was observed in the right putamen, right middle frontal gyrus, and right inferior frontal gyrus ($p < 0.05$, FDR-corrected; **Table 3**). These regions exhibited greater activation under incongruent than under congruent conditions. However, no brain regions were activated more by the congruent than by the incongruent condition.

Main Effect of Group

A main effect of group (PHB group vs. controls; $p < 0.05$, FDR-corrected; **Table 2**) was observed in the bilateral inferior parietal areas, right middle frontal gyrus, and right inferior frontal gyrus. The control group exhibited increased activation in the bilateral inferior parietal areas and the right middle and inferior frontal gyri relative to the PHB group ($p < 0.05$, FDR-corrected; **Table 3**). No brain regions were activated more in the PHB group than in controls.

Condition × Group Interaction Effects

Significant condition × group interactions ($p < 0.05$, FDR-corrected; **Table 4**, **Figure 3**) were identified in the right DLPFC and right inferior parietal cortex.

In follow-up *t*-tests using the extracted BOLD signal changes for each ROI, participants with PHB exhibited significantly less activation in the right DLPFC in the incongruent condition [$t_{(43)} = 4.46$, $p < 0.01$, Cohen's $d = 1.33$] relative to healthy controls, whereas no significant group difference was found in the congruent condition [$t_{(43)} = 0.48$, $p > 0.05$, Cohen's $d = 0.14$; **Figure 3a**]. A similar pattern of brain activation was observed in the right inferior parietal cortex: Compared to controls, individuals with PHB exhibited diminished activation in the right inferior parietal cortex during the incongruent conditions [$t_{(43)} = 4.28$, $p < 0.01$, Cohen's $d = 1.28$], but no significant group difference was observed during the congruent conditions [$t_{(43)} = 0.60$, $p > 0.05$, Cohen's $d = 0.18$; **Figure 3b**].

Correlation Analyses

To confirm the functions of ROIs in cognitive control, we conducted the correlation analyses between the behavioral data (i.e., response time and response accuracy) and BOLD signal changes for each ROI (i.e., the right DLPFC and right inferior parietal cortex). There are significant correlations between them (Supplementary Materials, **Figure S1**).

The relationship between standardized measurement scores (i.e., SAST-R and HBI scores) and BOLD signal changes for each ROI (i.e., the right DLPFC and right inferior parietal cortex) were calculated for all participants with PHB. Negative correlations were observed between standardized measurement scores and BOLD signal changes in the right inferior parietal cortex (SAST-R: $r = -0.64$, $n = 23$, $p < 0.01$; HBI: $r = -0.48$, $n = 23$, $p < 0.01$) and right DLPFC (SAST-R: $r = -0.51$, $n = 23$, $p < 0.01$; HBI: $r = -0.61$, $n = 23$, $p < 0.01$; **Figure 4**).

TABLE 2 | Mean hit rates and response latencies in Stroop test conditions.

	Control group ($n = 22$)	PHB group ($n = 23$)
Hit rate in congruent conditions	97.35 (3.29)	95.74 (8.99)
Hit rate in incongruent conditions	89.45 (14.37)	82.14 (22.01)
Response time in congruent conditions	601.77 (81.44)	602.04 (61.44)
Response time in incongruent conditions	762.00 (140.14)	784.35 (126.27)

TABLE 3 | Imaging results: main effects of condition and group ($p < 0.05$, FDR-corrected).

Brain regions	Side	No. of voxels in cluster	*F*	x, y, z MNI coordinates		
MAIN EFFECT OF CONDITION						
Incongruent > Congruent						
Putamen	R	63	2.61	30	−8	−6
Middle/inferior frontal gyrus	R	51	3.07	52	14	30
(BA 8, 9, 47)		33	2.96	52	21	2
Congruent > Incongruent						
No regions						
MAIN EFFECT OF GROUP						
Control Group> PHB Group						
Inferior parietal cortex (BA 40)	R, L	85	4.01	42	−37	38
				−42	−36	48
Middle/inferior frontal gyrus	R	47	2.54	42	25	38
(BA 9)						
PHB Group > Control Group						
No regions						

PHB, problematic hypersexual behavior; R, right; L, left; BA, Brodmann area.

TABLE 4 | Imaging results: interaction effects of option × group ($p < 0.05$, FDR-corrected).

Brain ROIs	Side	No. of voxels in cluster	*F*	x, y, z MNI coordinates		
INCONGRUENT CONDITIONS						
Control Group > PHB Group						
Dorsolateral prefrontal cortex	R	35	2.28	40	28	38
Inferior parietal cortex	R	66	2.35	48	−66	32

PHB, problematic hypersexual behavior; ROI, region of interest.

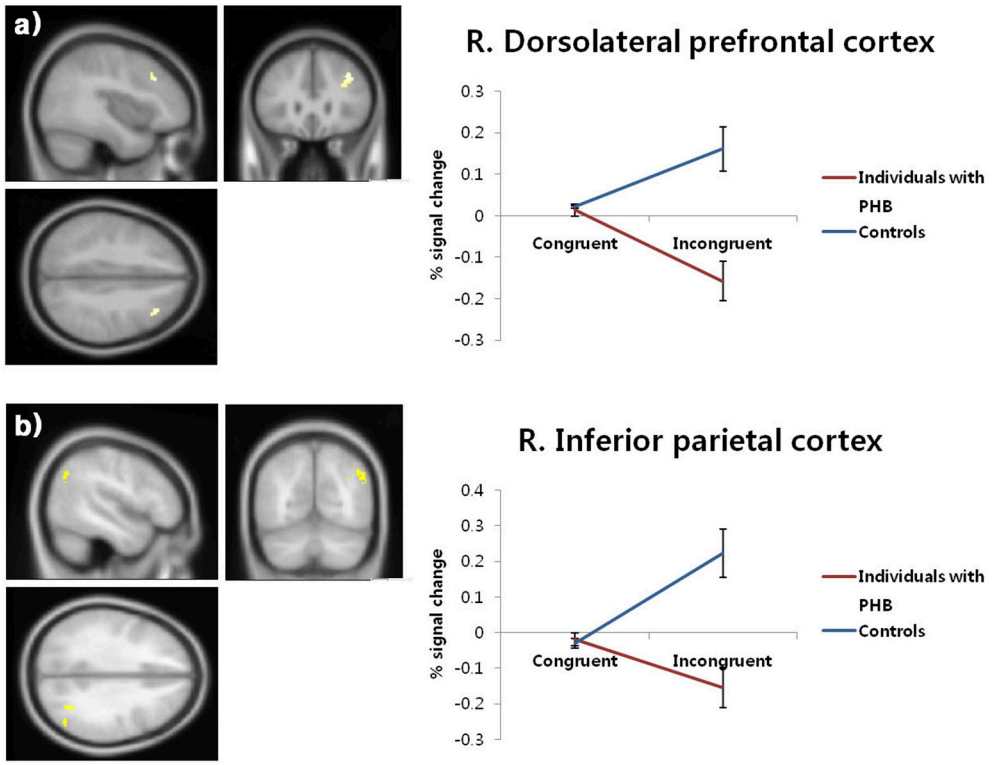

FIGURE 3 | Brain activation patterns in the right dorsolateral prefrontal cortex **(a)** and right inferior parietal cortex **(b)**. The graphs depict the extracted signal change averaged across voxels from each region, displaying condition × group interactions ($p < 0.05$, FDR-corrected). FDR, false discovery rate; PHB, problematic hypersexual behavior; R. DLPFC, right dorsolateral prefrontal cortex; R. IPC, right inferior parietal cortex.

DISCUSSION

The present study aimed to elucidate the neural mechanisms underlying impairments in executive control among individuals with PHB. As hypothesized, individuals with PHB exhibited diminished executive control associated with decreased activation of the DLPFC and right inferior parietal cortex during incongruent Stroop trials. Furthermore, decreased BOLD signal changes in the DLPFC and inferior parietal cortex during incongruent Stroop trials were associated with higher SAST-R and HBI scores in individuals with PHB. We also identified other brain areas besides the region of interest (DLPFC) during the Stroop task. The right putamen in the basal ganglia and middle and inferior frontal gyri were more activated during the incongruent condition compared to the congruent condition, which is consistent with previous studies of the Stroop effect (32, 34). The group differences in the inferior parietal cortex and middle and inferior frontal gyri during the Stroop task are in line with results from patients with other addictive behaviors (35).

With regard to task performance, individuals with PHB exhibited higher error rates than healthy controls in the incongruent condition. The Stroop task requires the cognitive inhibition of automatic responses (e.g., word reading); specifically, the target action in the incongruent condition can only be performed correctly if the incongruent stimulus (the word's meaning) is cognitively inhibited. Shorter response times and increased response accuracy are thought to reflect better cognitive flexibility and inhibition (36). Therefore, poor performance in individuals with PHB can be interpreted as reflecting impaired executive control. This observation is consistent with the findings of previous studies regarding behavioral addiction (15, 16).

Based on the results of this study, we infer that the behavioral characteristics of PHB may be due to decreased activity in the right DLPFC and right inferior parietal cortex. Goldstein and Volkow (25) suggested that slower task performance and higher error rates during incongruent Stroop task conditions are a hallmark of PFC dysfunction. Studies evaluating the Stroop task in addiction (i.e., substance dependence and behavioral addiction) have reported reduced activity in the right PFC, including the DLPFC, during incongruent conditions compared to congruent conditions (15, 26, 37, 38). The findings of the current study are consistent with these previous reports and further elaborate upon their results by showing a negative correlation between activation of these brain areas and PHB severity.

The DLPFC is associated with higher-order cognitive control functions such as monitoring and manipulating information in working memory (39). Milham et al. (40) proposed two roles for the DLPFC during Stroop task performance: (1) biasing

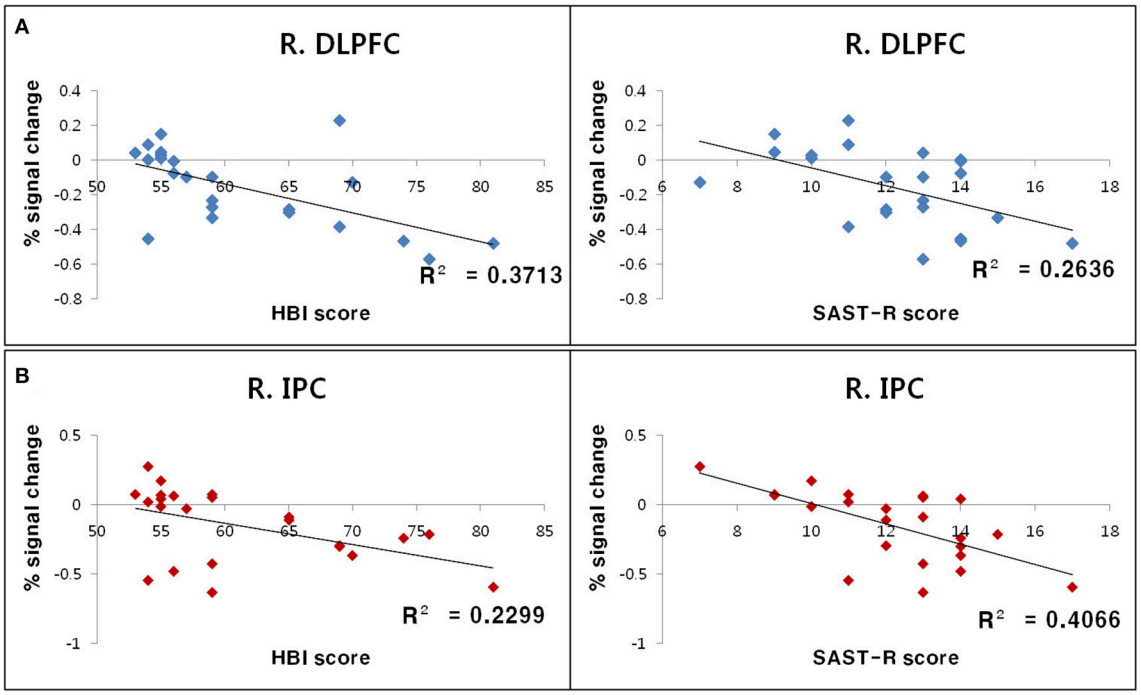

FIGURE 4 | Results of correlation analyses between standardized measurement scores and BOLD signal changes in ROIs during the incongruent Stroop condition. **(A)** Negative correlations between the percent signal change in the R. DLPFC and HBI score (left) as well as SAST-R score (right). **(B)** Negative correlations between the percent signal change in the R. IPC right and HBI score (left), as well as SAST-R score (right). BOLD, blood oxygen level-dependent; HBI, Hypersexual Behavior Inventory; R. DLPFC, right dorsolateral prefrontal cortex; R. IPC, right inferior parietal cortex; ROI, region of interest; SAST-R, Sexual Addiction Screening Test-R.

the selection of task-relevant representations within working memory, and (2) modulating activity in a posterior processing system (e.g., amplifying neural activity within the task-relevant processing system). The former role refers to the process of discriminating, selecting, and manipulating task-relevant (i.e., graphic) rather than task-irrelevant (i.e., semantic) information. The latter role describes the process of activating brain regions in the task-relevant processing system in order to allocate and maintain attentional resources for the discrimination of task-relevant information. The DLPFC is closely interconnected with the posterior visual processing area (e.g., the parietal lobe and primary visual cortex) and is thought to amplify neural activity via these direct neuronal connections (41–44). Brain imaging studies revealed that DLPFC activation is accompanied by activation of the parietal lobe during incongruent Stroop conditions (21, 22, 45). These data are supported by the results of the present study, which identified co-activation of the DLPFC and parietal lobe in the control group during incongruent conditions. The inferior parietal cortex is associated with visual attention (46) and helps to maintain selective attentional control by allowing one to disregard irrelevant stimuli. In one study of working memory task performance, increasing levels of incongruent stimuli produced greater activation of the posterior parietal cortex (47). Therefore, reduced activity in the right DLPFC and inferior parietal cortex in individuals with PHB might represent deficits in the ability to discriminate relevant information and disregard irrelevant information. These deficits in executive control may make it more difficult for individuals with PHB to suppress sexual cravings or behaviors.

The limitations of the present study are as follows. First, this study only evaluated the current mental status of individuals with PHB; therefore, our results do not address the causal nature of the relationship between executive control deficits and PHB. Second, we used the SAST and HBI scales to evaluate participant hypersexuality. They measure constructs related to psychological factors such as sexual motivation and sexual shame, as well as those related with sexual behavioral factors including frequency. Recent studies on sex and pornography addiction suggest that psychological factors are more important than sexual behavioral factors to develop addictive behaviors (48–50). These findings indicate a possibility for different effects between psychological factors and behavioral factors in executive control of sex and pornography addiction. Therefore, it is important to determine how each factor affects executive control and identify which are more important in developing the sex and pornography addiction. In future studies, we plan to test the associations between each factor and executive control by eliminating the confounding effects of other factors. Third, this study only investigated heterosexual Asian male participants. Future studies should include participants of different genders, sexual orientations, and ethnic backgrounds to provide more generalizable insights into PHB. Although the individuals with PHB in this study met the proposed criteria for PHB used in previous studies (2, 28), there are no formal diagnostic criteria for

PHB. Thus, a clinical diagnostic definition of PHB is required in order to improve the reliability of PHB studies. Finally, it would be interesting to identify whether the findings are the same for the PHB group with thoughts (e.g., fantasies) only vs. individuals who actually engage in problematic behaviors. However, the sample size in this study was relatively small, and our participants had a high level of sexual fantasies and also frequently engaged in problematic behaviors. For that reason, it was hard to distinguish the two groups. We hope to include this group comparison in future studies by recruiting more subjects.

Despite the aforementioned limitations, the present study is useful for understanding the characteristics and relevant neural mechanisms of PHB. In summary, individuals with PHB show poorer task performance and decreased activation in the PFC during the Stroop interference task compared to normal controls. Our findings validate the presence of impaired executive control and possible prefrontal dysfunction in individuals with PHB, similar to findings in other problematic excessive behavior conditions.

ETHICS STATEMENT

All participants provided their written informed consent after being thoroughly informed about the details of the experiment. The Chungnam National University Institutional Review Board (IRB) approved the experimental and consent procedures (approval number: 01309-SB-003-01; Daejeon, South Korea). All participants received financial compensation (50 US dollars) for their participation.

AUTHOR CONTRIBUTIONS

J-WS contributed to conception and experimental design, or acquisition of data, or analysis, and interpretation of data, and J-HS contribute substantially to interpretation of data and drafted the article or revised it critically for important intellectual content.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2018.00460/full#supplementary-material

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Ventral Striatal Reactivity in Compulsive Sexual Behaviors

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Compulsive Sexual Behaviors (CSB) are a reason to seek treatment. Given this reality, the number of studies on CSB has increased substantially in the last decade and the World Health Organization (WHO) included CSB in its proposal for the upcoming ICD-11. Sixty percent of the neuroimaging studies on CSB published since 2014 aimed to examine similarities and differences between brain mechanisms underlying CSB, gambling disorder, and substance use disorders. One of the crucial brain circuits involved in addiction is the reward system involving the ventral striatum (including nucleus accumbens). There are two distinct theories describing ventral striatal activity in addictions: Incentive Salience Theory (IST) and Reward Deficiency Syndrome (RDS). IST describes increased ventral striatal activations during the anticipation of addiction-related reward, while RDS describes decreased ventral striatal reactivity both during the anticipation of the reward and during the reward processing. Here, we aim to investigate how the findings on ventral striatal reactivity in CSB support each of these two addiction frameworks. For this purpose, we conducted a systematic review of neuroimaging studies on CSB available in Pubmed, EBSCO, and Google Scholar between 2005 and 2018. We found nine relevant research papers. Only four of these studies directly investigated processing of erotic cues and/or rewards and reported findings related to ventral striatum activations. Three of these studies indicate increased ventral striatal reactivity for erotic stimuli, which is consistent with IST and does not support predictions based on RDS. Therefore, the current state of this data suggest that CSB is related to increased ventral striatal reactivity during the anticipation of erotic stimuli.

Keywords: compulsive sexual behaviors, problematic pornography use, hypersexuality, ventral striatum, nucleus accumbens

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INTRODUCTION

Compulsive Sexual Behaviors (CSB) are a reason to seek treatment for both males (1–3) and females (4). The most commonly reported symptoms of CSB concern time spent viewing pornography (mainly on the Internet) and excessive masturbation (5–7). Other reported types of behaviors include risky casual sexual relations, anonymous sex, and use of paid sexual services (8).

The number of studies on CSB has increased substantially during the last decade (9, 10) and the World Health Organization (WHO) included CSB as an impulse control disorder (11) in its proposal for the upcoming ICD-11 (12). According to proposed criteria (very similar to those previously proposed by Kafka (6), we may recognize CSB Disorder if following symptoms are observed over a period of at least 6 months:

1. Excessive time spent on sexual fantasies, urges, or behaviors repeatedly interferes with other important (non-sexual) goals, activities, and obligations, i.e., pornography viewing has become a central interest in one's life, so that family duties or work obligations are neglected;
2. The subject engages repeatedly in these sexual activities in response to dysphoric emotional states, i.e., sexual activity has become a rigid strategy of mood regulation;
3. And/or in response to stressful situations; e.g., during stressful events at work;
4. Despite repeated attempts, the subject fails to control or significantly reduce these sexual activities, i.e., the subject makes numerous unsuccessful attempts to limit problematic activities, but invariably loses control over them after a couple of days;
5. The subject continues these sexual activities despite the risk of physical or emotional harm to self or to others, i.e., engaging in frequent sexual behavior despite serious consequences for relationships (e.g., break-up) or threat of job loss.

The frequency and intensity of these sexual activities lead to clinically significant personal distress or dysfunction in important aspects of life and do not result from exogenous substance use (e.g., drug abuse or medication), bipolar disorder, or paraphilia.

PATTERNS OF VENTRAL STRIATAL ACTIVATIONS ACCORDING TO THEORETICAL FRAMEWORKS OF ADDICTIONS

One of the crucial brain circuits involved in addiction is the reward system connecting such brain structures as the ventral tegmental area (one of the principal dopamine-producing areas in the brain) with the ventral striatum, mesocortical pathways, and cerebral cortex, especially the orbitofrontal and mediofrontal cortex (13–16). Anatomically, the ventral striatum in humans and non-human primates includes the nucleus accumbens, the region between the caudate nucleus and ventral putamen to rostral internal capsule, the olfactory tubercle, and the rostrolateral portion of the anterior perforated space adjacent to the lateral olfactory tract (17, 18). However, human connectivity studies suggest that the ventral striatum includes the nucleus accumbens and a larger region of the medial caudate nucleus and rostroventral putamen (19).

The ventral striatum receives cortical input from the orbital frontal cortex and anterior cingulate cortex in addition to dopaminergic input from the midbrain. The same region projects output to the ventral pallidum and to the ventral tegmental area, which project output back to the prefrontal cortex through the medial dorsal nucleus of the thalamus. This circuit is an integral part of the cortico-basal ganglia system (19). Different nodes of this network play different roles in such aspects of reward processing as motivation and hedonic pleasure (20, 21). The ventral striatum (especially the nucleus accumbens) is probably the most extensively studied brain region in the context of reward processing (22, 23), demonstrating activation during the anticipation and receipt of different types of rewards (24, 25).

Of the many addiction theories which are of interest, here, we would like to focus on two which allow for very clear predictions about ventral striatal activation and its link to addictive behaviors: Incentive Salience Theory [IST, (26–28)] and Reward Deficiency Syndrome [RDS; (29, 30)].

The Incentive Salience Theory framework, proposed by Robinson and Berridge (28), distinguishes between two basic components of motivated behavior—"liking" and "wanting." "Liking" is linked directly to the *experienced* value of the reward, usually carried by an unconditional stimuli such as heroine consumption; on the other hand, "wanting" is related to the *expected* value of the reward, often carried by a conditional stimuli (for example, the presence of people with whom one used to take drugs). Studies on substance and gambling addiction show that learned conditional stimuli (so called *cues*) related to addiction evoke increased responses in the ventral striatum as well as increased motivated behavior (manifested with shorter reaction times) among addicted individuals, while responses to the reward itself remain unchanged or undergo blunting over time (26, 31). Thus, according to IST, if CSB disorders share neural mechanisms with addictions, we should see an increased Blood-Oxygen-Level-Dependent (BOLD) response in the ventral striatum specifically for cues signaling erotic/sexual rewards, followed by higher motivation to obtain them (measured as shorter RTs) among individuals with CSB when compared to other cues predictive for other types of rewarding stimuli.

The Reward Deficiency Syndrome theory (29, 30) posits that individuals with addictive behaviors have a general deficit in recruiting brain reward pathways, resulting in chronic hypoactivation of these circuits and supposedly reduced pleasurable experience from rewards. Addictive behaviors, such as substance use or gambling, are consequently initiated to compensate for this reward deficiency and to stimulate the brain's reward circuitry (32). According to RDS, if a group of individuals with CSB is similar to subjects with substance and gambling addictions, than we should see decreased ventral striatal activations in the CSB group in response to the cue and during reward processing when compared to healthy controls.

Before discussing the results of published studies, it is worth mentioning that according to our understanding, IST and RDS are not contradictory, but rather complementary, approaches. It may seem counterintuitive since IST predicts increased ventral striatal activations for cues related to erotic/sexual reward, while RDS predicts decreased ventral striatal activations for such cues in the case of CSB individuals when compared to healthy controls. But for the sake of better understanding, we need to take the origins of both frameworks into account. RDS describes an inborn, genetically-determined tendency for hypoactivation of reward circuits. The RDS framework relates this innate trait to specific gene mutations, *except* for in the case of addictions, in which this tendency is related to non-specific mutations (20, 30, 33). On the other hand, IST assumes that incentive salience of some types of cues can be acquired through the regular conditioning and learning processes; however, in the case of individuals with a specific phenotype [for example, sign-trackers:

animals that are more prone to fast learning of cues predictive for rewards (34, 35)], this learning process can be much faster.

Therefore, we can imagine that some individuals with the phenotype described by RDS have generalized hypoactivation for any type of rewards and their associated cues, and present with lower activations of the ventral striatum when compared to the general population. However, at the same time, these same individuals have learned that some types of stimuli or substances provide them with greater pleasure—thusly, all cues associated with these greater pleasure-inducing stimuli acquire high incentive salience, per conditioning (as described in IST). For these specific cues, this group's ventral striatum can be more activated than when compared to the general population and when compared to different types of cues. With this prediction, we aim to review available neuroimaging data on ventral striatal activations in CSB.

If CSB is more related only to IST, then we should find more studies showing increased ventral striatal activations during expectation for erotic stimuli among individuals with CSB as compared to healthy controls. If CSB is more related to the RDS, then we should see more studies which demonstrate decreased ventral striatal reactivity for any type of rewards among CSB subjects when compared to healthy controls, and possibly decreased reactivity of the ventral striatum during the expectation of the reward, as well.

METHODS

For the purpose of this review, we searched Google Scholar, Pubmed, and EBSCO databases for scientific papers published in peer-reviewed journals (excluding conference abstracts) between January 1, 2005 and February 22, 2018. We only included publications which utilized functional magnetic resonance imaging (fMRI), as we are interested in the BOLD response of the ventral striatum and included keywords such as compulsive sexual behavior, pornography, sex addiction, hypersexuality, hypersexual disorder, problematic pornography use, and internet pornography addiction. The search was performed on February 22 and February 25, 2018. We only included articles published in English. We have found nine publications which met our search criteria (**Table 1**), six of which specifically examined ventral striatal activations during erotic cue or erotic reward processing (36–42). Inclusion and/or exclusion of all listed publications was discussed by two judges. As the overall number of publications was nine (and seven reporting any effects related to the ventral striatum), we did not select studies based on the methods of CSB diagnosis; therefore, we describe the specific methods used for subjects classification in **Table 1**.

REVIEW OF EXISTING DATA ON VENTRAL STRIATAL ACTIVATIONS IN CSB

First, we will discuss studies directly addressing cue and reward processing. Among the seven studies reporting ventral striatal activations for erotic cues or rewards, two were conducted on a sub-clinical population [frequent pornography users; (38, 39) not fulfilling criteria of CSB] and the remaining five were conducted on clinical populations fulfilling criteria of CSB [either subjects who were presenting with a variety of CSB (37, 40–42) or individuals seeking treatment specifically for problematic pornography use (36)]. Two studies were conducted on the same population (37, 42). All studies used erotic pictures, but one utilized explicit video clips (37). In Kühn and Gallinat (38), Seok and Sohn (40), and Banca et al. (42), authors compared ventral striatal reactivity between erotic and neutral pictures, in Voon et al. (37), between explicit and exciting videos, in Brand et al. (39), between preferred and non-preferred erotic pictures, and in Gola et al. (36) between erotic pictures and monetary rewards and between cues predictive for erotic pictures and for monetary gains.

DISCUSSION

Taking into account the very limited body of experimental publications (seven) reporting activations of ventral striatum during processing of erotic and non-erotic stimuli in populations meeting the criteria of CSB or in sub-clinical populations, deriving any strong conclusions at this moment would be premature. Therefore, we would first like to discuss the available results, then propose their interpretations in the context of IST and RDS theories.

Among non-problematic pornography users, an inverse relationship between right striatum (more precisely caudate) volume and frequency of pornography consumption was observed (38). The same study also reported a negative correlation between the amount of pornography consumption and functional reactivity of the left putamen during sexual stimuli watching. Alternatively, Voon et al. (37) showed that men meeting CSB criteria (6) as compared to those without CSB, demonstrated an increased striatal reactivity for sexually explicit videos. Interestingly, CSB patients watching exciting videos (namely, presentations of extreme sports) showed lower activations in the ventral striatum when compared to controls (37). Seok and Sohn (40) showed higher activation of the left caudate nucleus in response to erotic pictures in the CSB group when compared to controls and lower activation for neutral pictures in the left caudate nucleus. Brand et al. (39), similarly to Voon et al. (37), showed increased BOLD responses in the ventral striatum in response to preferred sexual pictures when compared to non-preferred ones, and that this activity positively correlated with scores on the Internet Addiction Test Modified for Cybersex in a sub-clinical population (39). The fifth study (36) used a different paradigm than the four previously discussed. Instead of simply presenting different types of stimuli (e.g., erotic, exciting, or neutral pictures), this study used a modification of the incentive delay task, a task previously used in studies of gambling disorder (46). This task has two important properties: (1) it disentangles cue- and reward-related phases related to anticipation and outcome, respectively, and (2) it provides a possibility to compare "addiction-related" stimuli (in this case, erotic pictures) with another potent reward (monetary gains). In this study, men with and without CSB differed in their striatal responses to cues predicting erotic pictures, but not in their responses to erotic pictures. CSB subjects when compared to control subjects showed increased activation of ventral striatum

TABLE 1 | Research publications on CSB or pornography use using functional resonance imaging.

