Chapter 4
Functional Imaging Study of Internet Gaming Disorder

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4.1 Introduction

Internet gaming is now among the most popular recreational activities worldwide. While the Internet enables access to online games 24 h a day, smartphones further enable access from any location. However, loss of control over the time spent engaged in online gaming may have negative consequences. Owing to the significant difference between generalized internet addiction and internet gaming disorder (Davis 2001; Montag et al. 2015) and the potentially adverse impacts of IGD on the health of internet users, the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) proposed diagnostic criteria specific for internet gaming disorder (IGD) in 2013. It defined addiction to Internet gaming among the conditions for further study of Section III, and suggested that more evidence was needed before IGD can be included as a standard disorder in the DSM system (American Psychiatric Association 2013). Several neurobiological and neurocognitive studies have evaluated the neuropsychological mechanisms of IGD (e.g., Dong et al. 2012a, b; Han et al. 2010; Ko et al. 2009a). Although some of the proposed clinical

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C. Montag and M. Reuter (eds.), *Internet Addiction*, Studies in Neuroscience, Psychology and Behavioral Economics, DOI 10.1007/978-3-319-46276-9_4

presentations and diagnostic criteria for IGD resemble those for substance addiction (Ko et al. 2006; Ko et al. 2012), no studies have conclusively determined whether IGD shares similar mechanisms with substance use disorder. Since neurobiological mechanisms of the substance use disorder have been extensively researched in the past decade (Volkow et al. 2010), studying the neurobiological mechanisms of IGD might reveal whether they resemble those in substance use disorder.

The present chapter reviews functional magnetic resonance imaging (fMRI) studies of internet gaming disorder. The review includes reports of the use of fMRI, including arterial spin-labeled fMRI, for analyzing task-related performance, resting functional connectivity, or effective connectivity.

4.2 Functional Magnetic Resonance Imaging

fMRI is a functional technique used to record cerebral hemodynamic changes during a specific task to demonstrate possible brain mechanisms of a specific neurocognitive function (Tejado et al. 2010). Analyses of blood-oxygen level dependent (BOLD) contrast, i.e., the difference in magnetic susceptibility between oxyhemoglobin and deoxyhemoglobin, enable the indirect study of hemodynamic changes based on variation in magnetic signals (Huettel et al. 2009). By comparing MR signals obtained while the subject is resting and while the subject is performing a specific task, this technique can reveal hemodynamic changes related to a specific neurocognitive response.

For evaluating mechanisms of psychiatric disorders, fMRI is preferable to PET and SPECT because it does not require radiation exposure. Other advantages include its wider availability and lower expense. Moreover, fMRI provides superior spatial and temporal resolution (Tejado Lde et al. 2010). However, isolating the hemodynamic change associated with a specific stimulus is very difficult. The paradigm must be well designed to avoid artifacts and misinterpretation. Further, since the BOLD signal provides only an indirect estimation of cerebral blood flow (CBF), the fMRI should be interpreted cautiously. The combination of fMRI techniques with insights from PET provides more direct insights into the biochemical mechanism of human behaviors.

4.3 Use of fMRI for Studying IGD

fMRI is among the most important imaging tools for investigating mechanisms of addiction, including response to a substance, vulnerability to addiction, characteristics, or symptoms of addictive behavior, and consequences of addiction (Fowler et al. 2007). As fMRI is widely available in industrialized countries, which tend to have the highest prevalence of IGD and IA, the present chapter reviews fMRI results reported in brain studies of subjects diagnosed with IGD. The fMRI results should be interpreted cautiously since the hypotheses in some of these studies have not been supported by further psychopathology, cognition, or physiology studies. Additionally, before beginning a new fMRI study, a rational hypothesis must be derived based on previous evidence obtained in brain imaging studies. Therefore, a literature review of applications of fMRI for studying IGD is timely.

4.3.1 Task-Related fMRI Study

A task-related fMRI study typically uses visual, auditory, or other stimuli, to provoke two or more different cognitive processes in the subject. The typical design has two conditions, an experimental condition, and a control condition. The goal of evaluation is to test the hypothesis that the signal differs between the two conditions. The trials are designed to alternate between the experimental and control condition (Glover 2011).

Classic experimental designs in fMRI represent the block or event-related design. In a block design, each block will have a duration of a certain number of fMRI scans, about 20–30 s, and within each block, only one condition (such as pictures from a computer game) is presented. Although the block design is considered optimal for detecting activation, numerous cognitive processes may occur within 20–30 s. Therefore, other approaches, such as the event-related design, are also used in fMRI studies. Event-related designs enable the researcher to detect changes in the BOLD hemodynamic response in response to specific events. Event-related designs are presented in a randomized sequence, and the between-stimuli duration is varied. Therefore, an event-related design is better able to characterize the timing of the change in amplitude of the hemodynamic response in the form of the BOLD signal.

For example, in the Go/Nogo task, an fMRI study with an event-related design can distinguish the BOLD response to the Go, Nogo, and failed inhibited trials. Therefore, an fMRI study is preferable for assessing the functional anatomy of response inhibition and error processing (Criaud and Boulinguez 2013). Both the block design and event-related design have been used to study IGD, particularly in the cue-induced reactivity paradigm. Such paradigms confront IGD patients with pictures from their favorite computer game while they are in an fMRI setting and their brain activity is being recorded. These designs have also been used to study reward sensitivity, inhibitory control, and risk decision.

