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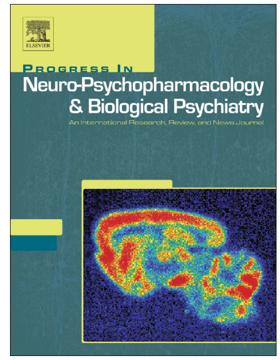

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Meta-analyses of the functional neural alterations in subjects with Internet gaming disorder: similarities and differences across different paradigms

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Abstract

Internet gaming disorder (IGD) has become a global public health concern due to its increasing prevalence and potential negative consequences. Researchers have sought to identify which brain regions are associated with this disorder. However, inconsistent results have been reported among studies due to the heterogeneity of paradigms and subjects.

The present research aimed to combine the results of individual studies to provide a more coherent and powerful explanation. By selecting 40 studies utilizing a qualified whole-brain analysis, we performed a comprehensive series of meta-analyses that employed seed-based *d* mapping. We divided the existing experimental paradigms into 3 categories: game-related cue-reactivity, executive control, and risk-reward-related decision-making tasks.

We divided all studies into three subgroups according to their paradigms. In cue-reactivity tasks, patients with IGD exhibited significant hyperactivation in the bilateral precuneus and bilateral cingulate and significant hypoactivation in the insula, but there were no differences in the striatum. In executive control tasks, patients with IGD displayed significant hyperactivation in the right superior temporal gyrus, bilateral precuneus, bilateral cingulate, and insula and hypoactivation in the left inferior frontal gyrus. In risky decision-making paradigms, IGD patients exhibited significant hyperactivation in the left striatum, right inferior frontal gyrus, and insula and hypoactivation in the left superior frontal gyrus, left inferior frontal gyrus, and right precentral gyrus.

Our study aimed to discover the similarities among all studies and to explore the uniqueness of the different paradigms. This study further confirmed the critical role of reward circuitry and executive control circuitry in IGD but not under all conditions.

Keywords:

Internet gaming disorder; executive function; reward system; fMRI; meta-analysis

Introduction

One of the negative consequences of the Internet is Internet gaming disorder (IGD), which has been defined as a chronic recurrent disorder characterized by compulsive game seeking, uncontrolled game playing, and the decision to play despite the negative consequences (van Rooij et al. 2017). IGD is usually conceptualized as a type of behavioral addiction (Petry and O'Brien 2013; WHO 2017) that pathologically leads to problematic behaviors, serious psychological distress, and even physiological damage (Dong et al. 2017b). In addition, IGD is widespread worldwide, particularly in young adults (Weinstein et al. 2017b).

The prevalence rate of IGD is believed to affect approximately 0.3% to 27.5% of people worldwide, depending on the population, location and other characteristics (Mihara and Higuchi 2017; Przybylski et al. 2017), with higher rates in Asian (Yu and Cho 2016; Higuchi et al. 2017) and adolescent populations (Kuss and Griffiths 2012; Zhang et al. 2018). In China, the number of online game users has reached 483 million, accounting for 58.4% of the total Internet users (CNNIC 2019). In summary, IGD affects an individual's health and social development (Ramesh and Igor 2016), particularly in adolescents (Paulus et al. 2018). A cohort study showed that nearly four-ninths of IGD patients who completed an 8-week psychotherapy program had recovered (Han et al. 2018). Although several studies have demonstrated that IGD can be treated, there have been a lack of randomized and well-controlled trials on IGD (Gentile et al. 2017). Treatment of IGD is another research topic and is focused on the mechanisms underlying the development, maintenance, and relapse of IGD (Dethier et al. 2017).