References	Subjects	Classification criteria and questionnaires	Aims and methods	Ventral striatal coordinates	Type of cue/ reward	Description of results
Miner et al. (43)	8 CSB and 8 controls; heterosexual males	Clinical interview using Structured Clinical Interview for DSM-IV, with extra section added to assess the symptoms of CSB Compulsive Sexual Behavior Inventory	Aims: investigate white matter micro-structure and behavioral inhibitory processes in men with CSB Methods: diffusion tensor imaging and Go—No Go Task	Not reported	None	This study was investigating performance in go-no go task, and there was no task related directly to cue or reward processing
Voon et al. (37)	19 CSB and 19 controls; heterosexual males	Clinical interview using CSB diagnostic criteria by Kafka Internet Sex Screening Test and extensive investigator-designed questionnaire	Aim: investigate neural correlates of cue reactivity comparing sexually explicit video cues with non-sexual cues in subjects with and without CSB Methods: passive viewing of video during functional magnetic resonance imaging	$x = 18, y = 2, z = -2$	Video clips of explicit sexual, erotic, non-sexual exciting, money, and neutral	Exposure to sexually explicit sexual videos in CSB compared to control subjects was associated with stronger ventral striatal response. Exposure to exciting non-sexual videos in CSB compared to control subjects was associated with weaker ventral striatal response. (Contrast: CSB > Control Subjects)
Kühn and Gallinat (38)	64 healthy heterosexual males	No CSB populations, but authors assessed time spent on pornography use and symptoms of CSB by Internet Sex Screening Test and Sexual Addiction Screening Test	Aim: investigate neural correlates associated with frequent of pornography use in a healthy population Methods: voxel-based morphometry, resting state functional connectivity, functional magnetic resonance imaging during Cue-Reactivity Task	$x = 11, y = 5, z = 3$ and $x = -24, y = 2, z = 4$	60 explicit sexual images and 60 non-sexual images	Negative association between reported pornography hours per week and gray matter volume in the right striatum as well as with functional activity during a sexual cue–reactivity paradigm in the left putamen. (Parametric modulation of BOLD by amount of pornography use)
Seok and Sohn (40)	23 CSB and 22 controls; heterosexual males	Clinical interview using CSB diagnostic criteria by Kafka Sexual Addiction Screening Test-R and Hypersexual Behavior Inventory	Aims: investigate sexual desire in men with CSB and identify neural correlates of enhanced desire Methods: passive viewing of images during functional magnetic resonance imaging	$x = -38, y = -32, z = 2$	34 images depicting naked women and sexual activity, and 20 non-sexual images	Higher activation of left caudate nucleus for erotic pictures in CSB group when compared to controls. Lower activation for neutral pictures in left caudate nucleus in CSB group when compared to controls. (Contrast: CSB > Control Subjects)
Banca et al. (42)	23 CSB and 40 controls; heterosexual males	Clinical interview using CSB diagnostic criteria by Kafka Internet Sex Screening Test and extensive investigator-designed questionnaire	Aims: investigate novelty-seeking and cue-conditioning in individuals with CSB, investigate neural correlates of cue-conditioning in men with CSB Methods: conditioning imaging task and habituation during functional magnetic resonance imaging	$x = 2, y = 8, z = -10$	Colored patterns as a cue and sexual, monetary, and neutral image as a reward	Decreased ventral striatal activations among CSB subjects (when compared to control) as a response for lack of erotic or monetary reward. (contrast: CSB > Control Subjects)
Brand et al. (39)	19 healthy heterosexual males	Internet Addiction Test modified for cybersex, Hypersexual Behavioral Inventory	Aim: investigate neural responses to pornographic material that is consistent with subjects' sexual preferences compared to pornographic material Methods: picture valuation task and picture choice task during functional magnetic resonance imaging	$x = 14, y = 8, z = -8$ and $x = -8, y = 6, z = -10$	Explicit sexual images in 3 categories: interactions between a man and a woman, between 2 men, and between 2 women	Increased ventral striatal activation in response to preferred vs. non-preferred erotic pictures. Positive correlations between ventral striatal activation (during presentation of erotic pictures) and score in Internet Addiction Test (s-IAT) (44) (Contrast: Preferred erotic pictures > Non-preferred erotic pictures)

(Continued)

TABLE 1 | Continued

References	Subjects	Classification criteria and questionnaires	Aims and methods	Ventral striatal coordinates	Type of cue/ reward	Description of results
Klucken et al. (41)	20 CSB and 20 control heterosexual males	Clinical interview using CSB diagnostic criteria by Kafka	Aim: investigate differences in neural activity associated with appetitive conditioning and connectivity in men with and without CSB Methods: appetitive conditioning paradigm during a functional magnetic resonance imaging	$x = -15$, $y = -1$, $z = -2$	2 colored squares as a cue and 21 erotic pictures as a reward	This study explores group differences in neural activity associated with appetitive conditioning and shows decreased coupling between the ventral striatum and prefrontal cortex in the CSB vs. control group. (Contrast: CSB > Control Subjects)
Gola et al. (36)	28 CSB and 24 control heterosexual males	Clinical interview using CSB diagnostic criteria by Kafka Sexual Addiction Screening Test-R and extensive investigator-designed questionnaire	Aim: investigate neural correlates of sexual and non-sexual incentives in men with and without CSB Methods: incentive delay task during functional magnetic resonance imaging	$x = -12$, $y = 10$ $z = -6$ and $x = 12$, $y = 10$, $z = -4$	Erotic, monetary, and control symbols as cues, erotic images and money as a reward	This study use incentive delay task with 2 types of rewards—erotic and monetary. Men with and without CSB differed in their striatal responses to cues predicting erotic pictures but not in their responses to erotic pictures or monetary rewards. CSB subjects when compared with control subjects showed increased activation of ventral striatum specifically for cues predicting erotic pictures but not for cues predicting monetary gains. (Contrast: CSB > Control Subjects)
Seok and Sohn (45)	17 CSB and 19 control heterosexual males	Clinical interview using CSB diagnostic criteria by Kafka Sexual Addiction Screening Test-R and Hypersexual Behavior Inventory	Aim: investigate gray matter deficits and resting- state abnormalities in individuals with CSB Methods: voxel-based morphometry, resting state functional connectivity	Not reported	None	This study was investigating gray matter deficits and resting-state connectivity in CSB

specifically for cues predicting erotic pictures, but not for cues predicting monetary gains. Relative sensitivity to cues predicting erotic pictures vs. monetary gains was significantly related to the increased behavioral motivation to view erotic images (suggestive of higher "wanting"), severity of CSB, amount of pornography use per week, and number of weekly masturbations. Excepting Kühn and Gallinat (38), the other reviewed studies suggest increased sensitivity either to erotic stimuli (37, 39) or to the cues predicting erotic stimuli (36) among people with higher scores in CSB.

Of the other studies not strictly related to cue or reward processing, Banca et al. showed decreased ventral striatal activations among CSB subjects when compared to controls as a response to lack of erotic or monetary reward in a conditioning task (42). Klucken et al. (41) showed decreased coupling between the ventral striatum and prefrontal cortex in the CSB vs. control group during appetitive conditioning [in a similar task to Banca et al. (42)].

CONCLUSIONS

If we focus strictly on ventral striatum activity in all the above mentioned studies, then a consistent schema of results emerges: preferred erotic pictures (39), explicit videos (37), or cues predicting erotic pictures (36) evoke stronger ventral striatal activations than other types of stimuli among people with CSB (or frequent pornography users) when compared to controls. Data provided by Kühn and Gallinat (38) and collected from a non-clinical sample also suggest decreased ventral striatum volumetry among healthy individuals who use more pornography; however, recent findings (47) do not confirm this difference in ventral striatum volume between individuals meeting CSB criteria and controls. As of yet, there is no study on a population meeting CSB criteria, testing BOLD responses for erotic stimuli, and examining volumetric changes at the same time, so any speculation on the relations between striatal volumetry and reactivity would be premature at this point.

CONSISTENCY WITH REWARD DEFICIENCY SYNDROME

To examine published results in the light of RDS, we need to look at the differences in ventral striatal activations between CSB (or sub-clinical populations) and control groups. RDS predicts hypoactivation for rewarding stimuli and for cues predicting such stimuli in between group comparison. None amongst the four studies examining reactivity for erotic stimuli (36–39) indicates such hypoactivation in the case of erotic stimuli. However, in Voon et al. (37), the CSB group when compared to controls presents visible hypoactivation of ventral striatum for non-erotic exciting stimuli [in Seok and Sohn (40), there is visible hypoactivation in CSB individuals when compared to controls for neutral stimuli]. Opposite results are presented in Gola et al. (36) where there is no difference in BOLD response for monetary rewards between CSB and control subjects. Three (36, 38, 39) out of four available studies speak clearly against predictions formulated based on the RDS framework. However, it is important to bear in mind the differences between the groups in these studies. While in Voon et al. (37), subjects who met CSB criteria presented a variety of problematic sexual behaviors, in Gola et al. (36) all individuals who met CSB criteria presented with problematic pornography use as a dominant problem. Similarly, in two (38, 39) other studies on sub-clinical populations, ventral striatal activations and volumetry correlated with the amount of pornography use. There is not enough data to formulate any strong conclusions, but some hypothesis for future studies can be formulated.

From our point of view, it is worth investigating whether CSB can be distinguished into two subtypes characterized by: (1) dominant interpersonal sexual behaviors, and (2) dominant solitary sexual behaviors and pornography watching (48, 49). Based on analogous findings on alcohol abuse, each of these subtypes could be related to the different genotypes and patterns of ventral striatal activations for cues and rewards (50, 51). We propose to examine in future studies whether a subtype defined by interpersonal sexual behaviors can be characterized by a higher degree of novelty seeking and ventral striatal hypoactivity as proposed by RDS, while a subtype related to predominant problematic pornography viewing and solitary sexual activity can be characterized instead by increased ventral striatal reactivity for erotic cues and rewards without hypoactivation of reward circuits.

CONSISTENCY WITH INCENTIVE SALIENCE THEORY

According to IST, learned cues (conditional stimuli) related to addiction evoke increased responses in the ventral striatum and evoke increased motivated behavior (i.e., shorter reaction times and higher accuracy) among addicted individuals, while responses to the reward itself remain unchanged or undergo blunting over time (26, 31). Thus, according to IST, if CSB shares mechanisms with addictions, we should see an increased BOLD response in the ventral striatum specifically for cues signaling erotic/sexual rewards among individuals with CSB when compared to healthy controls and when compared to the reaction for cues predicting other rewards.

Reading each of the presented publications (36–39) separately, one might gather that all data consistently indicate mechanisms proposed by IST, namely, higher sensitization for erotic stimuli. But one very important question emerges: How to interpret these erotic stimuli in the laboratory setup? If one assumes that an erotic picture or video plays the role of cue, then increased ventral striatal reactivity among subjects with CSB (in comparison with controls) would speak in favor of the addiction hypothesis. However, if one assumes that erotic stimuli play the role of reward, then these results do not necessarily support the predictions formulated in the IST framework. From our perspective, [for details, see Gola et al. (9)] in many real life situations, visual sexual stimuli such as the naked body of a sexually attractive partner increase sexual arousal and lead to approach behaviors initializing dyadic sexual activity and ending with orgasm (52). In this case, we argue that sexual stimuli play the role of cue (conditional stimuli), while orgasm plays the role

of (primary) reward (unconditional stimuli). This may be the case particularly for healthy controls and for CSB subjects with dominant interpersonal sexual behaviors.

Our reasoning is similar for most cases of solitary sexual activity, especially for healthy subjects. Most common visual sexual stimuli are pornographic videos or photos (cues), which increase sexual arousal and lead to masturbation ending with orgasm (reward). But in the research (9), we observe the following: (1) people experience pleasure while viewing erotic pictures and videos, possibly accompanied by genital reaction; (2) their rewards-related brain activity is correlated with these pleasurable feelings in response to visual sexual stimuli; (3) they are willing to exert effort to view these stimuli, similar to other rewarding stimuli, such as money; and (4) we also see conditioning for cues predictive of sexual stimuli. Thus, we claim that visual sexual stimuli may have rewarding value and, that in a laboratory setup [like in study (36)], can play the role of reward. For CSB individuals with dominant solitary behaviors and pornography watching, this may also be the case in real life situations, as many of them report pornography binges wherein orgasm is intentionally delayed to maintain hours of pleasure in pornography viewing (2). Therefore, according to our view, the results of the available studies support predictions of IST and show either increased ventral striatal reactivity for erotic stimuli [which may play the role of cue for subsequent sexual activity (37, 39)] or for cues predicting erotic pictures, which *per se* is a rewarding stimuli (36).

SIMILARITIES TO SUBSTANCE USE AND GAMBLING DISORDER

Most recent meta-analysis (32) of 25 studies on ventral striatal activations in substance addictions and pathological gambling suggest that during reward anticipation (exposition to cue), individuals with substance and gambling addictions showed decreased striatal activation as compared with healthy control individuals. During reward outcome, individuals with substance addiction showed increased activation in the ventral striatum, whereas individuals with gambling addiction showed decreased activation in the dorsal striatum compared with healthy control individuals. According to the authors, striatal hypoactivation in individuals with addiction during reward anticipation and in individuals with gambling addiction during reward outcome is in line with the RDS theory of addiction. It is important to note that all of the studies included in this meta-analysis were using monetary incentives; therefore, described patterns of reactivity for cues and rewards were non-specific for certain substance related addictions. The only study with CSB subjects—which can be directly compared to the studies reviewed in Luijten et al. (32)—is Gola et al. (36), which uses the monetary incentive delay task. Here, no hypoactivation of ventral striatum in CSB (compared to controls) was observed. We see a need to conduct studies comparing CSB individuals with populations addicted to substances or gambling using standard tasks such as monetary incentive delay task to directly investigate similarities and differences between CSB and addictions in ventral striatum reactivity.

SUMMARY AND FUTURE DIRECTIONS

The amount of available studies on CSB (and sub-clinical populations of frequent pornography users) is constantly increasing. Among currently available studies, we were able to find nine publications (**Table 1**) which utilized functional magnetic resonance imaging. Only four of these (36–39) directly investigated processing of erotic cues and/or rewards and reported findings related to ventral striatum activations. Three studies indicate increased ventral striatal reactivity for erotic stimuli (36–39) or cues predicting such stimuli (36–39). These findings are consistent with IST (28), one of the most prominent frameworks describing brain functioning in addiction. The only support for another theoretical framework which predicts hypoactivation of the ventral striatum in addiction, RDS theory (29, 30), comes partially from one study (37), where individuals with CSB presented lower ventral striatal activation for exciting stimuli when compared to controls.

The current state of the data allows us to conclude that CSB is related to increased ventral striatal reactivity for erotic stimuli and cues predictive for such stimuli. However, many basic questions allowing for direct comparisons with substance addictions and pathological gambling remain unaddressed. We see a need for studies directly comparing CSB individuals with populations addicted to substances (to verify predictions based on RDS) as well as more experimental work on cue and reward processing in CSB (for further verification of predictions based on IST). Future studies should also try to control for dominant patterns of CSB (e.g., solitary vs. interpersonal sexual activity).

We also want to note that the ventral striatum is only one brain region related to reward processing and learning, and that a much more complex picture of CSB can be presented when we are able to integrate knowledge on whole brain activity.

LIMITATIONS

Our review has limitations related to the small number of fMRI research with CSB patients. Due to this limitation, we tried to include all studies, despite obvious differences in the diagnostic methods, and criteria they imply (see **Table 1**), what results with non-homogenous samples. Secondly, we took quite a broad definition of ventral striatum, including a larger region of the medial caudate nucleus and rostroventral putamen with nucleus accumbens (19). We hope that an increasing body of evidence will allow for more specific analysis in the future.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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BRIEF RESEARCH REPORT
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Aggression and Harm-Avoidant Trait Impede Recovery From Internet Gaming Disorder

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Background: Relatively little is known about which neuropsychological factors promote recovery from Internet gaming disorder (IGD).

Methods: With informed consents, a cohort study was conducted in Seoul metropolitan area, South Korea, to investigate the course of IGD in youths. At baseline, we assessed psychosocial measures and gaming related measures such as Young's Internet Addiction Test (IAT) and the Aggression Questionnaire. The Balloon Analog Risk Task was also performed to study risk-taking behavior. A total of 60 subjects demonstrating three or greater criteria in the diagnostic interviews on IGD and the IAT score of 50 or above were included. After brief parental coaching at baseline, the participants were followed up at 3 and 6 months ($n = 31$). The baseline characteristics were compared between the non-improved group (<10% improvement in IAT score) and the improved group (≥30% improvement in IAT score) using Mann-Whitney *U*-test or chi-squared tests with a two-tailed statistical significance of 0.05.

Results: The non-improved group and the improved group did not demonstrate significant differences regarding demographics or the IAT scores at baseline. However, the IAT scores were significantly higher in the non-improved group at both 3 and 6 months. The non-improved group was also more likely to display higher aggression and harm avoidance than the improved group at baseline.

Discussion: Youths with excessive gaming problems should be evaluated for aggression and harm avoidance since they contributed to a worse prognosis. For those with high aggression or harm avoidance, more active therapeutic interventions should be considered.

Keywords: gaming disorder, hostility, harm avoidance, recovery, prognosis, course, risk-taking

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INTRODUCTION

With the release of the 11th International Classification of Diseases draft, internet gaming disorder (IGD) is anticipated to become the second formalized addictive behavior disorder after gambling disorder.

However, most of the previous studies were cross-sectional with only 13 longitudinal studies reported in a recent systemic review (1). Moreover, there is a major limitation among them since

all of these studies relied on self-reports to evaluate IGD. In addition, none provided answers to the important question of how the clinical course would be in patients diagnosed with IGD.

To the best of our knowledge, the current study is the first study to investigate the course of IGD established by clinical assessments. In addition to IGD measures, various psychological and neurocognitive measurements were administered to explore factors that promote or undermine recovery from IGD. The identification of hindering factors for IGD recovery will inform us as to which patients may require more clinical resources or attention to facilitate recovery.

METHODS

Procedures

This is a multi-center study that shares many designs with the Internet user Cohort for Unbiased Recognition of gaming disorder in Early adolescence (iCURE) study conducted at schools (2). While the iCURE was aimed at studying the natural course of IGD, this study intends to investigate the clinical course of the IGD affected subjects.

All recruitment was done in three university hospitals in Seoul and Uijeongbu, South Korea. Patients who visited our addiction or child-adolescent clinics either voluntarily, by referral from the local community mental health services, or by referral from the school iCURE research team were eligible for inclusion.

Participants were assessed at baseline, 3, 6, and 12 months, respectively, with the final examination being optional. At baseline, a 15–20 min of brief parents/guardians coaching session was provided with a pocket parental guidance of 12 written pages. This study was reviewed and approved by the institutional review board of Uijeongbu St. Mary's Hospital, the Catholic University of Korea (UC15ONMI0072).

Participants

From August 2015 to January 2018, a total of 130 participants were recruited. Prior to participation, written informed consent was attained from both the patients and their parents/guardians. To ensure the severity of the gaming problem, we included 60 subjects, who demonstrated three or greater positive criteria in the diagnostic interviews on IGD and a baseline Internet Addiction Test (IAT) score of 50 or above. Thirty-one subjects who remained as participants in the study at the 6-month follow-up mark were finally included.

Measurements

Diagnostic Interviews

The participants underwent face-to-face interviews with clinical psychologists using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) IGD criteria in addition to the symptom of "craving." The nine DSM-5 IGD criteria were assessed as suggested by the DSM-5 working group (3). "Craving," an important addiction symptom but not addressed by the DSM-5 was also assessed by verifying whether the interviewee experienced "strong urges to game" or "difficulties with suppressing gaming desires."

The psychiatric comorbidity was also assessed by the Korean Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children (4).

Neuropsychological Assessments

Baseline intelligence was measured using the Korean Wechsler Intelligence Scale for Children for participants under 16 years of age and the Korean Wechsler Adult Intelligence Scale for those aged 16 years or older. In addition, the four main components of verbal comprehension index, perceptual reasoning index, working memory index, and processing speed index were also scored.

The Balloon Analog Risk Task (BART) was completed using the E-prime software (Psychology Software Tools, Sharpsburg, PA, USA). A left-side button was pressed to inflate the balloon as many times as the participants wished before reaching an explosion point to earn 10 scores for each unexploded ballooning attempt. Before the explosion, the participants could press a right-side button to stop the ongoing task and save the scores before losing by an explosion. After instruction, they performed 10 trials prior to the real experiment of 100 BART. The total saved scores and BART index were recorded. The BART index indicates the average frequency for ballooning in the unexploded trials. A high BART index indicates a stronger risk-taking trait while a low BART index indicates a higher harm avoidance trait (5).

Self-Measurements

This study shares the majority of its study design with the iCURE study in regard to the self-measurements. For details, readers are advised to read the published protocol (2). For conciseness, the list and the internal consistencies of self-measurements will be provided as followings. The IAT (Cronbach $\alpha = 0.889$) (6), the Korean Scale for Internet Addiction (Cronbach $\alpha = 0.96$) (7), and the Short version of the Smartphone Addiction Scale (SAS-S) (Cronbach $\alpha = 0.967$) (8) were used to assess problems related to digital media usage. In addition, psychological characteristics were measured using Barratt Impulsiveness Scale-11 (Cronbach $\alpha = 0.79$–0.83) (9), the Attention Deficit Hyperactivity Disorder Rating Scale (ARS) (Cronbach $\alpha = 0.82$–0.89) (10), the Aggression Questionnaire (Cronbach $\alpha = 0.889$) (11), and the Rosenberg Self-Esteem Scale (Cronbach $\alpha = 0.75$–0.87) (12).

Statistical Analyses

The inter-group comparison was performed according to the IGD recovery status after stratifying the included subjects according to the change in IAT score from baseline. At 6 months, those with an equal or greater than 30% reduction in IAT score from the baseline were defined as the improved group ($n = 10$). In contrast, those with worsening or a less than 10% improvement in IAT were classified as the non-improved group ($n = 11$). To identify factors that influence IGD recovery, the baseline characteristics were compared between the two groups. The Mann–Whitney U test and chi-squared/Fisher's exact tests were performed for continuous variables and categorical variables, respectively. Analyses were done using the SPSS Statistics for Windows, version 18 (SPSS Inc., Chicago, IL, USA) with a two-tailed statistical significance of 0.05.

RESULTS

No significant differences were found between the improved group and the non-improved groups in terms of the baseline demographics, digital media use measurements, or co-morbid psychiatric disorders (**Table 1**).

However, the non-improved gamers demonstrated significantly higher aggression (79.6 ± 16.8 vs. 61.3 ± 11.5, $p = 0.010$). They also displayed lower BART index values (27.1 ± 9.2 vs. 37.1 ± 9.3, $p = 0.024$).

In the improved gamers, the ARS score (24.6 ± 11.6 vs. 14.8 ± 10.1, $p = 0.043$) was significantly higher and the perceptual reasoning index score (91.1 ± 14.1 vs. 108.4 ± 20.0, $p = 0.043$) was significantly lower when compared with the non-improved group.

TABLE 1 | Comparison between the non-improved and the improved groups at baseline.

	Non-improved group ($n = 11$)	Improved group ($n = 10$)	*p*
Age (years)	13.8 ± 3.0	12.2 ± 2.2	0.152
Male†	9 (81.8%)	8 (80%)	> 0.999
Female†	2 (18.2%)	2 (20%)	> 0.999
DIGITAL MEDIA USE MEASUREMENTS			
Number of positive IGD criteria*	5.1 ± 1.7	5.1 ± 1.7	0.973
Internet Addiction Test score	59.7 ± 5.6	68.6 ± 15.3	0.173
Korean Scale for Internet Addiction score	89.6 ± 13.7	82.5 ± 25.2	0.605
Smartphone Addiction Scale-Short score	35.6 ± 11.4	34.0 ± 12.9	0.918
PSYCHIATRIC COMORBIDITIES†			
Depression (+)	2 (18.2%)	2 (20%)	> 0.999
Attention deficit hyperactivity disorder (+)	3 (27.3%)	4 (40%)	0.659
PSYCHOLOGICAL MEASUREMENTS			
Rosenberg Self-Esteem Scale	26.6 ± 5.5	28.7 ± 6.2	0.468
Barratt Impulsiveness Scale-II	62.6 ± 8.6	54.4 ± 5.3	0.085
Aggression Questionnaire	79.6 ± 16.8	61.3 ± 11.5	0.010
ARS	14.8 ± 10.1	24.6 ± 11.6	0.043
NEUROCOGNITIVE ASSESSMENTS			
BART index	27.1 ± 9.2	37.1 ± 9.3	0.024
Full Scale Intelligent Quotient	99.6 ± 18.7	88.1 ± 11.8	0.089
Verbal Comprehension Index	99.2 ± 16.6	98.8 ± 11.8	1.000
Perceptual Reasoning Index	108.4 ± 20.0	91.1 ± 14.1	0.043
Working Memory Index	98.6 ± 16.5	87.6 ± 13.8	0.123
Processing Speed Index	90.4 ± 13.2	83.8 ± 15.1	0.353

*†Fisher's exact test; *Nine IGD DSM-5 criteria plus "craving." IGD, Internet gaming disorder; ARS, Attention Deficit Hyperactivity Disorder Rating Scale; BART: Balloon Analogue Risk Task.*

Although there were no significant differences between the two groups at baseline, the IAT scores of the improved group were significantly lower at both 3 and 6 months than were the non-improved group's IAT scores. For SAS-S score, the difference became significant at 6 months, with lower scores demonstrated by the improved group. Although not significant, the number of positive IGD symptoms on the clinical interview also showed a tendency of improvement in the improvement group (**Figure 1**).

DISCUSSION

This study is the first to demonstrate the potential value of aggression and harm avoidance in the prognosis of IGD. Aggression has been repeatedly reported as a risk factor for IGD (13–15). High harm avoidance has been suggested as a vulnerable characteristic of IGD or substance use disorders (16, 17). The first strength of this study lies in its longitudinal design that enables inference on causality. Gamers with such risk factors were more likely to continue their gaming problems and to have a lower chance of self-recovery.

Gamers may regard online gaming platforms as an environment that meets their demand to release aggression or to reduce tension without inflicting adversary reactions from others. In numerous cross-sectional studies, aggression displayed an association with IGD (13–15). Aggression may also impede IGD recovery due to a failure in giving up the self-serving role of gaming to release their hostility. Moreover, gamers with high aggression could also be less compliant with parental guidance attempts to address their gaming behaviors. Further studies are required to reveal the mechanism of aggression as a poor IGD prognostic factor.

In typologies of alcohol use disorder and gambling disorder, the antisocial/impulsive type showed higher addiction severity (18–21). Recently, a theoretical IGD typology was suggested as "aggressive/impulsive," "emotionally vulnerable," and "socially conditioned" IGD subtypes (22). Our findings indicate that the IGD group with high aggression that corresponds to the antisocial/impulsive type in other addictive disorders may also have a worse prognosis.

To gamers with a high harm-avoidant trait, the virtual environment created by gaming may act as "a place to find peace." They may regard virtual interpersonal interactions as relatively harmless compared to those that are in person in their daily lives. The secureness provided by gaming platforms in the context of social interactions may interact with the high harm-avoidant trait and in turn, undermines recovery from IGD. Therefore, screening and early interventions for high harm avoidance may improve the IGD treatment outcome.

The second major strength of this study is our effort to control parental influence. Parents may exert a significant influence on their children's gaming behavior, especially when their bond is strong and they communicate effectively. The IGD of children was negatively associated with autonomic and accepting parenting styles or the participation in enhanced social activities with their parents (23, 24). However, the majority of children reported rare or no supervision by their parents on their

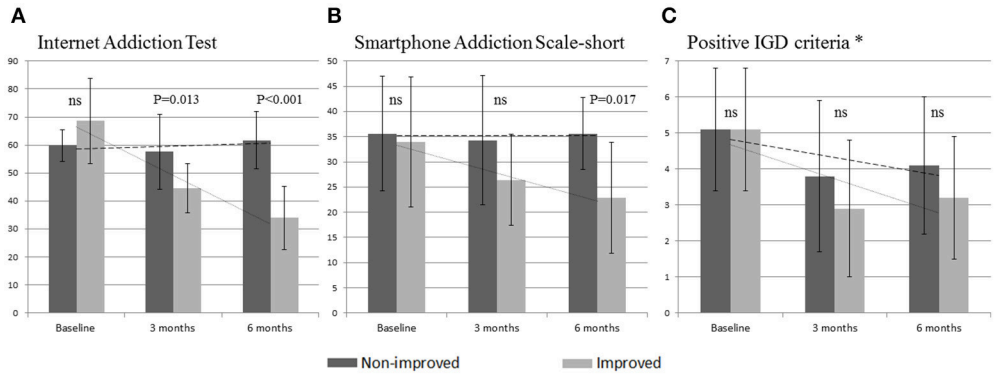

FIGURE 1 | Longitudinal comparison of digital media use measures between the non-improved and the improved groups. **(A)** Changes of Internet Addiction Test scores. **(B)** Changes of Smartphone Addiction Scale-short. **(C)** Changes in number of positive IGD symptoms. *Nine IGD DSM-5 criteria plus "craving"; IGD, Internet gaming disorder; ns, not significant; bar in the middle indicates SD.

computer use duration and this lack of rule was reported as a risk factor for excessive use (25).

In addition to the strength of parent-child relationships, the effectiveness of parental guidance may vary widely according to the difference in parental knowledge on gaming issues. IGD is yet to be formalized in the medical system. Thus, awareness about the addictive potentials of this particular behavior may vary across households. Moreover, parents may not seek professional treatment immediately due to excessive concerns about labeling their children with an addiction stigma despite being aware of the potential harms.

Therefore, providing accurate information on IGD and parental coaching may decrease the gaps in IGD knowledge between households. We tried to minimize such variations by providing clear and uniform instruction to the parents. The parental coaching provided in this study included brief instruction on communication skills, setting rules, monitoring, and providing positive feedback to their offspring. However, no interventions were provided to the participants *per se* to better observe the clinical course of IGD.

However, there are also a number of limitations in this study. First, the sample size is relatively small and the possibility of selection bias cannot be ruled out. In addition to the small initial enrollment, only 31 subjects remained in the study at 6 months and contributed to the smaller final sample. However, our secondary analysis of baseline characteristics between the drop-outs and the final participants did not reveal any significance in terms of demographics or psychological variables. Second, although we provided parental coaching, it was brief and the actual levels of parental understanding or execution were not assessed. Thus, parental confounding factors may not have been fully eliminated. Third, the use of IAT, a self-measured tool, as a primary outcome is a major limitation of our study and objective measurements should be utilized to overcome such limitation. Fourth, the levels of aggression and harm avoidance of the participants were not measured by biological markers such as genetic polymorphisms or functional imaging that may further elucidate the mechanism. However, regardless of the underlying mechanisms, the worse longitudinal outcome observed warrants more clinical attention.

The excessive gaming problems displayed by some children are likely to be first noticed by their parents. This may become a major parental concern because, in addition to having direct health consequences, IGD may impede necessary skill development or future career opportunities for the affected children. Parents will likely become curious about the prognosis of their already-affected children. Our findings may provide some answers, in that the gaming problems of children with high aggression and harm avoidance are less likely to resolve spontaneously. The assessment of aggression and harm avoidance levels may be clinically useful in predicting the clinical course of IGD. Active therapeutic approaches like cognitive behavior therapy should be considered in this identified risk group.

AUTHOR CONTRIBUTIONS

S-YL conducted the analyses and drafted the manuscript. HL and SB took a part in drafting. Y-SK developed the concept and supervised the writing of the manuscript. HJ and HY further developed the concept. All authors contributed editorial comments on the manuscript.

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Longitudinal Changes in Neural Connectivity in Patients With Internet Gaming Disorder: A Resting-State EEG Coherence Study

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Aims: The present study investigated neural connectivity associated with treatment responses in patients with Internet gaming disorder (IGD) using resting-state electroencephalography (EEG) coherence analyses.

Methods: We included 30 patients with IGD and 32 healthy control subjects (HCs). Of the IGD patients, 18 completed an outpatient treatment that included pharmacotherapy with selective serotonin reuptake inhibitors for 6 months. Resting-state EEG coherence and self-report questionnaires were used to evaluate clinical and psychological features pre- and post-treatment, and data were analyzed using generalized estimating equations.

Results: Compared with HCs, patients with IGD showed increased beta and gamma intrahemispheric coherence and increased delta intrahemispheric coherence of the right hemisphere at baseline. After 6 months of outpatient management, patients with IGD exhibited improvements in IGD symptoms compared with baseline, but they continued to show increased beta and gamma intrahemispheric coherence compared with that of HCs. No significant EEG coherence changes between the pre- and post-treatment assessments were detected in any band in the IGD group.

Conclusion: These findings suggest that significantly greater intrahemispheric fast-frequency coherence may be an important neurophysiological trait marker of patients with IGD.

Keywords: internet gaming disorder, EEG, coherence, fast frequency band, treatment response

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INTRODUCTION

Internet gaming disorder (IGD) is characterized by a pattern of excessive and repetitive use of Internet-based games (1). IGD has received increasing attention due to various negative consequences affecting normal daily life, academic and job performance, and psychological functioning (1, 2). Patients with a behavioral addiction, such as IGD, share certain clinical features, including impulsivity, craving, and the inability to control harmful behavior (3, 4). Recent studies have used neuroimaging and neurophysiological techniques to investigate the structural and

functional changes in the brain associated with impulsivity or response inhibition to enhance our understanding of the characteristics of IGD (5–7).