4.3.1.1 The fMRI for Analyzing Cue-Induced Reactivity in IGD or IA (Ko et al. 2009a)

Ko et al. (2009a, b) recruited ten adults who met the diagnostic criteria for IGD according to psychiatric interviews and ten healthy controls without IGD. All subjects in the experimental group were addicted to the same online game.

This block design study of the cue-induced craving paradigm performed fMRI scans while the subjects were shown screenshots of video games. The significance threshold was set to $p < 0.0005$, and the cluster size was >50 voxels. The experimental results revealed that, compared to controls, the IGD group had higher activations in the right orbitofrontal cortex, bilateral anterior cingulate, right dorsolateral prefrontal cortex (DLPFC), right nucleus accumbens, and right caudate nucleus. The authors suggested that these areas may be considered neural substrates of the cue-induced gaming urge in IGD. The results also indicated that cue-induced brain reactivity in IGD resembles that in substance use disorder.

Ko et al. (2013a) recruited 15 adults with IGD, 15 remitted subjects, and 15 healthy controls. Internet gaming disorder was diagnosed according to the modified diagnostic criteria of IA (DCIA) observed in psychiatric interviews (Ko et al. 2009b). All subjects recruited for the study had been diagnosed with addiction to the same online game for at least one year. All subjects in the remission group had a history of addiction to the same online game, and all had been in remission from IGA for at least six months, according to DCIA criteria. In this event-related study of the cue-induced craving paradigm, subjects viewed screenshots of online gaming activity while undergoing fMRI scans. The significance threshold in the between-group analyses was $p < 0.001$, and the cluster size was >10 voxels. Compared to the control group, the IGD group showed higher activations in the bilateral DLPFC, precuneus, left posterior cingulate, parahippocampus and right anterior cingulate in response to gaming cues. The authors hypothesized that these brain areas are associated with the gaming craving activated by cue exposure. The authors suggested that the activation pattern was consistent with the model of substance use disorder developed earlier by Volkow et al. (2010). Lastly, compared with the remission group, the IGA group had higher activation over the right DLPFC (BA46), left parahippocampus (BA19), and left middle temporal gyrus (BA 39). Therefore, the authors suggested that the DLPFC and parahippocampus are potential markers of cue-induced brain activation in subjects currently in a state of addiction to online gaming.

Han et al. (2010) recruited 11 adults diagnosed with IGD and 8 healthy controls. The IGD diagnoses were based on a self-report questionnaire combined with a score of at least 50 on the internet addiction test (IAT) (Widyanto and McMurran 2004; Young 1998). In this block design study, all subjects viewed online gaming cues while undergoing fMRI scans. The significance threshold for a correction in the False Discovery Rate for 100 adjacent voxels was set to $p < 0.05$.

The results showed that, compared to controls, subjects with IGD had higher brain activation in response to gaming cues over the left occipital lobe, DLPFC, and parahippocampus. However, after six weeks of treatment with bupropion extended-release tablets (SR), the subjects showed significant decreases in β values over the DLPFC ($p = 0.04$) and in craving scores ($p = 0.04$). Therefore, the authors suggested that the effects of bupropion SR on the brain activity of craving for online gaming among subject with IGD.

Lorenz et al. (2013) recruited eight adult males with IGD and nine healthy controls. The recruitment criteria for the experimental group of males with IGD were at least three of the following six criteria for IGA within the last 12 months: craving, impaired control of playing, withdrawal, development of tolerance, progressive neglect of other pleasure, and playing despite harmful consequences. The healthy controls were casual computer game players who were familiar with WoW, World of Warcraft, the online role player game. All subjects underwent fMRI scans while viewing screenshots of WoW in short presentation and long presentation trials of the dot probe task. The dot probe task is designed to assess attention bias. Participants are instructed to indicate the location of this dot as quickly as possible.

In the dot probe paradigm, subjects with IGD show an attentional bias toward stimuli with a positive valence. Analyses of the fMRI data revealed that the experimental group had a different activation in short presentation trials (with the contrast computed as [(WoW > neutral) > (positive emotion picture > neutral)]) in areas known to be associated with craving in addiction (e.g., ventral visual path, right hippocampus, and right inferior frontal gyrus). However, this activation pattern was only observed when stimuli were presented for durations shorter than 2 s. The stimulus duration related modulation of connectivity strength from the right inferior gyrus to cue-reactivity related regions suggested the presence of an inhibiting effect during the long presentation trials.

The authors further hypothesized that subjects with IGD might reveal inhibition of motivation-related brain regions in long presentation trials but not in short presentation trials. An explorative post hoc psychological interaction analysis was used to test for altered functional connectivity between the right inferior frontal gyrus and other brain areas. The analysis revealed significant group differences in the presentation duration dependent modulation of coupling strength between the right inferior gyrus and areas related to cue-reactivity, which was consistent with the hypothesis of the authors of that study.

However, these results should be interpreted cautiously because of the small sample size. Furthermore, the complex contrast [(WoW > neutal) > (positive emotion picture > neutral)] made it difficult to explain the significant activation. That is, the significant difference in subtraction might result from, not only the higher response to the WoW pictures, but also the lower response to the positive emotion pictures.

