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Review Article

Neurobiological findings related to Internet use disorders

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In the last 10 years, numerous neurobiological studies have been conducted on Internet addiction or Internet use disorder. Various neurobiological research methods – such as magnetic resonance imaging; nuclear imaging modalities, including positron emission tomography and single photon emission computed tomography; molecular genetics; and neurophysiologic methods – have made it possible to discover structural or functional impairments in the brains of individuals with Internet use disorder. Specifically, Internet use disorder is associated with structural or functional impairment in the orbitofrontal cortex, dorsolateral prefrontal cortex, anterior cingulate cortex, and posterior cingulate cortex. These regions are associated with the processing of reward, motivation, memory, and cognitive control. Early neurobiological research results in this area indicated that Internet use disorder shares many similarities with substance use disorders, including, to a certain extent, a shared pathophysiology. However, recent studies suggest that differences in biological and psychological markers exist between Internet use disorder and substance use disorders. Further research is required for a better understanding of the pathophysiology of Internet use disorder.

Key words: Internet addiction, Internet gaming disorder, Internet use disorder, neurobiology, neuroimaging.

IN THE PAST decade, an increasing number of studies have investigated excessive Internet use, which leads to behavioral addiction. Various activities that the Internet offers, such as gaming, shopping, and social networking, have hedonic qualities. Vulnerable individuals come to use the Internet obsessively and excessively, and their social and occupational functions are impaired. This pathological phenomenon, which has recently shown a dramatic increase, is called Internet addiction (IA) or Internet use disorder (IUD). Internet gaming disorder (IGD), which has a particularly high prevalence among male adolescents, is a specific form of IUD and has been the most extensively investigated form thus far.[1–6] Behavioral addictions, such as gambling disorder and IUD, share certain clinical characteristics with substance addiction, including the development of tolerance, psychological and/or physical withdrawal symptoms, excessive behavior, loss of control, and cravings.[5] Furthermore, changes in the brains of individuals with IUD and gambling disorder demonstrate similarities to those observed in substance use disorders (SUD). This implies that IUD and SUD are likely to share at least a subset of similar underlying neurobiological mechanisms.[7]

The purpose of this review is to summarize the major studies that have implemented neurobiological methods to investigate structural and functional changes that occur in the brains of individuals with IUD or IGD. Typical neurobiological methods used in these studies are neuroimaging and neurophysiologic techniques, as these enable the identification of the involved brain areas. The various neuroimaging techniques used include structural magnetic resonance imaging (sMRI), such as voxel-based morphometry (VBM) and diffusion tensor imaging (DTI); functional magnetic resonance imaging (fMRI); and nuclear imaging, such as positron emission tomography (PET) and single photon emission computed tomography (SPECT). Neurophysiologic studies using electroencephalogram (EEG) to study

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IUD are also discussed in this review. This review covers the studies on IA, IUD, and IGD together, without distinction, and uses these terms as they were presented in the original works.

SEARCH STRATEGIES AND CRITERIA

Literature from December 2005 to December 2015 was searched in the Web of Science and Google Scholar databases using the keywords 'Internet addict*', 'compulsive Internet', 'video gam*', 'Internet gam*', and 'excessive Internet use'. Review articles were included if associated with our topic.

Study inclusion criteria were as follows: (i) studies were peer-reviewed, in English, and published from December 2005 to December 2015; (ii) studies used imaging techniques, such as magnetic resonance spectroscopy (MRS), PET, SPECT, sMRI, and fMRI (such as DTI, VBM, arterial spin labeling [ASL], and regional homogeneity [ReHo]); and/or (iii) studies used neurophysiologic techniques (such as EEG and event-related potential); pharmacogenetic techniques (such as PET with a radioactive dye); or molecular genetic testing (such as acetylcholine receptor polymorphisms).

Eighty-four studies satisfied the inclusion criteria. Excluding duplicative studies that used similar research methods, sMRI was used in 13 studies, and fMRI, in 38. Ten studies employed PET, and one study employed SPECT. Fourteen studies used EEG. If two or more neurobiological techniques were implemented within the same study, studies are discussed below in all relevant sections. Due to the large number of studies, only pioneering studies are discussed, such as those that discovered neurobiological changes before and after treatments or utilized specific neurobiological techniques for the first time. We found some inconsistency between similar studies, which might be explained by newer methods and larger sample sizes of follow-up studies. The main studies discussed in this review are summarized in Table 1.[8–26] Brief information about the remaining studies can be found in the supplemental tables (Tables S1–S6, Supporting Information).

FINDINGS FROM MRI STUDIES

sMRI studies show that decreased gray matter density is associated with IUD

sMRI offers superior spatial resolution and is useful for determining changes in anatomic structures. Studies employing MRI on IGD patients revealed structural damage to specific brain regions. Various sMRI techniques have been used in order to study the characteristics of brain structure, discussed in turn below.

VBM is a neuroimaging technique that involves voxel-wise comparisons of gray and white matter in different groups of subjects. Using VBM, Zhou *et al.* showed that IA adolescents have low gray matter density in the left anterior cingulate cortex (ACC), left posterior cingulate cortex (PCC), left insula, and left lingual gyrus.[10] Yuan *et al.* also used VBM to study IA adolescents but found a decrease in gray matter density in the bilateral dorsolateral prefrontal cortex, supplementary motor area, orbitofrontal cortex (OFC), cerebellum, and left rostral ACC.[27] Furthermore, Weng *et al.* showed reduced gray matter density in IGD individuals localized to the right OFC, bilateral insula, and right supplementary motor area.[28] Although all three studies similarly found reduced gray matter density in the brains of subjects with IA or IGD, the regions exhibiting gray matter atrophy did not correspond fully between studies. This discrepancy may be due to technical differences between the three studies.