Several neuroimaging studies have investigated the dysfunctional connectivity in patients with IGD. For example, Zhang (8) reported a decreased amplitude of low fluctuations in the orbitofrontal cortex and posterior cingulate cortex in young adults with IGD compared with controls. They also found that patients with IGD exhibited enhanced interactions in the default mode and executive control networks compared with controls. Additionally, patients with IGD showed increased connectivity in sensorimotor brain networks and altered interhemispheric resting-state functional connectivity in the prefrontal lobe, including the bilateral superior frontal gyrus, inferior frontal gyrus, and middle frontal gyrus (9, 10). These findings suggest that patients with IGD have impairments in reward-related processing, general cognitive functioning, and impulse control.

Although neuroimaging studies have identified the brain structures involved in resting-state activities, they provide limited information in terms of the temporal dynamics of neural networks in the brain. Electroencephalographic (EEG) coherence is useful for measuring abnormalities in functional brain organization with high temporal resolution (11). EEG coherence measures the consistency of phase differences in two brain regions and reflects the synchronization between neural populations and cortical connectivity (12). Increased coherence between two EEG electrodes suggests functional integration of two brain regions, whereas decreased coherence reflects the unrelated activities of two neural populations (13, 14).

A few studies that have investigated brain connectivity using resting-state EEG have reported that adolescents with an Internet addiction showed increased gamma coherence among the parietal, right temporal, and occipital areas compared with healthy controls (HCs) (15). Patients with IGD also exhibited enhanced intrahemispheric gamma coherence compared to controls (16). Furthermore, increased intrahemispheric connectivity within the fronto-temporal area may be associated with repetitive online gaming (17). These consistent findings indicate that altered gamma phasic synchrony is associated with hyperarousal in the sensory system as well as with an abnormal excitatory system. However, it remains unclear whether altered neural connectivity in patients with IGD is a trait marker or a state marker associated with the severity of IGD. A few studies using EEG coherence have shown abnormalities in brain connectivity in individuals with substance use disorder (SUD), which has a brain mechanism similar to that of IGD (7, 18, 19). For example, long-term abstinent as well as non-abstinent alcohol-dependent participants showed increased bilateral, intrahemispheric, and posterior EEG coherence (18). Similarly, abstinent heroin-dependent individuals exhibited increased left intrahemispheric gamma coherence compared to HCs (19). These findings suggest that enhanced neural connectivity is not normalized after a long period of abstinence or treatment and may reflect an endophenotype for SUD. Therefore, longitudinal studies with patients with IGD could help us understand the pathophysiology of and develop treatment interventions for IGD.

To the best of our knowledge, no studies have investigated longitudinal changes in resting-state EEG coherence following treatment of patients with IGD. Thus, we investigated cortical connectivity associated with treatment responses in patients with IGD to understand its underlying mechanism and to elucidate whether the altered phasic synchrony in individuals with IGD is a state or a trait marker. Based on previous findings (16, 17, 20), we hypothesized that patients with IGD would exhibit increased fast-frequency coherence at baseline and that this neurophysiological index would be sustained even though their IGD symptoms improved after 6 months of outpatient management.

MATERIALS AND METHODS

Participants

This longitudinal study included 62 male participants aged 18–38 years who were recruited from the SMG-SNU Boramae Medical Center and the surrounding community in Seoul, Republic of Korea. Thirty patients were classified as having IGD based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition and diagnosed by a clinically experienced psychiatrist (1). Thirty-two participants served as HCs. The present study included only those patients who spent more than 4 h/day and/or 30 h/week playing Internet games. Additionally, Young's Internet Addiction Test (Y-IAT) was used to assess the severity of IGD symptoms (21). Baseline clinical assessments and an EEG scan were performed on all participants. Since baseline assessments, 18 of the 30 patients with IGD who had comorbid depressive or anxiety symptoms continued pharmacotherapy with serotonin reuptake inhibitors (SSRIs) using the average daily doses: escitalopram at 15.83 $\pm$ 9.17 mg, fluoxetine at 50.00 $\pm$ 9.17 mg, or paroxetine at 30.00 $\pm$ 14.14 mg. No drugs other than SSRIs were used in this study. After 6 months of continued treatment, they completed follow-up assessments including clinical measures and EEG recording. The primary treatment outcome was the change in the IAT score from pre- to post-treatment. HC participants who played Internet games $<$ 2 h/day were recruited directly from local communities. None of the participants had a history of intellectual disability, psychotic disorder, or neurological disorder, and all were right-handed. Participants with an estimated IQ of $<$ 80 were excluded.

This study was approved by the Institutional Review Board of SMG-SNU Boramae Medical Center, Republic of Korea. All participants provided written informed consent after having received information about the study.

EEG Recordings

EEG Data Collection

Detailed information about the EEG recordings and data collection procedure were presented in our previous study (16). Resting-state EEG was recorded for 10 min (4 min with eyes closed, 2 min with eyes open, and 4 min with eyes closed) in an electrically shielded and soundproofed room with dim lights. Participants were instructed to relax and avoid any body movements and drowsiness. EEG activity was recorded from 64 electrodes based on the modified International 10–20 system in conjunction with vertical and horizontal electrooculograms

and a mastoid reference electrode. The ground channel was located between the FPz and Fz electrodes. The EEG signals were recorded continuously using a 0.1–60 Hz online bandpass filter and a 0.1–50 Hz offline bandpass filter at a sampling rate of 1,000 Hz. Electrode impedances were kept at <5 KΩ.

All EEG data were analyzed with NeuroGuide software (NG Deluxe 2.6.1, Applied Neuroscience; St. Petersburg, FL, USA) for the coherence analysis, and 19 of the 64 channels were driven by the NeuroGuide montage set as follows: FP1, FP2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2. Artifacts due to eye blinks and movements during EEG recordings were eliminated by the automatic NG Deluxe 2.6.1 system and were visually detected.

Coherence

The coherence analysis methods were presented in Park et al. (16). To summarize, resting-state EEG data were transformed into the frequency domain using the fast Fourier transformation algorithm with the following parameters: epoch = 2 s, sampling rate = 128 samples/s (256 digital time points), frequency range = 0.5–40 Hz, and a resolution of 0.5 Hz with a cosine taper window to minimize leakage. The NG 2.6.1 program was used to obtain the coherence values. The accepted epochs of the EEG data were computed for each of the following frequency bands: delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–25 Hz), and gamma (30–40 Hz). Furthermore, the intrahemispheric coherence for each band was examined using the F3–C3, F3–T3, F3–P3, C3–T3, C3–P3, and T3–P3 electrode pairs on the left hemisphere and the F4–C4, F4–T4, F4–P4, C4–T4, C4–P4, and T4–P4 electrode pairs on the right hemisphere. Interhemispheric coherence was computed between electrode pairs F3–F4, C3–C4, T3–T4, and P3–P4.

Psychological Assessments

Wechsler Adult Intelligence Scale

The Korean version of the Wechsler Adult Intelligence Scale was administered to all participants to calculate their IQ (22–24).

Questionnaires

The Korean version of all questionnaires have been validated (25–28).

Young's IAT (Y-IAT)

The Y-IAT was used to measure the severity of Internet addiction. All 20 items are rated on a five-point scale from 1 to 5. Thus, total scores range from 20 to 100 (21, 28). The Cronbach's alpha for this study was 0.97.

Beck depression inventory-II (BDI-II)

The BDI-II was administered to assess the severity of depressive symptoms (26, 29). Each item is rated on a four-point scale from 0 to 3, and total scores for all 21 items can range from 0 to 63. The Cronbach's alpha for this study was 0.95.

Beck anxiety inventory (BAI)

The BAI includes a total of 21 items and addresses the intensity of anxiety symptoms (25, 30). Responses are rated on a four-point scale, and scores range from 0 to 3. The total BAI score, which ranges from 0 to 63, is obtained by summing all 21 items. The Cronbach's alpha for this study was 0.94.

Barratt impulsiveness scale-11 (BIS-11)

The BIS-11, which was used to measure impulsivity (27, 31), is a 30-item self-report questionnaire that includes three subscales that measure impulsivity (attention, motor, and non-planning). Each item is rated on a four-point scale from 1 to 4. The Cronbach's alpha for this study was 0.79.

Statistical Analysis

The baseline demographic and psychological variables were analyzed by independent *t*-tests, whereas differences in the psychological variables before and after treatment were analyzed by paired *t*-tests. Separate generalized estimating equations (GEEs) were used to assess the group effects in the EEG data for each frequency band to examine the correlations among repeated measurements (32, 33). Intra- and interhemispheric coherence values were analyzed by the GEEs using the following factors at baseline and at the end of the 6-month outpatient treatment period, respectively: intrahemispheric coherence was analyzed according to group (IGD and HC) × region (fronto-central, fronto-temporal, fronto-parietal, centro-temporal, centro-parietal, and temporo-parietal) × hemisphere (left and right); and interhemispheric coherence was evaluated according to group (IGD and HC) × region (frontal, central, temporal, and parietal). In these analyses, we controlled for education and BDI-II, BAI, and BIS-11 scores to identify group differences. All statistical analyses were performed using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

Demographic and Psychological Variables Before and After Treatment

The patients with IGD did not differ from the HCs in terms of age or IQ. However, significant differences in education, BDI-II, BAI, and BIS-11 scores were observed between the two groups. The demographic and psychological characteristics of the IGD and HC groups are presented in **Table 1**. After 6 months of treatment, patients with IGD had significantly lower Y-IAT scores but not lower BDI-II, BAI, or BIS-11 scores compared with their baseline data (**Table 2**).

EEG Coherence

Baseline EEG Coherence Data

The statistical analysis using the GEEs of intrahemispheric coherence revealed significant main group effects in the beta and gamma bands at baseline after adjusting for demographic and psychological variables (**Table 3**). Specifically, patients with IGD [M (standard error of the mean; S.E.M.) = 48.95 (69.463)] exhibited significantly increased beta intrahemispheric coherence than did HCs [M (S.E.M.) = 41.68 (70.187)]. Patients with IGD [M (S.E.M.) = 58.65 (111.862)] also showed significantly higher coherence in the gamma band than did HCs [M (S.E.M.) = 46.03 (113.029)]. Additionally, an

TABLE 1 | Demographic and psychological characteristics of the study groups at baseline.

Characteristics	IGD patients ($N = 30$)	Healthy controls ($N = 32$)	t	p
Age (years)	23.27 ± 5.15	24.97 ± 3.70	1.50	0.139
Education (years)	12.93 ± 1.83	14.61 ± 2.39	3.044	0.004**
IQ	113.83 ± 13.22	119.53 ± 9.81	1.918	0.061
Y-IAT	69.27 ± 14.78	29.29 ± 8.53	−12.992	<0.001***
BDI-II	18.45 ± 10.27	3.71 ± 3.89	−7.256	<0.001***
BAI	15.24 ± 13.14	5.81 ± 5.43	−3.590	0.001**
BIS-11	68.69 ± 13.15	55.23 ± 8.87	−3.590	<0.001***

Mean ± SD
***$p < 0.01$; ***$p < 0.001$.*
IQ, Intelligence quotient; Y-IAT, Young's Internet Addiction Test; BDI-II, Beck Depression Inventory-II; BAI, Beck Anxiety Inventory; BIS-11, Barratt Impulsivity Scale-11.

TABLE 2 | Changes in the clinical characteristics of patients with Internet gaming disorder (IGD) before and after treatment.

Characteristics	Before ($N = 18$)	After ($N = 18$)	t	p
Y-IAT	71.33 ± 12.12	58.80 ± 22.10	2.454	0.028*
BDI-II	19.31 ± 10.27	19.94 ± 14.67	−0.340	0.738
BAI	18.56 ± 15.51	18.19 ± 16.90	0.248	0.807
BIS-11	69.50 ± 10.16	67.86 ± 9.73	1.827	0.091

Mean ± SD scores for Y-IAT, BDI-II, BAI, and BIS-11.
**$p < 0.05$.*

interaction effect was revealed for group × hemisphere. The IGD group [M (S.E.M.) = 49.11 (68.393)] had significantly increased delta intrahemispheric coherence in the right hemisphere compared to the HC group [M (S.E.M.) = 42.36 (69.106)]. An analysis of interhemispheric coherence did not reflect a significant main effect of group, an interaction effect of group × region, or a group × hemisphere interaction.

Changes in EEG Coherence Data Following Treatment

No significant EEG coherence changes were observed in any of the pre-treatment or post-treatment bands in the IGD group. However, a main effect of group was observed in beta and gamma coherence at the post-treatment assessment (**Table 3** and **Figure 1**). Specifically, patients with IGD [M (S.E.M.) = 53.66 (75.338)] showed increased beta intrahemispheric coherence compared with HCs [M (S.E.M.) = 40.54 (77.143)]. Intrahemispheric coherence for the gamma band was significantly higher in patients with IGD [M (S.E.M.) = 61.41 (126.700)] than HCs [M (S.E.M.) = 46.51 (129.734)] at the post-treatment evaluation. Additionally, according to the post hoc analysis, there was an interaction effect of group × region in alpha coherence but no significant group differences.

DISCUSSION

To our knowledge, this is the first study to investigate longitudinal changes in neural connectivity measured by EEG coherence in patients with IGD. Participants with IGD exhibited increased intrahemispheric EEG coherence in the beta and gamma bands at baseline. However, these abnormal phase synchrony patterns were not normalized after 6 months of pharmacotherapy, even though the patients with IGD showed significant improvements in their IGD symptoms. Accordingly, our results indicate that increased beta and gamma coherence during the resting state may be an important neurophysiological trait marker of patients with IGD.

The IGD group showed significantly greater fast-frequency intrahemispheric coherence than did the HC group at baseline. Beta band activity on the resting EEG is considered to predispose a patient to substance use and is an electrophysiological marker of hyperexcitability due to an excitation–inhibition imbalance in the brain (34, 35). Increased intrahemispheric beta coherence has been related to the vulnerability factor for IGD (17, 36). For example, Youh et al. (17) showed that increased beta coherence in the frontotemporal area was more common in patients with comorbid IGD and major depressive disorder (MDD) compared to patients with only MDD. The authors suggested that enhanced beta coherence may reflect excessive online gaming and indicate the altered neural synchronization between brain regions in patients with IGD.

The increased EEG gamma coherence before treatment is consistent with a previous study (16). Gamma activity is commonly thought to reflect a variety of neural functions, including response inhibition and distribution of attentional resources (37–40). Our research group has reported that increased gamma intrahemispheric coherence is related to dysfunctional impulse control, the reward system, and the severity of IGD symptoms (16). Furthermore, Choi et al. (41) determined that increased gamma activity during a resting state is related to inhibitory impairment and trait impulsivity in patients with IGD. Taken together, these findings suggest inefficient neural synchrony and functional connectivity in patients with IGD.

After 6 months of outpatient management, the patients with IGD exhibited improvements in their IGD symptoms compared with baseline, but they still showed increased beta and gamma intrahemispheric coherence compared with HCs. A few studies conducted using SSRIs reported that pharmacotherapy reduces IGD symptoms (20, 42). Serotonin is thought to play an important role in depression, anxiety, and impulsivity (43). Therefore, treatment with an SSRI appears to be effective in reducing the severity of IGD. However, the present study did not find improvements in altered intrahemispheric coherence in the beta and gamma bands after 6 months of SSRI treatment. These findings suggest that increased fast-frequency coherence can be considered a potential trait marker of IGD rather than a state marker.

The present study was subject to certain limitations. First, our results may be of limited generalizability because the number of participants in this study was relatively small and only male

TABLE 3 | Effects on EEG intrahemispheric coherence controlling for the effects of demographic (education) and psychological (scores on the BDI-II, BAI, and BIS-11) characteristics before and after treatment.

	Comparison between IGD at pre-treatment and HC			Comparison between IGD at post-treatment and HC		
	χ^2	*p*	*Post hoc*	χ^2	*p*	*Post hoc*
DELTA						
Group	1.958	0.162		0.436	0.509	
Group × Region	5.886	0.317		7.705	0.173	
Group × Hemisphere	6.625	0.010*	Right, IGD: pre > HC	1.343	0.246	
Group × Region × Hemisphere	6.661	0.757		5.453	0.859	
THETA						
Group	0.409	0.522		2.165	0.141	
Group × Region	4.089	0.537		8.568	0.128	
Group × Hemisphere	3.656	0.056		1.210	0.271	
Group × Region × Hemisphere	4.740	0.908		7.095	0.716	
ALPHA						
Group	1.074	0.300		0.527	0.468	
Group × Region	9.478	0.091		13.950	0.016*	
Group × Hemisphere	0.627	0.428		0.419	0.518	
Group × Region × Hemisphere	5.473	0.857		3.277	0.974	
BETA						
Group	7.058	0.008**	IGD: pre > HC	14.074	0.000***	IGD: post > HC
Group × Region	8.326	0.139		9.068	0.106	
Group × Hemisphere	0.186	0.667		0.002	0.964	
Group × Region × Hemisphere	6.104	0.806		6.563	0.766	
GAMMA						
Group	8.118	0.004**	IGD: pre > HC	6.355	0.012*	IGD: post > HC
Group × Region	0.972	0.965		2.709	0.745	
Group × Hemisphere	0.122	0.726		0.076	0.782	
Group × Region × Hemisphere	3.736	0.958		5.028	0.889	

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

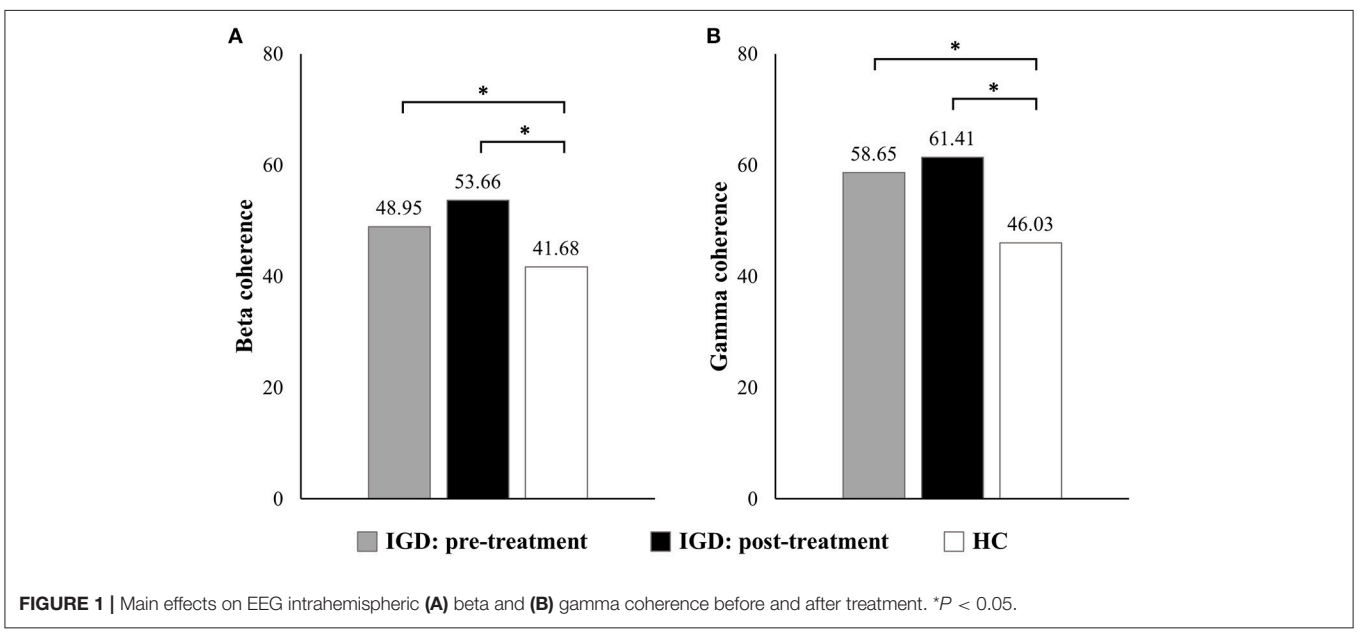

FIGURE 1 | Main effects on EEG intrahemispheric **(A)** beta and **(B)** gamma coherence before and after treatment. *$P < 0.05$.

participants were included. Second, the present study utilized typical outpatient care rather than well-organized treatment modalities. However, this study focused on the changes in phase synchrony patterns in patients with IGD rather than the treatment effects. Thus, additional studies will be needed to elucidate the effect of specific pharmacotherapy treatment on the neurophysiological markers of patients with IGD. Third, all patients with IGD included in this study had comorbid symptoms of depression or anxiety, which may have had confounding effects. Thus, psychological covariates were controlled in the final analysis to control for these comorbid symptoms.

Overall, the present study found that, at baseline, patients with IGD had increased intrahemispheric coherence in the fast-frequency band compared to the HC group. However, this abnormal neural connectivity was sustained after 6 months of outpatient treatment, indicating that the increased beta and gamma coherence during the resting state can be a considered neurobiological marker for the pathophysiology of IGD. The present research will contribute to a better understanding of the neurophysiological networks underlying IGD.

AUTHOR CONTRIBUTIONS

J-SC and SK conducted the design and concept of the study. SP conducted the analyses and led the writing of the manuscript. J-SC guided and supervised the writing of the manuscript. HR, J-YL, AC, and D-JK contributed to conducting the study.

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Factors Statistically Predicting At-Risk/Problematic Internet Use in a Sample of Young Adolescent Boys and Girls in South Korea

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Aims: This study aimed to investigate in a gender-sensitive manner factors related to at-risk/problematic Internet use (ARPIU) in a sample of young Korean adolescents. Given prior findings, we hypothesized we would observe specific temperamental, social and biological measures that would statistically predict ARPIU in boys and girls, respectively.

Method: Subjects included 653 middle-school students from Chuncheon, Korea who completed measures assessing Internet addiction, mood, temperament, and social interactions. Finger digit (2D:4D) ratios were also assessed. Chi-square and logistic regression models were conducted.

Results: Among boys and girls, the ARPIU and non-ARPIU groups showed differences in temperament, mood, social tendencies, and gaming behaviors. In boys, IAT correlated inversely with the 2D:4D digit ratio and novelty-seeking and positively with reward-dependence scores when controlling for BDI scores; these relationships were not found in girls. Multivariate analyses showed that among boys, novelty-seeking, harm avoidance, self-transcendence, and daily time spent gaming statistically predicted ARPIU. Among girls, daily time spent gaming, number of best friends, self-directedness, and cooperation statistically predicted ARPIU.

Conclusion: ARPIU was linked to specific temperamental, behavioral and biological characteristics, with specific relationships observed in boys and girls. Specific risk factors may exist for boys and girls with respect to their propensities to developing ARPIU, suggesting the need for gender-sensitive approaches to prevent ARPIU in youth.

Keywords: adolescent, gender difference, addictive behavior, biomarkers, exploratory behavior, internet

INTRODUCTION

Concerns have been raised that specific types and patterns of Internet use may be problematic for adolescents and their development, and specific youth may be particularly vulnerable to developing problematic Internet use (PIU). As such, identifying features associated with PIU may help in prevention and other intervention efforts. Considering gender-related differences is important

in targeting such interventions and optimizing care. In some studies, PIU has been reported to approximately two-fold more frequent in males as compared to females (1, 2), although other studies report less robust gender-related differences in prevalence (3). Boys and girls also differ with respect to types of online activities performed; for example, boys may spend more time gaming and girls may spend more time chatting and blogging (4). The latter findings suggest that PIU in girls may particularly related to social factors, consistent with females as compared with males tending to report more problems with social networking (5). Gender-related differences have been observed in temperamental features linked to PIU. Temperament may involve biological-based individual differences in reactivity and self-regulation (6) and may be assessed using instruments such as Cloninger's temperament character inventory (TCI) (7). Using the TCI, PIU in boys was linked to high novelty-seeking and harm-avoidance and low reward-dependence, and in girls PIU was linked to high harm-avoidance, low reward-dependence and cooperativeness (8).

Other factors may relate importantly to PIU in a gender-specific fashion. One biologically based physical characteristic, the second to fourth digit length ratio (2D:4D ratio), has been proposed as a possible marker linked to psychological characteristics in males. The 2D:4D ratio differs according to gender/sex, with males typically exhibiting lower ratios (9, 10). This sexually dimorphic feature typically appears around the 9-week point of the prenatal period, and it remains relatively constant from week 14 to adulthood (10, 11). The 2D:4D ratio in part reflects the level of exposure to sex hormones during the prenatal period, with high exposures to testosterone or high sensitivities of testosterone receptors prenatally lowering 2D:4D ratios in males and higher estrogen levels in females increasing 2D:4D ratios (11–13). Several previous studies had conducted to investigate the relationship between 2D:4D ratio and PIU. PIU (14) and problematic video-gaming (15) were associated with low 2D:4D ratios. However, Muller et al. (16) reported the association of 2D:4D and Internet gaming disorder only in females.

Given the above findings, additional research into behavioral, psychological, and biologically based physical factors related to PIU in males and females warrant additional investigation. The most appropriate thresholding for PIU has been debated (17), and data suggest that the more stringent thresholding used in diagnostic criteria for behavioral as compared to substance addictions may miss clinically relevant groups (18). Given that youth may have their developmental trajectories may be negatively impacted by engagement in sub-diagnostic engagement in risk behaviors, we opted to investigate PIU using a relatively liberal threshold (which we term at-risk/PIU, or ARPIU), as we have in prior studies (19–22).

In the current study, we aimed to assess a multiple behavioral, temperamental and physical factors may relate to ARPIU in male and female young middle-school students in South Korea. We based our hypotheses on existing data on PIU from different counties and age groups, with the understanding that environmental, cultural and other factors may have important influences that may alter relationships. We hypothesized that we would identify different factors related to ARPIU in boys and girls. For example, we hypothesized that time spent gaming, novelty-seeking, and the 2D:4D ratio would be related to ARPIU in boys and not girls, whereas time spent chatting and other social factors would be related to ARPIU in girls but not boys.

Abbreviations: BDI, Beck depression inventory; IAT, Young's internet addiction test; TCI, temperament character inventory; JTCI, junior temperament character inventory; NS, novelty seeking; HA, harm avoidance; RD, reward dependence; P, persistence; SD, self-directedness; CO, cooperativeness; ST, self-transcendence; 2D, second digit length; 4D, fourth digit length.

METHODS

Participants

This study involved 665 junior middle-school students (in second and third grades) who resided in Chuncheon city, Gangwon province, South Korea. Two classrooms by school and grade were randomly selected. Participants voluntarily accepted to take the survey and were informed of its purpose and methods. Data were analyzed from 653 students [male: 388 (59.3%), female: 265 (40.5%)] due to exclusion of left-handed individuals (12 students, 2%) given assessment of 2D:4D ratio on the right hand only. The survey was conducted from April 1st, 2013 to June 30th, 2013. The study was approved by the Institutional Review Board (IRB) of Hallym University Chuncheon Sacred Heart Hospital. Each participant submitted a written informed consent form after receiving a full explanation of the study's purpose and procedure. Before this process, letters were sent through the school to parents informing them of the purpose of the survey, its methodology, and the procedure by which they could deny permission for their child to participate in the survey if they wished their child to be excluded, as has been done previously (3).

Questionnaire Components

Participants were asked to complete questions regarding general demographic characteristics including age, gender, self-rated school achievement (above 10% highest, 11–30%, 31–70%, 71–90%, below 10% lowest), the status of family and friends ("living with parents," "experience of having been bullied by others or having bullied others," and "number of best friends"), unhealthy behaviors like drinking and smoking ("experience of drinking," "experience of smoking"), and online activities ("purpose of using Internet," "self-assessment of Internet addiction," "Need to use the Internet," "average minutes of daily Internet use," and "average minutes usually spend daily playing games on the Internet").

Internet Addiction Test (IAT)

The Internet addiction test (IAT) consists of 20 questions using Likert responses (23) and was adapted for use in Korean populations (24). The IAT assesses multiple domains related to PIU including obsessive behaviors, financial losses, underachievement, negligence at home, problems with interpersonal relationships, behavioral problems and emotional changes. A score of 50 or more on the IAT was used to define at-risk problematic Internet use (ARPIU), as done previously

(23). The internal consistency as measured using Cronbach's for the IAT was 0.92.

Junior Temperament and Character Inventory (JTCI)

Following the Temperament and Character Inventory (TCI) developed by Cloninger for adults (7), the Junior Temperament Character Inventory (JTCI) was developed for youth (25). This study used a Korean version of the questionnaire (26). The JTCI evaluates personality, divided into four temperaments and three characteristics. Temperaments consist of novelty-seeking, harm-avoidance, reward-dependence, and persistence. Characteristics consist of self-directedness, cooperativeness, and self-transcendence. The JTCI consists of a total of 108 yes/no questions. The internal consistency as measured using Cronbach's for the JTCI was 0.76.

Depression Scale

The Beck Depression Inventory (BDI) as adapted by Lee (27) was used. The instrument consists of questions along a four-point scale, with the minimum total score being zero points and the maximum 63 points. The scale includes 21 questions regarding emotional, cognitive, motivational and physical aspects of depression. Higher scores reflect more severe depression (Cronbach's Alpha coefficient: 0.86).

Measurement of 2D:4D Ratio

As described previously (10), finger length was measured by putting the right hand on the floor with the right palm facing up, spreading the thumb and collecting the remaining four fingers. The second (index) and fourth (ring) finger length was directly measured from the tip of the finger to the basal crease up to 0.01 mm using a Vernier caliper (28). This measure was conducted by two separate investigators and calculated the mean of the two measurements. The correlations between the two raters was 0.93, indicating excellent inter-rater reliability.

Study Procedure

Surveys and tests were conducted in classrooms. To receive sincere answers on the survey, questionnaires were collected without providing any personally identifiable information. Prior to the surveys and tests, the prepared instruction regarding the intent, purpose and the guaranteed anonymity of the survey was given, and the survey was completed over a 50-min period.

Statistics

Two groups were generated reflecting an ARPIU group and non-ARPIU group. *T*-test and chi-square analyses were performed to investigate between-group differences on demographic factors and patterns of Internet use. Correlation analyses (Pearson's) and partial correlations adjusted for BDI scores were used to investigate relationships between IAT, JTCI, and 2D:4D ratio measures. Multivariate binary logistic regression models were analyzed to identify factors statistically predictive of ARPIU.

RESULTS

Sociodemographic Characteristics and Patterns of Internet Use by ARPIU Overall and by Gender

The ARPIU group was comprised 32.6% of the sample and was predominately male (42.3% of boys vs. 18.5% of girls, $\chi^2 = 40.5$, $p < 0.01$). The ARPIU and non-ARPIU groups showed largely similar sociodemographic characteristics with respect to household structure, academic achievement, drinking and smoking behaviors, and numbers of best friends (**Table 1**). The ARPIU and non-ARPIU differed on Internet-use-related characteristics, with the ARPIU group being more likely to report gaming, having experience buying gaming items, feeling like they were addicted to the Internet, and having felt a need to cut back on their Internet use (**Table 1**). These findings largely extended to both boys and girls. However, among girls, those with ARPIU differed from those without ARPIU on numbers of best friends, with the non-ARPIU appearing more likely to report four or more best friends (**Table 1**).