The elevated prevalence rate of and the unclear treatment options for have led to research on the neural mechanisms of IGD. The focus on the similarities between behavioral addiction and substance addiction (Griffiths 2017) has led researchers to apply the research methods used in substance addiction to IGD (Smith et al. 2015), and some similar conclusions were reached. The behavioral analysis showed that IGD patients have uncontrolled cravings (Kim et al. 2018), extensive playing time (Dong et al. 2010), and over engagement despite the negative consequences (Bertran and Chamarro 2016). According to fMRI studies, IGD patients exhibit significantly higher attention to game-related cues than healthy controls (Choi et al. 2014), and the relevant brain regions are mainly located in the prefrontal lobe (Ahn et al. 2015). IGD patients show impairments in executive control functions (Nuyens et al. 2016), and the relevant brain regions, usually designated as the executive control network, include the dorsolateral prefrontal cortex (dlPFC) and dorsal anterior cingulate cortex (dACC) (Ding et al. 2014). IGD patients exhibit disadvantageous decision making (Pawlikowski and Brand 2011), and the relevant brain regions include regions involved in valuation (nucleus accumbens (NAcc) and ventromedial prefrontal cortex (vmPFC)), exploration (medial temporal lobe, precuneus, and dorsomedial prefrontal cortex), and executive control (orbitofrontal cortex (OFC), dlPFC and dACC) (Qi et al. 2016b). In particular, in delay-discounting tasks, IGD patients are insensitive to long-term gains and losses and choose short-term gains (Buono et al. 2017).

Taking theoretical considerations and empirical research results into account, Brand et al. proposed the Interaction of Person-Affect-Cognition-Execution (I-PACE) model to describe these features of IGD. The I-PACE model suggests that a specific Internet-use disorder (e.g., IGD) is considered to be the consequence of interactions among predisposing factors such as Internet-related cognitive biases (e.g., craving), reduced executive functioning and disadvantageous decision-making (Brand et al. 2016). According to the I-PACE model (Brand et al. 2016) and a cognitive-behavioral model of IGD (Dong and Potenza 2014), we divided the paradigms of fMRI studies into 3 categories, namely, cue-reactivity paradigms, executive function paradigms, and risky decision paradigms. (1) Cue-reactivity paradigms use game-related and game-unrelated stimuli in a simple but robust manner to study the craving process in IGD and HCs. (2) Executive function paradigms include go/no-go tasks, Stroop tasks, dot-probe paradigms, and working memory tasks. (3) Risky decision paradigms usually provide feedback about winning and losing to subjects via reality-simulated guessing tasks and risk-taking tasks.

fMRI has been widely used to understand neural underpinnings by examining the key brain regions associated with IGD (Gentile et al. 2017). However, these results are difficult to interpret (Weinstein et al. 2017a); some issues hindered the final conclusions because the neural circuitry that predominates during the tasks and the nature of the response strongly depend on the study methodology, particularly paradigms and fMRI parameters. In general, four major problems regarding this issue have been identified. First, during the screening process, different scales and different criteria are often used to screen IGD patients and matched healthy controls (King et al. 2013). Additional details are listed in Table 1. Second, neuroimaging studies usually rely on small sample sizes, rendering conclusions less reliable (Button et al. 2013). These two issues underpower the conclusions and increase the false-positive rate (Yarkoni et al. 2011), which may be offset by conducting a meta-analysis (Hu et al. 2015). According to a meta-analysis that includes all tasks, IGD patients show hyperactivation in the bilateral medial frontal gyrus (MFG), the left cingulate gyrus, the left medial temporal gyrus and the fusiform gyrus (Meng et al. 2015). However, this meta-analysis did not consider the following issues.

Third, studies often include overlapping data from the same set of participants, and the results for different contrasts are not independent (Turkeltaub et al. 2012) (e.g., the researcher publishes two papers based on one set of data) (Qi et al. 2015, 2016a). Even in the same paradigm, redundant pathways subserve the same brain function. Fourth and most importantly, multiple paradigms are used to test different functions, making the combination of these results into one meta-analysis difficult and leading to substantial problems. In other words, the use of one meta-analysis for pooling multiple paradigms and contrasts is impossible. However, if we perform a meta-analysis using only a specific type of paradigm, such as the cognitive action control paradigms (e.g., go/no-go or Stroop tasks), a broad perspective of IGD may be lacking. Meanwhile, increasing numbers of studies are using different tasks. Thus, a meta-analysis designed to address the differences between paradigms is needed.

The aims of the current study are to explore the characteristics of brain activities in participants under different paradigms and to compare these characteristics.