Many of the brain regions found to be altered in the IA brain by VBM have been linked previously to functions contributing to the development of addictive or compulsive behaviors. For example, damage to the prefrontal cortex (PFC) occurs in other addictive disorders. Gray matter atrophy of the PFC is associated with a loss of control of behavior, which is an important characteristic of IA. Furthermore, the OFC regulates impulse control and decision-making, and the dorsolateral PFC and rostral ACC are responsible for cognitive control.[29] Functional neuroimaging studies suggest that activity in the insula triggers the explicit motivation to use addictive drugs.[30] The VBM study results also correspond to those of previous studies showing that the PFC and insula contribute to the underlying mechanism of SUD.[31]

Yuan *et al.* combined sMRI with a behavioral test, confirming that during late adolescence, individuals with IGD had impaired cognitive control in a Stroop color–word test compared to a control group. In these individuals, cortical thickness was decreased in the left lateral OFC, insula, lingual gyrus, right postcentral gyrus, entorhinal cortex, and inferior parietal cortex.[8] The reduced cortical thickness of the left lateral OFC in IGD subjects was correlated with the

Table 1. Summary of neurobiological findings related to Internet use disorders

Study	Subjects	Neurobiological changes compared to controls
sMRI		
Yuan *et al.*, 2013[8]	18 male addicts and 18 male controls	Gray matter density IGD group showed decreased gray matter density in left anterior cingulate cortex, left posterior cingulate cortex, left insula, and left lingual gyrus
Lin *et al.*, 2012[9]	17 addicts (2 females and 14 males) and 16 controls (2 females and 15 males)	Diffusion tensor image Subjects with IA showed significantly lower FA in orbitofrontal white matter, corpus callosum, cingulum, inferior fronto-occipital fasciculus, corona radiation, and internal and external capsules
Zhou *et al.*, 2011[10]	18 addicts (2 females and 16 males) and 15 controls (2 females and 13 males)	Voxel-based morphometry IA adolescents had lower gray matter density in the left anterior cingulate cortex, left posterior cingulate cortex, left insula, and left lingual gyrus
fMRI		
Feng *et al.*, 2013[11]	15 addicts (2 females and 13 males) and 18 controls (4 females and 14 males)	Arterial spin-labeling perfusion fMRI Adolescents with IGA showed significantly higher global cerebral blood flow in the left inferior temporal lobe/fusiform gyrus, left parahippocampal gyrus/amygdala, right medial frontal lobe/anterior cingulate cortex, left insula, right insula, right middle temporal gyrus, right precentral gyrus, left supplementary motor area, left cingulate gyrus, and right inferior parietal lobe. Lower cerebral blood flow was found in the left middle temporal gyrus, left middle occipital gyrus, and right cingulate gyrus
Liu *et al.*, 2010[12]	19 addicts (8 females and 11 males) and 19 controls (8 females and 11 males)	Resting fMRI; regional homogeneity Adults with IGD showed increased ReHo in the cerebellum, brainstem, right cingulate gyrus, bilateral parahippocampus, right frontal lobe (rectal gyrus, inferior frontal gyrus, and middle frontal gyrus), left superior frontal gyrus, left precuneus, right postcentral gyrus, right middle occipital gyrus, right inferior temporal gyrus, left superior temporal gyrus, and middle temporal gyrus
Hong *et al.*, 2013[13]	12 male addicts and 11 male controls	Resting fMRI; inter-regional connectivity Adolescents with IA showed more impaired connections involving cortico-subcortical circuits
Ko *et al.*, 2009[14]	10 male addicts and 10 male controls	Block design, gaming cue induced reactivity Adults with IGD showed activated brain regions in right orbitofrontal cortex, right nucleus accumbens, bilateral anterior cingulate and medial frontal cortex, right dorsolateral prefrontal cortex, and right caudate nucleus
Dong *et al.*, 2011[15]	12 male addicts and 12 male controls	Event-related, Stroop task Adults with IGD showed increased activation in the orbitofrontal cortex in gain trials and decreased anterior cingulate activation in loss trials
Dong *et al.*, 2012[16]	14 male addicts and 13 male controls	Reality-simulated guessing task Adults with IGD showed greater BOLD signal in the anterior and posterior cingulate cortices during incongruent Stroop trials
Han *et al.*, 2010[17]	11 male addicts and 8 male controls	Treatment response, fMRI with StarCraft cue IGD subjects showed decreased craving for Internet video game play, total game play time, and cue-induced brain activity in dorsolateral prefrontal cortex after a 6-week period of bupropion
Liu *et al.*, 2013[18]	14 addicts and 14 controls	Magnetic resonance spectroscopy Subjects with IAD showed decreased N-acetylaspartate-to-creatine ratio and choline-containing-compounds-to-creatine ratio in the bilateral frontal lobe white matter
Hou *et al.*, 2012[19]	5 male addicts and 9 controls	Single photon emission computed tomography Individuals with IAD showed decreased dopamine transporter expression level of striatum, and the volume and weight of bilateral corpus striatum as well as the (99m)Tc-TRODAT-1 uptake ratio of corpus striatum/the whole brain were greatly reduced in individuals with IAD

Table 1. (*Continued*)

Study	Subjects	Neurobiological changes compared to controls
PET		
Kim *et al.*, 2011[20]	5 male addicts and 7 male controls	11C-raclopride PET Individuals with IA showed reduced levels of dopamine D2 receptor availability in subdivisions of the striatum, including the bilateral dorsal caudate and right putamen
Park *et al.*, 2010[21]	11 male addicts and 9 male controls	18F-fluorodeoxyglucose PET Overusers had increased glucose metabolism in the right middle orbitofrontal gyrus, left caudate nucleus, and right insula, and decreased metabolism in the bilateral postcentral gyrus, left precentral gyrus, and bilateral occipital regions
Tian *et al.*, 2014[22]	12 male addicts and 14 male controls	11C-N-methylspiperone PET A significant decrease in glucose metabolism was observed in the prefrontal, temporal, and limbic systems. Dysregulation of D2 receptors was observed in the striatum, which was correlated to years of overuse. A low level of D2 receptors in the striatum was significantly associated with decreased glucose metabolism in the orbitofrontal cortex
Neurophysiology		
Yu *et al.*, 2009[23]	10 IUD subjects and 10 controls	EEG/Event-related potentials Excessive Internet use resulted in a significant decrease in the P300 amplitudes and a significant increase in the P300 latency in all electrodes
Molecular genetics		
Han *et al.*, 2007[24]	79 addicts and 75 controls	*Taq1A1* allele of the dopamine D2 receptor The *Taq1A1* and low activity (COMT) alleles were significantly more prevalent in the excessive Internet game playing group relative to the comparison group
Lee *et al.*, 2008[25]	91 IA subjects and 75 controls	Allelic variant of the serotonin transporter gene The homozygous short allelic variant of the serotonin transporter gene (*SS-5HTTLPR*) was more frequent in the excessive Internet use group
Montag *et al.*, 2012[26]	131 IA subjects and 132 controls	Nicotinic acetylcholine receptor subunit alpha 4 (*CHRNA4*) The T-variant (CC genotype) of the rs1044396 polymorphism on the *CHRNA4* gene occurred significantly more frequently in the IA group