Comparisons of Internet Use, JTCI and 2D:4D Between the ARPIU and Non-ARPIU Groups Overall and by Gender

The ARPIU group as compared to the non-ARPIU reported spending more time per day using the Internet and gaming, more depression, and greater novelty seeking, harm avoidance and self-transcendence (**Table 2**). The ARPIU group as compared to the non-ARPIU also reported less reward dependence, persistence, self-directedness and cooperativeness, and demonstrated lower 2D:4D scores (**Table 2**). While all of these relationships were also found among boys and most were found between girls, the ARPIU and non-ARPIU did not differ at $p < 0.05$ on the measures of novelty seeking, persistence, self-directedness and cooperativeness, and their 2D:4D ratios were not different (**Table 2**).

Correlations Among IAT Scores, BDI Scores, JTCI Scores, and 2D:4D Ratios Overall and by Gender

IAT scores correlated with BDI scores, scores on all subscales of the JTCI, and the 2D:4D digit ratio in the overall sample (**Table 3**). These findings extended to both boys and girls with the exception of novelty seeking, self-transcendence, and 2D:4D ratio in girls not being significant at $p < 0.05$ (**Table 3**). The 2D:4D ratio was also modestly correlated with BDI scores and reward dependence, cooperativeness in the overall sample only (**Table 3**). However, when controlling for BDI scores, the 2D:4D digit ratio remained correlated with IAT and reward dependence scores overall and among boys, and was also correlated with novelty-seeking overall and among boys (**Table 3**).

Factors Statistically Predicting ARPIU by Gender

A stepwise multiple regression analysis was performed using the independent variables of Internet using characters, BDI,

TABLE 1 | Sociodemographic characteristics and internet-use behaviors stratified by ARPIU-involvement status and gender.

Variable	Total [*N* (%)]		χ^2	*p*-value	Boys [*N* (%)]		χ^2	*p*-value	Girls [*N* (%)]		χ^2	*p*-value
	ARPIU 213 (32.6)	**Non-ARPIU 440 (67.4)**			**ARPIU 164 (42.3)**	**Non-ARPIU 224 (57.7)**			**ARPIU 49 (18.5)**	**Non-ARPIU 216 (81.5)**		
Living with parents (Yes)	188 (87.9)	396 (90.9)	0.937	0.63	149 (90.99)	209 (93.3)	0.80	0.67	39 (79.6)	187 (86.6)	2.48	0.29
Academic average grade												
Above 10%	21 (9.9)	46 (10.5)	7.33	0.12	17 (10.4)	26 (11.6)	6.56	0.16	4 (8.2)	20 (9.3)	5.35	0.25
11–30%	33 (15.5)	96 (21.9)			28 (17.1)	56 (25.0)			5 (10.2)	40 (18.6)		
31–70%	87 (40.8)	181 (41.2)			69 (42.1)	88 (39.3)			18 (36.7)	93 (43.3)		
71–90%	55 (25.8)	97 (22.1)			37 (22.6)	46 (20.5)			18 (36.7)	51 (23.7)		
Below 10%	17 (8.0)	19 (4.3)			13 (7.9)	8 (3.6)			4 (8.2)	11 (5.1)		
Drinking, life time (Yes)	43 (20.1)	86 (19.5)	0.03	0.47	34 (20.7)	58 (25.9)	1.39	0.14	8 (16.3)	28 (13.0)	0.39	0.34
Smoking, life time (Yes)	62 (29.0)	97 (22.1)	3.63	0.06	58 (35.4)	73 (32.7)	0.29	0.33	4 (8.2)	24 (11.2)	1.10	0.22
Number, best friends												
One or less	13 (7.6)	31 (8.1)	0.79	0.85	8 (6.2)	11 (5.7)	0.57	0.90	5 (12.5)	20 (10.5)	10.65	0.01
2–3 persons	75 (43.9)	153 (39.8)			48 (36.9)	77 (39.7)			26 (65.0)	76 (40.0)		
4–5 persons	45 (26.3)	108 (28.1)			38 (29.2)	50 (25.8)			7 (17.5)	58 (30.5)		
More than five persons	38 (22.2)	92 (24.0)			36 (29.7)	56 (28.9)			2 (5.0)	36 (18.9)		
Purpose of using internet												
Searching information	29 (14.3)	124 (32.0)	75.94	< 0.01	15 (9.5)	45 (21.2)	36.75	< 0.01	14 (31.1)	79 (45.1)	11.69	0.01
Chatting, mailing	15 (7.4)	26 (6.7)			8 (5.1)	12 (5.7)			7 (15.6)	14 (8.0)		
Gaming	137 (67.5)	122 (31.5)			128 (81.0)	111 (52.4)			9 (20.0)	11 (6.3)		
Others	22 (10.8)	115 (29.7)			7 (4.4)	44 (20.8)			15 (33.3)	71 (40.6)		
Experienced buying game-items (Yes)	141 (66.5)	202 (46.0)	24.24	< 0.01	116 (71.6)	128 (57.4)	8.16	< 0.01	25 (51.0)	74 (34.3)	5.52	0.06
Felt being addicted to internet (Yes)	73 (34.4)	32 (7.3)	77.62	< 0.01	59 (36.4)	22 (9.8)	40.11	< 0.01	14 (28.6)	10 (4.7)	27.46	< 0.01
Need to cut down using internet (Yes)	130 (61.0)	111 (25.3)	78.30	< 0.01	97 (59.5)	68 (30.5)	32.40	< 0.01	32 (65.3)	43 (20.0)	40.27	< 0.01

TABLE 2 | Comparisons of BDI, TCI, and 2D:4D ratio by gender.

	Total sample (*N* = 653)			Boys (*N* = 388)			Girls (*N* = 265)		
	ARPIU (*N* = 213)	Non-ARPIU (*N* = 440)		ARPIU (*N* = 164)	Non-ARPIU (*N* = 224)		ARPIU (*N* = 49)	Non-ARPIU (*N* = 216)	
	Mean ± SD	Mean ± SD	*p*-value	Mean ± SD	Mean ± SD	*p*-value	Mean ± SD	Mean ± SD	*p*-value
Time for internet (minutes)	137.47 ± 96.27	83.96 ± 72.32	<0.01	141.10 ± 101.13	89.28 ± 79.40	<0.01	126.91 ± 78.16	78.31 ± 63.65	< 0.01
Time for gaming (minutes)	93.90 ± 83.21	38.58 ± 55.58	<0.01	107.61 ± 83.09	58.17 ± 63.31	<0.01	48.83 ± 67.46	17.75 ± 35.80	< 0.01
BDI	11.74 ± 6.53	9.20 ± 6.65	<0.01	10.77 ± 5.46	8.57 ± 5.77	<0.01	14.15 ± 8.32	9.74 ± 7.28	< 0.01
NS	8.70 ± 3.08	7.65 ± 3.04	<0.01	8.68 ± 3.03	7.48 ± 3.20	<0.01	8.73 ± 3.29	7.84 ± 2.87	0.06
HA	12.37 ± 4.34	10.55 ± 4.49	<0.01	12.24 ± 4.38	9.95 ± 4.53	<0.01	12.84 ± 4.26	11.18 ± 4.38	0.02
RD	4.97 ± 1.88	5.85 ± 1.97	<0.01	4.97 ± 1.88	5.56 ± 1.93	<0.01	4.98 ± 1.90	6.15 ± 1.98	< 0.01
PS	2.84 ± 1.26	3.26 ± 1.37	<0.01	2.92 ± 1.23	3.52 ± 1.35	<0.01	2.59 ± 1.37	2.99 ± 1.33	0.06
SD	9.68 ± 3.66	12.01 ± 3.66	<0.01	10.01 ± 3.63	12.41 ± 3.71	<0.01	8.57 ± 3.57	11.59 ± 3.56	< 0.01
CO	12.50 ± 3.26	13.78 ± 3.03	<0.01	12.22 ± 3.23	13.63 ± 3.14	<0.01	13.41 ± 3.23	13.92 ± 2.90	0.28
ST	4.83 ± 2.35	4.31 ± 2.40	<0.01	4.82 ± 2.34	4.27 ± 2.53	0.03	4.88 ± 2.45	4.34 ± 2.25	0.14
2D:4D	0.96 ± 0.04	0.97 ± 0.04	<0.01	0.949 ± 0.03	0.955 ± 0.03	0.05	0.981 ± 0.04	0.985 ± 0.05	0.58

Tested by Independent sample t-test. BDI, Beck depression inventory; JTCI, junior temperament character inventory; NS, novelty seeking; HA, harm avoidance; RD, reward dependence; P, persistence; SD, self-directedness; CO, cooperativeness; ST, self-transcendence.

Temperament and Character factors, Finger digit ratio which showed significant correlation with the online game addiction score from Pearson's correlation analysis by gender. **Table 4** shows the results of the multivariate logistic regression analysis of factors statistically predicting ARPIU in boys and girls. The amount of time spent playing games on the Internet was a predicting factor for ARPIU in both gender groups (**Table 4**). In boys, novelty seeking, harm avoidance and self-transcendence were predictive factors; in girls, self-directedness and the number of best friends were predictive factors (**Table 4**).

DISCUSSION

The present study investigated factors related to ARPIU in a sample of young adolescent Korean students, with a focus on gender. Our *a priori* hypotheses were partially supported in that time spent gaming and novelty seeking were factors predictive of ARPIU in boys and social factors were linked in girls. However, other aspects were not hypothesized, such as that time spent gaming would also predict ARPIU in girls. Implications of the findings are discussed below.

Purposes for Using the Internet

This study's results showed that the non-ARPIU group used the Internet mainly for searching for information (32.0%) and gaming (31.5%), whereas the ARPIU group used the Internet mainly for gaming (67.5%), especially in boys (81.0%). In ARPIU girls, the Internet was used mainly for searching for information (31.1%), gaming (only 20.0%), chatting (15.6%), and other purposes (33.3%). These findings are thus largely similar to those reported previously from other samples (29). Gender may relate importantly to the reasons underlying Internet use and the patterns and types of Internet use. One hypothesis was that males would be more likely to use the Internet problematically for seeking new and exciting experiences, for example through gaming, while females would be more likely to use the Internet problematically when connecting socially through chatting and other means. Other findings only partially support our hypotheses. Whereas for boys novelty seeking and time spent gaming were factors linked to ARPIU and statistically predicted ARPIU in logistic regression analyses, chatting was not linked *per se* to ARPIU in girls (in part perhaps due to the nature of the assessment question). However, the finding linking fewer best friends to ARPIU in girls, with this measure statistically predicting ARPIU in girls in the logistic regression models, suggest that social factors may be particularly relevant to ARPIU among young Korean adolescents. Given the increasing Internet use over time, it will be important to monitor for ARPIU in youth (and other age groups), particularly as the majority of the adolescent boys (90.2%) in South Korea play on-line games (30) and that the use of the Internet to connect socially (e.g., via social networking and other processes) has also been increasing over time (31).

Depression, Temperament and Character, and Digit Ratio

Correlations among IAT scores, BDI scores, JTCI scores, and 2D:4D ratios were identified in this study. The IAT scores showed positive correlations with BDI, consistent with prior findings in other populations (32, 33). Perhaps due to depressive symptoms, adolescents might experience difficulties in learning and engaging in social activities, and thus may use the Internet as a means of avoiding stress (34).

Internet addiction scores showed positive correlations with novelty-seeking, harm-avoidance, and self-transcendence scores

TABLE 3 | Correlations among IAT scores, BDI scores, JTCI scores, and 2D:4D ratios.

		IAT	BDI	NS	HA	RD	P	SD	CO	ST
BDI	T	0.226**								
	B	0.215**								
	G	0.310**								
NS	T	0.158**	0.247**							
	B	0.195**	0.312**							
	G	0.109	0.198**							
HA	T	0.222**	0.435**	0.008						
	B	0.274**	0.458**	0.052						
	G	0.215**	0.423**	−0.062						
RD	T	−0.257**	−0.337**	−0.140**	−0.312**					
	B	−0.191**	−0.322**	−0.151**	−0.387**					
	G	−0.275**	−0.379**	−0.125*	−0.238**					
PS	T	−0.184**	−0.192**	−0.307**	−0.175**	0.135**				
	B	−0.278**	−0.247**	−0.315**	−0.161**	0.144**				
	G	−0.167**	−0.137*	−0.303**	−0.181**	0.179**				
SD	T	−0.299**	−0.491**	−0.341**	−0.468**	0.295**	0.432**			
	B	−0.310**	−0.487**	−0.349**	−0.446**	0.321**	0.403**			
	G	−0.357**	−0.510**	−0.331**	−0.499**	0.283**	0.470**			
CO	T	−0.237**	−0.272**	−0.318**	−0.305**	0.392**	0.217**	0.419**		
	B	−0.241**	−0.326**	−0.339**	−0.362**	0.392**	0.204**	0.442**		
	G	−0.157**	−0.251**	−0.287**	−0.241**	0.364**	0.288**	0.407**		
ST	T	0.133**	0.167**	−0.037	0.074	−0.003	0.011	−0.178**	0.023	
	B	0.148**	0.146**	−0.045	0.015	0.013	0.036	−0.196**	0.077	
	G	0.112	0.200**	−0.024	0.172**	−0.020	−0.026	−0.153*	−0.063	
2D:4D	T	−0.156**	0.096*	−0.074	0.069	0.101**	−0.019	−0.044	0.081*	0.018
	B	−0.139**	0.059	−0.055	−0.015	0.063	0.022	0.027	0.042	−0.033
	G	0.035	0.082	−0.110	0.116	0.031	0.045	−0.087	0.031	0.089
2D:4D#	T	−0.189**		−0.152**	−0.056	0.121*	0.048	0.055	0.095	0.061
	B	−0.174**		−0.141*	−0.028	0.138*	0.038	0.055	0.090	0.015
	G	0.010		−0.109	0.102	0.059	0.054	−0.056	0.036	0.074

*$p < 0.05$, **$p < 0.01$, tested by Pearson's correlation, #Partial correlation between IAT scores, JTCI scores, and 2D:4D ratios when con trolling for BDI scores. T, total sample; B, only boys; G, only girls; IAT, Young's internet addiction test; BDI, Beck depression inventory; JTCI, junior temperament character inventory; NS, novelty seeking; HA, harm avoidance; RD, reward dependence; P, persistence; SD, self-directedness; CO, cooperativeness; ST, self-transcendence.*

and negative correlations with reward-dependence, persistence, self-directedness, and cooperativeness scores and 2D:4D ratio in boys; however, in girls, novelty-seeking, self-transcendence, and 2D:4D ratio relationships were not statistically significant at $p < 0.05$. The positive correlation between Internet addiction score and novelty-seeking were in line with prior findings linking sensation-seeking and impulsivity to Internet addiction (32, 33), and the positive correlation between Internet addiction scores and harm-avoidance (35) suggest that individuals experiencing difficulty in making interpersonal relationships with others in real life (perhaps due to shyness, anxiety, and difficulties in social adaptation) may be particularly vulnerable to using the Internet in problematic fashions.

Reward dependence, persistence, self-directedness, cooperativeness had significant correlations with IAT score in both gender groups. Reward dependence reflects a propensity for being cynical, apathetic, insensitive to social situations, and indecisive and not feeling positive emotions easily. These results are consistent with prior findings reporting that Internet addiction is linked to loneliness and limited social relationships (35). Persistence showed negative correlations with Internet addiction scores. This finding suggests that

TABLE 4 | Factors statistically predicting ARPIU by gender.

Gender	Factors	*B*	S.E.	Wald	*p*-value	Exp (*B*)	95% C.I.
Boy	Time spent gaming	0.006	0.002	11.449	0.001	1.006	1.003–1.010
	NS	0.136	0.043	9.831	0.002	1.146	1.052–1.247
	HA	0.118	0.031	14.676	< 0.001	1.126	1.060–1.196
	ST	0.152	0.057	7.056	0.008	1.164	1.041–1.303
Girl	Time spent gaming	0.009	0.004	4.938	0.026	1.009	1.001–1.017
	Number of best-friends (Ref: less than one persons)	−0.567	0.256	4.915	0.027	0.567	0.343–0.936
	SD	−0.302	0.068	19.639	< 0.001	0.739	0.647–0.845

Multivariate stepwise binary logistic regression analysis. B, β values are the estimated unstandardized regression coefficients. S.E., standard error; C.I., confidence interval; NS, novelty seeking; HA, harm avoidance; RD, reward dependence; SD, self-directedness; CO, Cooperativeness; ST, self-transcendence.

tendencies for Internet addiction may be linked to not feeling a motivation to act when no reward or a small reward is given; speculatively, individuals with low persistence may turn to the Internet (perhaps for gaming) which may provide more instant gratification. Negative correlations were also seen between Internet addiction and self-directness scores. Low self-directness reflects a tendency to pursue shorter- as opposed to than longer-term goals; as such individuals with ARPIU may seek goals through immediate responses from the Internet (36). A negative correlation was seen between Internet addiction and cooperativeness. Low cooperativeness may interfere with the establishment of social relationships, and such tendencies may lead to social isolation and tendencies to use the Internet (over direct interpersonal social relations) and develop ARPIU. Given the similarities in these relationships across gender groups, these features may reflect general tendencies linked to ARPIU.

A negative correlation was seen between Internet addiction scores and 2D:4D ratio in the overall sample and in boys but not girls. Further, the finding persisted when controlling for severity of depressive features. These results resonate with findings linking low 2D:4D ratios to sensation-seeking and risk-taking (37–39), substance addictions like alcohol dependence (40) and Internet addiction in other groups such as Turkish college students (41). Taken together, multiple factors (male sex, low 2D:4D ratios, and specific temperamental features) may relate importantly to ARPIU.

Subtyping of Internet Addiction

The results of this study lay the groundwork for examining the extent to which there may exist subtypes of Internet addiction, similar to those reported in alcohol-use disorders (42). First, factors relating to Internet addiction tendency may vary by gender, with factors like novelty seeking being particularly relevant for males. Second, the biologically influenced 2D:4D ratio, linked to prenatal testosterone exposure, suggests a biological factor linked to novelty seeking and ARPIU in males, particularly when accounting for depressive symptoms. The notion that individuals with high and low depressive features is suggested and warrants additional investigation.

Limitations

There are limitations to this study. First, the participants included solely junior middle-school students in South Korea. While age may not substantially influence some factors (e.g., 2D:4D ratios), future studies should examine the extent to which the findings extend to other populations (e.g., different ages and cultural backgrounds). Second, only right-handed 2D:4D ratios were assessed. Given potential differences in correlations between psychological measures and handedness (43), future studies should consider handedness. Third, clinical assessment through structured interview was not conducted given subject burden, and future studies should consider more precise psychiatric assessments.

CONCLUSION

This study found both gender-specific and shared features across gender groups that related to ARPIU in young adolescents from South Korea. A common finding that time spent gaming on the Internet statistically predicts ARPIU across genders suggest the relevance of public health guidelines related to Internet gaming among youth. The extent to which there may exist subtypes of individuals with Internet-use problems warrants additional study, particularly if such groups may benefit from specific interventions.

AUTHOR CONTRIBUTIONS

S-KL and MP designed the study. Y-JK wrote the protocol. S-KL, DR, and MP managed the literature searches and analyses (including the statistical analysis). Y-JK, S-KL, and MP wrote the first draft of the manuscript. S-KL and Y-JK managed the entire surveys. S-KL, MP, and FC contributed to the analysis and interpretation of data for the work, revised the work. All authors contributed to and have approved the final manuscript.

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Component Model of Addiction Treatment: A Pragmatic Transdiagnostic Treatment Model of Behavioral and Substance Addictions

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Behavioral addictions such as gambling, video games, sex, and shopping share many clinical features with substance use addictions including etiology, course, and neurobiology. Yet, the treatment of behavioral and substance use addictions tends to be separated. However, we argue that a more effective and efficient treatment approach is to conceptualize behavioral and substance use addictions as different expressions of a common underlying disorder and, in treatment, to address the underlying mechanisms common to both. To this end, the article presents a developing transdiagnostic treatment model of addictions that targets underlying similarities between behavioral and substance use addictions, called the component model of addiction treatment (CMAT). The CMAT is transdiagnostic in that it can be used in the treatment of both behavioral and substance use addictions. It is pragmatic in that it targets component vulnerabilities, which are enduring, yet malleable, individual psychological, cognitive, and neurobiological characteristics that are common to all addictive disorders and have been demonstrated to be modifiable. A working model of CMAT is presented, including proposed component vulnerabilities: lack of motivation, urgency, maladaptive expectancies, deficits in self-control, deficits in social support, and compulsivity, as well as their potential intervention possibilities. Future directions and potential implications of the CMAT are discussed.

Keywords: addictive disorders, treatment, transdiagnostic, substance use disorders, behavioral addictions

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COMPONENT MODEL OF ADDICTION TREATMENT: A PRAGMATIC TRANSDIAGNOSTIC TREATMENT MODEL OF BEHAVIORAL AND SUBSTANCE ADDICTIONS

The publication of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (1) marked a significant shift in the field of addictive disorders. For the first time in history, a behavior, as opposed to a psychoactive substance was classified as an addiction. Specifically, gambling disorder (previously called pathological gambling) was moved from the Impulse Control Disorders section of the DSM to the Substance Related and Addictive Disorders section. The re-classification of gambling disorder occurred due to decades of accumulating evidence that gambling disorder shares many commonalities with substance use disorders, which have been well elucidated and summarized in the existing literature (2).

In addition to gambling, internet gaming disorder (i.e., video game addiction) is currently listed in section Unified Theories of Addictive Disorders of the DSM-5 Emerging Measures and Models as a potential psychiatric disorder pending further empirical investigation. Likewise, gaming disorder is included alongside gambling and substance use disorders in the upcoming edition of the International Statistical Classification of Diseases and Related Health Problems—11th Revision (ICD-11) (3). The inclusion of gaming disorder in the DSM-5 and ICD-11 stems from empirical research delineating the similarities between gaming disorder and gambling (4), as well as substance use disorders (2). The inclusion of the aforementioned behavioral addictions in the manual of psychiatric disorders speaks to the rising relevance of behavioral addictions in both research and treatment in the fields of psychology and psychiatry.

BEHAVIORAL AND SUBSTANCE ADDICTIONS: TWO SIDES OF THE SAME COIN?

The past several decades have seen a remarkable growth in the research of behavioral addictions (2). Similarly to gambling and internet gaming, empirical research has examined other compulsive behaviors which have been postulated as behavioral addictions. These behaviors include, but are not limited to: compulsive buying, sex addiction, binge eating, work addiction, exercise addiction, and smartphone addiction (2, 5–8). The overlapping feature common to all behavioral addictions is the failure to resist an impulse or urge, leading to persistent engagement in the behavior (e.g., video games, shopping) despite recurring harms (2).

Despite the similarities between behavioral addictions and substance addictions, there is a debate in the empirical literature as to whether behavioral addictions should be classified as "new" psychiatric disorders (9). Furthermore, there has been a trend in the "scope creep" of behavioral addictions, whereby an increasing number of everyday activities have been proposed as addictive disorders, including for example tanning addiction (10), tango addiction (11), and fortune telling addiction (12). However, what is remarkable when examining the relationship between addictive disorders including both behavioral and substance addictions is the similarities rather than the differences. Indeed, there is considerable overlap in etiological (e.g., onset, natural course), phenomenological (e.g., cravings, pre-occupations), and clinical (e.g., treatment strategies, co-morbidities) presentations across addictive behaviors (2). For instance, behavioral addictions such as gambling and internet gaming disorder, much like substance use disorders, tend to have their onset in late teens or early twenties and follow a variable course of lapses and recoveries (13, 14). Behavioral and substance addictions also tend to share similar risk factors. Adverse childhood experience or childhood trauma such as physical and emotional abuse have been linked to increased risk of developing a variety of addictive disorders including addiction to alcohol, gambling, video games, shopping, and sex (15). In addition, dysregulation in underlying neurobiology such as the dopamine reward system has been found in problematic engagement with gambling (16), video games (17), and shopping (18), and both behavioral and substance addictions share similar executive functioning deficits as demonstrated by deficits in decision making and difficulties in delaying rewards (2).

Importantly, the considerable overlap shared across addictive disorders may have potential treatment implications. Specifically, both behavioral and substance addictions share common clinical processes that may be targeted in treatment. For example, impulsivity, the tendency to act rashly without forethought, has been found to be a key characteristic in a wide array of behavioral addictions including gambling (19), video games (20), sex (21), and shopping (22). Compulsivity is present in both behavioral (23) and substance addictions (24). Emotional dysregulation or low distress tolerance has been associated with gambling (25), compulsive shopping (26), and binge eating (27) and may increase the severity of the addictive behaviors (28). Lack of social supports and interpersonal conflicts have also been demonstrated to negatively affect the onset and severity of substance use disorders such as alcohol (29) and a variety of behavioral addictions (30, 31).

Although there are similarities between behavioral and substance addictions, there are also important neurological differences. For instance, whereas the role of neurotransmitters, specifically dopamine, is robustly implicated in substance use disorder, especially stimulants, the role of neurotransmitters is less clear when it comes to behavioral addictions such as gambling (32). Indeed, a recent meta-analysis of 25 studies on reward processing found increased activation in the ventral striatum during reward outcomes for substance use disorders, whereas gambling addiction was associated with decreased activation in the dorsal striatum (33). Neurological differences have also been found in internet gaming disorder. Compared to alcohol use disorder, internet gaming disorder has been associated with stronger functional connectivity in the left ventromedial prefrontal cortex (34). That said, what is known is that engaging in both behavioral and substance addictions results in the activation of the dopamine reward system, with continued engagement being associated with structural and functional changes (2). In these ways, behavioral addictions closely mimic the hallmark characteristics of substance use disorders (35).

UNIFIED THEORIES OF ADDICTIVE DISORDERS

The similarities among addictive disorders, including behavioral addictions have been noted for decades. Indeed, theoretical models of addictive disorders that view addictions as a common disorder rather than distinct disorders have been proposed as early as in the 1980s (36). The general theory of addictions by Jacobs (36) placed emphasis on two predisposing factors that make an individual at risk for developing an addiction: (i) chronic hypo or hyperarousal and (ii) maladaptive schemas of oneself as inferior. Jacobs (36) argued that coping with negative emotions by engaging in an addictive behavior is a key maintaining factor of addictions. In addition, Jacobs (36) delineated a process model

of addictions, which includes three phases: (i) Phase I, the initial discovery in which one learns that engagement in addictive behaviors can alleviate negative affect, (ii) Phase II, the phase in which the positive reinforcing effects of the addictive behavior become over-learned and lead to compulsive-like behaviors and are thus resistant to change, and (iii) Phase III, the phase in which the individual actively avoids experiencing the aversive state that the addictive behavior was alleviating by continuing to engage in the addictive behavior despite the continued harms. Jacobs (36) argued that the predisposing factors and the three phases are uniform across all addictive behaviors.

Orford (37, 38), in his excessive appetites model of addictions, emphasized psychological processes that lead to an appetitive behavior such as alcohol use, smoking, gambling, drug use, eating, and sex that may become excessive. Orford's highlighting of psychological processes was a significant contribution given many theories of addictions focused on the physiological processes that result from ingestion of a psychoactive substance. The focus on psychological processes acknowledges a range of activities that may lead to impairments with excessive engagement. In other words, this theory provides a conceptual model of addictions that allows for the inclusion of behavioral addictions. The excessive appetites theory of addictions shares overlapping components with the general theory model of addiction, including learning processes in which people associate addictive behavior with alleviation of negative affect (i.e., emotional regulation).

The syndrome model of addiction (39) introduced the concept of multiple and interacting biopsychosocial antecedents, manifestations, and consequents of addictive disorders. Shaffer et al. (39) described the addiction syndrome as a cluster of signs and symptoms related to a common underlying dysfunction. The presence of a syndrome suggests commonalities between different expressions of addictive behaviors, and these commonalities share similar etiologies. The environment, which allows repeated interactions with a specific substance or behavior, determines the specific addiction. An important contribution of the syndrome model of addiction is the acknowledgment that there are, as well, unique features associated with each specific addictive behavior, despite the underlying syndrome. For example, if a person repeatedly engages in alcohol use, then the manifestation of the addiction syndrome and its consequences will have some characteristics that uniquely reflect problems associated with alcohol such as high blood pressure, liver cirrhosis, and pancreatitis. Conversely, if one interacts repeatedly with a slot machine, then the manifestation of this syndrome will have some features that uniquely reflect gambling such as chasing losses and financial debt. Internet gaming may lead to sleep disturbances such as insomnia given the significant amount of time an individual can spend playing video games (40). However, the various expressions of addiction will also share common manifestations and sequelae such as psychological distress, the use of addictive behavior to cope with negative affect and impairments in family life, and work life.

The components model of addiction also conceptualizes addictive disorders based on their commonalities (41). According to this model, all addictive behaviors consists of six core components: (i) salience, which refers to the addictive behavior becoming the most important activity in a person's life and may manifest as pre-occupation or craving; (ii) mood modification which refers to subjective enhancement such as getting high or alleviating negative affect, in other words, coping; (iii) tolerance which is the need to increase the frequency, duration, or amount of a particular addictive behavior to get the same effects; (iv) withdrawal symptoms, which are unpleasant physiological and psychological effects experienced when an addictive behavior is discontinued; (v) conflict that can be either personal and interpersonal that arise due to continued engagement in addictive behaviors; and (vi) relapse, which refers to the reversion back to previous levels of engagement when attempting to reduce an addictive behavior. Griffiths (41) argued that for a behavior or substance to be conceptualized as an addiction, all of the above components need to be demonstrated.

The above models are similar in that they each postulate, in one fashion or another, the commonalities between addictions. However, there are also important differences. The syndrome model of addictions (39) acknowledges that despite the similarities across addictions, there also exists unique manifestations. Orford privileged certain addictions (e.g., alcohol, nicotine, gambling, food, and sex) as "excessive appetites" whereas the other models remain relatively impartial, with the exception of noting that alcohol and gambling are the prototypical substance and behavioral addiction respectively. Additionally, each model presents strengths and weaknesses. For example, the general theory of addictions (36) was the first to propose a unified theory of addictions. However, the model was based on gambling, and thus was unable to take into account the proliferation of behavioral addictions that exists today. A strength of the excessive appetites model (38) is expanding the scope of behavioral addictions to include food and sex. A potential weakness of this model is a minimal focus on physiological processes of addictions. An important contribution and strength of the syndrome model of addictions (39) is introducing the concept of unique manifestations in addictions. Lastly, a strength of the components model of addictions (41) is providing a model that reduces the similarities of addictions to six core components. However, a potential weakness of such a parsimonious model is the exclusion of other components, which may be important characteristics of both behavioral and substance addictions (e.g., compulsivity).