We hypothesize that overlapping characteristics exist among the three paradigms, which will indicate the common dysfunction neural network for IGD that is consistent with findings from individuals with substance addictions. Specifically, for all types of paradigms, IGD patients exhibit significant differences in activity in the default mode network (), frontoparietal control network (FPN), attention network (ATN), and insula involving multiple cognitive functions (Brand et al. 2016). We also hypothesize that different paradigms have specific characteristics that are driven by their paradigm's features. IGD patients will display different activities in the reward network for the cue-reactivity task. Specifically, IGD patients will exhibit higher cue-induced activations in the ventral and dorsal striatum involving reward anticipation compared with HCs (Starcke et al. 2018). IGD patients will display different activities in the FPN for executive function tasks. Specifically, IGD patients will exhibit higher task-related activations in the ACC and posterior cingulate cortex (PCC) involving cognitive control and lower task-related activations in dlPFC involving habit control (Dong et al. 2015b). IGD patients will display different activities in the FPN and limbic network for decision-making tasks. Specifically, IGD patients will exhibit higher reward-related activations in the NAcc and dorsal striatum involving reward anticipation and lower reward-related activations in the vmPFC and OFC involving reward evaluation (Brand et al. 2016).

Materials and Methods

Inclusion and exclusion criteria for selecting studies

The following inclusion criteria were used: (1) peer-reviewed, original articles; (2) direct comparison between IGD patients and HCs; (3) a diagnosis of IGD based on the DSM-5 (Kuss et al. 2017) or other published scales with high reliability and validity (e.g., Chen Internet Addiction Scale, Youngs' Internet Test); (4) whole-brain analysis of task-based fMRI results that reported peak coordinates of the activation areas with *T*, *p* or *Z*-values; and (5) articles written in English.

The following exclusion criteria were used: (1) different studies using the same group of subjects; (2) absence of multiple comparison correction; and (3) other fundamental biological/clinical/mechanistic issues that may affect the final conclusions (e.g., control subjects with other mental illnesses).

Database searches and study selection

Two authors (HZ and GD) independently searched PubMed (http://www.pubmed.org), Google Scholar (http://scholar.google.com), Web of Science (http://apps.webofknowledge.com), and the Cochrane library (http://www.cochranelibrary.com/) for articles published from June 1, 2008, to June 1, 2018, using the following search terms: "pathological video gamers" or "Internet game disorder" or "online game disorder" or "cyberspace game disorder" or "computer game disorder" or "video game disorder" or "Internet game addiction" or "video game addiction" or "Internet gaming disorder" together with "fMRI" or "neuroimaging" and "task".
The search was refined by "DOCUMENT TYPES: (ARTICLE) AND LANGUAGES: (ENGLISH)". Based on these searches, we created a database of references. In addition, studies were identified using HistCite (http://interest.science.thomsonreuters.com/forms/HistCite/). The two authors independently screened titles and abstracts and deleted duplicates and records that did not meet the inclusion criteria. Full articles were then checked carefully by each author to produce separate inclusion lists. This procedure adhered to the preferred item selection method for systematic reviews and meta-analysis guidelines (Panic et al. 2013), and the full details are shown in Figure 1.

Insert Figure 1 here

Criteria for paradigm classification

In previous meta-analyses, if an article employed more than one comparison, researchers usually selected only one. However, with ES-SDM 5.141, we are able to combine the results of this iterative measurement to achieve more reliable results (Norman et al. 2016). According to the I-PACE model and previous databases, we divided the paradigms of fMRI studies into 3 categories. (1) Cue-reactivity paradigms evoke addiction-related neural activity and are evaluated using cue-induced reactivity tasks, and three studies reported the mean effect of gaming-related stimuli (the cue stimuli – neutral stimuli) (Lorenz et al. 2013; Liu et al. 2014; Han et al. 2016). (2) Executive function paradigms evoke executive-related neural activity and are evaluated using go/no-go tasks, Stroop tasks, dot-probe task, and working memory task. (3) Risky decision-making paradigms evoke decision-related neural activity and are evaluated using guessing task, risk-taking tasks, delay-discounting task, Wisconsin Card Sorting task (WCST), the S-R task, odd-even pass task, cup task, and balloon analog risk task.