BOLD, blood-oxygen lev7el-dependent signal; COMT, catechol-O-methyltransferase; EEG, electroencephalogram; FA, fractional anisotropy; fMRI, functional magnetic resonance imaging; IA, Internet addition; IAD, Internet addiction disorder; IGA, Internet gaming addiction; IGD, Internet gaming disorder; IUD, Internet use disorder; PET, positron emission tomography; ReHo, regional homogeneity; sMRI, structural magnetic resonance imaging.

degree of cognitive impairment in the color–word Stroop task. Similarly, the degree of reduction in cortical thickness in the left precentral gyrus, precuneus, and lingual gyrus of IGD adolescents was associated with the duration of addiction.[32] In other studies using the same method, a reduction in OFC thickness was found in male adolescents with IA.[33] As a decrease of OFC thickness has previously been shown in the brains of subjects with drug and behavioral addictions, this implies that IGD development may involve brain regions similar to those involved in these conditions.[33,34]

In contrast to their findings in the OFC, Yuan *et al.* also reported an increase in cortical thickness in the left precentral cortex, precuneus, middle frontal cortex, and inferior and middle temporal cortices in IGD subjects.[8] The precuneus is responsible for processing visual imagery, attention, and memory retrieval and is well known as a region involved in cue-induced craving.[35] The inferior and middle temporal cortices also participate in gaming cue-induced craving. Thus, the increase in cortical thickness in these areas is likely to be related to gaming cue-induced craving.[36]

DTI is another sMRI method used to quantify the status of white matter tracts via fractional anisotropy (FA), which measures the diffusivity of water molecules in the brain. This method is also used for

visualizing white matter tracts.[37] Dong *et al.* reported that the FA increased in the thalamus and left PCC of IGD patients compared to that of healthy controls.[38] Lin *et al.* confirmed these findings, showing that the FA of IA subjects was low in a broad range of brain regions, including the orbitofrontal white matter and corpus callosum, and that no brain region exhibited a higher FA level than controls.[9] Another DTI study reported that the FA of white matter in the right parahippocampal gyrus decreased and the FA increased in the left posterior limb of the internal capsule in adolescents with IA compared to the control group.[27] Collectively, these studies indicate that IA may cause impairments in both white matter and gray matter or, alternatively, that the changes to these brain structures can predispose individuals to IA. However, the brain regions where the alteration of FA occurs vary from study to study. Thus, further research into this matter is required.

Finally, in studies using proton MRS, individuals with IA showed a decrease in the ratio of N-acetylaspartate (NAA) to creatine (Cr) in the bilateral frontal lobe white matter and an increase in the ratio of choline-containing compounds to Cr.[18] NAA is considered a marker of neurons, and Cr is a metabolite that maintains a regular density despite neuronal loss. Therefore, a decrease of NAA/Cr ratio in certain brain regions may imply the loss or malfunction of corresponding neurons.[39] These research findings imply a decline in frontal lobe functioning in IA patients.

fMRI studies identify IA brain activity associated with reward and addiction

fMRI studies measure changes in blood oxygen in the brain to localize brain regions where neuronal activity is occurring. The increase of blood flow provides the active brain regions with more glucose and oxygen. Thus, an index of brain activity can be obtained by determining the oxyhemoglobin-to-deoxyhemoglobin ratio (distinguished on the basis that deoxygenated hemoglobin is paramagnetic and oxygenated hemoglobin is diamagnetic). Regional brain function can be studied indirectly by measuring the contrast of blood-oxygen level-dependent (BOLD) signal while performing cognitive tasks or before and after providing cues. ASL perfusion MRI can measure the absolute quantification of cerebral blood flow (CBF), and the increase of CBF is related to regional neuronal activity.[40]

Feng *et al.* investigated changes in resting CBF in adolescent IGD patients using ASL perfusion fMRI.[11] The CBF of IGD patients in a resting state was measured and compared to that of healthy controls. In the brains of IGD patients, an increase in CBF was observed in multiple regions, including the left inferior temporal lobe, fusiform gyrus, left parahippocampal gyrus, amygdala, right medial frontal lobe, ACC, left insula, right insula, right middle temporal gyrus, right precentral gyrus, left supplementary motor area, left cingulate gyrus, and right inferior parietal lobe. A decrease was observed in the left middle temporal gyrus, left middle occipital gyrus, and right cingulate gyrus. Of these brain regions, the amygdala and hippocampus belong to a circuit involved in learning and memory that is related to cue-induced craving.[41] The insula is associated with an impairment in self-awareness,[42] and the prefrontal cortex is associated with executive functions.[31] All of these brain regions have been associated previously with addiction. However, it is yet unclear whether the increased CBF is a primary consequence due to addiction itself or a secondary reaction to compensate for addiction-induced brain damage.