Ko et al. (2013b) recruited an experimental group of 16 adults with concurrent IGD and nicotine dependence and 16 healthy controls. The recruitment criteria for the experimental group were psychiatric interview results indicating that the subject met both the diagnostic criteria for Internet addiction (Ko et al. 2009b) and the DSM-IV criteria for nicotine dependence (American Psychiatric Association 2000). Additionally, all subjects in the experimental group were currently addicted to the same game. In contrast, the healthy controls had no history of IGD or nicotine dependence. All subjects then underwent fMRI scans while viewing screenshots of computer games, photographs associated with cigarette smoking, and neutral stimuli. The selection of stimuli in this event-related design was based on the cue-induced reactivity paradigm. The analysis identified the brain correlates of gaming urge (game cue-reactivity of the comorbid group—that of the control group) and smoking craving (smoking cue reactivity of the comorbid group—that of the control group). Conjunction analysis is defined as "the joint refutation of multiple null hypotheses" (Friston et al. 2005). That is, it identifies a significant difference in the activation of a brain area during two different tasks. Conjunction analysis with conjunction null hypothesis (Nichols et al. 2005) was performed ($p < 0.05$ with small volume correction) to identify the brain correlates common to both gaming and smoking. The results demonstrated activations over the bilateral parahippocampal gyrus, precuneus, left DLPFC, and anterior cingulate were significantly higher in the IGD group than in controls. The literature suggests that the brain correlates of cue-induced gaming urge resemble those of cue-induced substance craving (Han et al. 2010; Ko et al. 2009a, 2013a). However, these conclusions are not based on a direct comparison between BOLD response to gaming urge and substance craving in addicts craving for the Internet or nicotine only. Furthermore, even if a study had used a similar design to compare the BOLD response to gaming use of IGD subjects and that to substance craving of a drug abuser, the comparison might have been biased by differences in subject characteristics between two disorders. The present study included a comorbid group to enable comparisons of brain activation between cue-induced gaming urge and cue-induced smoking craving in the same brain. The comparisons showed that, before subtracting the reaction of the control group, the gaming cue-activated a brain pattern similar to that activated by the smoking cue in the comorbid group. After subtracting the reaction of the control group, the comorbid group showed that cue-induced gaming urge and cue-induced smoking craving activated the parahippocampus and the anterior cingulate. A further conjunction analysis showed significant activation of the bilateral parahippocampal gyrus by both the gaming urge and smoking craving. Therefore, the parahippocampus may be associated with mechanisms of cue-induced brain activities common to both IGA and nicotine dependence.

Liu and his colleagues had recruited 39 male subjects with internet gaming disorder and 23 male matched healthy controls to complete a cue reactivity task under fMRI scanning. Subjects with IGD demonstrated higher brain activity over ventral and dorsal striatum (Liu et al. 2016). They also claimed the similarity in cue-induced craving response between IGD and substance use disorder.

Summary of Gaming Cue-Induced Reactivity

Despite the different designs in the aforementioned studies of gaming cue-induced reactivity, they all reported cue-induced reactivity over the parahippocampus, anterior cingulate, precuneus, striatum, and DLPFC (Han et al. 2010; Ko et al. 2009a, 2013a, b; Lorenz et al. 2013). These consistent results indicate that these areas participate in brain reactivity to the cue-induced gaming urge.

One of the most consisted results is the parahippocampus. The literature agrees that the parahippocampus has a role in cue-induced craving in substance use disorder (Skinner and Aubin 2010). The parahippocampus receives input from the nucleus accumbens and amygdala and evaluates the behavioral significance of sensory information (Salzmann et al. 1993). It also provides a contextual representation function and is an important afferent pathway to the hippocampus (Rudy 2009). Thus, it may contribute to the emotional response produced by cues such as screenshots of online gaming activity. Exposure to gaming cues causes the hippocampus to produce an emotional response based on contextual memory. By integrating contextual representations with their emotional significance, the parahippocampus contributes to the craving for an online gaming experience. It may explain why both the gaming urge and smoking craving cause a strong activation of the bilateral parahippocampal gyrus (Ko et al. 2013b). However, as a limitation on the number of subjects and the design of the study, other critical brain regions responsible for cue-induced craving were not repeatedly proved in these studies, such as nucleus accumbens or DLPFC. Thus, a well-designed study with adequate sample size under effective definition was necessary to prove the similarity in craving response between IGD and substance use disorder.

4.3.1.2 fMRI Studies Focus on Response Inhibition Task

Ding and his colleagues had recruited 17 male adolescents with internet gaming disorder and 17 male matched healthy controls to complete Go/Nogo task under fMRI scanning. There is no difference in behavior performance. Subjects with IGD demonstrated higher activation during N-Go trials in the left superior medical frontal gyrus, right anterior cingulate cortex, right frontal gyrus, left inferior parietal lobule, left precentral gyrus, and left precuneus and cuneus based on AlphaSim correction. This result suggested that the prefrontal cortex may be involved in the circuit correlated with impulsivity, during its impaired among adolescents with IGA.

Ko and his colleagues had recruited 26 male adults with internet gaming disorder for more than two years and 23 male matched healthy controls to complete event-related designed Go/Nogo task under fMRI scanning (Ko et al. 2014). There is no difference in behavior performance. Subjects with IGD demonstrated higher activation when processing response inhibition over the left orbital frontal lobe and bilateral caudate nucleus than controls in small-volume FWE correction. Further, the activation for error processing over the right insula was lower in the subjects with IGD than the control group. This result suggested that adults with IGD have impaired insular function in error processing and greater activation of the frontostriatal network to maintain their response inhibition performance.