Meta-analysis of studies

In the current study, the meta-analysis was conducted using the anisotropic effect-size version of the Seed-based *d* Mapping (AES-SDM) software package (http://www.sdmproject.com), version 5.141. AES-SDM is a reliable and effective voxel-based meta-analysis software that has been used and published in multiple studies (Alegria et al. 2016). This software can combine hyperactivation and hypoactivation in one analysis, while other MRI meta-analysis approaches (e.g., ALE, MKDA) include only one side. Hypoactivation is also important for IGD. Our meta-analysis was conducted in seven steps. 1) We prepared files for the AES-SDM software to collect raw information and main outcomes from the included studies to create the SDM table. 2) AES-SDM uses an anisotropic non-normalized Gaussian kernel to recreate Hedges' effect-size map and an effect-size variance map for the comparison between IGD patients and

HCs from peak coordinates and effect sizes for each included study (Radua et al. 2012). A mean map was then created by a voxel-wise calculation using a random-effects model, which was weighted by sample size and variance for each comparison, as well as inter-study heterogeneity. Statistical significance was determined using standard permutation tests. The isotropic full width at half maximum (FWHM) in SDM was set to 20 mm, and the randomization time was set to 50, which provides excellent control for false positives, according to previous studies. 3) A mean comparison of the functionally activated regions between IGD patients and HCs was performed. 4) A subgroup analysis was performed for three key paradigms: game-related cue reactivity, executive control, and risk-reward-related decision making (Radua et al. 2010). 5) Meta-regression analyses of symptom severity were applied to examine potential confounding variables (e.g., online time) (Radua et al. 2014). 6) We conducted a jackknife sensitivity analysis using subgroups of datasets stratified by the area (China, Taiwan, and Korea) in which adult subjects lived, corrected for multiple comparisons using statistical parametric mapping (SPM) software, and reported Young's Internet addiction test scores and typical smoothing kernels (FWHM=7–8 mm or 5-6 mm) to assess the robustness of the results. 7) The statistical heterogeneity of individual clusters was examined using a random-effects model. All the thresholds were $p < 0.005$, uncorrected with peak height $z \geq 1$ and cluster extent=10 voxels. For each significant patient-control comparison, Egger's test was used to assess the asymmetry of the funnel plot as a measure of potential publication bias (Norman et al. 2016).

Results

Included studies and characteristics

Based on the selection criteria (Figure 1), this study included 40 articles with 766 IGD patients and 700 HCs. Seven studies examined IGD in adolescents (N=123, mean age=15.19 years). The mean age of IGD patients was 21.19 years. Most subjects were male (751 males, 98.05%). The average gaming time of IGD patients was 36.56 hours/week (4 studies did not report this item). We recorded all scales used in the 40 studies, comprising 36 studies from Asian countries (China mainland, 20; Taiwan, 6; and Korea, 10), 3 from Germany and 1 from The Netherlands. Based on the paradigms used and addiction loop theory, we divided the 61 comparisons into 3 main categories: cue reactivity (12 comparisons), executive control (17 comparisons, including 3 error effects, 10 inhibitions, 2 switches, and 2 working memory), risk reward (24 comparisons, including 8 win outcomes, 4 loss outcomes, 4 risks, and 8 decisions), and others (8 total, including 5 emotion, 2 self-concept, and 1 embodiment). All comparisons were consistent between pairs of IGD patients and well-matched HCs. The clinical characteristics and other details of the included studies are shown in Table 1.

Insert Table 1 here

Activity results from all studies

In all tasks, compared with HCs, IGD patients exhibited significant hyperactivation in the bilateral precuneus, bilateral cingulate (ACC, middle cingulate cortex (MCC), PCC), left precentral gyrus (BA 44 and BA 6; LPG), right inferior frontal gyrus (BA 45; IFG), and left frontal orbito-polar tract. IGD patients also displayed significant hypoactivation in the left inferior network (BA 45, BA 47, BA 48, and IFG).

Insert Table 2 and Figure 2 here

Subgroup analysis

The subgroup meta-analysis of these studies was divided into 3 categories based on the paradigms and addiction loop theory, as shown in Table 1 and the methods section.

Cue-reactivity task

Compared with HCs, patients with IGD exhibited significant hyperactivation in the bilateral precuneus (BA7), bilateral cingulate, left precentral gyrus (BA 6), and right inferior frontal gyrus (BA 45 and BA 48). Patients with IGD displayed significant hypoactivation in the insula (BA 48) and right postcentral gyrus (BA 6), as shown in Table 3 and Figure 3.

Insert Table 3 and Figure 3 here

Executive function tasks

Compared with HCs, patients with IGD displayed significant hyperactivation in the right superior temporal gyrus (STG, BA 48), bilateral precuneus, bilateral cingulate, and right caudate nucleus (BA 25). Patients with IGD exhibited significant hypoactivation in the left inferior frontal gyrus (BA 44, BA 45, and BA 48), as shown in Table 4 and Figure 4.