Functional connectivity impairments were also observed in IUD patients. Ding *et al.* showed that, in comparison to healthy controls, IGD patients' functional connectivity increased in the bilateral cerebellum posterior lobe and middle temporal gyrus and decreased in the bilateral inferior parietal lobe and right inferior temporal gyrus.[43] In another study that researched resting-state functional connectivity in IA adolescents, functional connectivity decreased mainly in cortico-subcortical circuits, particularly with prefrontal and parietal cortices.[13] In subcortical brain regions, the bilateral putamen was largely invaded. Similar to these results, a decrease in resting-state functional connectivity has been observed in the frontoparietal network in patients with cocaine and heroin use disorders, with a relative sparing of temporal regions.[44,45]

ReHo is a voxel-based measurement of brain activity in a resting-state. It assesses the similarity or synchronization of the time series of certain voxels and their adjacent voxels.[46] Liu *et al.* implemented the ReHo method to study the cerebral functioning characteristics of IA undergraduates in a resting state. In comparison to healthy controls, ReHo in the brains of IA undergraduates increased significantly

in the inferior parietal lobe, left posterior cerebellum, and left middle frontal gyrus and decreased in temporal, occipital, and parietal brain regions.[12] The differences in brain regions showing increased versus decreased regional homogeneity are informative. The temporal lobe region is responsible for processing auditory information, comprehension, and linguistic memory, and the occipital lobe is responsible for processing visual information. The cerebellum has various functions, including the regulation of cognitive activity, whereas the cingulate gyrus incorporates sensory information and is associated with monitoring conflicts. Hippocampi are part of the mesocorticolimbic system related to reward pathways. These results imply that in IA patients, the synchronization of sensory–motor coordination increases but the synchronization of visual and auditory brain activity decreases.

fMRI studies show increased activity in IA brain areas involved in impulsivity and craving

Impulsivity is often exhibited by IA patients.[47] Response inhibition (the ability to suppress a preplanned motor action) is known to decline when impulsivity occurs. Impulsivity is generally assessed through stop-signal tasks or Go/NoGo tasks.[48] Ko *et al.* assessed the changes in brain activation during response inhibition and error processing in IGD patients and healthy controls using fMRI. All participants answered questionnaires on IA and impulsivity and performed event-related Go/NoGo tasks while undergoing fMRI scans. IGD patients scored higher on impulsivity than healthy controls and showed higher brain activity in the left OFC and bilateral caudate nucleus when processing response inhibition. The insula and ACC were activated in both IGD patients and healthy controls during error processing. Right insular activity was lower in the IGD group than in the control group.[49] OFC has previously been associated with response inhibition.[50] These studies show that the frontostriatal network takes part in response inhibition and that both the ACC and insula, which are part of the salience network, are involved in error processing.[51] Collectively, changes in the activation of these brain regions may explain the loss of control during online gaming in IGD patients.

Dong *et al.* studied the neural correlations of response inhibition in male subjects with IA using an event-related fMRI and Stroop color–word task.[16] The Stroop color–word task is an assessment tool for inhibitory control, which is one of the aspects of cognitive control. In incongruent Stroop trials, the IA group showed stronger BOLD signaling in the ACC and dorsal PCC in comparison to the control group. The ACC is a brain region known to be involved in conflict monitoring and cognitive control.[52] Therefore, higher ACC activity in incongruent Stroop trials may imply a decline in cognitive efficiency. The PCC is part of the default mode network and performs attentional processes.[53] Increased dorsal PCC activity implies incomplete disengagement of the default mode network and an impairment in optimizing the tasks related to attentional resources in IA subjects.

In an attempt to define the neural substrates of cue-induced gaming urge in IGD patients, Ko *et al.* showed participants gaming pictures while fMRI scans were taken. The IA group showed higher activity in the right OFC, right nucleus accumbens, bilateral anterior cingulate, medial frontal cortex, right dorsolateral prefrontal cortex (DLPFC), and right caudate nucleus in comparison to the control group. These activated brain regions were positively correlated with self-reported gaming urges[14] and resembled activated regions in the brains of drug addicts who reported cravings.[54]

Similarly, Dong *et al.* compared reward and punishment processing in IA male subjects and healthy controls. All participants had fMRI scans while performing a reality-simulated task of imagining the situation of gaining or losing money in a card game. The IA group showed an increase of OFC activity in the gain trial and a decrease of ACC activity in the loss trial.[15] The OFC is known to be activated by reward,[55] the ACC, by losses.[56] Therefore, these results indicate a relative increase of reward sensitivity and a decrease of loss sensitivity in the IA group in comparison to the control group.

Another study by Ko *et al.* made a comparison of cue-induced craving in IGD subjects, IGD subjects in remission, and healthy controls.[36] These researchers found that the bilateral DLPFC, precuneus, left parahippocampus, posterior cingulate, and right anterior cingulate were more active in response to gaming cues in the IGD group than the control group. The remission group showed lower activity in the right DLPFC and left parahippocampal gyrus than the IGD group. Thus, activity levels in these regions may be used as indicators of the current level of addiction to Internet gaming.

fMRI also may be useful in determining the effects of certain treatments on IUD. Han *et al.* studied whether 6-week treatment with bupropion reduces the craving for Internet game play and video game cue-induced brain activity in individuals with IGD.[17] In response to video game cues, the IGD group showed higher activity in the left occipital lobe, left dorsolateral PFC, and left parahippocampal gyrus than the control group. After the bupropion treatment, the IGD group exhibited decreases in the degree of craving, total time spent on gaming, and cue-induced brain activity in the DLPFC. The clinical improvement and the changes in brain activity were similar to those when smokers with tobacco use disorder were treated with bupropion.[57]

Finally, a study by Han *et al.* compared the brain activity of university students before and after playing video games for 7 weeks.[58] When Internet video-game cues were suggested, the excessive Internet gaming group (playing more than 2520 min) showed an increase of brain activity in the ACC and OFC in comparison to the general player group (playing less than 2520 min). These results resemble the brain activity exhibited by individuals with SUD after a small dose of a substance is injected and substance cues are suggested.[59,60] This indicates that brain activation may not cause excessive playing of Internet video games but instead may be a consequence.

FINDINGS FROM NUCLEAR IMAGING STUDIES

In the field of neuroscience, studies on brain neuron activity and disease processes are conducted using nuclear imaging. PET and SPECT are nuclear imaging methods that are characterized by high sensitivity and show clinical utility with a variety of nuclear imaging agents.[61] Glucose consumption, CBF, and oxygen consumption can be quantified as indices of brain energy metabolism using SPECT and PET. In addition, the binding-site density for specific neurotransmitters can be measured by PET and SPECT using specific neuroreceptor radiotracers.