Dong et al. (2012a, b) recruited 12 adults with IGD and 12 healthy controls. Subjects were classified into an internet addiction disorder (IAD) group if they had a score of 80 or higher on the self-report questionnaire developed by Young (1998) (and psychometrically tested by Widyanto and McMurran 2004). Subjects with IA also met the criteria of the Chinese Internet addiction test (Wang et al. 2009). All participants were asked to perform a color-word Stroop task while undergoing an fMRI scan. The IAD and control groups showed no performance difference. The difference in BOLD signal during the Stroop effect between IAD and control groups was calculated as ((IAD incongruent-IAD congruent)-(control incongruent-control congruent)) with a false discovery rate set at a threshold of $p < 0.05$. The IAD group revealed higher activity over the anterior and posterior cingulate compared to the control group. The authors suggest that adults with IAD have impaired inhibitory control and diminished efficiency of cognitive control.

Zhang and his colleagues had recruited 19 male subjects with internet gaming disorder and 21 male-matched-healthy controls to complete an addiction Stroop task under fMRI scanning. Subjects with IGD demonstrated higher cue-induced activity over inferior parietal lobule, the middle occipital gyrus and the dorsolateral prefrontal cortex (Zhang et al. 2016a). The authors claimed that subjects with IGD had impaired visual and cognitive control ability while dealing with gaming-related words. However, in the analysis, the author calculated the response for the word stimulating (IGD related words – neutral words), but not the Stroop effect. It might limit the generalization of the result to indicate the cognitive control function.

All of these studies mentioned above claimed a deficit in cognitive control and demonstrated higher brain activation over inferior frontal lobe and anterior cingulate. However, all these studies could not demonstrate the deficit in behavior performance in cognitive tasks. The cognitive control is the essential ability to success in gaming. The ability could be well trained and prerequired to get the winning feeling in the game to have a positive reinforcement effect. Thus, whether they have a deficit in cognitive control should be provided in a future study. On the other side, other function involving response inhibition, such as error processing, could be another factor contributed to their daily life functional impairment and deserved further studied.

4.3.1.3 Other Tasks fMRI Study for Rewarding Sensitivity and Risk Taking

Dong et al. (2011) recruited 12 males with IGD and 12 healthy controls. Subjects were enrolled in the IGD group based on a score of 80 or higher on the self-report questionnaire developed by Young to test for internet addiction (Widyanto and McMurran 2004). All subjects in the IGD group also met the criteria of the Chinese internet addiction test (Wang et al. 2009). They were required to complete a reality-simulated guessing task. The subjects need to choose one of two cards in 245 guessing trials. Depending on the color of the chosen card the subjects either win (red playing cards) or lose (black playing cards) 10 Dollars. In the win condition, the IGD group revealed higher activation of the orbitofrontal cortex than controls. Under the loss condition, the IGD group revealed lower activation of the anterior cingulate than controls. The authors claimed that the IGD group had higher reward sensitivity but lower loss sensitivity.

Chun and his colleagues had recruited 19 male adolescents with internet gaming disorder and 19 male-matched-healthy controls to discriminate swear, negative, and neutral words under fMRI scanning (Chun et al. 2015). There is no difference in behavior response. Adolescents with IGD demonstrated lower activation in the right

OFC related to cognitive control and in the dorsal anterior cingulate cortex (dACC) related to social rejection during the swear word condition in FDR correction. This result suggested that the alterations in emotional processing among adolescents with IGD.

Lin and his colleagues had recruited 19 male adolescents with internet gaming disorder and 21 male matched-healthy controls based on IAT. They completed probability discounting task under fMRI scanning (Lin et al. 2015a). Subjects with IGD prefer the probabilistic options to fixed ones and short reaction time. They had lower activation in the inferior frontal gyrus and the precentral gyrus in choosing the probabilistic options in the alphasim correction. The author claimed that subjects with IGD had impaired risk evaluation which might contribute to why they continue playing online games despite the risks of widely known negative consequence.

Wang and his colleagues had recruited 19 subjects with internet gaming disorder and 21 matched-healthy controls based on IAT and DSM5 IGD criteria. They completed probability discounting task under fMRI scanning (Wang et al. 2016a). Subjects with IGD preferred the risky to the fixed options and showed shorter reaction time. They had higher task-related activity in default mode network (DMN) and less engagement in the executive control network (ECN) when making the risky decisions. The authors claimed this result could be the reason for why subjects with IGD continue to play online games despite the potential negative consequences.

Qi and his colleagues had recruited 23 male adolescents with internet gaming disorder and 24 male matched-healthy controls based on Yang Diagnostic Questionnaire and IAT. They completed balloon analog risk task under fMRI scanning (Qi et al. 2015). Subjects with IGD had complete more pump in the task. There are no significant differences in other indicators of the task. Subjects with IGD demonstrated lower modulation of the risk level of the activation of the right dorsolateral prefrontal cortex (DLPFC) during the active BART under alphasim correction. The author claimed a critical decision-making-related brain region is less sensitive to risk among subjects with IGD.

Dong and his colleagues had recruited 20 subjects with internet gaming disorder and 16 male-matched healthy controls based on IAT. They complete risk decision task under fMRI scanning (Dong and Potenza 2016). Subjects with IGD selected more risk-disadvantageous trials and demonstrated less activation of the anterior cingulate, posterior cingulate and middle temporal gyrus when they are undergoing risk taking. They had shorter response times and activated lower over the inferior frontal and superior temporal gyri when decision-making. The authors claimed that deficit in executive control in selecting risk-disadvantageous choices among subjects with IGD.