Insert Table 4 and Figure 4 here

Risky decision-making tasks

Compared with HCs, patients with IGD presented significant hyperactivation in the left striatum and right inferior frontal gyrus (IFG; orbital part, BA 11). Patients with IGD exhibited significant hypoactivation in the left superior frontal gyrus (medial part, BA 32), left inferior frontal gyrus (IFG; triangular part, BA 45), right precentral gyrus (BA 6), and left median network (cingulum), as shown in Table 5 and Figure 5.

Insert Table 5 and Figure 5 here

Meta-regression analysis and publication bias

According to the meta-regression analysis, as game time increased, IGD patients exhibited significant hyperactivation and hypoactivation in many brain regions, as shown in Figure S4. The jackknife sensitivity analyses and Egger's test did not reveal publication bias in this meta-analysis, as shown in Figures S2 and S3 and Tables S3 and S4.

Discussion

Patients with IGD displayed similar and different alterations in functional neural activity across different paradigms. Compared with HCs, patients with IGD showed significant hyperactivity in the bilateral precuneus, bilateral cingulate, left precentral gyrus, and right inferior frontal gyrus and hypoactivation in the left inferior gyrus. The subgroup analyses stratified by the 3 categories of paradigms showed 2 interesting findings: 1) under the cue-reactivity paradigm, IGD patients did not display abnormal activation in key regions of the reward network such as the VS or DS; and 2) functional differences in the activity of the insular cortex exist across all paradigms. Other than these findings, the other findings were broadly consistent with our hypothesis that common brain features in IGD patients exhibit significant differences in activity in the DMN, FPN, and ATN, while the effect was not uniform across paradigms.

Therefore, our results showing that the functional abnormalities observed in patients with IGD differed between the three different types of paradigms also provided empirical support for the theoretical I-PACE model. The I-PACE model proposed that specific Internet-use disorders are thought to result from interactions between predisposing factors (such as neurobiological and psychological structures), regulators (such as coping styles and Internet-related cognitive bias), and mediators (such as reduced executive function capabilities) (Brand et al. 2016). The cue-reactivity paradigm is the A (affective response) component of this model. Reduced executive function and inhibitory control constitute the E (executive) component of the model. Disadvantageous decision making is related to a mixture of components E and C (cognitive response) in this model.

Results from all 40 studies

The most recent meta-analysis of structural states and task states reported that IGD patients exhibit hyperactivation in the bilateral ACC and PCC, precuneus, caudate, posterior inferior frontal gyrus (IFG), dlPFC, and right middle occipital cortex and hypoactivation in the left anterior IFG, right precentral and postcentral gyri and right posterior insula in 27 fMRI comparisons (Yao et al. 2017). We used a new method combined with multiple comparisons in the same study to obtain similar results. These brain regions are thought to be part of the DMN, FPN, and ATN, and alterations in these networks are important neural signatures of IGD (Weinstein and Lejoyeux 2015; Weinstein et al. 2017a). These three brain networks are usually activated during cue reactivity, executive control and risk decision-making tasks (Palaus et al. 2017). The development of addiction may be conceptualized as a three-stage model: binge/intoxication stage, withdrawal/negative stage, and preoccupation/anticipation (craving) stage that worsens over time and involves neuronal changes in the brain reward, stress and executive function systems (Koob and Volkow 2016). These results helped us to confirm that IGD significantly altered the pattern of neural activity, and the regions displaying altered activity were mainly concentrated in the ACC, PCC, dlPFC, and precuneus.

The DMN, FPN, and ATN play separate and interactive roles in the development of IGD. The DMN plays a major role in the healthy and diseased human brain (Raichle 2015). Many addiction studies reported changes in the DMN (Ma et al.