In a study using 18F-fluoro-deoxyglucose (18F-FDG) PET imaging, males with IGD showed an increase in glucose metabolism in the right middle OFC, left caudate nucleus, and right insula, and a decrease in the bilateral postcentral gyrus, left precentral gyrus, and bilateral occipital regions in comparison to the control group.[21] This finding indicates that the neurobiological mechanism of IGD is related to the OFC, striatum, and sensory regions, which are responsible for impulse control, reward processing, and somatic representation of previous experiences, respectively.[31]

PET has shown that impairments in dopaminergic systems can occur in the brains of IA or IGD patients. Koepp *et al.* performed pioneering work using PET to demonstrate striatal dopamine release levels when playing a video game.[62] As the binding potential of 11C-raclopride to dopamine D2 receptors decreases when the endogenous dopamine density becomes higher, it is possible to estimate the density of endogenous dopamine by measuring the changes in the binding potential of the radioligand. In the results of this study, the binding capacity of 11C-raclopride to dopamine receptors in the striatum decreased during video game play in comparison to baseline levels, indicating an increase in dopamine release and binding. The changes in binding potential while playing a video game were similar to those following the injection of amphetamines or methylphenidate, suggesting that gaming activity induces changes in dopaminergic activity comparable to psychoactive substances. Kim *et al.* measured the D2 dopamine receptor availability in the brains of IA patients using PET and the radioligand 11C-raclopride.[20] Consistent with the previous findings by Koepp *et al.*, individuals with IA showed decreased dopamine D2 receptor availability in the bilateral caudate and left putamen compared to the control group, which indicated a decrease of dopamine activity.

The dopamine transporter is a plasma membrane protein that actively transports dopamine from the extracellular space into presynaptic neurons.[63] Hou *et al.* measured dopamine transporter levels in IA patients using 99mTc-TRODAT-1 SPECT and found that the striatal dopamine transporter levels of the IA group decreased compared to the control group.[19] Similar results have been reported in patients with SUD.[64,65]

Tian *et al.* used PET with 11C-N-methylspiperone (11C-NMSP) and 18F-FDG to study dopamine D2 receptor levels and glucose metabolism in the brains of male subjects with IGD during a break and after playing an Internet game.[22] A decrease of glucose metabolism was observed in the prefrontal, temporal, and limbic systems of the IGD group. The binding of 11C-NMSP decreased in the right inferior temporal gyrus during a break in the IGD

group in comparison to the control group. Striatal 11C-NMSP binding in the IGD group significantly increased after playing an Internet game, indicating a decrease in dopamine D2 receptors. Furthermore, a significant positive correlation was observed between striatal 11C-NMSP binding and orbitofrontal 18F-FDG activity, showing that the striatal–prefrontal pathways take part in the dysregulation of striatal D2 receptors. The mechanisms of loss of control and compulsive behavior found in IGD patients may be associated with this dysregulation of striatal D2 receptors. Collectively, several lines of evidence support that IA is associated with impairments in the dopaminergic systems of the brain.

FINDINGS FROM NEUROPHYSIOLOGIC STUDIES

EEG measures the neuronal activity of the cerebral cortex by placing multiple electrodes on certain areas of the scalps of participants.[66] Event-related potentials are a method for studying brain–behavior relationships by measuring time-locked EEG activities.[67] According to the research by Yu *et al.*, a decrease of P300 amplitudes and longer P300 latencies were observed in IA patients compared to healthy controls.[23] Similarly, a decrease of P300 amplitudes was also observed in patients with SUD.[68] IAD patients receiving cognitive behavioral therapy for 3 months exhibited significantly decreased P300 latencies, indicating that cognitive function impairment in IA patients can be improved through psychological treatment.

According to the study by Dong *et al.*, compared to healthy controls, IA patients showed lower NoGo-N2 amplitude, higher NoGo-P3 amplitude, and longer NoGo-P3 peak latency in event-related brain potentials while performing the Go/NoGo tasks.[69] This suggests that the activation is decreased in the conflict-detection stage of IA patients and that more cognitive control is required in the next step of inhibiting tasks. The same research team conducted a study on cognitive control using the color–word Stroop task.[70] In the study on event-related potentials, the IAD group demonstrated longer reaction time and more response errors in incongruent conditions in comparison to the control group, reflecting a possible impairment in executive control.

FINDINGS FROM MOLECULAR GENETIC STUDIES

Attempts have been made to find genetic changes that convey a predisposition for IUD. Researchers investigated dopamine D2 receptors and genetic polymorphisms in the genes encoding enzymes that break down dopamine. It was discovered that the *Taq1A1* allele of the *DRD2* gene and the low-activity allele of catechol-O-methyltransferase (COMT) appeared more frequently in the excessive Internet video game-playing group relative to the control group. The *DRD2 Taq1A1* allele was associated with high reward-dependence.[24,71]

Previous studies have also suggested that excessive Internet use shares a phenotype with depression to some extent. Adolescents with problematic Internet use showed a higher frequency for a homozygous short allelic variant of the serotonin transporter gene (*SS-5HTTLPR*), greater harm avoidance, and higher Beck Depression Inventory scores.[25] Montag *et al.* investigated the genetic polymorphisms of nicotinic acetylcholine receptor subunit alpha 4 (*CHRNA4*) in IA patients. The T-variant (CC genotype) of the rs1044396 polymorphism on the *CHRNA4* gene was more frequent in the IA group than in the control group.[26] Evidence for molecular genetic variants in the serotonergic, dopaminergic, and acetylcholinergic neurotransmitter pathways have been described for both IUD and SUD.[26,72,73]

DIFFERENCES BETWEEN IUD AND SUD PATIENTS

Although the above literature indicates that IUD and SUD share at least some common underlying neurobiological mechanisms, recently, several studies have suggested that differences exist in brain activities between IUD and SUD patients. Han *et al.* reported that patients with alcohol dependence had positive functional connectivity from the DLPFC to striatal areas whereas patients with IGD had negative connectivity from the DLPFC to striatal areas.[74] Furthermore, Kim *et al.* declared that patients with IGD had decreased regional homogeneity from the PCC to inferior temporal cortex, compared to patients with alcohol dependence.[75] Finally, using quantitative EEG, Son *et al.* showed that lower absolute beta power could be used as a potential trait marker of IGD whereas higher

absolute power in the delta band may be a potential marker for alcohol dependence.[76]

CONCLUSIONS

Recently, research into the neurobiology of IUD has increased remarkably. The majority of studies have examined the similarities and differences between SUD and behavioral addictions using various neuroimaging techniques. Based on the past research on IUD, we conclude that IUD is associated with structural or functional impairments in the OFC, dorsolateral PFC, ACC, and PCC regions, which are involved in the processing of reward, motivation, memory, and cognitive control. IUD is also associated with impairment of dopamine D2 receptor function, which is associated with dysregulation in the OFC. These results correspond to those of SUD studies and, thus, IUD and SUD may share certain underlying neurobiological mechanisms. However, there are many differences in neurobiological mechanisms between different addictive drugs. For example, opiate addiction and psychostimulant addiction are behaviorally and neurobiologically distinct from each other. Similar findings can also be observed in behavioral addictions. Moreover, recent studies directly comparing IGD and SUD report differences between the two disorders.