ALL FOR ONE OR ONE FOR ALL? TOWARD A TRANSDIAGNOSTIC TREATMENT OF ADDICTIONS

The aforementioned theories have all alluded to the potential treatment implications of viewing addictive behaviors as a common underlying disorder. Yet, a unified transdiagnostic treatment model for addictive disorders has not emerged. In contrast, the trend over the past number of decades in

the development of evidence-based treatments for addictive disorders as well as other mental health disorders has been the development of single diagnosis protocols. Indeed, disorder-specific protocols are readily available for both substance and behavioral addictions (42, 43). That said, the diversity in treatment programs are likely the result of responding to the needs of clients, whereas the training of clinicians likely impacts the management of different disorders.

Although protocols have not been developed that capitalize on common underlying factors for addictions, clinicians often intuitively target the underlying similarities in the treatment of their clients' addictions, regardless of whether the presenting problem is alcohol, cannabis, gambling, or sex. Indeed, it has been argued that due to increased demand for treatment, the field of addictions treatment has out of necessity, utilized a more holistic approach and has applied a broader focus on examining processes that underlie multiple problem areas (44). Providing support for this supposition, evidenced-based treatments for addictions such as cognitive behavioral therapy (CBT) for substance use disorders (44, 45) and motivational enhancement therapies (46) use the same treatment strategies regardless of the specific substance or behaviors. In addition, there exists a multitude of 12-step programs for distinct addictive behaviors such as alcohol (Alcoholics Anonymous), cocaine (Cocaine Anonymous), gambling (Gamblers Anonymous), sex (Sexaholics Anonymous), and eating (Overeaters Anonymous). 12-step programs largely operate independently and are disorder-specific, emphasizing each groups' need to embrace "singularity of purpose." That is, an individual who is experiencing problems with alcohol will attend Alcoholics Anonymous, whereas an individual experiencing problems with gambling will attend Gamblers Anonymous and individuals experiencing both disorders are encouraged to attend both groups. However, regardless of which 12-step program an individual attends, the principles of the program and the 12-steps remain very similar. Implicitly then, the treatment of addictions may closely resemble a transdiagnostic approach in practice.

To summarize, there exists a considerable overlap between behavioral and substance addictions, including in psychological processes that may be targeted in treatment. In this light, we present a developing transdiagnostic treatment model for addictions that takes advantage of the underlying commonalities that have been shown to be amiable to change across both behavioral and substance use addictions.

TRANSDIAGNOSTIC TREATMENTS

The term transdiagnostic treatment is used variably to describe a number of different approaches to providing treatment. Sauer-Zavala et al. (47) recently distinguished among three broad categories, all of which have empirical support for their efficacy. The first of these are universally applied therapeutic principles. Treatments such as psychodynamic and CBT models are transdiagnostic in the sense that they are designed to be applied to a variety of presenting conditions. Included in this category are mindfulness-based interventions and acceptance and commitment therapy (ACT) (48). The second type of transdiagnostic treatments are modular treatments that provide clinicians with a number of evidence-based treatment strategies that can be applied according to individualized patient needs. The Harvard University's modular approach to therapy for children with anxiety, depression, or conduct problems (MATCH) (49) is a well-regarded example. The third type of transdiagnostic treatments are interventions that specifically target shared mechanisms that have been implicated in the etiology or maintenance of a group of disorders. These models target what are presumed to be core features of groups of disorders, such as avoidance coping related to high neuroticism, which is targeted by the Unified Protocol for transdiagnostic treatment of emotional disorders (50), and preoccupation with body weight and shape, which is targeted by Fairburn's Enhanced CBT model for eating disorders (51).

Emerging research suggests that transdiagnostic treatments lead to superior outcomes when compared to control conditions and treatment as usual. A meta-analysis of 24 randomized control trials for transdiagnostic treatments for anxiety and depression found medium to large effect sizes in favor of transdiagnostic treatments compared to no treatment control conditions, such as waitlists, and small but significant effect sizes when compared to disorder-specific treatments such as treatment for social anxiety. It has been argued that a benefit of transdiagnostic treatments is that they treat not only the presenting problem, but can also concurrently treat co-occurring problems (47). For example, transdiagnostic treatments for anxiety disorders have demonstrated modest but significant improvements in symptoms of depression, without explicitly treating the depressive disorder itself (50). This is an immense benefit of transdiagnostic treatments in that co-morbidity is the rule rather than the exception in psychiatric disorders (52), including addictive disorders (53).

Applied to the treatment of addictions, rather than targeting a specific addictive behavior, which is the traditional treatment approach, it may be possible to simultaneously influence a variety of current and emerging addictive behaviors by targeting common underlying mechanisms (i.e., component vulnerabilities). This flexible approach benefits not only "traditional" addictions such as gambling disorder or substance abuse, but uncommon and underserved behavioral addictions such as video games, compulsive shopping, sex addiction, and others, which clinicians who specialize in substance use addictions might not feel competent in being able to treat (6). Herein, we define component vulnerabilities as enduring yet malleable individual characteristics that are linked to different expressions of addictive disorders. Some of these vulnerabilities include lack of motivation, the disposition to act rashly when experiencing strong emotions, deficits in self-control, expectancies, and motivations for engagement in addictions, family and social support deficits, executive functioning deficits, and compulsivity.

POTENTIAL BENEFITS OF TRANSDIAGNOSTIC TREATMENT FOR ADDICTIONS

Similar to transdiagnostic treatments for other psychiatric disorders such as anxiety (50), a transdiagnostic treatment approach to addictive disorders would have several benefits compared to the current treatment model of targeting specific addictions. First, treatment would be more efficient. This is because both behavioral and substance addictions are highly co-morbid with one another. For instance, gambling disorder frequently co-occurs with substance use disorders, with point prevalence rates of 58% for any substance use disorder (54). Similarly, previous research has found that substance use disorders co-occur up to 38% with internet use disorder, 46% with compulsive buying, and 64% with sex addiction (2). Additionally, in a large representative sample of Canadian adults, 40% of participants who reported experiencing problems with an addictive behavior in the past 12 months, reported problems with two or more substance or behavioral addictions, with high co-occurrence of both substance and behavioral addictions in individuals (6).

It has long been speculated that the reason for the high degree of co-occurrence of addictive disorder is due to the underlying psychological mechanisms that link two addictive disorders (47). Recent research provides empirical support for this assertion. For example, negative urgency, which is the tendency act rashly under intense negative affect has been suggested to be an important construct that underlies the co-occurrence of gambling and nicotine use (55) as well as alcohol use disorder (56). Thus, rather than taking a sequential approach to treatment by treating first the substance use disorder and then the behavioral addiction or vice versa, the treatment of the co-occurring addictions can proceed in an integrated fashion by targeting the underlying component vulnerability. In the above example, it is possible to influence the alcohol, gambling, and nicotine use by targeting negative urgency, the underlying mechanism that is leading to the expression of all three addictions. Targeting component vulnerabilities in treatment is likely to lead to improvements in not only the primary addiction but also in any secondary addictions that may be present.

The second benefit of transdiagnostic treatments is cost-efficiency (57). There currently exists a variety of treatments for addictive disorders, including for example, psychoanalytic, narrative therapy, solution-focused brief therapies, cognitive behavioral therapy, acceptance-based commitment therapies, and motivational enhancement therapies among others (2, 44, 58–60). In addition to this, several unique therapies have been developed for specific behavioral addictions (42, 61). It is virtually impossible for clinicians to learn and become competent in delivering the dozens of treatment approaches that currently exist or learn new treatments for specific addictive disorders, let alone the unwieldy training costs. A more fruitful approach is to train clinicians in a unified treatment approach that can be used for both behavioral and substance addictions. Indeed, while many treatment models for addictions exists, there is a high degree of overlap in the mechanisms that lead to treatment outcomes (39). Relatedly, the ability for clinicians to treat both behavioral and substance use addictions will allow current services to expand their scope of practice versus creating new services for emerging behavioral addictions.

This approach is in contrast to the current model of treatment services for behavioral addictions. For example, with the expansion of legalized gambling in the 1990s, many jurisdictions funded gambling-specific treatment services that were administratively separate from substance abuse services. A similar trend is beginning to occur for behavioral addictions, where specialized treatment programs are starting to be developed (62). Unfortunately, the creation of specific treatment centers for behavioral addictions may have several unintended consequences, including perpetuating the idea that behavioral addictions represent "unique" psychiatric disorders, despite the empirical literature highlighting considerable overlap between behavioral and substance addictions (2). Clinically, the creation of specific treatment centers maintains the separation of treatment of behavioral and substance addictions, which can be problematic as individuals experiencing problems with emerging addictive disorders, including video gaming, may not be able to access the services they need. Further, for individuals with multiple addictive disorders, it may present confusion as to which treatment services to seek and may result in multiple referrals.

A third benefit to targeting underlying commonalities is that it may decrease the likelihood of individuals engaging in a concept known as addiction substitution. Addiction substitution occurs when an individual who recovers from one addictive behavior (e.g., alcohol) then substitutes their dependency to another addiction (e.g., gambling). Although the empirical literature on addiction substitution is sparse, what is known is that there is considerable change, both increases, and decreases, in other addictive behaviors during recovery. For example, in a large national representative sample of adults from the United States, Blanco et al. (63) found that 13% of people who recovered from a substance use disorder at Time 1, reported having developed a new onset of substance use disorder at Time 2. Furthermore, Hodgins et al. (64) found that among recovered cannabis users, only a small minority (14%) reported no change in other addictive behaviors. Indeed, most people reported that their addictive behaviors either increased (26%), decreased (39%), or both increased and decreased (21%). Interestingly, treatment seeking cannabis users were more likely to report decreasing other substance use and less likely to report an increase in other substance use upon recovery compared to cannabis user who utilized self-directed change. A potential reason for these findings may be due to the fact that in treatment, it is more likely that some aspects of the component vulnerabilities will be addressed as compared to self-directed change, in which the focus may be on the specific addictive behavior.

CANDIDATE COMPONENT VULNERABILITIES (TRANSDIAGNOSTIC MECHANISMS)

Harvey et al. (65) have distinguished between transdiagnostic factors that are descriptively transdiagnostic and those that are mechanistically transdiagnostic. Descriptively transdiagnostic factors are those that are present across disorders but are not etiological or maintaining conditions. Mechanistically transdiagnostic factors are those shown to be causally linked to multiple disorders. In our pragmatic model we include both types of these factors as both can be can targeted in treatment. Over time, empirical evidence will reveal which vulnerabilities are, in fact, important treatment targets. **Figure 1** outlines our developing component model of addiction treatment, highlighting the component vulnerabilities and the corresponding intervention possibilities. With the exception of motivation, the model does not assume a temporal sequencing of the component vulnerabilities to be addressed in treatment. Rather, the clinical decision of sequencing would be determined by individual client needs, specifically assessing which of the component vulnerabilities are most likely to lead to, and maintain the expression of the addictive disorder for each client.

Our pragmatic list of vulnerabilities is not meant to be comprehensive, but it is representative of psychological processes to date that, although enduring, are amenable to change. Furthermore, while we acknowledge that evidence supports high genetic liability among addictions (66), the genetic level of analysis is not currently easily translated into personalized treatment and thus we have omitted the genetic component vulnerability from the model. In contrast, our treatment model focuses on component vulnerabilities that can be directly targeted in treatment and have been shown to be important processes in the expression of both behavioral and substance addictions. In our opinion, we view the component vulnerabilities as culturally invariant because they represent psychological processes that are innate human conditions. While we acknowledge that in certain cultures, a candidate component vulnerability may be more or less likely to play a central role in the expression of an addictive behavior, in all cultures we would expect all the component vulnerabilities listed below to exist to varying degrees.

DEFICITS IN MOTIVATION FOR CHANGE

A cardinal characteristic of addiction is the failure to engage in change despite knowledge that recovery is indeed feasible and, furthermore, that changing the pattern of the addictive behavior is in the best interest of the individual (67). In fact, DiClemente stated that change is the antithesis of addiction (67). While most people do make an attempt to change their addictive behaviors, it typically occurs after several years, and with the accumulation of negative consequences (68, 69). Providing support for this assertion, only 15% of people are actively engaged in removing a problematic behavior from their behavioral repertoire (70). Indeed, ambivalence about change is common among people who engage in a wide array of addictive behaviors including behavioral addictions (71). Unfortunately, however, low motivation has been shown to predict poorer treatment outcomes, including premature treatment termination (72). Thus, prior to addressing the component vulnerabilities listed below, we argue that motivation to engage in change must be addressed if treatment is to be successful and, as such, we consider motivation to change to be an overarching component vulnerability in **Figure 1**.

Motivational enhancement therapies (MET) (46), including motivational interviewing (MI) (70) represent a potential intervention possibility in helping to increase the motivation of clients in overcoming their addictive disorders and to engage in the required treatment processes. MET is a type of client-centered therapy that helps to address ambivalence and enhance an individual's internal motivation to engage in behavioral change. MET assumes that motivation is dynamic and that people are at different stages of motivation when it comes to overcoming addictive behaviors. The goal of MET is to evoke change talk in a supportive and collaborative environment and foster the client's own internal motivation to engage in change (44). Decades of empirical evidence, including randomized controlled trials, support the use of MET in the treatment of addictive disorders. Several meta-analyses have found that MET is associated with significantly improved outcomes when compared to non-treatment controls and is equivalent to other treatments (73). Specifically, motivational enhancement and interviewing have been supported in the use of a wide variety of addictive behaviors, including alcohol, tobacco, marijuana, and gambling (74). In addition, a recent meta-analysis found that pre-treatment motivational interviewing was associated with greater treatment engagement compared to comparison groups in a variety of mental health settings (75).

The potential benefits of enhancing motivation to improve treatment outcomes for addictive behaviors have also been noted by incorporating motivation enhancement as an adjunct to other treatments (76). McKee et al. (77) found that although there were no differences between participants who received one session of motivational enhancement therapy combined with three sessions of cognitive behavioral therapy compared to those who only received the cognitive behavioral therapy in reduced cocaine use, the inclusion of motivational interviewing resulted in greater treatment attendance following the treatment intervention as well as greater desire for abstinence. In a sample of substance users who also presented with co-occurring gambling problems, Petry et al. (78) found that a combination of motivational enhancement and cognitive behavioral therapy led to greater improvements in gambling outcomes than a brief single session intervention. Motivational interviewing has also been combined with acceptance and commitment therapy with promising results (79).

In addition to helping to resolve ambivalence and enhancing motivation to change, MET can also help clarify and specify individuals' goals for change. Having adaptive and realistic goals is important in facilitating effective self-control of actions and emotions. Moreover, in addictive disorders, establishing clear goals to moderate or cease addictive involvement is an important part of treatment.

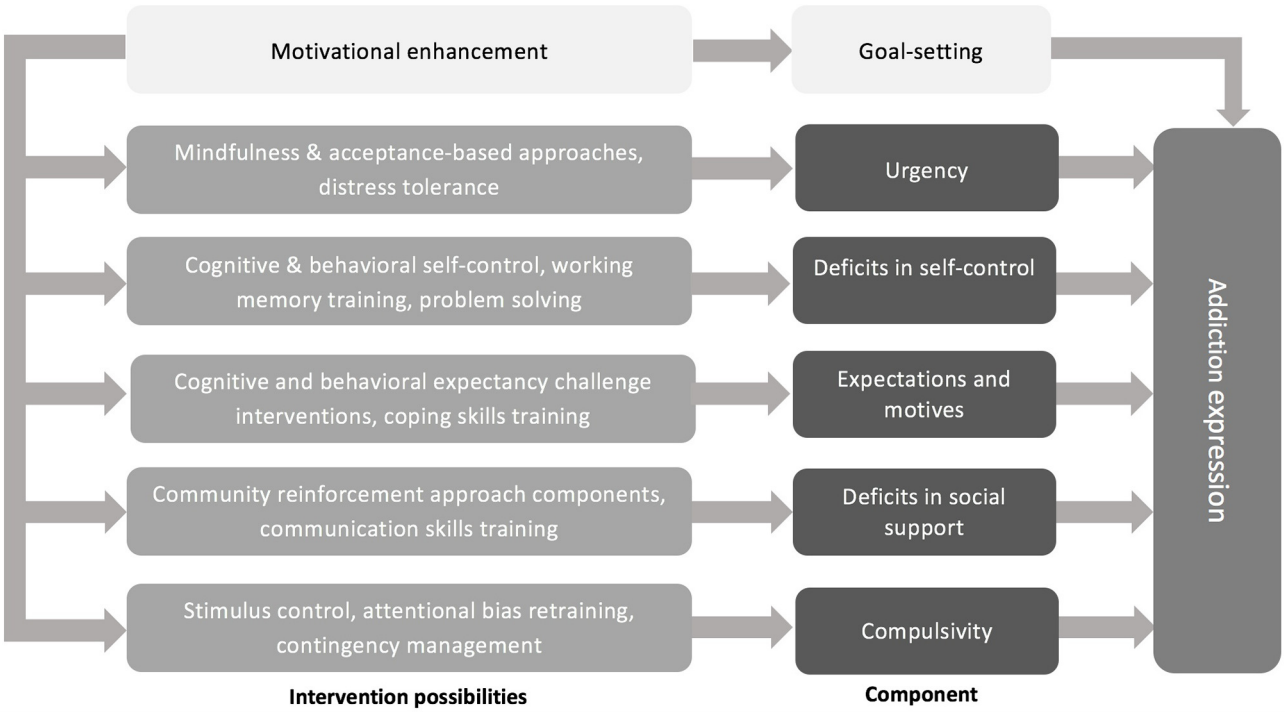

FIGURE 1 | A working model of the component model of addictions treatment depicting component vulnerabilities and the corresponding intervention possibilities.

NEGATIVE URGENCY

Urgency is the disposition to act in rash, ill-advised ways when experiencing intense positive (positive urgency) or negative (negative urgency) affect (80). Negative urgency is the integration of negative affect and impulsivity. In this way, negative urgency helps to explain why people engage in impulsive actions, for example addictive behaviors when emotionally dysregulated (81). Urgency is one of the facets of impulsivity that has received increasing empirical attention given its hypothesized association in the etiology and maintenance of addictions. Negative urgency, in particular, has been robustly associated with substance use disorders such as alcohol (82) as well as behavioral addictions such as gambling (83), video games (84), compulsive buying (85), binge eating (86), and sex (87).

In a meta-analysis of 96 studies (N = 32,167) examining the relationship between facets of impulsivity and its association with problematic alcohol use, Coskupinar et al. (82) found that while impulsivity, in general, was related to alcohol use, negative urgency was the only facet of impulsivity that predicted alcohol dependence and drinking-related problems. The association between negative urgency has also been documented in longitudinal studies with behavioral addictions. In a large sample of Canadian adults (N = 1,002), Farstad et al. (86) found that negative urgency was the only facet of impulsivity that predicted problematic gambling and binge eating, suggesting negative urgency may be an important transdiagnostic mechanism in the expression of both gambling disorder and binge eating disorder, and a component of impulsivity that needs to be addressed in treatment. Indeed, negative urgency has been related to poorer treatment outcomes including relapse in substance use disorder (88). Furthermore, a meta-analysis examining changes in facets of impulsivity reported that sensation seeking and negative urgency were the only facets of impulsivity that significantly decreased during treatment (88).

Distress tolerance is a construct that is related to urgency in that it reflects perceived and actual capability to withstand negative emotional or physical states. Lower distress tolerance, as assessed with simple behavioral tasks (e.g., breath holding, hand grip persistence), also predicts negative treatment outcomes, including increased relapse across substance abuse, smoking, and gambling disorder (89). In addition, distress intolerance amplifies the distress-terminating effects of addictive behaviors (90). Thus, the inability to tolerate negative emotions appears to be an important factor in the etiology and maintenance of both substance and behavioral addictions.

Distress tolerance can be targeted in skills and exposure-based treatments, in which individuals practice cognitive and behavioral tolerance techniques in the context of negative affect. Bornovalova et al. (91) provide preliminary evidence that a six session Skills for Improving Distress Intolerance Program added to residential substance use disorder treatment showed both improvement in distress tolerance skills and clinical outcomes compared with supportive counseling. Furthermore, among smokers with a history of early relapses, people who were randomly assigned to a distress tolerance treatment were over six times more likely to be abstinent compared to a standard

smoking cessation treatment, with the effects being maintained, albeit diminishing overtime (92). More recently, Stein et al. (93) assessed the effects of including a distress tolerance intervention to buprenorphine in the treatment of opioid dependence. At 3 months, 36.5% of people randomly assigned to the distress tolerance program were opioid negative compared to 28% of people who were randomly assigned to the health education program. Although not statistically significant, the distress tolerance intervention led to a small reduction in opioid use. In sum, the literature provides promising support for targeting distress tolerance in the treatment of addictive behaviors.

A recent advancement in the treatment of psychiatric disorders has been the emergence of a body of empirical literature supporting the use of mindfulness-based therapies in the treatment of psychiatric disorders including addictive disorders (94). Mindfulness is broadly defined as attending to the present moment in a non-judgmental manner and reaching a state of awareness that can be cultivated through formal and informal practice (95). Mindfulness is included as a component in dialectical behavior therapy and acceptance and commitment therapy as a technique to promote non-judgmental acceptance of internal physiological, cognitive, and emotional experiences (44). Similarly, mindfulness-based cognitive therapy [MBCT; (79)] is provided to reduce the likelihood of relapse into major depression by encouraging observation versus reaction to negative cognitions. Recently, mindfulness based interventions have been developed in the treatment of addictive disorders (e.g., Mindfulness Based Relapse Prevention) with promising results (96). A systematic review concluded that mindfulness-based interventions have demonstrated support for reducing severity of a wide variety of addictions, including behavioral addictions (97). Interestingly, the authors found that combining mindfulness-based interventions with other active treatments led to the greatest efficacy, suggesting the importance of mindfulness as an intervention strategy in addictive behaviors.

In practice, mindfulness-based interventions help individuals become aware of their specific triggers and increase an individual's ability to stay in the moment with discomforting states (96). In this way, cultivating mindfulness may help individuals become less behaviorally reactive when experiencing negative affect. Indeed, it has been found that a mechanism by which mindfulness helps improve mental health functioning is through lessening cognitive and emotional reactivity (91, 98). Although empirical studies testing the mechanisms by which mindfulness-based interventions lead to improved outcomes for addictive disorders are sparse, there is preliminary support that one potential mechanism is reduction of negative urgency. A review of mindfulness-based interventions for substance use concluded that mindfulness meditation enhances peoples' emotion regulation skills, which is a component of urgency as well as reducing drug use (99). Additionally, in a sample of smokers, Spears et al. (100) found that greater self-efficacy for managing negative affect without turning to nicotine use was a mechanism by which mindfulness-based interventions led to improved outcomes compared to usual care. Thus, there is increasing support for urgency as a potential intervention target in the treatment of addictive disorders.

DEFICITS IN SELF-CONTROL

Self-control refers to the ability to focus awareness beyond immediate stimuli (101). It involves the ability to purposely direct one's actions toward a goal (102), which may involve short terms goals such as limiting the time spent playing video games, not stopping at the bar on the way home, as well as long terms goals such as abstaining from an addictive behavior. This vulnerability has been examined in various research lines showing that addicted individuals have significant deficits, including shortened time perspective and self-control resource depletion. It has been suggested that people have a finite amount of self-control capacity, known as the resource depletion model, whereby if individuals use their self-control capacity for multiple tasks, less becomes available for other tasks (103).

A related construct to deficits in self-control is deficits in executive functioning. Executive functioning are cognitive functions that direct the ability to organize, plan, problem-solve, and coordinate thought and action toward goal-directed behavior, thus facilitating self-control (104). It consists of several top-down cognitive processes such as inhibitory control and working memory (105). It is now well established that deficits in executive functions measured by tasks such as the Iowa Gambling Task and Wisconsin Card Sorting Task have been implicated in a wide array of addictions including both substance use disorders (2, 106) and behavioral addictions (107, 108).

There are several intervention possibilities to increase individuals' self-control capacity, including working memory training to improve executive functions (109). Several empirical studies support the use of working memory training in the treatment of addictions. Houben et al. (110) randomly assigned problem drinkers to 25 sessions of working memory training or control tasks. They found that participants who completed the working memory training showed improvements not only in working memory but reduced alcohol intake at 1 month follow up. Importantly, the reduction in problematic drinking was mediated through improvements in working memory. Additionally, preliminary evidence suggests that computerized tasks such as the Dual N-Back task can enhance executive functions and may show promise in the treatment of addictions (111).

Self-control training has also been shown to improve self-control and help with smoking cessation (112). There are a variety of tasks to improve self-control ranging from strengthening one's hand grip to avoiding sweets and implementation intentions, which are if-then statements created to help with high-risk situations (113). There is now empirical evidence to support that self-control capacity can be enhanced through deliberate practice (103). Goal management training (114), designed to remediate executive dysfunction, has been shown to be effective in improving response inhibition and decision-making in individuals with alcohol problems (115).

Problem-solving therapy is another transdiagnostic approach to addressing deficits in self-control that impede effective problem resolution (116). A central component of this approach is training individuals to use a structured process to identify possible solutions to well-defined problems to combat cognitive

and emotional overload, biased cognitive processing of emotion-related information, and ineffective problem-solving strategies (116). Although problem-solving therapy has demonstrated empirical support for the treatment of other psychiatric disorders, specifically depression (117) and is included as a treatment intervention in some treatment manuals for addictive disorder (43), to our knowledge, no studies have directly tested the potential of problem solving therapy in the treatment of addictions.

EXPECTANCIES AND MOTIVES

Cognitive expectancies for the effects of addictive behaviors have been found to be an etiological and maintaining factor of addictive disorders (118). To this end, two types of dysfunctional beliefs have been identified: permissive beliefs and anticipatory beliefs (45). Permissive beliefs are thoughts that provide a justification for engaging in addictive behaviors, for example, *"it has been a long week; I deserve this."* On the other hand, anticipatory beliefs are thoughts in regard to what engaging in addictive behavior will do for the individual, such as *"drinking will help me feel better."* Both types of beliefs may serve to maintain and exacerbate engagement in addictive behaviors. CBT has been identified as the gold standard treatment for a variety of substance use disorders (119, 120), including behavioral addictions such as gambling (121). A component of CBT is helping individuals identify and challenge maladaptive cognitions that are maintaining the addictive behavior (44). Specific cognitive and behavioral substance use expectancy challenge interventions have also shown efficacy (122, 123). For example, a meta-analysis involving 14 studies with 1,415 participants found that compared to control conditions, expectancy challenge interventions resulted in reducing positive expectancies in regard to alcohol. Importantly, expectancy challenge interventions also resulted in improved treatment outcomes for problem drinking (122). Restructuring of maladaptive cognitions have also demonstrated efficacy as a treatment target for gambling disorder (124).

Relatedly, motives for why people engage in addictive behaviors have been prospectively linked to problematic engagement in a variety of addictive disorders (57, 125). Generally, speaking, three primary motives for engaging in addictive disorders have been identified. These motives include: (i) enhancement motives (i.e., engaging in addictive behaviors to enhance excitement and positive affect), (ii) social motives (i.e., engaging in addictive behaviors for social benefit), and (iii) coping motives (i.e., engaging in addictive behaviors to alleviate negative affect). The empirical literature has consistently found that of all the motives, coping motives has been robustly associated with problematic engagement of addictive behaviors, including both behavioral and substance addictions (56, 126). Moreover, our recent work suggests that common motives underlie comorbid alcohol, gambling, and eating problems (127, 128).

Coping skills training is based on the premise that people engage in addictive behaviors to alleviate negative affect (129). If an individual's only means of coping is to engage in addictive behaviors, then an effective treatment strategy would be to help individuals develop more adaptive ways of coping. Adaptive coping skills can vary widely from practicing intrapersonal skills including relaxation training to interpersonal skills such as practicing refusal skills. Coping skills training has been shown to lead to greater treatment improvements as an adjunctive therapy (130, 131). In a sample of marijuana users, Litt et al. (131), tested the mechanisms of behavior change in one of four conditions; control, motivational enhancement plus coping skills, contingency management, and combination of all three active treatments. The results found that longer term abstinence of marijuana was predicted most strongly by the use of coping skills. Coping skills training has also been demonstrated to reduce problem drinking up to 12 months post treatment (130). Moreover, in individuals addicted to gambling, Petry et al. (132) found that regardless of whether problem gamblers were randomly assigned to attend a self-help group or self-help plus professional treatment, coping skills increased over time, although those who received professional treatment reported greater increases in coping skills. Importantly, increased coping skills partially mediated improved treatment outcomes at 2-month post treatment.

DEFICITS IN SOCIAL SUPPORT

Deficits in social support have been consistently linked to the expression of addictive disorders, including alcohol (29), cannabis (133), illicit drugs (134), as well as behavioral addictions such as gambling (135) and video games (31). Furthermore, lack of social support has been associated with poorer treatment outcomes (136), and increases the chance of relapse (137). For instance, interpersonal conflicts may result in increases in negative affect, which then leads an individual to engage in addictive behaviors as a means of coping (138). Enabling, that is, the well-intentioned but unhelpful behaviors of friends or family is another concept that has been shown to increase the use of addictive behaviors (139).

Interventions that enhance and reinforce social and family supports are well supported in the treatment of addictive disorders (138). For example, a therapeutic benefit offered by 12-step programs is social support such as access to a sponsor (140). Additionally, family-based therapies and behavioral couples therapy have shown efficacy in the treatment of a variety of addictive disorders (141–143). An approach that has garnered increasing support in the treatment of addictions is the community reinforcement and family training (CRAFT) approach. The CRAFT approach, involves including concerned significant others of addicted individuals in treatment to engage the addicted individual, as well as to teach social skills (144). There now exists support for the use of CRAFT in the treatment of various addictive behaviors including alcohol, cocaine, and opioid dependence (145). The CRAFT approach has also demonstrated some support in the use of behavioral addictions (145–147). In a study of 31 concerned significant others of individuals addicted to

gambling, those who received a manual based on CRAFT principles reported greater reduction of gambling in their loved ones. Training in communication skills has been shown to result in increased relationship satisfaction (148) and has demonstrated some support in the treatment of addictive disorders (149). Providing support for the use of communication skills training in the treatment of addictions, Monti et al. (150) found that among problem drinkers, those who received communication skills training in conjunction with coping skills training reported greater reduction in problematic drinking up to 12 months compared to those who received a control treatment.

COMPULSIVITY, MALADAPTIVE PERSEVERATION OF BEHAVIOR

Compulsivity refers to repetitive engagement in a behavior (151). It is also termed impairment of control. Although, compulsivity shares overlap and is often confused with impulsivity, compulsivity is conceptualized to be a distinct construct from impulsivity (151). Importantly, it has been proposed that whereas impulsivity plays a prominent role in the development of addictive behaviors, compulsivity emerges overtime and maintains addictions through a cycle of negative reinforcement (152). In other words, compulsivity serves to maintain addictions through rigid patterns of coping strategies in response to negative affect.