2011); the addiction studies included individuals with a pathological gambling habit (Jung et al. 2014), alcohol dependence (Arcurio et al. 2015), a cigarette smoking habit (Tang et al. 2016), methamphetamine dependence (Ipser et al. 2018), and cocaine addiction (Ding and Lee 2013). Neurological abnormalities in the DMN, as well as in the precuneus, PCC, and IFG, may contribute to the behavioral inhibition deficits associated with IGD-related cognitive dysfunction (Dong et al. 2017a; Wang et al. 2017a). The FPN is the key brain network for predicting and monitoring action outcomes (Zubarev and Parkkonen 2018). Some addiction studies reported changes in the FPN (Costumero et al. 2017), including studies examining cocaine-dependent people (Barrós-Loscertales et al. 2011) and smokers (Clewett et al. 2014). Consistent with previous studies, the right IFG in the ATN showed abnormalities in IGD (Hong et al. 2018). Resting-state fMRI also revealed various internal architectures that support dynamic interactions between the DMN, FPN, and ATN (Avelar-Pereira et al. 2017). An independent component analysis suggested that Internet addiction is associated with imbalanced interactions among the DMN, FPN, and salience network (Wang et al. 2017a). In combination with behavioral studies (van Holst et al. 2012), changes in these brain networks observed in IGD have been shown to disrupt attention, executive control, and automated information processing (Vatansever et al. 2017).

The insula was another brain region that consistently showed abnormalities across different paradigms. This result is consistent with some findings of substance addiction studies, such as the relationship between neural activity in the insular cortex in cravings in deprived smokers (Gu et al. 2016). The insula is postulated to be involved in (1) motivation processing in addiction (Engelmann et al. 2012), (2) the control or inhibition of addictive behaviors (Menon and Uddin 2010), and (3) the acceptance of medical-related physical conditions (Naqvi et al. 2014). In addition, the insula has been suggested to function as a neurobiological gate for the development of compulsive behaviors (Belin-

Rauscent et al. 2016). Insular activation during reward anticipation reflects the duration of illness in abstinent pathological gamblers (Tsurumi et al. 2014). The increased functional connection between the left frontoparietal network and anterior insula predicts steeper devaluation of delayed rewards in smokers (Clewett et al. 2014). Some IGD studies focused on this area have shown that impaired anterior insular activation is associated with poor risky decision making (Lee et al. 2016), and increased insular cortical thickness is associated with symptom severity in IGD (Wang et al. 2018). Our findings also provide evidence that the insula contributes to how addicted individuals feel (craving), remember, control, and make decisions about (risk-reward decision) their addictive behaviors (Naqvi and Bechara 2010).

Results from the cue-reactivity task

Addiction-related cues have been considered a trigger for relapses and may also provide targets for more effective addiction-cessation interventions (Carter and Tiffany 1999). Repeated exposure to drug-related cues (e.g., drugs, people, places) can lead to craving and drug-seeking behaviors (Gardner 2011). A recent meta-analysis of cue-reactivity in behavioral addiction also confirmed that patients with behavioral addiction showed higher responsiveness to addiction-related cues than HCs (Starcke et al. 2018). Specifically, gaming cues are the trigger of game-seeking behaviors in IGD patients (Wang et al. 2017b).
We found a similar pattern in a previous meta-analysis of behavioral addiction to that in the cue-reactivity paradigm (Starcke et al. 2018). The previous meta-analysis showed that patients with a behavioral addiction have higher activations in response to addiction-relevant cues than control participants in the median cingulate, inferior frontal gyrus, caudate, and precentral gyrus (Starcke et al. 2018). In this meta-analysis, for the cue-reactivity task, patients with IGD exhibited significant changes in the DMN, ATN, and FPN that were also detected in the analysis of all 40 studies, providing support for the hypothesis that abnormalities in these brain networks may be stable manifestations in

patients with IGD.

However, in contrast with our hypothesis, IGD patients rarely have activation differences in the reward network. Substance addiction studies strongly suggest that drug-related cues cause greater brain activation in addicts than HCs and usually include the ventral tegmental area (VTA), ventral striatum (VS), dorsal striatum (DS), amygdala, ACC, PFC, insula, and hippocampus (Chase et al. 2011; Milella et al. 2016; Moeller and Paulus 2018). Phasic excitation of dopaminergic neurons projecting from the VTA to the VS is crucial for behavioral regulation and cue priming (Schultz 2007). Another meta-analysis of IGD also showed caudate hyperactivation in a subgroup (8 studies used the cue-reactivity paradigm) associated with reward (Yao et al. 2017). In addition, a diffusion tensor imaging study of patients with IGD reported increased white matter integrity in tracts linking the reward circuitry and sensory/motor control systems (Dong et al. 2018). Interestingly, in our subgroup analysis, reward-related brain regions did not show activation differences, such as in the VS and DS. According to I-PACE, neural correlates between cue reactivity and craving have been confirmed in individuals with IGD (Brand et al. 2016).