Research on the treatment of IUD is in its initial phase, and much work remains to be done. In order to develop IUD-specific treatments, the neurobiological mechanisms underlying IUD must first be elucidated. Randomized controlled clinical trials of the effectiveness of pharmacotherapies for IUD are yet to be conducted. Furthermore, PET studies using new radiotracers should be used to determine the efficacy of pharmacotherapy and to predict treatment results. Further study should include both male and female subjects, as female participants have rarely been included in IA and IGD studies. In addition, longitudinal studies are needed to fully understand the dynamics of these conditions, as IA and IGD patients are often adolescents or young adults.

The majority of studies have been conducted in East Asia. To generalize the findings, further studies should involve subjects with various ethnic or cultural backgrounds. Additional studies using a larger number of participants should be conducted in order to reduce inconsistencies resulting from multiple small studies using relatively few participants. Despite the fact that our knowledge of IUD has significantly increased recently, a consensus on the operational definition and diagnosis of IUD has still not been achieved. This is due in part to inconsistencies in the selection of study participants. Therefore, future research should more precisely define the selection criteria for participants.

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DISCLOSURE STATEMENT

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design of the study: S.R.; acquisition and analysis of data: B.P., D.H.H., S.R.; drafting the manuscript and tables, B.P., D.H.H., S.R.

REFERENCES

1. Niemz K, Griffiths M, Banyard P. Prevalence of pathological internet use among university students and correlations with self-esteem, the General Health Questionnaire (GHQ), and disinhibition. *Cyberpsychol. Behav.* 2005; **8**: 562–570.
2. Yen JY, Ko CH, Yen CF, Wu HY, Yang MJ. The comorbid psychiatric symptoms of internet addiction: Attention deficit and hyperactivity disorder (ADHD), depression, social phobia, and hostility. *J. Adolesc. Health* 2007; **41**: 93–98.
3. Tsai HF, Cheng SH, Yeh TL *et al.* The risk factors of internet addiction – a survey of university freshmen. *Psychiatry Res.* 2009; **167**: 294–299.
4. Lin MP, Ko HC, Wu JY. Prevalence and psychosocial risk factors associated with internet addiction in a nationally representative sample of college students in Taiwan. *Cyberpsychol. Behav. Soc. Netw.* 2011; **14**: 741–746.
5. Goel D, Subramanyam A, Kamath R. A study on the prevalence of internet addiction and its association with psychopathology in Indian adolescents. *Indian J. Psychiatry* 2013; **55**: 140–143.
6. Mueller KW, Glaesmer H, Brahler E, Woelfling K, Beutel ME. Prevalence of internet addiction in the general population: Results from a German population-based survey. *Beha. Info. Technol.* 2014; **33**: 757–766.
7. Leeman RF, Potenza MN. A targeted review of the neurobiology and genetics of behavioural addictions: An