The incentive-sensitization theory of addictions provides empirical support for the role of compulsivity in the manifestation of addictive disorders (153). According to this theory, liking, (i.e., the hedonistic aspect of addictions) and wanting (i.e., the compulsive aspect of addictions) are two separate states. Although individuals at first engage in addictive behaviors for the hedonistic aspect, over time and with repeated engagement, individuals continue to "want" to engage in the addictive behavior without "liking" it. In other words, engaging in addictive behaviors may become a compulsion that is cue-dependent, triggered by certain situations, people, places or internal states. The incentive-sensitization theory has been applied to substance use disorders (154) as well as with behavioral addictions (153). Support for the incentive-sensitization theory comes from attentional bias research, in which problematic engagement with addictive behaviors is associated with a preferential view toward addiction-related stimulus to substances such as alcohol (155) and behaviors such as gambling (156), video games (157), food (158), and shopping (159).

Stimulus control, attentional bias retraining, and contingency management may represent potential intervention possibilities for this component vulnerability. These approaches may prevent the activation of the sensitized networks that mediate the motivation processes in compulsively engaging in the addictive behavior (154). Stimulus control is based on the principle of classical and operant conditioning and helps individuals avoid or reduce the learned association between addiction-related cues and the desire to engage in the addictive behavior. For example, stimulus control may involve avoiding certain places, people or things that have become associated with the addictive behavior. Stimulus control has been shown to be a very frequently used change strategy in recovery from addictions (160) and case studies have demonstrated the potential for the use of stimulus control in the treatment of addictions (161).

Attentional bias retraining is also another potential treatment possibility. Attentional bias refers to an unconscious process by which addicted individuals attend to addiction related cues, and subsequently have difficulties disengaging with the cues, which is thought to increase cravings and the risk of use (162). There have now been several meta-analyses that support the use of attentional bias modification in the treatment of addictive behaviors, which have demonstrated significant improvements in reducing attentional bias (162) Although the effects of attentional bias training on decreasing cravings remains unsupported, attentional bias training has demonstrated improved treatment related outcomes in problem drinkers including decreased length of stay in treatment as well as delaying the onset of relapse (163).

Contingency management is based on the principles of reinforcement and provides people tangible rewards (e.g., gift cards) for evidence of behavioral change, for example maintaining abstinence. There now exists several treatment studies supporting the use of contingency management in the treatment of a wide variety of addictive disorders, including alcohol, gambling, stimulant use, cannabis, nicotine, and opioids (164). The improved treatment outcomes not only include increased retention but also a reduction of addiction-related symptoms.

COMPONENT MODEL OF ADDICTION TREATMENT

The CMAT (**Figure 1**) is a transdiagnostic treatment in that it can be used in the treatment of both behavioral and substance addictions. It is pragmatic in that it targets component vulnerabilities that are common to both, and that has been demonstrated to be modifiable. Importantly, the CMAT is empirically grounded in that the component vulnerabilities have all been empirically shown to be important etiological and maintaining factors for addictive behaviors and can be targeted in treatment. It is a hybrid of the three broad categories of transdiagnostic treatments described by Sauer-Zavala et al. (47). It draws upon treatment models that can be universally applied to addictive and mental health disorders, such as MET and ACT. It is also modular in that remediation of any of the specific components can be emphasized based on the specific presenting needs and treatment progress of individual clients. Finally, the CMAT fits the third category of transdiagnostic treatments identified by Sauer-Zavala (47) in that the hypothesized components included in this treatment model have been found to be core mechanistic features of addictive disorders.

In our opinion, we believe that all the components below are necessary yet insufficient in and of themselves as an effective treatment for addictions. In other words, for effective treatment, all components would need to be addressed to varying degrees. The components and their related treatment interventions are also not conceptualized as independent, but rather are linked. Indeed, treatment interventions likely impact multiple vulnerabilities. In addition, we advocate that the components listed below be individualized by modifying the varying degrees of focus on each of the components. For example, while urgency, social support, and maladaptive expectancies are all important treatment components, some individuals may require greater intervention in urgency, while others may require more focus on changing maladaptive cognitions. In this way, the CMAT is flexible in nature, without changing the underlying protocol depending on the addictive behaviors. Furthermore, we believe that the CMAT can be delivered as an individual therapy and as a group treatment, specifically as part of a step-cared approach for the treatment of addictions. This is because the components do not have to be addressed sequentially in treatment. This allows the treatment to proceed by addressing each of the components delivered via a group format. Thereafter, referrals for individualized treatments can be made based on individual needs to target the specific components. Thus, the CMAT will require clinicians to be skilled in the delivery of multiple therapeutic interventions. Clinicians will also need to be flexible in adapting the intervention possibilities based on client needs in order to address the component vulnerabilities that are maintaining the addictive behavior.

The goals of treatment (i.e., harm reduction or abstinence) will likely be dependent on several factors including the preference of the client and the clinicians views of recovery. Indeed, there is currently no one agreed upon definition of recovery, and there are multiple pathways that an individual can take to overcome their addiction (165). Furthermore, whether the goal of treatment is harm reduction or abstinence may depend on whether the addictive behavior is a behavioral or substance addiction. This is because, whereas the traditional goal of treatment for substance use disorders has been abstinence based (165), such an approach may not be possible when it comes to primary rewards such as sex and food. This has led to traditional abstinence-based 12 step programs to make exceptions such as no extramarital sexual intercourse, opposed to all sexual intercourse in the case of Sexaholics Anonymous (166) and the avoidance of certain food groups in the case of Overeaters Anonymous (167). However, these approaches have led to concerns, for example restricting any sexual activity for individuals who are not married and the potential development of disordered eating caused by avoiding certain food groups. Thus, in the case of certain behavioral addictions, harm-reduction approaches may be more appropriate. Harm-reduction approaches aim to reduce the negative consequences of addictions, as well as increase an individual's well-being. Importantly, harm-reduction has been shown to be effective in the treatment of both behavioral and substance addictions (89).

UNIQUE DIFFERENCES IN ADDICTION AND ITS POTENTIAL TREATMENT IMPLICATIONS

In line with Shaffer et al. (39), we recognize that different expressions of addictive disorders present with unique differences that may have important treatment implications. For example, there are differences regarding physical dependency between behavioral and substance addictions. While the presence of withdrawal symptoms are well-established for substance use disorders, it is disputable in the case of behavioral addictions (168). A recent systematic review concluded that the evidence base for withdrawal symptoms in internet gaming disorder is underdeveloped (169). Furthermore, withdrawal symptoms of behavioral addictions have largely manifest as psychological symptoms such as irritability and restlessness (168), rather than physiological symptoms, although physiological symptoms of withdrawal have been observed in gambling disorder (170, 171). The debate regarding the presence of withdrawal symptoms is not limited to behavioral addictions. Until recently, the presence of withdrawal symptoms in cannabis use disorder was debated, and was only included in the DSM-5 due to accumulating evidence (1). In a similar vein, more research is needed to demonstrate the concept of tolerance and withdrawal for behavioral addictions. The presence of withdrawal symptoms is an important factor that needs to be taken into account in the treatment of addictions as they are associated with increased risk of relapse (89). As such, a greater emphasis on the management of withdrawal symptoms may be warranted for certain addictions.

There are also differences in the physical dependency of addictions. For example, heroin, cocaine and barbiturates have been identified as having the greatest physical dependency (172). Additionally, different addictions are associated with varying degrees of both personal and interpersonal harms, with alcohol having been identified as the most harmful (173). The differences in physical dependency between addictive behaviors have basic treatment implications. For example, the risk of overdose is greater for substance use disorders, such as opioids (174) whereas the risk of overdose does not apply to behavioral addictions. Physiological individual differences may also influence the development of certain addictions, including alcohol (e.g., *ALDH2* and *ADH1B*) (175). Although physical dependence has yet to be demonstrated in behavioral addictions, certain behaviors have greater potential to lead to the development of addictive behaviors. Indeed, whereas there are countless behaviors, only a handful have been proposed to lead to addiction-related symptoms, suggesting certain compulsive behaviors have greater dependency potential than others (176).

Lastly, the negative consequences vary depending on the addictive behavior, which need to be taken into treatment considerations. For instance, the risk of sexually transmitted infections are greater for intravenous drug use (39) and compulsive sexual behaviors (177), whereas financial consequences may play a more prominent role in compulsive shopping (178) and gambling disorder (179). Additionally,

individuals with gambling problems may benefit from a specific focus on the "gamblers fallacy" (i.e., erroneous cognitions about the ability to control the chance of an outcome). Individuals involved with illicit drugs, may face greater legal consequences and as such may require focus on the potential legal consequences associated with their illicit substance use. It would be of benefit for clinicians to be cognizant of these important differences and tailor the treatment accordingly.

CURRENT AND FUTURE DIRECTIONS

Although the CMAT is grounded in empirical research, studies are needed to test out the assumptions of the CMAT model as there is currently no data that speak to the efficacy of the CMAT. Furthermore, studies are needed to determine whether the component vulnerabilities listed represent important mechanisms that account for treatment efficacy across a range of addictive disorders. Indeed, while we found generally strong support for the intervention possibilities listed in the CMAT model for substance use disorders, more empirical evidence is needed in the treatment of behavioral addictions, specifically other than gambling disorder. It is our hope that the model inspires both basic and applied research on these issues. Furthermore, there are likely other component vulnerabilities that have yet to be elucidated and may represent important mechanisms which can be targeted in treatment. To this end, we are currently engaging in a program of research that aims to identify and provide further empirical support for the components in the CMAT model through a multi-method approach with diverse populations. For example, we are currently conducting a quantitative study using a lay-epidemiological approach to identify the most important symptoms for 10 addictive behaviors (e.g., alcohol, cannabis, gambling, video games, sex, etc.) from people with lived experiences to identify commonalities as well as unique manifestations. Furthermore, we are assessing common clinical processes (e.g., impulsivity-compulsivity) that may be important across people seeking treatment for a variety of addictive disorders including both behavioral and substance addictions.

In regard to the CMAT, we are in the midst of developing a treatment protocol and will be testing the effectiveness of the treatment model and whether improvements are mediated by the component vulnerabilities on an individual basis, as well as a treatment protocol that will be delivered in a group format in Canada. Furthermore, we will be piloting the treatment protocol in Brazil to test whether the treatment model can be applied across diverse cultures. Future directions will involve creating an assessment tool that will have clinical validity in helping treatment providers determine which component vulnerabilities are the most important to target in treatment. Additionally, we have begun a program of research that also aims to address the treatment needs of co-occurring addictions and mental health concerns. Indeed, concurrent disorders tend to be the rule rather than the exception in addictions treatment (6). Importantly, similar component vulnerabilities have been implicated in the etiology and maintenance of mental health disorders including negative urgency (56) and impulsivity (39). To this end, we have assessed whether similar component vulnerabilities represent common factors that exacerbate the severity of mental health and addictive disorders. For example, we have found that heightened levels of impulsivity mediate the relationship between dual diagnosis of gambling and psychosis, and increased gambling severity (180). Relatedly, we have found that maladaptive expectancies mediate the relationship between co-morbid gambling and depression, and increased gambling severity. We are extending this line of work with non-treatment seeking samples as well as examining component vulnerabilities that are important in the co-morbid expression of mental health disorders and other behavioral and substance use addictions.

While we remain cautiously optimistic about the potential benefits of the CMAT, we would like to note where alternate treatment approaches may be more appropriate. First, is in the treatment of opioid dependence, which often involve the use of pharmacological treatments such as opioid agonists. In a review assessing the effectiveness of the addition of psychosocial intervention along with opioid agonists, the inclusion of psychosocial interventions did not lead to improved treatment outcomes including treatment retention, adherence to treatment or abstinence from opioid use (181). Further, the authors found that these null-results held regardless of the type of therapy intervention. In our review of the literature on the component vulnerabilities, we also found some evidence to suggest that the use of psychosocial interventions such as cue-exposure may have deleterious effects on the treatment of opioid dependence (182).

Secondly, one of the hypothesized benefits of the CMAT is in the treatment of co-morbid addictions. However, we should note that both behavioral and substance use addictions are also highly co-morbid with other mental health disorders, with high prevalence rates of co-morbid mood and anxiety disorders (54, 183). While we believe that several of the components listed in our CMAT model may be applicable to co-occurring substance use and mental health concerns, our literature review was limited to component vulnerabilities implicated across addictive disorders, as opposed to component vulnerabilities in co-occurring mental health and addictions. Thus, caution is warranted in applying our model to co-occurring addictions and mental health concerns, and we advise the use of concurrent disorder treatments in these instances.

The current and future directions noted above are only the start of an ongoing program of research. To the extent that new evidence emerges identifying new component vulnerabilities, and advancements are made in the treatment of addictive disorders, the CMAT will be revised to reflect the latest evidence base in the treatment of addictive disorders. Indeed, it is our hope through an ongoing process that the CMAT will represent an evidenced-based treatment for both behavioral and substance addictions, including addictive disorders that are well recognized, as well as emerging addictive disorders.

CONCLUSION

Addictive disorders represent one of the most common psychiatric disorders in the general population and are associated with significant degradation in psychological, physical, and

social impairments (184). The treatment of addictions has advanced significantly in the past several decades, with the development of evidence-based treatments (44). However, the recent proliferation of behavioral addictions has created the need for the development of a unified treatment for addictive disorders, which may help to increase the efficiency, effectiveness, and accessibility of addictions treatment for traditional and emerging addictions. The CMAT represents to our knowledge, the first attempt in developing a unified treatment approach to addictions. It is our hope that the presentation of the CMAT will generate further research in transdiagnostic mechanisms across addictive disorders and in turn, facilitate the creation of a unified treatment of addictions that may help people live a life free from their addiction.

AUTHOR CONTRIBUTIONS

HK wrote the first draft of the manuscript. DH wrote parts of the manuscript and edited subsequent versions.

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OPINION
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Introducing Precision Addiction Management of Reward Deficiency Syndrome, the Construct That Underpins All Addictive Behaviors

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Worldwide daily, millions of people are unable to combat their frustrating and even fatal romance with getting high; for some, "high" may be just experiencing feelings of well-being. The neuroscience community conducts and funds, outstanding research using sophisticated neuroimaging and molecular-genetic applied technology to improve understanding of the complex functions of brain reward circuitry that has a key role in addiction symptomatology. While it is widely accepted that dopamine is a major neurotransmitter implicated in behavioral and substance addictions, there remains controversy about how to modulate dopamine clinically to treat and prevent various types of addictive disorders. A prudent approach may be biphasic; a short-term blockade followed by long-term dopaminergic upregulation. The goal of treatment would be to enhance brain reward functional connectivity volume, and target reward deficiency and the stress-like anti reward symptomatology of addiction. Such phenotypes can be characterized using the Genetic Addiction Risk Score (GARS)®. Dopamine homeostasis may thus be achieved via "Precision Addiction Management" (PAM)®, the customization of neuronutrient supplementation based on the GARS test result, along with a behavioral intervention.

INTRODUCTION

Following almost three decades of genetic-based research related to identifying and characterizing addiction-related Reward Deficiency Syndrome (RDS), a paradigm shift is proposed in the prevention and treatment of all types of addictive behaviors. The novel adoption of "Precision Addiction Management" (PAM) based on genetic predisposition is imminent. Certainly, more research is necessary to further pinpoint the most appropriate candidate genes. However, an accelerated personalized, precision tool can be useful for the identification of highly convergent candidate gene single nucleotide polymorphisms (SNPs), associated in populations with RDS. Research directed toward improving treatment of substance use disorders in underserved populations is the basis of an NIH grant awarded to Drs. Kenneth Blum and Marjorie Gondré-Lewis. The research team is confident that eventually, the scientific community will seriously support new research directed toward the up-regulation of dopamine in mesolimbic structures with the goal of restoring homeostasis.

The interrelatedness of reward circuitry and the prefrontal cortices of the brain were not well-understood in the early sixties. The importance of the core neurotransmitters was not recognized. The functions of serotonin, GABA, dopamine, and acetylcholine were unknown, and endorphins were not even a part of our scientific acumen. The 1956 doctrine of Jellinek shocked the world when he proposed the concept of alcoholism as a disease, without much scientific evidence the idea was not generally accepted (1). However, most addiction scientists at that time agreed, in part, that deficiencies or imbalances in brain chemistry-perhaps genetic in origin –contributed to the cause of alcoholism.

REWARD DEFICIENCY SYNDROME (RDS)

In the early 70s, Blum investigated the theorized neurochemical mechanisms of some psychoactive drugs (alcohol and opioids) that had been observed initially in the work of Virginia Davis, Gerald Cohen, Michael Collins and others, as being related to the interface of alcohol and opioid use disorders (2–6). Following many other foundational studies from around the world, the Royal Society of Medicine published the RDS concept in 1996 (7). To date, there have been 150 articles in PUBMED, and the SAGE Encyclopedia of Abnormal and Clinical Psychology published a definition in 2017 (8). The RDS concept arose from the findings that dysfunction in the dopaminergic system are implicated in reward mechanisms in the brain and lead to substance seeking behavior and non-substance addictive behaviors (7) like pathological gambling (9–11), Tic Disorders (12, 13), Tourette's syndrome (14), and attention deficit hyperactivity disorder (ADHD) (15–17).

Mark Gold's "Dopamine Depletion Hypothesis," proposed an important role for dopamine in the effects of cocaine. He observed that the development of chronic cocaine use disorder (CUD) was due to the euphoric properties of cocaine and followed the acute activation of central dopamine neurons. Overstimulation of these neurons and excessive synaptic metabolism is thought to result in dopamine depletion which may underlie dysphoric aspects of cocaine abstinence and cocaine urges (18). Neurochemical disruptions caused by cocaine are consistent with the concept of "physical" rather than "psychological" addiction (19). The proposal that followed this research was to treat CUD with dopamine agonist therapy. The powerful dopamine D2 agonist bromocriptine was found to reduce cocaine craving significantly after a single dose (20). The suggestion was that bromocriptine might be an effective, non-addictive pharmacological treatment for those with CUD and open trials indicated that low-dose bromocriptine might be useful in cocaine detoxification. In 1995, Lawford et al. administered bromocriptine or placebo to subjects with alcohol use disorder (AUD), in a double-blind study, they found that the most significant improvement in craving and anxiety occurred in the bromocriptine treated subjects with the Dopamine Receptor D2 (DRD2) A1 allele and attrition was highest in the placebo-treated A1 subjects (21). Unfortunately, we now know that chronic administration of this D2 agonist induces significant down-regulation of D2 receptors, thereby making it an ineffective deterrent to relapse and preventing its clinical use (22, 23).

THE CASCADE OF REWARD NEUROTRANSMISSION

The Ventral Tegmental Area (VTA)-Nucleus Accumbens (NAC) pathway is part of a series of parallel integrated circuits within the "Brain Reward Cascade," which involves the hypothalamus, dorsal raphe and substania nigra. The net release of dopamine is due to the interrelatedness of serotonergic, endorphinergic, endocannabinoidergic, GABAergic, glutaminergic, and dopaminergic neurotransmitter signaling. The VTA is the site of dopaminergic neurons, which tell the organism whether an environmental stimulus (like natural rewards, drugs of abuse, stress) is aversive or rewarding. While a less understood brain region, the pre-frontal cortex, including the anterior cingulate cortex and orbitofrontal cortex, provides executive control of choices such drug reinstatement as being pleasurable (reward). Most recently even the dorsal raphe which contains both serotonergic and glutaminergic neurons impact the GABA input at the substania nigra (24). Therefore, for reward processing while net dopamine released at the NAC (reward site) is key, it is impacted by many neurotransmitter systems. Neurotransmitter interaction at the mesolimbic brain region induce "reward" when dopamine well-known as an anti-stress and pleasure neurotransmitter is released from the neuron and interacts with a nucleus accumbens dopamine D2 receptor. Reward produced to maintain our drives is the consequence of a cascade of neurotransmission. Initially, the release of serotonin stimulates enkephalin, then, inhibits GABA at the substantia nigra and ventral tegmental area. GABA regulates the release of DA at the nucleus accumbens. Studies indicate that balancing dopamine, possibly via dopamine D2 agonists, especially when availability of this molecule, based on genes and even epigenetics, is compromised, has important therapeutic application which has been proposed by NIDA scientists (25).

A consensus of the literature suggests dysfunction in the brain reward cascade is caused by the genetic sequence variations that cause a hypodopaminergic trait. This trait leads to multiple drug-seeking behaviors; the brain of that person requires a dopamine fix to feel good. Reduced dopamine release causes individuals to crave dopamine and have a high risk for multiple addictive, impulsive and compulsive behaviors that have been shown release dopamine (26).

Non-drug behaviors like gambling (27) and high-risk drug use are reinforced by surges of dopamine activation in the nucleus accumbens via the D1 receptors of the direct striatal pathway and inhibition of the indirect corticostriatal pathway via D2 receptors. Chronic drug administration enhances the brain's reactivity to drug cues, reduces sensitivity to non-drug rewards and causes neuroplastic changes in glutamatergic inputs to the striatum and midbrain dopamine neurons. Self-regulation is weakened, and sensitivity to stressful stimuli and dysphoria is increased. These long-lasting drug-induced impairments call for interventions designed to mitigate and if possible reverse them (28).

THE DEVELOPMENT OF PRECISION ADDICTION MANAGEMENT

Blum et al. proposed that KB220Z; a mild neuro-nutrient formulation, can stimulate the D2 receptor (29). Blum's group advocates instigating dopamine release, to cause the induction of D2-directed mRNA to direct the proliferation of D2 receptors in the brain (30). For example, DNA-directed compensatory overexpression of the DRD2 receptors (a form of gene therapy), resulted in a significant reduction in alcohol craving behavior in alcohol-preferring rodents (31) and self-administration of cocaine (32). Thus, based on this model enhanced bioavailability of D2 receptors was shown to reduce craving.

Studies that showed rats with depleted neostriatal dopamine display increased sensitivity to dopamine agonists estimated to be 30–100 x in the 6-hydroxydopamine (6-OHDA) rotational model (33) were the basis for "denervation supersensitivity" (34). Denervation supersensitivity was identified as a putative physiological mechanism to help explain the enhanced sensitivity following intense acute dopaminergic D2 receptor activation in the face of hypodopaminergia. In contrast, promotion of long-term (chronic low vs. intense acute) dopaminergic activation by lower potency dopaminergic repletion therapy has been shown in clinical and neuro imaging studies, to be an effective modality when used to treat RDS behaviors including Substance Use Disorders (SUD), Attention Deficit Hyperactivity Disorder (ADHD), obesity and others, without side effects (35).

An unprecedented number of clinical studies validating this patented nutrigenomic technology for re-balancing brain chemistry, and optimizing dopamine sensitivity and function have been published. Here clinicians and neuroscientists are encouraged to continue to embrace the concept of "dopamine homeostasis" and search for safe, effective, validated and authentic means to achieve a lifetime of recovery, instead of reverting to anti-dopaminergic agents. Anti-dopaminergic agents are doomed to fail because chronic use continues and exacerbates hypodopaminergia while promoting powerful D2 agonists like bromocriptine and L-Dopa compromises needed balance (36). Increased resting state functional connectivity as well as an increased neuronal recruitment has been demonstrated acutely on fMRI in both animal and humans within 15 (animal) to 60 (human) minutes post administration of neuro nutrient therapy. These studies demonstrate neuronal dopamine firing in brain areas involved in reward processing and possible induced neuroplasticity and "dopamine homeostasis" (37, 38). The comprehensive role of dopamine as the mesolimbic system neurotransmitter underlying motivational function supports the low potency dopaminergic repletion therapy concept; sustainable, mild activation of D2 receptors (30).

PRECISION ADDICTION MANAGEMENT (PAM)

The system is a holistic therapeutic model for treating RDS that includes the Genetic Addiction Risk Score (GARS) test for genetic risk predisposition and customization of neuronutrient supplementation to target the individual genetic allele variation, based on the GARS test results, and thereby deliver (PAM)® to patients.

See **Figure 1** for an example of how simple genotyping for identified SNPs in individuals could identify targets for precision nutrigenomics treatment. **Figure 1** shows the PCR amplification of four variants of dopamine receptor D4 (DRD4). Multiple repeats of DRD4 variants are associated with disorders within the RDS spectrum (39–41). In the figure, six different 48 bp repeat sequences are identified, from 2 repeats (2R) to 8R. The DRD4, DRD2, catechol-O-methyltransferase (COMT) are among genes within the mesolimbic reward pathway with SNPs that contribute to RDS, see **Figure 2**.

THE DEVELOPMENT OF THE GENETIC ADDICTION RISK SCORE (GARS)

There are many examples of association studies involving genes and polymorphisms especially of the ten reward genes measured in the GARS test. Alleles of genes that affect the synthesis, degradation, reception, and transport of neurotransmitters (like enkephalin, serotonin, GABA, and dopamine) and enzymes like Monoamine Oxidase (MOA) A and COMT in the reward pathway of the brain were candidates for selection for the GARS test if they contributed to hypodopaminergia. Comings and Blum proposed that functional defects in the genes for these neurotransmitters result in dopamine deficit, later identified as RDS. They suggested that individuals with hypodopaminergia are at risk for seeking reward from RDS behaviors to satisfy their lack of natural rewards (42). Some examples of functional research and studies that associated RDS behaviors with the risk alleles of the genes and second messengers that comprise the GARS test follow.

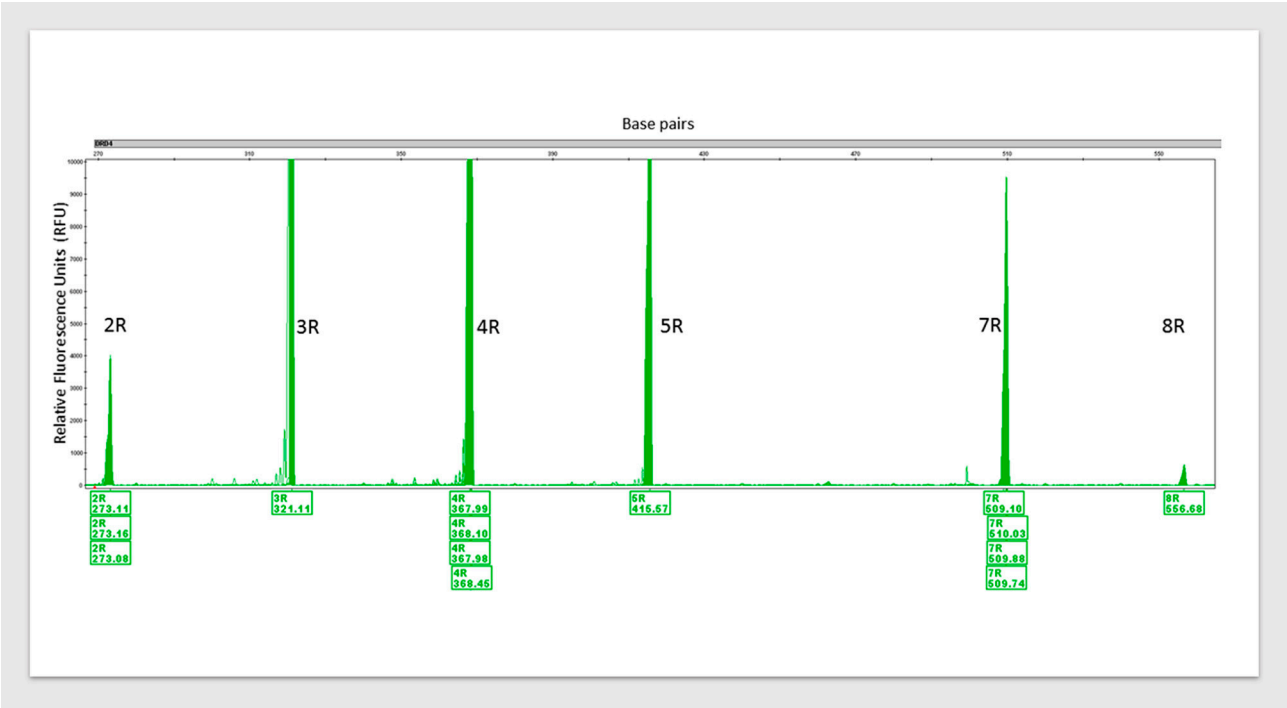

FIGURE 1 | An example of PCR amplification of variants of dopamine receptor D4 (DRD4). *DRD4* (Dopamine Receptor 4) variants detected via polymerase chain reaction (PCR) amplification with multiple control samples. 2R to 8R = six different 48 base pair (bp) repeat sequences. 2R repeats = 48 bp twice, 3R = thrice and so forth. Peak height (y-axis) indicates fluorescence signal amplitude, peak location (x-axis) indicates fragment size (bp). Fragment sizes are shown below the peaks (base pairs). Humans carry two copies of this variant and their lengths are from 2R to 11R. Carrying one or both variants at 7R+ increases the risk of developing RDS. This is one of the eleven established risk variants assessed by the GARS test.

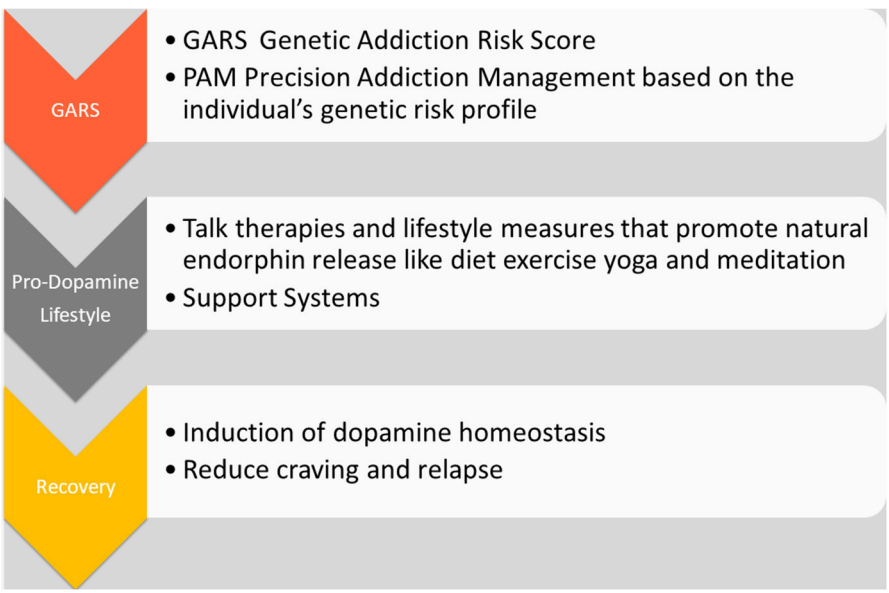

FIGURE 2 | The Precision Addiction Management system. The schematic illustrates various elements related to "Precision Addiction Management (PAM)" and shows the interrelatedness of genetic testing, utilizing a patented Genetic Addiction Risk Score (GARS) and a customized polymorphic matched nutraceutical therapeutic adjunct KB220PAM.

THE CHARACTERIZATION OF PHENOTYPES FOR THE GARS

The Dopamine Receptor DRD1 Gene

The dopamine receptor DRD1 gene encodes the most abundant dopamine receptor in the central nervous system: the D1 subtype (43). While the D2, D3, and D4 receptor subtypes inhibit adenylyl cyclase activity, the D1 receptor stimulates a critical brain molecule adenylyl cyclase, which activates cyclic AMP (required for proper nerve brain function). The nucleotide guanidine (G) can be replaced by the adenine (A) and roughly a quarter of the human population carries one or two copies of this risk variant allele. Peer-reviewed studies involving the DRD1 gene show that carriers have an increased risk for many substance abuse and novelty seeking (NS) reward deficiency behaviors. In one of hundreds of association studies, Liu et al. looked at drug dependence and impulsive behavior and found that DRD1 gene polymorphisms are related to heroin dependence in a Chinese Han population, however, two of eight SNPs did not associate with impulsivity (44). Huang et al. found a significant association between the DRD1 and Nicotine Dependence (ND) (45). Recently they explored differential allelic expression of the DRD1 modulated by microRNA miR-504 (46). Other positive association studies on abusable drugs related to the D1 polymorphisms provide informative data indicating risk (47–50).