Wang and his colleagues had recruited 18 subjects with internet gaming disorder and 21 matched healthy controls based on IAT. They completed a delay discounting task under fMRI scanning (Wang et al. 2016b). They demonstrated the executive control network and the basal ganglia network were associated with IGD.

Subjects with IGD had stronger FC when selecting small and now options. Further, the delay discounting rates were positively correlated with the modulation of the two networks. They claimed that the IGD patients had enhanced reward sensitivity and impaired ability to control the impulsivity.

Summary of Task fMRI Studies

Most study all claimed a deficit on risky evaluation or executive control in risky decision-making task. However, subjects with IGD had an adequate behavior performance. For example, they all had an adequate result with short reaction time. How could conclude their impairment? Further, there are many studies with the similar design or designed by the same team. These studies could reasonably recruit some repeated subjects. However, the brain regions corresponding for the deficit on risk decision were different in these studies. In fact, the effect of IGD on cognitive function is controversial. Since most illegal substances are known to have damaging effects on the brain, a reasonable assumption is that they impair cognitive function. However, most online games exercise many specific cognitive functions (Granic et al. 2014). Further, since perfect performance in online gaming requires good cognitive function and decision-making, particularly under risk, the hypothesis that online gaming produces a deficit in cognitive function or risk decision is questionable. Further studies to compare the cognitive functions and behavioral characteristics of decision-making among subjects with IGD and causal gamer are needed to clarify the role of cognitive functions in the process of addiction to online gaming.

4.3.2 Resting fMRI Study

A growing body of evidence shows that several neural circuits exhibit spontaneous activity at rest. These slow-frequency fluctuations are temporally correlated within spatially distinct but functionally related networks. Studies consistently show that, in healthy subjects, numerous networks in this resting-state functional connectivity represent specific patterns of synchronous activity (Rosazza and Minati 2011). Evaluation of resting-state functional connectivity provides an opportunity to characterize distributed circuit abnormalities in neuropsychiatric illnesses. For example, seed analyses of the amygdala, insula, and nucleus accumbens have revealed reduced functional connectivity in subjects with opioid dependence (Upadhyay et al. 2010). Representing the specific neurobiological network underlying reward, affective and cognitive processes regarding functional connectivity may reveal possible mechanisms of addictive disorder (Sutherland et al. 2012).

4.3.2.1 Regional Homogeneity of IGD

Dong et al. (2012a, b) recruited 15 males diagnosed with IGD according to the Young Internet addiction scale (Widyanto and McMurran 2004) and 14 healthy comparison subjects. The cut-off point in this study was 80. Regional homogeneity (ReHo) was evaluated in a resting-state during an 8-min fMRI scan. The significance threshold was set to $p < 0.05$ FDR correction. Comparisons with controls showed that the IGD subjects had higher ReHo in the brain stem, inferior parietal lobe, left posterior cerebellum, and left middle frontal gyrus. However, the IGD subjects had lower ReHo in the temporal, occipital, and parietal brain regions.

Liu recruited 19 college students with Internet addiction and 19 controls (Liu et al. 2010). The diagnoses of IA were based on a version of the Young diagnostic questionnaire modified by Beard and Wolf (2001) (Beard and Wolf 2001). Regional homogeneity was evaluated by 9-min fMRI scans with the subjects in a resting-state. Subjects with IA increased ReHo over the cerebellum, brainstem, right cingulate gyrus, bilateral parahippocampus, right frontal lobe, left superior frontal gyrus, left precuneus, right inferior temporal gyrus, left superior temporal gyrus and middle temporal gyrus.

Kim and his colleagues had recruited 16 subjects with internet gaming disorder and 14 subjects with alcohol use disorder and 15 healthy controls to complete a resting-state fMRI scanning (Kim et al. 2015). The result demonstrated increased ReHo in the posterior cingulate cortex (PCC) and decreased ReHo in the right superior temporal gyrus (STG) among subjects with IGD. The authors had suggested higher ReHo in the PCC may be a common neurobiological feature of IGD and AUD and that lower ReHo in the STG may be a candidate neurobiological marker for IGD.

Lin and his colleagues had recruited 35 subjects with internet gaming disorder and 36 matched healthy controls to complete Whole-brain voxel-based analysis (Lin et al. 2015b). Comparing to healthy subjects those with IGD demonstrated lower fALFF values in the cerebellum, posterior lobe, and higher fALFF values in superior temporal gyrus. The author had suggested these altered brain regions had been suggested to associated with the executive function and decision-making.

Although these three studies run the same way with the same analyzing way, except fALFF, they did not report the similar data. The heterogeneity of IGD and the limited in sample size might contribute to the difference in results. Further, as the physiological, psychological, or cognitive implication of regional homogeneity and fALFF had not been concluded now, it is difficult to have a clear clinical implication based on these results.

4.3.2.2 Functional Connectivity Study: The Most Published fMRI Studies of IGD in Recent Three Years

Hong et al. (2013) recruited 12 adolescents diagnosed with IA based on the Young Internet Addiction Scale (Widyanto and McMurran 2004) and 11 healthy control subjects. Functional connectivity was evaluated by fMRI scans performed for 6 min 45 secs with the subjects in a resting state. Compared to the control group, the IA group showed lower functional connectivity spanning a distributed network. Most of the impaired connections involved the subcortical brain region. No between-group differences were noted in the average clustering coefficient, the characteristic path length, or the small-worldness ratio, an indicator of the extent to which the synchronization networks of cortical neurons exhibit the small-world topology. This result suggested that, in this group, IA was associated with a large and widespread decrease in functional connectivity in the cortico-striatal circuit.