emerging area of research. *Can. J. Psychiatry* 2013; **58**: 260–273.
8. Yuan K, Cheng P, Dong T *et al.* Cortical thickness abnormalities in late adolescence with online gaming addiction. *PLoS One* 2013; **8**: e53055.
9. Lin F, Zhou Y, Du Y *et al.* Abnormal white matter integrity in adolescents with internet addiction disorder: A tract-based spatial statistics study. *PLoS One* 2012; **7**: e30253.
10. Zhou Y, Lin FC, YS D *et al.* Gray matter abnormalities in Internet addiction: A voxel-based morphometry study. *Eur. J. Radiol.* 2011; **79**: 92–95.
11. Feng Q, Chen X, Sun J *et al.* Voxel-level comparison of arterial spin-labeled perfusion magnetic resonance imaging in adolescents with internet gaming addiction. *Beha. Brain Funct.* 2013; **9**: 33.
12. Liu J, Gao X-P, Osunde I *et al.* Increased regional homogeneity in internet addiction disorder: A resting state functional magnetic resonance imaging study. *Chin. Med. J.* 2010; **123**: 1904–1908.
13. Hong S-B, Zalesky A, Cocchi L *et al.* Decreased functional brain connectivity in adolescents with internet addiction. *PLoS One* 2013; **8**: e57831.
14. Ko C-H, Liu G-C, Hsiao S *et al.* Brain activities associated with gaming urge of online gaming addiction. *J. Psychiatr. Res.* 2009; **43**: 739–747.
15. Dong G, Huang J, Du X. Enhanced reward sensitivity and decreased loss sensitivity in internet addicts: An fMRI study during a guessing task. *J. Psychiatr. Res.* 2011; **45**: 1525–1529.
16. Dong G, DeVito EE, Du X, Cui Z. Impaired inhibitory control in 'internet addiction disorder': A functional magnetic resonance imaging study. *Psychiatry Res.* 2012; **203**: 153–158.
17. Han DH, Hwang JW, Renshaw PF. Bupropion sustained release treatment decreases craving for video games and cue-induced brain activity in patients with internet video game addiction. *Exp. Clin. Psychopharmacol.* 2010; **18**: 108–117.
18. Liu J, Esmail F, Li L *et al.* Decreased frontal lobe function in people with internet addiction disorder. *Neural Regen. Res.* 2013; **8**: 3225–3232.
19. Hou H, Jia S, Hu S *et al.* Reduced striatal dopamine transporters in people with internet addiction disorder. *J. Biomed. Biotechnol.* 2012; **2012**: e854524.
20. Kim SH, Baik S-H, Park CS, Kim SJ, Choi SW, Kim SE. Reduced striatal dopamine D2 receptors in people with internet addiction. *Neuroreport* 2011; **22**: 407–411.
21. Park HS, Kim SH, Bang SA, Yoon EJ, Cho SS, Kim SE. Altered regional cerebral glucose metabolism in internet game overusers: A F-18-fluorodeoxyglucose positron emission tomography study. *CNS Spectr.* 2010; **15**: 159–166.
22. Tian M, Chen Q, Zhang Y *et al.* PET imaging reveals brain functional changes in internet gaming disorder. *Eur. J. Nucl. Med. Mol. Imaging* 2014; **41**: 1388–1397.
23. Yu H, Zhao X, Li N, Wang M, Zhou P. Effect of excessive internet use on the time–frequency characteristic of EEG. *Prog. Nat. Sci.* 2009; **19**: 1383–1387.
24. Han DH, Lee YS, Yang KC, Kim EY, Lyoo IK, Renshaw PF. Dopamine genes and reward dependence in adolescents with excessive internet video game play. *J. Addict. Med.* 2007; **1**: 133–138.
25. Lee YS, Han DH, Yang KC *et al.* Depression like characteristics of 5HTTLPR polymorphism and temperament in excessive internet users. *J. Affect. Disord.* 2008; **109**: 165–169.
26. Montag C, Kirsch P, Sauer C, Markett S, Reuter M. The role of the CHRNA4 gene in internet addiction. *J. Addict. Med.* 2012; **6**: 191–195.
27. Yuan K, Qin W, Wang G *et al.* Microstructure abnormalities in adolescents with internet addiction disorder. *PLoS One* 2011; **6**: e20708.
28. Weng C-B, Qian R-B, Fu X-M *et al.* Gray matter and white matter abnormalities in online game addiction. *Eur. J. Radiol.* 2013; **82**: 1308–1312.
29. Krawczyk DC. Contributions of the prefrontal cortex to the neural basis of human decision making. *Neurosci. Biobehav. Rev.* 2002; **26**: 631–664.
30. Naqvi NH, Bechara A. The hidden island of addiction: The insula. *Trends Neurosci.* 2009; **32**: 56–67.
31. Volkow ND, Wang G-J, Fowler JS, Tomasi D. Addiction circuitry in the human brain. *Annu. Rev. Pharmacol. Toxicol.* 2012; **52**: 321–336.
32. Hong S-B, Kim J-W, Choi E-J *et al.* Reduced orbitofrontal cortical thickness in male adolescents with internet addiction. *Behav. Brain Funct.* 2013; **9**: 11.
33. Everitt BJ, Hutcheson DM, Ersche KD, Pelloux Y, Dalley JW, Robbins TW. The orbital prefrontal cortex and drug addiction in laboratory animals and humans. *Ann. N. Y. Acad. Sci.* 2007; **1121**: 576–597.
34. Lucantonio F, Stalnaker TA, Shaham Y, Niv Y, Schoenbaum G. The impact of orbitofrontal dysfunction on cocaine addiction. *Nat. Neurosci.* 2012; **15**: 358–366.
35. Cavanna AE, Trimble MR. The precuneus: A review of its functional anatomy and behavioural correlates. *Brain* 2006; **129**: 564–583.
36. Ko C-H, Liu G-C, Yen J-Y, Chen C-Y, Yen C-F, Chen C-S. Brain correlates of craving for online gaming under cue exposure in subjects with internet gaming addiction and in remitted subjects. *Addict. Biol.* 2013; **18**: 559–569.
37. Alexander AL, Lee JE, Lazar M, Field AS. Diffusion tensor imaging of the brain. *Neurotherapeutics* 2007; **4**: 316–329.
38. Dong G, DeVito E, Huang J, Du X. Diffusion tensor imaging reveals thalamus and posterior cingulate cortex abnormalities in internet gaming addicts. *J. Psychiatr. Res.* 2012; **46**: 1212–1216.
39. Shiino A, Matsuda M, Morikawa S, Inubushi T, Akiguchi I, Handa J. Proton magnetic resonance spectroscopy with dementia. *Surg. Neurol.* 1993; **39**: 143–147.