The Dopamine Receptor DRD2 Gene

The dopamine receptor DRD2 gene encodes the second (D2) subtype of the dopamine receptor. While the D1 receptor subtype activates, the D2 receptor inhibits adenylyl cyclase activity and reduces the intracellular concentration of cyclic AMP (51). DRD2 located near Ankyrin Repeat and Kinase Domain Containing 1 (ANKK1) at chromosome 11 q23.2, is involved in signal transduction (52). The ***Taq A1*** genetic variant in ANKK1 equates functionally to 30–40% lower density of dopamine D2 receptors resulting in hypodopaminergic function (53). The DRD2 risk variant of interest (rs1800497) is downstream at chr11:113400106 where the nucleotide guanine (G) replaces the adenine (A). In 1986 inspired by a reported unconfirmed genetic association in depressed Amish subjects, Blum et al. discovered the first genetic association with a behavior, severe alcoholism, foundational work within the field of behavioral genetics (54). Initially, **Taq 1A** (rs1800497) was thought to be within the DRD2 gene, but as sequencing technology advanced and the location was corrected to exon 8 of the nearby ANKK1 gene. This risk allele is found in approximately 100 million people in the USA, with the highest frequency in Native Americans (85%) and the lowest among Western European Jews (6%).

The first of few examples of association studies is one from Singh, Ghosh, and Saraswathy. They looked at the role of dopamine receptors in susceptibility to alcohol dependence (AD) concerning three sites of the *DRD2* gene (-141C Ins/Del, TaqIB, and TaqID) and ***TaqIA*** site of ANKK1 gene among Meiteis of Manipur, a Mendelian population of India, in association with AD. They found ANKK1 TaqIA polymorphism significantly associated with AD (odds ratio = 2.13, 95% confidential interval 1.04–4.39, $P < 0.05$), whereas a borderline significance of the −141C Del allele was observed ($P = 0.059$) (55).

Panduro et al. analyzed DRD2/ANKK1 genotyped a cross-section of 680 unrelated subjects including two Native Amerindians groups (87 Nahuas and 139 Huicholes), and two Mestizos groups (158 subjects from Tepic, Nayarit and 296 subjects from Guadalajara, Jalisco) by PCR-RFLP and allelic discrimination assays. Heavy drinking was considered ≥300 g alcohol/week. They concluded that the DRD2/ANKK1 A1 allele was present at a high frequency in Mexican populations and the A1/A1 genotype associated with heavy drinking in Mestizos. The highest frequencies of the A1 allele, exhibited worldwide to date were documented among the Native Amerindians (56).

Wang et al. investigated whether predisposing genetic variants and personality traits may be specific to a particular class of addiction or common to all addictions. They recruited 175 opiate-dependent patients, 102 alcohol-dependent patients, and 111 putative healthy controls diagnosed using DSM-IV criteria and assessed with Tridimensional Personality Questionnaire (TPQ). They genotyped dopamine D2 receptor (DRD2), 5-HTT-linked promoter region (5-HTTLPR), and aldehyde dehydrogenase 2 (ALDH2) genes using Polymerase Chain Reaction (PCR). They concluded that both alcohol- and opiate-dependent patients, have common genetic variants in DRD2 and 5-HTTLPR but specific for ALDH2. They found higher NS and Harm Avoidance traits in both patient groups with the interaction with DRD2, 5-HTTLPR, and ALDH2 genes (57).

Merritt and Bachtell in their non-genetic physiological study looked for the expression of the D2 dopamine receptor subtype as predictive of D2 dopamine receptor function and cocaine sensitivity that would enable cocaine abuse in rats. Quinpirole [D2 dopamine receptor agonist] was used to classify rats as high (HD2) or low responders (LD2). Results demonstrated that HD2 rats have greater cocaine conditioned place preference, enhanced sensitivity to the locomotor stimulating properties of cocaine, and self-administer more cocaine compared to LD2 animals. These findings suggested that individual differences in D2 dopamine receptor sensitivity may be predictive of cocaine sensitivity and reward (58).

Persico, Bird, Gabbay, and Uhl tested the hypothesis that a DRD2 gene variant might be more prominent in polysubstance users who preferentially use psychostimulants than in addicts who prefer opiates and those with no drug preference. Their results were consistent with the hypothesis that DRD2 gene variants marked by Taq1 A1 and B1 polymorphisms may work, probably in concert with other genetic and environmental factors, to enhance vulnerability to psychostimulant abuse (59).

Noble et al. examined the allelic prevalence of the D2 dopamine receptor (DRD2) gene in male cocaine-dependent (CD) Caucasian (non-Hispanic) subjects to determine the relationship of DRD2 alleles to family history and selected behavioral measures. The data showed a strong association of the minor alleles (A1 and B1) of DRD2 with cocaine dependence and suggested that a gene, located on the q22-q23 region of chromosome 11, confers susceptibility to this drug disorder (19).

Wang et al. used the MassARRAY system to identify markers that contribute to the genetic susceptibility to heroin addiction. They compared 334 patients with heroin dependence, and 299 healthy controls who participated in the research. Their findings indicated a role for DRD2 polymorphism in heroin dependence

in the Chinese Han population and may be helpful for future genetic or neurobiological studies on heroin dependence (60). Most recently, Zhang et al. (61) found a 35.8 kilobases haplotype spanning ANKK1 and DRD2 is associated with heroin dependence in Han Chinese males (61).

The Dopamine Receptor DRD3 Gene

The dopamine receptor DRD3 gene encodes the D3 subtype of the five (D1–D5) dopamine receptors. As with D2 receptors, the activated D3 receptor inhibits adenylyl cyclase DRD3. Having a cytosine (C) instead of thymine (T) intensifies the effect of dopamine, magnifying the "high" observed with alcohol and cocaine to dangerous levels (62). The location of this receptor is within the older, more emotionally bent, limbic areas of the brain, including the pituitary gland, the olfactory bulb (smell) and the nucleus accumbens (cravings, aversions, reward). This gene demonstrates increased risks for alcohol, cocaine, and heroin dependence as well as RDS behaviors including ADHD, OCD, and even pathological aggression.

Thome et al. investigated the distribution of a dopamine D3 receptor gene polymorphism (Ball) in patients suffering from AD and compared with non-dependent controls. The allele A1 occurred significantly more frequently among patients compared to controls. Patients with the genotype A1/A2 showed significantly higher defined NS scores in the tridimensional personality questionnaire (TPQ) than patients with the genotype A1/A1. While this seems counter intuitive it can be explained by heterosis a well-known genetic phenomenon extensively discussed in the literature. There were significantly more individuals with higher NS scores and fewer individuals with lower NS scores than expected. The results of this study support the hypothesis of a genetically determined involvement of the dopaminergic system in AD (63).

Another study by Huang et al. investigated 13 single nucleotide polymorphisms (SNPs) spanning a region of the dopamine D(3) receptor gene (DRD3) to determine whether DRD3 is associated with ND. They studied a set of 2,037 subjects in 602 nuclear families representing two distinct American populations using three ND measures, namely, smoking quantity (SQ), the Heaviness of Smoking Index (HSI), and the Fagerström Test for ND (FTND). The results indicate that DRD3 associated significantly with ND in the European American cohort, and that rs6280, a functional polymorphism causing an amino acid change of serine to glycine (Ser9Gly) in the N-terminal extracellular domain of the D(3) receptor, likely is causative of the association between DRD3 and ND (64). Other positive association studies involving avoidant and obsessive personality traits and disorders, violent behavior and response to morphine reveal the importance of DRD3 polymorphisms in RDS (65–67).

The Dopamine Receptor DRD4 Gene

The dopamine receptor DRD4 gene that encodes for the receptor (subtype) D4. Dopamine receptors are responsible for neuronal signaling in the old reptilian mesolimbic system of the brain, which is an area that regulates emotions as well as RDS addictive behaviors. The DRD4 located on chromosome 11 at 11p15.5., is a G-protein receptor which is activated by the chemical messenger dopamine. Two different variants are measured in the GARS test. The first is a SNP located at rs1800955, −521 C>T and the risk allele is C. The second, is a Variable Number of Tandem Repeats (VNTR) located in intron 3, 48. The base–pair repeat; <7 is short, while if there are >7R, the risk allele is long VNTR equal or >7–11 repeats (68, 69). There are hundreds of studies of the DRD4 gene, and many of these studies have linked these risk variants to neurological and psychiatric conditions including schizophrenia, bipolar disorder, anhedonia, ADHD, Addictive behaviors, Parkinson's disease, eating disorders, and even anorexia nervosa (a non-eating repetitive RDS behavior). The underlying brain mechanism is D2-like in which the activated receptor inhibits the enzyme adenylate cyclase, thereby reducing the intracellular concentration of the second messenger cyclic AMP (required for cell function). The 7R allele appears to have been selected, for providing a survival advantage, about 40,000 years ago. It has been shown that compared to sedentary populations, the frequency of the 7R variant of *DRD4*, is much higher in nomadic populations suggesting its association with modern day "NS." One important feature is that good parenting (epigenetic) was associated with appropriate decision making even at the age of four. Thus, early knowledge of this 7R or greater risk variant could be very helpful to prevent risk for substance use: opiate, alcohol, cannabis, glucose, and nicotine as well non-substance RDS behaviors: ADHD, Novelty seeking, Conduct Disorder (CD), hypersexuality, pathological aggression, and others.

Multiple repeats of DRD4 variants are associated with disorders within the RDS spectrum. Gervasini et al. conducted research to determine the effect of functional polymorphisms and haplotypes of the DRD4 gene on general psychopathological symptoms of 273 eating disorder (ED) patients [199 with Anorexia Nervosa (AN) and 74 with Bulimia Nervosa (BN)] who completed the SCL-90R symptom inventory. They found that certain combinations of DRD4 variants haplotype *2 (non7R-TR long-C-C) associated with higher scores in the three global SCL-90R indices the Global Severity Index (GSI), the Positive Symptom Distress Index, (PSDI), and the Positive Symptom Total (PST) after Bonferroni correction ($p \leq 0.01$ in all instances). They also found that these polymorphisms may contribute to psychopathological features like Somatization, Obsessive-Compulsive, Anxiety, Phobic anxiety, Paranoid ideation, in BN patients (41).

In another example Dragan and Oniszczenko analyzed the association between the variable number tandem repeat (VNTR) DRD4 exon III polymorphism and intensity of PTSD symptoms in 107 (57 women and 50 men) survivors of a flood aged 14–62. PTSD symptoms were more intense for participants with at least one copy of the long (seven or eight repetitions) DRD4 allele than participants who did not have these alleles (40). Huang et al. used a transmission disequilibrium test of DRD4 exon III 48 bp variant-number-tandem-repeat polymorphism and tic disorder. Their results revealed an association between the longer alleles of DRD4 exon III 48 bp VNTR polymorphism and tic disorder accompanied with ADHD, thus suggesting a possible genetic risk factor of tic disorder with ADHD in Chinese (39). One interesting recent study by Ji et al. (70) involving epigenetics revealed that DNA methylation of *DRD4* may be responsible for the pathophysiology of drug addiction (70).

The Dopamine Transporter Gene

The dopamine transporter gene (DAT1/SLC6A3) gives instructions for the production of a membrane-spanning protein that controls the reuptake (recycling) of dopamine from the synapse. The dopamine transporter helps regulate the level of neurotransmitter present in the synapse and controls how long a signal resulting from neurotransmitter release lasts (71).

The function of DAT1 is to clear excess dopamine released from the pre-neuron into the synapse and prevent uptake into the receptors on the next neuron. Much research, both biochemical and structural, has been performed to obtain clues about the mechanism of reuptake.The activity of clearing dopamine from the synapse is dependent on the variant form of this gene. So under normal conditions, the dopamine active transporter protein pumps the chemical messenger dopamine out of the synaptic cleft back into the cytosol of the pre-neuron cell. The DAT1 gene is located on chromosome 5 at p15. The gene has a variable number tandem repeats (VNTR) at the 3′end of the gene and another in the intron 8 region (72). The importance here is that differences in the VNTR, for example, 10R vs. 9R have been shown to effect the basal level of expression (activity) of the transporter. Indeed it has been demonstrated that the 9R is a risk form because it has a much higher ability to clear DA from the synaptic cleft compared to the 10R allele (73). Therefore, carriers of the 9R are more prone to both substance and non-substance RDS addictive behaviors due to hypodopaminergia (low dopamine function). The regional brain distribution of the DAT includes high dopamine-containing neurons in the old reptilian limbic system similar to the DRD2 receptor distribution (74). The maximum expression of the DAT1 gene is found in a parts of the brain called the substantia nigra and ventral tegmentum area (75) [brain regions containing large amounts of the inhibitory chemical messenger GABA that fine-tunes dopamine release at the reward site]. It is also interesting that DAT is co-localized with the D2 receptors (76).

There exists over 2,700 studies (PUBMED 7-14-18) concerning the role of the DAT1 gene and predisposition for the use of substances: particularly, heroin, alcohol, cocaine, and nicotine dependence; and non-substance RDS behaviors: ADHD, depression (Anhedonia), and PTSD are included.

Sullivan et al. focus on the role of aberrant dopaminergic signaling, interaction with dopamine transporter DAT, a cocaine target, and the dopamine D2 receptor in subjects and controls from the Miami Dade County Brain Bank splicing polymorphism rs2283265 of DRD2, encoding D2 receptors, was shown to confer risk (odds ratio ∼3) of cocaine overdose/death. This risk was attributable to the minor allele of rs2283265 enhanced significantly in homozygous carriers of the main 6-repeat allele of DAT rs3836790to OR = 7.5 ($P = 0.0008$). In contrast, no significant risk to carriers of the minor 5-repeat DAT allele was demonstrated. The results demonstrated gene-gene-drug interaction affecting the risk of fatal cocaine intoxication (77).

Cinque et al. used transporter (DAT) knockout (KO) and heterozygous (HET) mice to investigate diseases with altered dopamine transmission such as attention-deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD). These diseases characterized by poor decision making and executive function have been studied using many animal models. DAT KO rats appeared less sensitive to rewarding stimuli than wild-type (WT) and HET rats: they also showed a prominent hyperactive behavior with a rigid choice pattern and a wide number of compulsive stereotypies. Moreover, when the effects of amphetamine (AMPH) and RO-5203648 were tested, the AMPH accentuated impulsive behaviors in WT and HET rats, it did not affect in DAT KO rats (78).

Monoamine Oxidase A Gene

Monoamine oxidase A, (MAO-A), an enzyme, is encoded by the MAOA gene in humans. Two neighboring gene family members MAOA and MAOB encode mitochondrial enzymes which catalyze the oxidative deamination (breaks down the molecules) of catecholamines, like dopamine, norepinephrine, and indoleamines like serotonin. This gene is associated with a variety of psychiatric disorders, including antisocial behavior. The MAOA gene located on only the X chromosome at Xp11.3, the short (p) arm of the X chromosome, at position 11.3. a crucial enzyme for healthy brain function degrades chemical messengers like dopamine and serotonin (79–82).

The risk variant is 4R found at the 3′ 30 base-pair Repeat (R) on X chromosome only. The 3.5R and 4R variants have been found to be more highly active than 3R or 5R. Carriers of the 3.5 and 4R may display hypodopaminergia (low dopamine function) whereby too much of dopamine is broken down in the presynaptic neuron which may result is less dopamine to be released into the synaptic cleft. The 4R has been associated with Alzheimer's disease, aggression, panic disorder, bipolar affective disorder, major depressive disorder, and ADHD. There are over 900 studies on the MAO-A gene showing risk for substance use disorder: alcohol, opioid, and nicotine dependence, as well as obesity, and RDS behaviors: harm avoidance, NS, and ADHD.

Regarding catabolism the studies reveal risk for MAOA, Wang et al. conducted a family-based association analysis of AD in the COGA sample in the Australian twin-family study and found support for an association of MAOA gene ($P = 4.14 \times 10(-4)$ for rs979606) and AD (83).

Ducci et al. investigated the interaction between a functional monoamine oxidase A (MAOA) locus and childhood sexual abuse (CSA). They tested whether MAOA-LPR influences the impact of CSA on alcoholism and antisocial personality disorder (ASPD) in a sample of 291 women, 50% of whom had experienced CSA. They also tested whether haplotypes covering the location of both MAOA and MAOB) genes predict risk for alcoholism and ASPD better than the MAOA-LPR locus alone. Three haplotypes showed the MAOA-LPR low activity allele. The most abundant was among alcoholics ($P = 0.008$) and antisocial alcoholics ($P = 0.001$). Independently from ASPD the MAOB haplotype associated significantly with alcoholism ($P = 0.006$), and antisocial alcoholism ($P = 0.03$) (84).

Tikkanen et al. found that the PCL-R symptom inventory total score predicts impulsive reconvictions among offenders with high-activity MAOA (6.8% risk increase for every one-point increase in PCL-R total score, $P = 0.015$) but not among offenders with low-activity MAOA. Antisocial behavior and attitudes were found to predict reconvictions in both high and low activity MAOA genotypes a17% risk increase and a 12.8% increase, respectively. In a meta-analysis, Yang et al. found an

association between MAO gene polymorphisms and smoking behavior. The meta-analysis showed the T allele in MAO-A C1460T reduced the risk of heavy smoking (OR = 0.66, 95% CI: 0.52–0.84; I(2) = 0.0%), especially in Caucasians. However, the active group in MAO-A VNTR increased the likelihood of smoking cessation failure in males (OR = 1.49, 95% CI: 1.01–2.22; I(2) = 0.0%) and the A allele in MAO-B G644A reduced the risk of heavy smoking in males (OR = 0.20, 95% CI: 0.04–0.98) (85).

Gorodetsky et al. investigated the interactive effect of MAOA-LPR genotype and a history of childhood trauma in predicting aggressive behaviors in a population of 692 male prisoners. Within the group not exposed to physical neglect (PN), carriers of the MAOA-LPR high-activity variant were more aggressive: (tR = 2.47, $P < 0.014$). They observed a crossover effect in that the increase in aggression scores with PN was greater in low-activity individuals (tR = 5.55, $P < 0.0001$) than in high-activity individuals (tR = 4.18, $P < 0.0001$). These findings suggested that childhood trauma and the functional MAOA-LPR polymorphism may interact to specifically increase the risk for over-aggressive behavior but not impulsivity or hostility. The MAOA-LPR low-activity variant may be protective against the development of aggressive behavior under low-stress conditions (86).

Vanyukov et al. looked for evidence of an association of a dinucleotide repeat polymorphism at the MAOA gene with early onset alcoholism/substance abuse. They found a correlation between the presence/absence of the disorder and the length of the MAOCA-1 repeat was significant in males only, with both increased risk for the disorder and lower age of onset of substance abuse associated with "long" alleles (repeat length above 115 bp) (87).

Tikkanen et al. looked at the relationship between MAOA the effects of heavy drinking and childhood physical abuse (CPA) on risk for severe impulsive acts of violence among violent alcoholic offenders. The sample population of 174 male impulsive, alcoholic, Finnish, violent offenders assessed after 8 years of non-incarcerated follow-up mostly exhibited antisocial (ASPD) or borderline personality disorder (BPD) or both. Logistic regression analyses demonstrated that both CPA and heavy drinking were significant independent predictors of recidivism in violent behavior (OR 5.2, $p = 0.004$ and OR 5.3, $p = 0.003$) among offenders having the high MAOA activity genotype (MAOA-H), but these predictors showed no effect among offenders carrying the low MAOA activity genotype (MAOA-L) (88). The work of Huang et al. (89) suggested the interaction of DRD2 rs1079597 and MAOA rs309850 3-repeat affects smoking intensity in young Taiwanese men (89).

The Catechol-O-methyltransferase Gene

The COMT gene (location 22q11.2) provides instructions for making an enzyme called COMT. Enzymes facilitate chemical reactions without the enzyme being changed (90). The gene makes two versions of COMT enzyme. The longer form, called membrane-bound catechol-O-methyltransferase (MB-COMT), is chiefly produced by nerve cells in the brain. The COMT enzyme destroys the dopamine molecule in the synapse and helps maintain appropriate levels of neurotransmitters (dopamine and norepinephrine) in the brain. In some people, there is a variation of a single protein building block (amino acid) in the enzyme (91). The amino acid valine (Val) replaces the amino acid methionine (Met), expressed as Val108/158Met. Carriers of two copies of MET have very heightened dopamine function because COMT activity is low and less dopamine is broken down, while two copies of Val, destroy more dopamine, and lower dopamine function (hypodopaminergia) is the result. The double copy (homozygote) of Val variant metabolizes dopamine at up to four times the rate of its Met counterpart. There have been over 2,400 studies involving the COMT gene. Val carriers are at increased risk for substance-related reward deficiency behaviors: including dependence on alcohol, cannabis, glucose; opiates/opioids, stimulants, and nicotine; or non-substance-related: ADHD, Oppositional Defiant Disorder, pathological aggression, panic disorder, anxiety, Obsessive-Compulsive Disorder (OCD) (92).

Hill et al. investigated caudate volume and working memory with brain scans and fMRI in offspring with childhood disorders followed until adolescence. They were tested for genotypic variation in the COMT and DRD2 genes. Caudate volume and working memory were reduced in association with externalizing disorders of childhood-adolescence and associated with variation in COMT and DRD2 genes (93).

Sery et al. performed a restriction analysis for the detection of the Val158Met polymorphism to look at the association between high-activity COMT allele and alcoholism in DNA samples from 799 subjects in total (279 male alcoholics and 120 female alcoholics, 151 male controls and 249 female controls). They found a significant difference between male alcoholics and male controls in allele and genotype frequencies ($p < 0.007$; and $p < 0.04$, respectively) (94).

Guillot et al. examined associations of COMT rs4680 with dimensionally and categorically measured gambling and drinking problems in a non-clinical sample (139 Caucasian adults). They found that COMT rs4680 was related to both dimensionally and categorically measured gambling and drinking problems and may be a genetic risk factor that contributes to the development of both problems 36 (95).

Enoch et al. looked for sex differences in the influence of COMT Val158Met on alcoholism and smoking in plains American Indians. They found that both male and female alcoholics were more likely to have at least 1 Val158 allele compared with non-alcoholics (0.95 vs. 0.88, $p < 0.05$). Approximately 30% of all participants were long-term, non-addicted light, social smokers (3.6±1.7 cigarettes/d); they had the same Val158Met frequencies as non-smokers (96).

The Opioid Receptor Genes

Three opioid receptors, mu, delta and kappa exert their pharmacological actions through the *Oprm1*, *Oprd1*, and *Oprk1* genes, respectively, and these genes have been cloned. A family of natural opiate-like endogenous peptides, (enkephalins, dynorphins, and endorphin), which are released by neurons activate opioid receptors in the brain. The mu (μ) opioid receptors (MOR), located on chromosome 6 at q24-q25, have a high affinity for the enkephalins and beta-endorphin, found in the brain. The prototypical μ-opioid receptor activator is the mu agonist morphine, the primary psychoactive alkaloid in opium. The primary purpose of the mu opiate receptor is the control of pain; it is also very involved in the regulation of dopamine

release in the reward site (nucleus accumbens) of the brain. One function of MOR, when activated by either endogenous natural opioids like enkephalins or opioid compounds like Fentanyl or Oxycontin, is to suppress the inhibitory chemical messenger GABA allowing for dopamine release at the reward site. These potent activators of MOR can cause overdose and death by blocking breathing. The risk variant of the MOR is the G allele 118A>G (p.Asn40Asp); SNP rs1799971). The definition of opioid is any synthetic narcotic that has opiate-like activities not derived from opium. The over-prescription of opioids (297 million in 2016) for pain relief, has been linked to the unwanted deaths (one person every 17 min dying from an overdose in America). Studies on the MOR variants are primarily related to substance use disorder: alcohol, food, opiate/opioid, and nicotine dependence; and RDS behaviors: overeating, inability to cope with stress, and PTSD. Carriers of the G allele have a reduced response to opioids (97) and exhibit hypodopaminergia.

Published studies reveal that polymorphisms in the Mu opioid receptor associate with drug dependence. A meta-analysis from Haerian and Haerian is a good example. They sort to resolve the question of whether the OPRM1 rs1799971 polymorphism associated with opioid dependence by evaluating evidence from 13 studies ($n = 9,385$), comprising 4,601 opioid dependents and 4,784 controls. These studies evaluated the association of the OPRM1 rs1799971 polymorphism with susceptibility to opioids. The analysis showed a significant association between this polymorphism and susceptibility to opioid dependence in overall studies under a codominant model, as well as susceptibility to opioid dependence or heroin dependence in Asians under an autosomal dominant model. They concluded OPRM1 rs1799971 might be a risk factor for addiction to opioids or heroin in an Asian population (98).

In another study Marini et al. examined the involvement of the mu-opioid receptor gene polymorphism A118G in the efficacy of detoxification of alcohol-dependent patients. They found that alcohol-dependent patients with the A/A genotype could have a faster restoration of their liver function than those with the A/G genotype: it might be possible that the presence of G allele confers on these patients a reduced ability in abstaining from drinking alcohol (99).

Wang et al. looked at genetic polymorphisms in the OPRM1 gene to determine if in methadone maintenance they are associated with changes in libido and insomnia in patients. The results obtained using dominant model analysis indicate that the OPRM1 SNPs rs1074287, rs6912029, rs12209447, rs510769, rs3798676, rs7748401, rs495491, rs10457090, rs589046, rs3778152, rs563649, and rs2075572 are significantly associated with change-in-libido side effects (adjusted $p < 0.042$). A recessive model analysis, of these SNPs, were found to be significantly associated with insomnia side effects in this cohort ($p < 0.009$). A systematic review and meta-analysis of six previous studies from Chamorro, et al. that analyzed the role of A118G polymorphism in response to naltrexone for AD. After meta-analysis, they found lower relapse rates in patients treated with naltrexone who carried the G allele, than patients who were homozygous for the A allele (OR: 2.02, 95% CI 1.26–3.22; $P = 0.003$) (100).

Bond et al. examined alterations in beta-endorphin binding and activity and the possible implications for opiate addiction. Their results show that SNPs in the mu opioid receptor gene can alter binding and signal transduction in the resulting receptor. This finding may have implications for normal physiology, therapeutics, and vulnerability to develop or be protected from diverse diseases including the addictive diseases. The object of this review is the mu opioid receptor gene, Oprm1 that generates 3 sets of proteins, each containing many variants. The review suggests these variants might be targeted to generate safer, effective analgesic drugs lacking respiratory depression, physical dependence, and reward behavior (101).

The Serotonin Transporter Gene

The serotonin transporter gene encoded by (SLC6A4) located with the 5-HTTLPR polymorphism on chromosome 17, occurs in the promoter region of the gene. Researchers report two variations in humans; a short (s) and a long (l). The 5-HTTLPR (serotonin-transporter-linked polymorphic region) is a degenerate repeat polymorphic region. There have been thousands of reports many related to behavioral, pharmacogenetic and RDS behaviors since the identification of the polymorphism in the 1990's. The risk variant involves a 43 base –pair 5′′ insertion/deletion, S' at SNP rs25531. Researchers found that long allele results in higher serotonin transporter mRNA transcription in human cell lines. Thus, the serotonin is swiftly released into the synaptic cleft; eliminated from the synapse into the pre-nerve cell resulting in low serotonin content in the synapse leading to reduced function. Sometimes the long A allele of SNP rs25531 is written LA. Some studies revealed that the risk form signifies a predisposition to affective disorders, depressive responses to life stress, hyperactivity, and slowing of the electroactivity (speed) of the brain. Carriers of the S' or LA variant are at risk for substance-related: alcohol, opiate/ opioid, nicotine, cocaine, cannabis, and glucose dependence; RDS addictive behaviors: ADHD, PTSD, and pathological gambling and even pain response (102–105).

The established role of the serotonin transporter and associated polymorphisms across the Brain Reward Cascade and addiction liability is exemplified by this study from Herman et al. They examined the association between a measure of sociopathy and 5-HTTLPR genotype in a sample of individuals from a multi-center alcohol treatment trial [Project MATCH]. Regression analysis revealed that males with the L'L' genotype (i.e., those homozygous for the L(A) allele) had lower socialization scores (i.e., greater sociopathy) than males who were carriers of the S' allele ($P = 0.03$). In contrast, women with the S'S' genotype had lower socialization scores than women with two L' alleles ($P = 0.002$) and tended to have lower Socialization Index of the California Psychological Inventory scores than women with one copy of the L' allele ($P = 0.07$). Among individuals with AUDs, the tri-allelic 5-HTTLPR polymorphism had opposite effects on socialization scores in men than women. The basis for this finding is unknown, but it may have implications for sub-typing alcoholics (106). Herman and Balogh explored polymorphisms of the serotonin transporter and receptor genes and susceptibility to substance abuse. They suggested that Genetic variations in the 5-HT system, such as SLC6A4, HTR1B, HTR2A, HTR2C, HTR3 (HTR3A, HTR3B, HTR3C, HTR3D, and HTR3E), likely play a role contributing to SUD patient heterogeneity (107).

Polsinelli, Levitan, and De Luca used a multiple-model meta-analysis to clarify the association between BN and 5-HTTLPR

using statistical models not used by previous meta-analyses and extend upon previous meta-analyses by including new samples. Data were pooled using dominant and additive models. Both models showed an association between the 5-HTTLPR polymorphism and BN that was non-significant (108).

Harkness et al. examined the moderating role of childhood emotional, physical and sexual maltreatment and the serotonin-transporter-linked promoter region (5-HTTLPR) polymorphism to stress generation in a cross-sectional community sample of 297 adolescents and young adults. Individuals with the risk s-allele of the serotonin transporter gene and a history of maternal emotional maltreatment or sexual maltreatment reported higher rates of dependent and dependent-interpersonal life events than those homozygous for the l-allele (109).

Liu et al. investigated the relationship between the serotonin transporter gene (SLC6A4) 5-HTTLPR genotypes, cocaine-dependence, and impulsivity in 98 healthy control and 243 treatment-seeking, cocaine-dependent subjects. They found that the impulsivity BIS-11 total score was associated positively with years of cocaine use for S'-allele carriers ($r = 0.26$, $P = 0.0006$, Pearson's correlation analysis), but not for L'L' genotype subjects ($r = 0.02$, $P = 0.87$) (110). It is noteworthy that Garbarino et al. (111), suggested that extreme bidirectional perturbations of serotonin signaling during development of one's DNA likely compound or synergize to facilitate enduring neurochemical changes resulting in insufficient or excessive 5-HT signaling, that could underlie the persistent behavioral characteristics of autism spectrum disorder (111).