Ding recruited 17 adolescents with IGD and 24 controls (Ding et al. 2013). The diagnoses of IGD were based on a modified version of the self-report Young diagnostic questionnaire developed by Beard and Wolf (2001). Default network resting-state functional connectivity was evaluated by 4400-s fMRI scans with the subjects in a resting-state. The default network was evaluated by the functional connectivity to the posterior cingulate as defined by WFU-Pick Atlas (Maldjian et al. 2003). The significance threshold was set at $p < 0.05$ with AlphaSim correction. The subjects with IGD exhibited increased functional connectivity (FC) in the bilateral cerebellum, posterior lobe, and middle temporal gyrus but decreased FC in the bilateral inferior parietal lobe and right inferior temporal gyrus. The author suggested that the alterations were partially consistent with those in subjects with substance use disorder.

Dong and his colleagues had recruited 35 subjects with internet gaming disorder and 36 matched healthy controls to complete a resting-state fMRI scanning (Dong et al. 2015a, b). Subjects with IGD demonstrated decreased FC in the executive control network and increased FC in the reward network. This result suggested that impairments in executive control lead to inefficient inhibition of cravings to gaming among subjects with IGD.

The same team had recruited 35 subjects with internet gaming disorder and 36 matched healthy controls to complete a resting-state fMRI scanning and a Stroop task inside of fMRI (Dong et al. 2015a, b). This result functional connectivity measures in executive control networks were negatively correlated with Stroop effect and positively correlated with brain activations in executive control regions across groups. The within-group analysis demonstrated positive trends were found between functional connectivity in ECNs and brain activations in Stroop task. The authors suggested that higher functional connectivity in ECNs may underlie better executive control and may provide resilience on IGD.

Han and his colleagues had recruited 78 adolescents with internet gaming disorder and 73 matched healthy controls to complete a resting-state fMRI scanning (Han et al. 2015a, b). Subjects with IGD demonstrated an over connectivity of the default mode and executive control networks.

Han and his colleagues had recruited 15 subjects with internet gaming disorder and 16 patient with alcohol use disorder to complete a resting-state fMRI scanning (Han et al. 2015a, b). Both groups had a positive functional connectivity between the dorsolateral prefrontal cortex (DLPFC), cingulate, and cerebellum. Further, both groups have negative functional connectivity between the DLPFC and the orbitofrontal cortex. These indicate both groups may share a problem with executive function. However, as no control group, we could not know whether this connectivity existed among healthy subjects.

Hong and his colleagues had recruited 12 adolescents with internet gaming disorder and 11 males matched controls to complete a resting-state fMRI scanning (Hong et al. 2015). Adolescents with Internet gaming disorder had lower connectivity between dorsal putamen and the posterior insula-parietal operculum. On the other hand, controls had lower function connectivity between the dorsal putamen and bilateral sensorimotor cortices. Although the author had claimed the result is indicating a biomarker of IGD, the same result was not reproduced by any other study.

Park and his colleagues had recruited 19 male adolescents with internet gaming disorder and 20 age-matched controls to complete a resting-state fMRI scanning (Park et al. 2015). A graph-theoretical approach was used to analyze functional magnetic resonance imaging data. Subjects with IGD had higher impulsiveness, and they had a higher global efficiency and lowered local efficiency in the functional network. The authors claim that their finding supported to the proposition that the brain of IGD could be in the state similar to pathological states in topological characteristics of functional networks in the brain.

Wang and his colleagues had recruited 17 male adolescents participants with internet gaming disorder and 24 healthy controls to complete a resting-state fMRI scanning (Wang et al. 2015). A voxel-mirrored homotopic connectivity (VMHC) was used to analyze functional magnetic resonance imaging data. Subjects with IGD had lower VMHC between the left and right superior frontal gyrus (orbital part), inferior frontal gyrus (orbital part), middle frontal gyrus and superior frontal gyrus in Alphasim correction. The authors claim the important role of altered interhemispheric rsFC in the bilateral prefrontal lobe in the brain mechanism in IGD.

Zhang and his colleagues had recruited 35 male adolescents participants with internet gaming disorder and 24 healthy controls to complete a resting-state fMRI scanning (Zhang et al. 2015). Subjects with IGD had lower functional connectivity between the VTA and right NAcc under AlphaSim correction. The authors claimed the possible neural functional similarities between individuals with IGD and individuals with substance addictions.

Ko and his colleagues had recruited 30 young adults with internet gaming disorder and 30 male matched controls to complete a resting-state fMRI scanning (Chen et al. 2016). Subjects with IGD had a lower FC with the left insula over the left dorsolateral prefrontal cortex (DLPFC) and orbital frontal lobe and a higher FC with the insula with the contralateral insula than controls in small-volume FEW correction. The authors claimed that the elevated interhemispheric insula FC may involve in the mechanism of IGD.

Zhang and his colleagues had recruited 19 young adults with internet gaming disorder and 19 male matched controls to complete a resting-state fMRI scanning (Zhang et al. 2016b). Subjects with IGD had a lower functional connectivity of left posterior insula over the bilateral supplementary motor area and middle cingulated cortex, FC of right posterior insula over right superior frontal gyrus, and decreased functional integration between insular subregions. The author claimed that the lower functional connectivity between the interoception and the motor/executive control regions could reflect reduced ability to inhibit online gaming among subjects with IGD.