The possible reasons for the result of our sub-analysis may include three aspects. 1) A previous meta-analysis included research that was primarily related to gambling addiction; of the six data sets, four included data on gambling (Starcke et al. 2018). Gambling addiction may have caused more neuroadaptive changes than IGD (Mallorquí-Bagué et al. 2017). 2) Behavioral addiction, unlike substance addiction, increases DA transmission in the VA modulated by reward predictability and habituation (Heinz et al. 2019). 3) The individuals with IGD in our meta-analysis who were most likely to be in the later stages of the addiction process were considered to be in the more compulsive stages of the disorder. Compared with direct gaming experience, the monotonous game-related stimulus becomes less important (Piazza and Deroche-Gamonet 2013).

Results from executive control tasks

Executive functions are a set of cognitive processes necessary for cognitive control behaviors, including selecting and monitoring behaviors to facilitate the achievement of the chosen goal (Hall 2017). Addiction is associated with decreased inhibitory control (Dalley et al. 2011; Ersche et al. 2012). Attention bias toward drug-related stimuli has been consistently reported in the addiction literature (Hester and Luijten 2014). Studies on subjects with IGD proposed that the failure of the executive control system was caused by their tendency to fail to properly regulate gaming behavior (Dong et al. 2015b). A previous behavioral meta-analysis showed that IGD patients have more impairment of response inhibition (Argyriou et al. 2017). In I-PACE, neural correlates of executive functions and inhibitory control have been confirmed in individuals with IGD, and attention has focused on the fronto-striatal circuits, based on evidence from structural and functional MRIs (Brand et al. 2016).

In this meta-analysis, in executive function tasks, IGD patients exhibited significant hyperactivation in the DMN, ATN, FPN, and sensorimotor network (SMN), as well as significant hypoactivation in the DMN and FPN. According to the literature, the most commonly altered brain region in IGD is the STG, which is composed of the right insula, right MTG, right STG, and right IFG. Structural MRI studies have also confirmed the involvement of these brain regions in IGD. A VBM study revealed a greater GM volume in the MTG of subjects with IGD (Sun et al. 2014). A recent surface-based morphometric study reported increased cortical thickness in the bilateral insula and right IFG and decreased thickness in the bilateral STG of subjects with IGD (Wang et al. 2018). fMRI studies of addiction using executive function tasks reported similar results. The inferior frontal gyrus is a core area underlying substance dependence and behavioral addictions (Luijten et al. 2014). The caudate is the key region of prefrontal-striatal circuits, and a previous study showed increased volumes of the caudate in IGD patients that were correlated with the response errors during (Cai et al. 2016)The current results of abnormal brain activity during executive functional tasks also provide support for the I-PACE model that the reduced executive capabilities mediate IGD (Brand et al. 2016).

Our results also revealed more varied patterns of brain activities during executive function paradigms, e.g., hyperactivation in the SMN and hypo-activation in the DMN and FPN. The SMN belongs to striato–subthalamic–pallido–thalamo–cortical networks, which distinguish between goal-directed and habitual behavior (Jahanshahi et al. 2015). Alterations in the SMN have been reported in some drug addicts, but this has never been considered a core feature of addiction. Interestingly, alterations in the SMN were found in all three subgroup analyses. Alterations in the SMN may reflect the complex sensory input and responses that are required during Internet gaming activities. These activities may also reinforce this behavioral addiction (Albergaria et al. 2018).

Results from decision-making tasks

Decision-making is a cognitive process that leads to a choice when an individual is presented with two or more possibilities. In this subgroup analysis, different paradigms were involved in the risk-reward decision-making process. These paradigms were designed to investigate the mechanisms underlying different decision styles (e.g., risk-taking) and sensitivities to rewards and penalties (e.g., impulsivity). In a typical delayed discounting task, participants would face a choice of an immediate but smaller reward versus a later but larger reward (Frederick et al. 2002). Substance addicts often exhibit high reward sensitivity and low punishment sensitivity in conjunction with deficits in executive control, which may contribute to high levels of risk-taking behaviors (Kahn et al. 2018). However, these factors may differ in IGD. According to behavioral research, impulsive decision making and personality traits might co-occur with IGD in adolescents, but not risk-seeking (Tian et al. 2018). Decision-making deficits under risky conditions are linked to poor inhibition that is specifically related to gaming cues in IGD (Yao et al. 2015).