40. Wolf RL, Detre JA. Clinical neuroimaging using arterial spin-labeled perfusion magnetic resonance imaging. *Neurotherapeutics* 2007; **4**: 346–359.
41. O'Brien CP, Childress AR, Ehrman R, Robbins SJ. Conditioning factors in drug abuse: Can they explain compulsion? *J. Psychopharmacol.* 1998; **12**: 15–22.
42. Naqvi NH, Bechara A. The insula and drug addiction: An interoceptive view of pleasure, urges, and decision-making. *Brain Struct. Funct.* 2010; **214**: 435–450.
43. Ding WN, Sun JH, Sun YW *et al.* Altered default network resting-state functional connectivity in adolescents with internet gaming addiction. *PLoS One* 2013; **8**: e59902.
44. Kelly C, Zuo XN, Gotimer K *et al.* Reduced interhemispheric resting state functional connectivity in cocaine addiction. *Biol. Psychiatry* 2011; **69**: 684–692.
45. Yuan K, Qin W, Dong M *et al.* Gray matter deficits and resting-state abnormalities in abstinent heroin-dependent individuals. *Neurosci. Lett.* 2010; **482**: 101–115.
46. Zang Y, Jiang T, Lu Y, He Y, Tian L. Regional homogeneity approach to fMRI data analysis. *Neuroimage* 2004; **22**: 394–400.
47. Lee HW, Choi J-S, Shin Y-C, Lee J-Y, Jung HY, Kwon JS. Impulsivity in internet addiction: A comparison with pathological gambling. *Cyberpsychol. Behav. Soc. Netw.* 2012; **15**: 373–377.
48. Aron AR, Shohamy D, Clark J, Myers C, Gluck MA, Poldrack RA. Human midbrain sensitivity to cognitive feedback and uncertainty during classification learning. *J. Neurophysiol.* 2004; **92**: 1144–1152.
49. Ko CH, Hsieh TJ, Chen CY *et al.* Altered brain activation during response inhibition and error processing in subjects with internet gaming disorder: A functional magnetic imaging study. *Eur. Arch. Psychiatry Clin. Neurosci.* 2014; **264**: 661–672.
50. Schoenbaum G, Roesch MR, Stalnaker TA. Orbitofrontal cortex, decision-making and drug addiction. *Trends Neurosci.* 2006; **29**: 116–124.
51. Seeley WW, Menon V, Schatzberg AF *et al.* Dissociable intrinsic connectivity networks for salience processing and executive control. *J. Neurosci.* 2007; **27**: 2349–2356.
52. Botvinick MM, Cohen JD, Carter CS. Conflict monitoring and anterior cingulate cortex: An update. *Trends Cogn. Sci.* 2004; **8**: 539–546.
53. Leech R, Sharp DJ. The role of the posterior cingulate cortex in cognition and disease. *Brain* 2014; **137**: 12–32.
54. Franken IH. Drug craving and addiction: Integrating psychological and neuropsychopharmacological approaches. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 2003; **27**: 563–579.
55. Gallagher M, McMahan RW, Schoenbaum G. Orbitofrontal cortex and representation of incentive value in associative learning. *J. Neurosci.* 1999; **19**: 6610–6614.
56. Petrovic P, Pleger B, Seymour B *et al.* Blocking central opiate function modulates hedonic impact and anterior cingulate response to rewards and losses. *J. Neurosci.* 2008; **28**: 10509–10516.
57. Weinstein A, Greif J, Yemini Z, Lerman H, Weizman A, Even-Sapir E. Attenuation of cue-induced smoking urges and brain reward activity in smokers treated successfully with bupropion. *J. Psychopharmacol.* 2010; **24**: 829–838.
58. Han DH, Kim YS, Lee YS, Min KJ, Renshaw PF. Changes in cue-induced, prefrontal cortex activity with video-game play. *Cyberpsychol. Behav. Soc. Netw.* 2010; **13**: 655–661.
59. Park MS, Sohn JH, Suk JA, Kim SH, Sohn S, Sparacio R. Brain substrates of craving to alcohol cues in subjects with alcohol use disorder. *Alcohol Alcohol.* 2007; **42**: 417–422.
60. McBride D, Barrett SP, Kelly JT, Aw A, Dagher A. Effects of expectancy and abstinence on the neural response to smoking cues in cigarette smokers: An fMRI study. *Neuropsychopharmacology* 2006; **31**: 2728–2738.
61. Jones T, Rabiner EA. The development, past achievements, and future directions of brain PET. *J. Cereb. Blood Flow Metab.* 2012; **32**: 1426–1454.
62. Koepp MJ, Gunn RN, Lawrence AD *et al.* Evidence for striatal dopamine release during a video game. *Nature* 1998; **393**: 266–268.
63. Torres GE, Gainetdinov RR, Caron MG. Plasma membrane monoamine transporters: Structure, regulation and function. *Nat. Rev. Neurosci.* 2003; **4**: 13–25.
64. Zahniser NR, Sorkin A. Rapid regulation of the dopamine transporter: Role in stimulant addiction? *Neuropharmacology* 2004; **47** (Suppl. 1): 80–91.
65. Verma V. Classic studies on the interaction of cocaine and the dopamine transporter. *Clin. Psychopharmacol. Neurosci.* 2015; **13**: 227–238.
66. Olejniczak P. Neurophysiologic basis of EEG. *J. Clin. Neurophysiol.* 2006; **23**: 186–189.
67. Reinvang I. Cognitive event-related potentials in neuropsychological assessment. *Neuropsychol. Rev.* 1999; **9**: 231–248.
68. Singh SM, Basu D. The P300 event-related potential and its possible role as an endophenotype for studying substance use disorders: A review. *Addict. Biol.* 2009; **14**: 298–309.
69. Dong G, Zhou H, Zhao X. Impulse inhibition in people with internet addiction disorder: Electrophysiological evidence from a Go/NoGo study. *Neurosci. Lett.* 2010; **485**: 138–142.
70. Dong G, Zhou H, Zhao X. Male internet addicts show impaired executive control ability: Evidence from a color-word Stroop task. *Neurosci. Lett.* 2011; **499**: 114–118.
71. Kim EY, Lee YS, Han DH, Suh DS, Kee BS. Temperament and genetic polymorphism in Korean male adolescents with internet addiction tendency. *J. Korean Neuropsychiatr. Assoc.* 2006; **45**: 468–475.
72. Le Foll B, Gallo A, Le Strat Y, Lu L, Gorwood P. Genetics of dopamine receptors and drug addiction: A comprehensive review. *Behav. Pharmacol.* 2009; **20**: 1–17.
73. Muller CP, Carey RJ, Huston JP, De Souza Silva MA. Serotonin and psychostimulant addiction: Focus on 5-HT1A-receptors. *Prog. Neurobiol.* 2007; **81**: 133–178.

74. Han JW, Han DH, Bolo N, Kim B, Kim BN, Renshaw PF. Differences in functional connectivity between alcohol dependence and internet gaming disorder. *Addict. Behav.* 2015; **41**: 12–19.
75. Kim H, Kim YK, Gwak AR *et al.* Resting-state regional homogeneity as a biological marker for patients with internet gaming disorder: A comparison with patients with alcohol use disorder and healthy controls. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 2015; **60**: 104–111.
76. Son KL, Choi JS, Lee J *et al.* Neurophysiological features of internet gaming disorder and alcohol use disorder: A resting-state EEG study. *Transl. Psychiatry* 2015; **5**: e628.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Summary of structural magnetic resonance imaging (MRI) findings on Internet use disorders.

Table S2. Summary of functional magnetic resonance imaging (MRI) findings on Internet use disorders.

Table S3. Summary of functional magnetic resonance imaging (MRI) findings on response to treatment in Internet use disorders. IA, Internet addiction; IGD, Internet gaming disorder.

Table S4. Summary of positron emission tomography (PET) findings on Internet use disorders. IA, Internet addiction; IGD, Internet gaming disorder.

Table S5. Summary of neurophysiologic findings on Internet use disorders. IA, Internet addiction; IGD, Internet gaming disorder.

Table S6. Summary of pharmacogenetics findings on Internet use disorders. IA, Internet addiction; IGD, Internet gaming disorder.