Zhang and his colleagues had recruited 74 young adults with internet gaming disorder and 41 male matched controls to complete a resting-state fMRI scanning (Zhang et al. 2016b). Subjects with IGD had higher FC of anterior insula over anterior cingulate cortex (ACC), putamen, angular gyrus, and precuneus. They also had higher FC of the posterior insula over postcentral gyrus, precentral gyrus, supplemental motor area, and superior temporal gyrus (STG). The authors claimed the key role of the insula in the manifestation of the core symptoms of IGD.

4.3.2.3 Summary of Resting fMRI Studies

The studies for resting fMRI among subjects with IGD extensively increased in the last three years. It is easier to run resting fMRI than to run task fMRI. Further, there are many ways to analyze resting fMRI data, such as regional homogeneity, default model, ICA analysis, seed analysis, voxel-mirrored homotopic connectivity, graph-theoretical approach, and small-world analysis. For the seed analysis, the selection of seed could make the result different. A variety of analysis could demonstrate resting FC in a different way. These differences make a head-to-had comparison impossible. Moreover, it is also difficult to find the similar result among above extensive studies to have a conclusion. The inconsistent results of these studies may have resulted from different definitions of IA, different indicators of functional connectivity, and different ages and numbers of subjects. The last three studies had the similar analysis way for insula connectivity. Two studies demonstrated a decreased FC to the frontal lobe, but one study show increased FC of anterior insula. The difference in subregion of insula to be the seed of analysis might contribute to their differences. Lastly, the indicator for FC in resting fMRI had implicated to explain the mechanism of psychiatric disorder. However, the interpretation of this connectivity was varied. For example, both lower connectivity and over connectivity were suggested to indicate the impaired function. Many studies claim some connectivity represent the executive function. However, the analyzed data was recruited under resting without executive performance. Thus, an over interpretation for the FC result of IGD without clear evidence should be prevented. Further, resting fMRI studies with clear definitions, such as diagnostic interviewing, adequate numbers of subjects, and clear hypotheses are needed to obtain additional data regarding functional connectivity in IGD. Further, since online gaming might also train the brain, some subjects with IGD could hypothetically show improved functional connectivity. However, other impairments in functional connectivity might contribute to their lack of control over their internet use. Thus, detailed studies of specific networks are still needed.

4.3.3 The Structure Analysis of IGD

Sun and his colleagues had recruited 18 subjects with internet gaming disorder and 21 matched healthy controls to complete Whole-brain voxel-based analysis (Sun et al. 2014). Mean kurtosis metrics (MK), radial kurtosis (K perpendicular), and axial kurtosis had been calculated and compared with $P < 0.05$ in AlphaSim corrected. The IGA group demonstrated diffusional kurtosis parameters that were significantly less in GM of the right anterolateral cerebellum, right inferior and superior temporal gyri, right supplementary motor area, middle occipital gyrus, right precuneus, postcentral gyrus, right inferior frontal gyrus, left lateral lingual gyrus, left paracentral lobule, left anterior cingulate cortex, and median cingulate cortex. VBM showed that IGA subjects had higher GM volume in the right inferior and middle temporal gyri, and right parahippocampal gyrus, and lower GM volume in the left precentral gyrus. This result suggested that. The lower diffusional kurtosis parameters in IGA suggest multiple differences in brain microstructure, which may contribute to the underlying pathophysiology of IGA.

Ko and his colleagues had recruited 30 young adults with internet gaming disorder and 30 male matched controls to complete a resting-state fMRI scanning (Ko et al. 2015). The subjects with IGD had a lower GMD over the bilateral amygdala than the controls. Further, the subjects with IGD had lower FC with the left amygdala over the left dorsolateral prefrontal lobe (DLPFC) and with the right amygdala over the left DLPFC and orbital frontal lobe (OFL). They also had higher FC with the bilateral amygdala over the contralateral insula than the controls. The results of this study suggested that the amygdala plays a very influential role in the mechanism of IGD. Its detailed role should be further evaluated in future study and should be considered in the treatment of IGD.

Cai and his colleagues had recruited 27 adolescents with internet gaming disorder and 30 age, gender, and education matched healthy controls to complete FreeSurfer to measure subcortical volume (Cai et al. 2016). They also complete the Stroop task outside of fMRI scanning. Subjects with IGD committed more incongruent errors during the task and demonstrated higher volumes of dorsal striatum and ventral striatum. The author claimed that the striatum might be implicated in the underlying pathology of IGD.

Lin and his colleagues had recruited 26 subjects with internet gaming disorder and 26 matched healthy controls based on a self-reported questionnaire. They were arranged to complete resting fMRI scanning to evaluated their gray matter density by using voxel-based morphometric analysis. (Lin et al. 2015c). Subjects with IGD had lower gray matter density over bilateral inferior frontal gyrus, left cingulate gyrus, insula, right precuneus, and right hippocampus. They also had lower white matter density in the inferior frontal gyrus, insula, amygdala, and anterior cingulate. The author had suggested that the altered brain regions involved in decision-making, behavior inhibition, and emotional regulation.

In conclusion, all study demonstrated a decreased gray matter density among subjects with IGD. However, all the results were not reproduced in any another study. Although the way to analyze the brain structure data was more consisted, the difference in sample recruiting, the stage of disorder (newly onset or chronic), and comorbidity could contribute to these difference in result.