The Gamma-aminobutyric Acid Receptor Subunits

GABA a neurotransmitter mediates neuronal inhibition by binding to the GABA/benzodiazepine receptor and opening an integral chloride channel. Gamma-aminobutyric acid receptor subunit alpha-3 (GABRA3) is a human protein that is encoded by the GABRA3 gene. GABA is the major inhibitory neurotransmitter that acts at $GABA_A$ receptors to fine-tune dopamine release in the reward site of the brain. Of the 16 identified and distinct subunits of GABA-A receptors, the GABRA3 gene located on Xq28, and the risk variant is CA-Repeat (171-201) whereby allele 181 results in higher activity. This risk allele if overexpressed will cause low dopamine function (hypodopaminergia) leading to SUD: including AD, and other RDS non-substance addictive behaviors and PTSD (112–117).

There are also association studies involving various polymorphisms of GABA receptors and RDS behaviors including alcoholism. An example is an extensive investigation, by Enoch et al. research to identify the functional locus of GABRA2 genotyped 24 SNPs across GABRG1 (gamma subunit) and GABRA2 in 547 Finnish Caucasian men (266 alcoholics), and 311 community-derived Plains Indian men and women (181 alcoholics). GABRG1 haplotypes and SNPs associated significantly with AUD whereas there was no association between AUD and GABRA2 haplotypes. Although of several common (>or = 0.05) haplotypes that spanned GABRG1 and GABRA2 (341 kb) emerged, three of which were present in both populations. One associated with AUD, the other two were more common in non-alcoholics determined by GABRG1. Three less-common extended haplotypes (<0.05) in the Finns, associated with AUD that was determined by GABRA2. These results suggest that there are likely to be independent, complex contributions from both GABRG1 and GABRA2 to alcoholism vulnerability (118).

Terranova et al. analyze the connection between AD and criminal behavior and GABA receptors by an integrated genetic-environmental approach that examined 186 alcohol-dependent males; group 1 ($N = 47$ convicted subjects) compared with group 2 ($N = 139$ no previous criminal records). Genetic results highlighted group 1 differences in genotype distribution ($p = 0.0067$) for SNP rs3780428, found on the intronic region of subunit 2 of the GABA B receptor gene (GABBR2) (119).

Massat et al. (120) found that the GABRA3 polymorphism may confer susceptibility to or may be in linkage disequilibrium with another gene involved in the genetic etiology of bi-polar depression (120). Cui et al. looked at the genetics of GABAergic signaling in nicotine and AD. Human genetic studies support the involvement of genes and variants in the GABAergic signaling system in the etiology of nicotine dependence and alcoholism based on linkage, association, and gene-by-gene interaction studies (121).

Finally, there are multitudes of genetic studies that associate specific behaviors with identified reward gene alleles (specific SNPs) within the mesolimbic pathway. These descriptions of the contribution made by polymorphisms (sequence variations) that effect the healthy function of reward genes, and this small sampling of association studies illustrate why the presence of these alleles in a gene panel indicate genetic risk for associated behaviors.

PROMOTING A PRO-DOPAMINE LIFESTYLE

A comprehensive treatment program that teaches a pro-dopamine lifestyle and uses urine drug screens like the Comprehensive Analysis of Reported Drugs (CARD) to monitor outcomes, and as a basis for therapeutic interactions, is suggested. Can a pro-dopamine lifestyle with gentle prolonged D2 agonist therapy overcome DNA polymorphisms by promoting positive epigenetic effects which can be transferred from generation to generation (32, 122, 123)? Holistic modalities like exercise (124), low glycemic index diet (125), mindfulness training, neurofeedback, yoga, and meditation are known to support reward neurotramsmission and naturally release dopamine the product of reward neurotransmission (126, 127). These holistic pro dopamine modalities supported by the 12 step fellowship, might induce feelings of well-being and thereby reduce craving and relapse. With this in mind, we wonder if we have been "licking our pups" enough? Could substance and non-substance seeking- behaviors be attenuated through nurturing (128) as suggested by David E. Smith in the late 60's "love needs care" (129)?

SUMMARY

These basic concepts underpin translational addiction-related research that can help the multitude of victims of genetically

induced RDS become the recipients of better therapeutic relapse-preventive tactics.

Finally, as neuroscientists and psychiatrists, working in the "addiction space" we encourage the global scientific community to take heed and reconsider the current utilization of dopaminergic blockade and instead adopt the goal of regaining dopamine homeostasis. Optimistically, early predisposition diagnosis through genetic testing; including pharmacogenetic and pharmacogenomic monitoring, with appropriate urine drug screening, and treatment with pro-dopamine regulators could conceivably reduce stress, craving, and relapse and enhance well-being in the recovery community. Following required basic and clinically directed research, the notion of genetically guided therapy may become a front-line technology with the potential to overcome, in part, the current heightened rates of substance abuse.

AUTHOR CONTRIBUTIONS

The original concept was developed by KB, DB, JN, PT, and RDB. The original draft was provided by KB and MG-L. The entire paper was carefully vetted by RDB, IE, MG-L, KB, EB, PT, DB, JN, and approved.

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Bupropion Shows Different Effects on Brain Functional Connectivity in Patients With Internet-Based Gambling Disorder and Internet Gaming Disorder

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Introduction: Internet gaming disorder (IGD) and gambling disorder (GD) share similar clinical characteristics but show different brain functional connectivity patterns. Bupropion is known to be effective for the treatment of patients with IGD and GD. We hypothesized that bupropion may be effective for the treatment of Internet-based gambling disorder (ibGD) and IGD and that the connections between the default mode network (DMN) and cognitive control network (CCN) would be different between ibGD and IGD patients after 12 weeks of bupropion treatment.

Methods: 16 patients with IGD, 15 patients with ibGD, and 15 healthy subjects were recruited in this study. At baseline and after 12 weeks of bupropion treatment, the clinical symptoms of patients with IGD or ibGD were assessed, and brain activity was evaluated using resting state functional magnetic resonance imaging.

Results: After the 12-week bupropion treatment, clinical symptoms, including the severity of IGD or GD, depressive symptoms, attention, and impulsivity improved in both groups. In the IGD group, the functional connectivity (FC) within the posterior DMN as well as the FC between the DMN and the CCN decreased following treatment. Moreover, the FC within the DMN in the IGD group was positively correlated with changes in Young Internet Addiction Scale scores after the bupropion treatment period. In the ibGD group, the FC within the posterior DMN decreased while the FC within the CCN increased after the bupropion treatment period. Moreover, the FC within the CCN in the ibGD group was significantly greater than that in the IGD group.

Conclusion: Bupropion was effective in improving clinical symptoms in patients with IGD and ibGD. However, there were differences in the pharmacodynamics between the two groups. After 12 weeks of bupropion treatment, the FC within the DMN as well as between the DMN and CCN decreased in patients with IGD, whereas the FC within the CCN increased in patients with ibGD.

Keywords: Internet gaming disorder, gambling disorder, bupropion, default mode network, cognitive control network

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INTRODUCTION

Internet-based gambling is a modified form of gambling using Internet-enabled devices, including computers, mobile phones, and digital television (1, 2). Due to the characteristics of online systems such as speed and ease of accessibility, internet-based gambling may have a rapid feedback system and provide easy access to variable betting options (1, 2). Over the last two decades, Internet gaming disorder (IGD) has been regarded as a mental disease characterized by the urge for game (gambling) play, extensive playing time, and harmful side effects (3). Due to the similarities between IGD and internet-based gambling disorder (ibGD) with respect to the clinical symptoms of excessive use and the potential adverse effects, several studies have suggested that IGD may be diagnostically similar to ibGD (4). Because of these diagnostic similarities, medications for gambling disorder (GD), including escitalopram and bupropion, have also been applied to IGD (5–8). However, there has been controversy regarding the classification of IGD as an addiction or impulse control disorder (3, 9, 10) as well as the differences in brain functional connectivity (FC) within the cognitive network between the two diseases (11). Therefore, a comparison of the effects of medication on the two diseases is warranted.

Among the several medications known to be effective for reducing the symptoms of GD (5, 6), bupropion has been suggested to improve the symptoms of IGD (8, 12). Bupropion is effective for treating patients with GD by decreasing gambling behavior and the amount of money spent (5, 6). Black et al. (5) reported that bupropion was effective and well tolerated in patients with GD (5). Dannon et al. (6) have suggested that bupropion is as effective as naltrexone based on its mechanism of regulating dopamine release. Bupropion acts to inhibit the reuptake of dopamine and norepinephrine by stimulating acetylcholine, hydroxytryptamine, gamma aminobutyric acid receptor, and endorphin signaling (13). These neurochemical systems may be associated with the urges, craving, and enjoyment accompanying gambling behaviors and addiction to drugs of abuse (14). The opioid antagonist naltrexone may block alcohol-induced dopamine release in the nucleus accumbens, which reduces the craving for alcohol and promotes abstinence (15). Studies have suggested that bupropion could improve the symptoms of IGD by improving comorbid depressive symptoms and inducing changes in brain activity (8, 16). Twelve weeks of bupropion treatment has been shown to improve IGD symptoms as well as depressive symptoms in patients with major depressive disorder and IGD (8). In another study, 6 weeks of bupropion treatment reduced the severity of IGD by decreasing brain activity within the dorsolateral prefrontal cortex in response to game stimulation (16).

In our previous study comparing the brain connectivity of the default mode network (DMN) and cognitive control network (CCN) between IGD and ibGD, both groups showed a similar decrease in FC in the DMN. However, FC within the CCN was increased in the IGD group but not the ibGD group (11). The DMN refers to functionally grouped areas that are synchronously deactivated during task performance and mainly activated during rest (17). The DMN was usually thought to consist of the posterior cingulate cortex (PCC), precuneus, medial frontal cortex (mPFC), ventral anterior cingulate cortex (ACC), and lateral (LP) and inferior parietal lobes (IP) (17). In patients with substance dependence, the brain FC within the DMN was positively correlated with impulsivity (18). In patients with GD, decreased FC within the DMN from the PCC to the left superior frontal gyrus, right middle temporal gyrus, and precuneus was reported. In addition, the severity of GD was negatively correlated with the FC from the seed PCC to precuneus (19). However, previous studies on FC within the DMN in IGD have shown variable findings (11, 12). The FC within the posterior parts of the DMN in patients with IGD was decreased (11). By contrast, FC between the DMN and the salience network was increased in patients with IGD (12).

The CCN is correlated with the process of employing executive functions, including attention, planning, and working memory for guiding appropriate behaviors to achieve specific goals (20). It includes the dorsal regions of the lateral prefrontal cortex (DLPFC), ACC, and parietal cortex (20). As gambling and Internet gaming are associated with goal-directed decision-making (21), several scholars have suggested that the FC within the CCN would be associated with gambling and IGD (22). Moreover, the conflict and uncertainty resulting from risky decision-making during gambling tasks can activate the dorsal prefrontal cortex (23).

We hypothesized that bupropion might be effective for the treatment of ibGD and IGD. However, the mechanism of bupropion action in the treatment of ibGD and IGD in terms of brain connectivity between DMN and CCN would differ. We hypothesized that bupropion would decrease the FC between the DMN and CCN in the IGD group, but would increase the FC within the CCN in the ibGD group.

MATERIALS AND METHODS

Participants

Of the 15 patients with IGD and 14 patients with ibGD who participated in our previous study comparing brain connectivity (11), 12 patients with IGD and 12 patients with ibGD agreed to participate in this study. In addition, seven patients with IGD and six patients with ibGD who visited the outpatient department of OO hospital were newly recruited in this study (**Figure 1**). All participants were screened with the DSM-IV structural clinical interview for assessing psychiatric comorbidity (24). During the follow-up period, three patients with IGD and three patients with ibGD dropped out because of voluntary termination and changes in medication. Finally, 16 patients with IGD and 15 patients with ibGD completed the study protocol (**Figure 1**). The inclusion criteria were as follows: (1) diagnosed with IGD based on the DSM-5 or determined to have ibGD. We used the diagnostic criteria of GD and adapted it to form the inclusion criteria for ibGD, but changed "problematic gambling" in the DSM-5 to "ibGD," (2) adult (>18 years old), (3) male, and (4) psychiatric medication-naïve. The exclusion criteria were as follows: (1) other comorbid medical or psychiatric diseases, (2) low intelligence quotient (IQ) (less than 80), (3) contraindications for MRI scanning such as claustrophobia and metal implantation, and (4) history of substance abuse with the exception of social alcohol drinking and smoking.

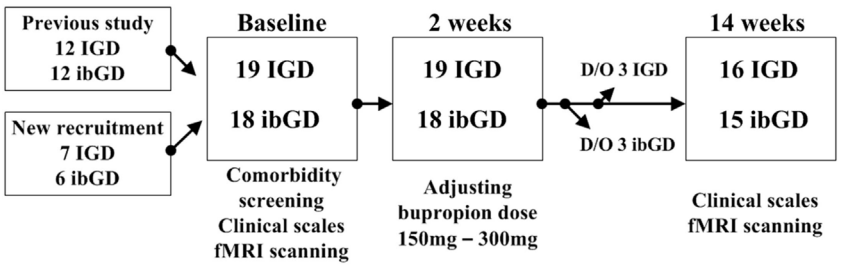

FIGURE 1 | Study procedure. Abbreviations: IGD, Internet gaming disorder; ibGD, Internet-based gambling disorder; D/O, dropped out; fMRI, functional magnetic resonance imaging.

Procedure

At baseline, all participants were asked to complete questionnaires for demographic data and clinical symptoms. The symptom severity of ibGD and IGD was assessed with the Yale-Brown Obsessive Compulsive Scale for pathologic gambling (YBOCS-PG) (25) and Young Internet Addiction Scale (YIAS) scores (26), respectively. Four more clinical symptom assessment scales were applied to all participants: the Beck Depression Inventory (BDI) (27) for depressive mood symptoms, the Korean ADHD Rating Scale (K-ARS) (28) for attention symptoms, and the Behavioral Inhibitory System and Behavioral Activation System scales for inhibitory and excitatory personal traits for aversive or appetitive motivations in behavior (29). The IQ of all participants was assessed using the Korean-Wechsler Adult Intelligence Scale (30). In addition, all participants were scanned to analyze brain FC *via* resting state functional magnetic resonance imaging (rs-fMRI). Both patients with IGD and ibGD were started on bupropion SR 150 mg/day, which was then increased to 300 mg/day. The decision to adjust the dose was made by a psychiatrist (Doug Hyun Han) at the second-week visit on the basis of tolerability and efficacy. At the end of 12 weeks of bupropion treatment, clinical scales and rs-fMRI scans were repeated in all participants (**Figure 1**). The Chung-Ang University Hospital Institutional Review Board approved the research protocol for this study, and written informed consent was provided by all participants.

MRI Acquisition and Preprocessing

Brain FC in the resting state was assessed using 3 T blood-oxygen-level dependent functional MRI (Philips Achieva 3.0 T TX MRI scanner; TR = 3 s; scan period, 12 min; 240 volumes; 128 × 128 matrix; 40 slices at a 4.0-mm slice thickness). Preprocessing consisted of despiking (AFNI: 3dDespike), motion correction (SPM 12b), coregistration to Magnetization Prepared RApid Gradient Echo image (SPM 12b), normalization to MNI space (SPM 12b), temporal detrend (Matlab: detrend.m), bandpass filtering (Matlab: idealfilter.m), and voxelwise regression of identically bandpass filtered time series of six head motion parameters (realignment steps with six rigid-body parameters characterizing the estimated subject motion for each subject), degraded cerebrospinal fluid, degraded white matter, and facial soft tissues (Matlab) as previously described (31). To address the possibility of micro-head movements affecting connectivity results (32), censoring of time points with a head motion >0.2 mm was performed, but no regression of the global signal was performed (31).

We extracted 12 regions of two brain networks [four from the DMN: mPFC, right/left lateral parietal cortex (LPRt/LPLt), and PCC; eight from the CCN: right/left DLPFC (DLPFCRt/DLPFCLt), right/left inferior PFC (IFGRt/IFGLt), right/left posterior parietal cortex (PPCRt/PPCLt), and right/left presupplementary motor area] from the AAL atlas of the brain (networks.nii/.txt/.info). Using the CONN-fMRI functional connectivity toolbox (ver.15; www.Nitrc.org/projects/conn), Fisher-transformed correlation coefficients were calculated for each pair of regions of interest in each subject. Between-group effects were considered significant with a cluster-level false discovery rate (FDR)q < 0.05, considering the multiple comparison correction over the correction of 66 pairs of 12 regions.

Statistics

Demographic and clinical characteristics of IGD, ibGD, and healthy comparison subjects were analyzed using analysis of variance (ANOVA) tests with statistical significance set at $p < 0.05$. The correlations between clinical scales and brain connectivity were assessed using Spearman correlation with statistical significance set at $p < 0.05$. All statistical assessments were performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Changes in Clinical Symptoms After 12 Weeks of Bupropion Treatment

At baseline, there were no significant differences in age, education years, and IQ between IGD patients, ibGD patients, and healthy comparison subjects. However, there were significant differences in BISBAS ($F = 6.56$, $p < 0.01$), BDI ($F = 4.68$, $p = 0.02$), K-ARS ($F = 24.09$, $p < 0.01$), YIAS ($F = 70.94$, $p < 0.01$), and YBOCS-PG ($F = 82.68$, $p < 0.01$) scores between the three groups. The *post hoc* test showed no significant differences in BDI, K-ARS, and BISBAS scores between the IGD and ibGD groups. The YIAS scores in the IGD group were higher than those in the ibGD group ($z = 4.58$, $p < 0.01$) while the YBOCS-PG scores in the ibGD group were higher than those in the IGD group ($z = 4.60$, $p < 0.01$) (**Table 1**).

After the 12-week bupropion treatment, the BDI ($z = -2.68$, $p < 0.01$), K-ARS ($z = -2.81$, $p < 0.01$), BISBAS ($z = -2.81$,

TABLE 1 | Demographic and clinical characteristics.

	IGD		ibGD		HC
	Baseline	Follow-up	Baseline	Follow-up	
Age	25.3 ± 5.2		25.0 ± 4.9		25.7 ± 4.7
Education year	12.8 ± 2.6		12.1 ± 2.5		13.1 ± 2.3
IQ	99.0 ± 12.5		97.7 ± 15.3		103.8 ± 9.9
Alcohol (yes/no)	10/6		10/5		12/3
Smoking (yes/no)	8/8		9/6		8/7
BDI	9.7 ± 56.2	5.7 ± 2.8	14.1 ± 8.3	9.4 ± 3.4	6.1 ± 4.2
K-ARS	13.0 ± 4.5	9.3 ± 3.1	18.8 ± 7.7	14.4 ± 4.9	5.4 ± 3.4
BISBAS	47.6 ± 4.9	47.6 ± 4.9	50.7 ± 6.0	50.7 ± 6.0	49.0 ± 8.1
YIAS	68.9 ± 8.8	54.8 ± 8.2	38.3 ± 9.0	36.5 ± 7.4	37.6 ± 6.6
YBOCS-PG	5.7 ± 2.2	5.1 ± 1.8	17.8 ± 4.6	12.2 ± 4.3	4.1 ± 1.8

IGD, Internet gaming disorder; ibGD, Internet-based gaming disorder; HC, healthy comparison subjects; IQ, intelligence quotient; BDI, Beck Depression Inventory; K-ARS, Korean ADHD Rating Scale; BISBAS, Behavioral Inhibitory System Behavioral Activation System; YIAS, Young Internet Addiction Scale; YBOCS-PG, Yale-Brown Obsessive Compulsive Scale for pathologic gambling.

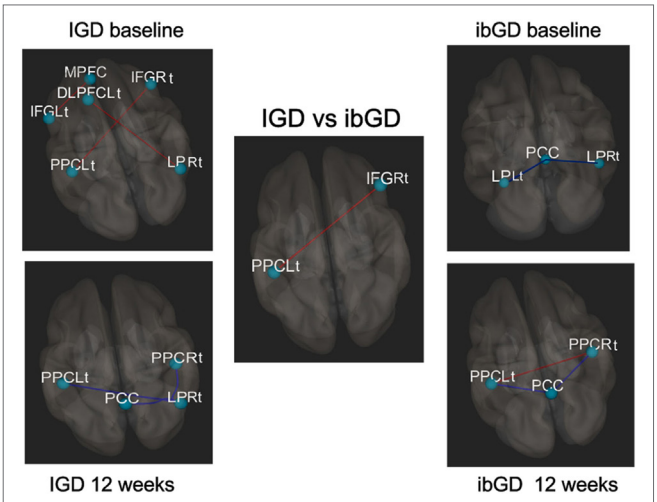

FIGURE 2 | Changes in brain functional connectivity after 12 weeks of bupropion treatment. Red line: increased functional connectivity (FC), blue line: decreased FC, In the IGD group at baseline, the functional correlation between the middle frontal gyrus (MPFC) and left inferior prefrontal cortex (IFGLt) (t = 3.39, FDRq = 0.0026), left dorsolateral prefrontal cortex (DLPFCLt) and right lateral parietal cortex (LPRt) (t = 3.34, FDRq = 0.0030), and left posterior parietal cortex (PPCLt) and IFGRt (t = 3.67, FDRq = 0.0013). At 12 weeks, the functional correlation between the posterior cingulate cortex (PCC) and LPRt (t = −3.26, FDRq = 0.0017), LPRt and PPCRt (t = −3.16, FDRq = 0.0023), and LPRt and PPCLt (t = −3.42, FDRq = 0.0012). In ibGD group at baseline, the functional correlation between the PCC and LPLt (t = −3.36, FDRq = 0.0014), PCC and LPRt (t = −3.26, FDRq = 0.0027). At 12 weeks, the functional correlation between the PCC and PPCLt (t = −3.23, FDRq = 0.0031), PCC and PPCRt (t = −3.25, FDRq = 0.0031). The functional correlation between the PPCLt and PPCRt (t = 3.12, FDRq = 0.0042). In the IGD vs ibGD comparison (repeated measure analysis of variance), the ibGD group showed increased FC between IFGRt and PPCLt (F = 3.67, p = 0.0013), compared with IGD group.

$p < 0.01$), and YIAS ($z = -2.81$, $p < 0.01$) scores improved in the IGD group while the BDI ($z = -2.09$, $p = 0.04$), K-ARS ($z = -2.81$, $p < 0.01$), BISBAS ($z = -2.81$, $p < 0.01$), and YBOCS-PG ($z = -2.80$, $p < 0.01$) scores improved in the ibGD group. However, there were no significant intergroup differences with regards to changes in the clinical scales during the 12-week period (**Table 1**).

Changes in Brain FC After 12 Weeks of Bupropion Treatment

In the IGD group at baseline, the FC between the MPFC and IFGLt (t = 3.39, FDRq = 0.0026), DLPFCLt and LPRt (t = 3.34, FDRq = 0.0030), and PPCLt and IFGRt (t = 3.67, FDRq = 0.0013) was higher than that in the healthy subjects. After 12 weeks of bupropion treatment, the FC between the PCC and LPRt (t = −3.26, FDRq = 0.0017), LPRt and PPCRt (t = −3.16, FDRq = 0.0023), and LPRt and PPCLt (t = −3.42, FDRq = 0.0012) were lower than baseline (**Figure 2**).

In the ibGD group at baseline, the FC between the PCC and LPLt (t = −3.36, FDRq = 0.0014) as well as PCC and LPRt (t = −3.26, FDRq = 0.0027) was lower than that in healthy subjects. After 12 weeks of bupropion treatment, the FC between the PCC and PPCLt (t = −3.23, FDRq = 0.0031) as well as the PCC and PPCRt (t = −3.25, FDRq = 0.0031) was decreased while that between PPCLt and PPCRt (t = 3.12, FDRq = 0.0042) had increased compared with baseline (**Figure 2**).

A repeated measures ANOVA revealed that the ibGD group showed increased FC between IFGRt and PPCLt (F = 3.67, p = 0.0013), compared with the IGD group (**Figure 2**).

Correlation Between the Changes in Clinical Scales and the Changes in Brain FC

In the IGD group, the functional correlation between PCC and LPRt was positively correlated with changes in YIAS scores from baseline to 12 weeks ($r = 0.69$, $p < 0.01$). In the ibGD group, the changes in FC between the PPCLt and PPCRt were negatively correlated with the changes in YBOCS-PG scores from baseline to 12 weeks ($r = -0.68$, $p < 0.01$) (**Figure 3**).

DISCUSSION

Changes in Clinical Symptoms in Response to Bupropion Treatment

In this study, 12-week bupropion treatment improved the severity of IGD and ibGD as well as the associated clinical symptoms in both patient groups. The effectiveness of bupropion for the treatment for IGD has been reported in previous studies (8, 16). Twelve weeks of bupropion treatment has been shown to reduce the severity of IGD as well as depressive symptoms in IGD patients with major depressive disorder (8). In a comparison of escitalopram and bupropion treatment, bupropion showed greater effectiveness in improving impulsivity and attention (12). The effectiveness of bupropion in patients with GD is a matter of debate (5, 6). Although Black et al. (5) reported the effectiveness and tolerability of bupropion in patients with GD, its effectiveness

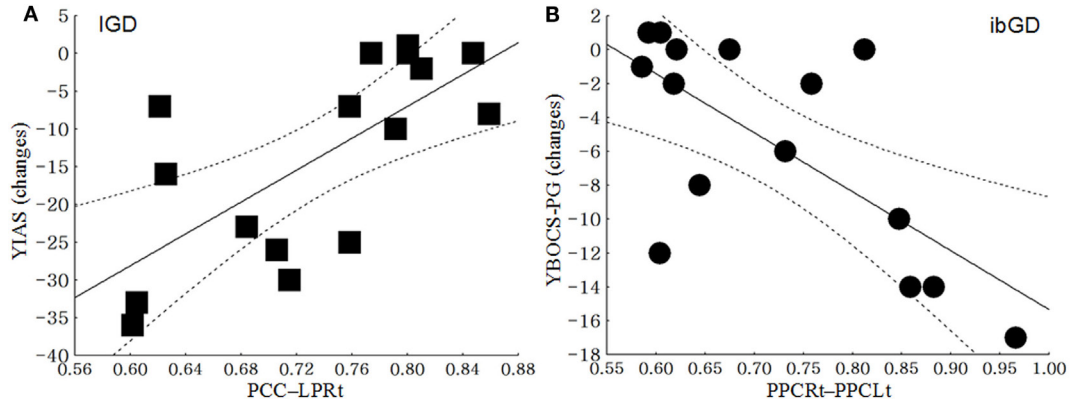

FIGURE 3 | Correlation between the changes in clinical scales and the changes in brain functional connectivity. **(A)** In the Internet gaming disorder (IGD) group, the functional connectivity between the posterior cingulate cortex (PCC) and right lateral parietal cortex (LPRt) was positively correlated with the changes in the Young Internet Addiction Scale scores from baseline to 12 weeks ($r = 0.69$, $p < 0.01$). **(B)** In the ibGD group, the changes in FC between the left posterior parietal cortex (PPCLt) and right posterior parietal cortex (PPCRt) were negatively correlated with the changes in the Yale-Brown Obsessive Compulsive Scale for pathologic gambling (YBOCS-PG) scores from baseline to 12 weeks ($r = -0.68$, $p < 0.01$).

in GD symptom reduction was not greater than that of placebo (5). However, Dannon et al. (6) declared that bupropion was as effective as naltrexone in patients with GD (6). Due to the dual action of bupropion with regards to the inhibition of norepinephrine and dopamine reuptake, it is thought to be effective for reducing impulsive behaviors in both IGD and ibGD patients (33, 34). Impulsivity is a well-known correlate of prototypical behavioral addictions with steep discounting of delayed rewards (35). This steep discounting of delayed rewards is associated with the dopamine-based neuromodulatory system (36).

Changes in Brain FC After 12 Weeks of Bupropion Treatment

In response to 12 weeks of bupropion treatment, the FC within the DMN as well as that between the DMN and CCN decreased in the IGD group, while the FC within the CCN increased in the ibGD group. The IGD and ibGD groups showed different brain FC patterns in response to bupropion treatment. In the IGD group, the FC within the posterior DMN as well as the FC between the DMN and CCN decreased after the 12-week treatment period. Moreover, the FC between the PCC and LPRt in the IGD group was positively correlated with changes in YIAS after the 12-week bupropion treatment period. These results were consistent with our previous study showing decreased FC within the DMN and between the DMN and the salience network (12). Decreased FC within the DMN may be associated with increased norepinephrine and dopamine, as observed in the DMN in response to the administration of atomoxetine (37). The dual action of bupropion in increasing norepinephrine and dopamine signaling is similar to the mechanism of action of modafinil (38). The increased FC within the DMN was thought to be related to impulsivity, risky decision-making, and attention deficits (17, 39). Therefore, decreasing the FC within the DMN and the FC between the DMN and other networks may reduce impulsive behavior, such as excessive Internet game-playing or gambling.

In the ibGD group, the FC within the posterior DMN decreased while that within the CCN increased after the 12-week bupropion treatment period. Moreover, the FC within the CCN (IFGRt – PPCLt) in the ibGD group was much higher than that in the IGD group. The FC within the CCN (PPCLt – PPCRt) in the IGD group was negatively correlated with changes in the YBOCS-PG scores after the 12-week bupropion treatment period. The failure of self-regulation in patients with GD is thought to occur due to failure in prefrontal-mediated top-down inhibitory control (40). The top-down circuitry is reported to be associated with decision errors (36) as well as dopamine transmission (41). In addition, areas of the fronto-parietal cortices are engaged in top-down attention and cognitive control (42). Therefore, the pharmacodynamic activity of bupropion (dopamine stimulation) may enhance the CCN (fronto-parietal areas) by promoting activity within the top-down circuitry in patients with ibGD. Taken together, IGD and ibGD appear to share similar characteristics of decreased impulsivity and decreased FC within the DMN after bupropion treatment. However, bupropion was more effective at increasing the FC within the CCN, which is associated with the correction of decision errors.

Limitations

There were several limitations in this study. First, the small number of subjects limits the generalizability of the results. Due to the small number of subjects, only two brain networks of interest were used to compare the FC changes between the two groups in response to bupropion treatment. Second, as this study did not have a placebo control group, we cannot rule out the possibility that we were seeing a placebo effect. Finally, because the healthy control subjects did not participate in follow-up assessments, we did not have a measure of test-retest variability. Future studies should include a larger number of subjects as well as follow-up information for healthy control subjects.

CONCLUSION

Bupropion shows promise for improving problematic behaviors in both IGD and ibGD. However, the pharmacodynamics

of bupropion differed between the two groups, whereby the FC within the DMN as well as between the DMN and CCN decreased in patients with IGD, whereas the FC within the CCN increased in patients with ibGD after 12 weeks of bupropion treatment.

ETHICS STATEMENT

The Chung-Ang University Hospital Institutional Review Board approved the research protocol for this study, and written informed consent was provided by all participants.

AUTHOR CONTRIBUTIONS

JH, SK, and DH contributed to patients' recruitment, data collection, and processing. SB, JH, and DH analyzed the data. All the authors participated to drawing up the manuscript, were involved to the intellectual workup for the article, and read and approved the final manuscript.

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