4.3.4 Arterial Spin-Labeled Perfusion Magnetic Resonance Imaging

Perfusion provides oxygen and nutrients to tissues and is closely tied to brain function, which is an essential indicator of psychiatric disorder. Arterial spin label (ASL) perfusion MRI offers absolute quantification of cerebral blood flow (CBF). In ASL technique, arterial blood water is magnetically labeled using radiofrequency irradiation. The magnetically labeled arterial water decays with T1 relaxation. Since ASL MRI provides absolute quantification of CBF, which is coupled to regional neural activity, it can also be used to measure resting brain function independently of any specific sensorimotor of a cognitive task (Detre et al. 2009).

Feng et al. (2013) recruited 15 adolescents with IGD and 18 controls (Feng et al. 2013). The diagnoses of IGD were based on self-reported results on the Young diagnostic questionnaire, as modified by Beard and Wolf (2001) (Beard and Wolf 2001). The subjects were arranged to undergo scanning with a 3T MRI scanner. Pseudocontinuous ASL perfusion images were collected by 3D fast spin echo acquisition with background suppression, 1500 ms labeling, and a postlabeling delay of 1500 ms. Multiple comparison corrections were performed with AlphaSim program at a combined threshold of $p < 0.05$ and a minimum cluster size of 54 voxels.

Compared with the control group, the IGD group showed higher CBF in the left inferior temporal lobe, left parahippocampal gyrus/amygdala, right medial frontal lobe/anterior cingulate, bilateral insula, right middle temporal gyrus, right precentral gyrus, left supplementary motor area, left cingulate, and right inferior parietal lobe. The CBF was decreased in the left middle temporal gyrus, left middle occipital gyrus, and right cingulate gyrus. The authors suggest that IGD is a behavioral addiction that may share similar neurobiological abnormalities with other addictive disorders.

4.4 Limitations and Controversial Issues in Previous fMRI Studies of IGD or IA

The major problem in fMRI studies of IGD is the extreme heterogeneity of the subjects resulting from their widely varied online gaming activities, variety in age, difference in disease stage, and the varied chronicity. If the aim of the study is identifying potential predictors of IA, a highly homogeneous group is needed.

However, that sample selection is limited by the constraints of minimizing confounds, e.g., that all participants with IGD need to be addicted to the same game in a study. This might explain why all studies had a limited sample size. Further, if the aim of the study is to discuss sequelae of IGD, a specific group with similar addiction experiences should be selected, which might explain why most research targets subjects with IGD for brain imaging studies. However, the wide variability in Internet games may result in different consequences. Further, most subjects with IGD had an above average performance in online gaming, which requires the presence of cognitive functions such as decision-making, attention, concentration, and response inhibition, even though their daily life function in the real world was impaired. Since most cognitive skills used in games are similar to those used in cognitive tasks of researches, a diagnosis of impaired brain function in a cognitive task should be made cautiously until the deficit is further evaluated or confirmed by a behavioral assessment. Thus, a rational hypothesis based on clinical experience and on the literature is essential before performing a brain imaging study.

Compared to other event-related studies (Murphy and Garavan 2004), the sample sizes used in fMRI studies of IGD have been small. Recruiting greater numbers of subjects would provide more robust results and would help prevent type II error. Furthermore, most studies have focused on male subjects despite reports of gender differences in factors associated with IA (Ko et al. 2007, 2008; Yeh et al. 2008). Although evaluations of brain reactions specific to males or to females are clearly needed, most studies have focused on males because males have a higher risk of IGD. Further studies are needed to study hypothesized mechanisms specific to females.

Finally, previous studies have not applied consistent definitions of IGD and IA. Since the DSM-5 has proposed diagnostic criteria for IGD, future works should consistently define IGD or IA according to DSM-5 criteria.

4.5 Future Studies of Internet Gaming Disorder

The findings of this literature review show that further fMRI studies are needed to investigate the following issues:

1. According to a previous review of event-related studies (Murphy and Garavan 2004), each group should have a minimum of 20 subjects.
2. Since the number of subjects is usually limited, psychiatric interviews are needed to identify IGD based on DSM-5 criteria (American Psychiatric Association 2013).
3. Before beginning a study, a rational hypothesis must be made based on clinical experience or on previous epidemiological, neurocognitive, molecular, or neurobiological studies.
4. Future studies should consider mechanisms specific to females.

5. An integrated team including a clinical psychiatrist, a psychologist, an expert in fMRI physiology, a brain imaging technician, and an expert in imaging data analysis would improve the design and implementation of an fMRI study.
6. Advanced design in task and advanced analyses such as psychological interaction analysis or dynamic caudal model could be used to explore and/or validate hypothesized mechanisms of IGD. However, such studies should only be put in place after a reasonable hypothesis is developed by an integrated team.
7. A hypothesis testing design that integrates psychopathology, prospective behavioral presentations, neurocognitive performance, neurophysiology, and brain imaging studies would help to achieve a comprehensive understanding of IGD.

4.6 Conclusion

Studies of gaming cue-induced reactivity have shown that the parahippocampus have similar roles in the gaming urge response. Most task studies suggest impairment in inhibitory control and decision-making. However, the mechanism had not been concluded now as the correlated brain region is different in the previous study. Thus, any conclusion regarding the mechanisms of IGD would be premature due to the many limitations of previous studies. Future work should apply the diagnostic criteria used in the DSM-5 when recruiting subjects with IGD. Further fMRI studies with adequate sample sizes of at least 20 participants, reasonable hypotheses, effective designs, and precise data analysis by integrated research teams, are needed for further elucidation of mechanisms of IGD.

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