In I-PACE, disadvantageous decision making is considered a dysfunctional interaction between reward seeking during cue-reactivity and executive function (Brand et al. 2016). Thus, the dysfunctional neuronal functions of IGD during decision-making tasks should include the reward system (Sercombe 2014) and the executive control network. In this meta-analysis, IGD patients exhibited significant hyperactivation in the visual network and limbic network, as well as significant hypoactivation in the SMN, ATN, FPN, and DMN. The left striatum and left caudate identified in this subgroup analysis belong to a limbic network that is crucial for the reward system (Yeo et al. 2011), the IFG, MCC and insula belong to the ATN, FPN, and DMN are expected and similar to those found in the subgroup analysis of executive function tasks. And these finding is consistent with the results of studies on substance addiction (Bustamante et al. 2014) and the meta-analysis of neurocognitive decision making in adolescents (Shablack et al. 2019). Functional connections may exist between reward-seeking and executive control systems during decision-making tasks, which has been emphasized by resting-state fMRI (Dong et al. 2015a).

Neural correlates of symptom severity

The results show that the severity of symptoms (gaming time (hours per week)) was positively associated with hyperactivation in the left inferior frontal gyrus and right insula and negatively associated with hypoactivation in the right dorsal striatum, right inferior frontal gyrus, and left precentral gyrus. A previous meta-analysis showed that online time (hours per week) was associated with hyperactivity in the left MFG (BA9) and the right cingulate gyrus (BA24) (Meng et al. 2014). These results may suggest an unbalance between the two systems, with the gaming time decreasing the neural substrate activation of the goal-directed system, which may reflect impairment in goal-directed behavior. As in substance addiction, the severity of symptoms reflects different stages of the addiction process, especially the transformation from goal-directed behavior and habit control behavior (Voon et al. 2017).

Limitations

First, meta-analyses of peak and effect sizes use data from published studies instead of raw data, which may decrease the accuracy of the results (Radua et al. 2012). Second, different studies adopted different statistical thresholds and multiple comparison corrections. Third, the heterogeneity of participants in the original literature included a variety of diagnostic criteria, comorbidities (e.g., smoking, alcohol abuse, anxiety, and depression), different contrast conditions and few female subjects (Table 1).

Conclusions

Based on the results, we conclude that different abnormal brain networks under dysfunction lead to IGD, in line with I-PACE. However, during the craving process, differential activation of brain regions in the reward network was not observed between IGD and HCs, which may be one of the differences between IGD and substance addiction. More interestingly, the insula was the brain region that consistently showed abnormalities across the different paradigms and may be the core brain region involved in IGD.

These three altered functions suggest that excessive gaming enhances cravings for gaming stimuli, impairs executive control ability, and leads to disadvantage decision making (e.g., focusing on an immediate, small reward and ignoring a delayed, larger reward). These findings show distinctive changes in the cingulate cortex, precuneus, striatum and insular neurons that may serve as functional biomarkers for IGD and have potential implications for future diagnosis and treatment practices.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest to report.

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Authors contributed as follows: protocol design, and meta-analysis, HZ and GD; data collection, MW and ZLW; manuscript preparation, YBH and HZ. All authors contributed edits and approved the content of the manuscript.

Supplementary data

Supplementary material

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Figure 1. Flow diagram of the literature search used in this meta-analysis (June 2008 to June 2018).

Figure 2. Brain response abnormalities in IGD patients compared with HCs in all 40 studies.

A: Compared with HCs, IGD patients exhibited significant hyperactivation in the a: bilateral precuneus and bilateral cingulate; b: left precentral gyrus; c: right inferior frontal gyrus; and d: left frontal orbitopolar tract and hypoactivation in the left inferior gyrus.

B: Comparison of the altered brain regions in the brain network reported by Shirer WR et al. in 2011.

C: Comparison of the altered brain regions in the brain network examined by Yeo et al. in 2011.

Figure 3. Brain response abnormalities in IGD patients during cue-reactivity tasks.

Compared with HCs, IGD patients displayed significant hyperactivation in the a: DMN, b: ATN, and c: FPN and hypoactivation in the d: SMN.

Figure 4. Brain response abnormalities in IGD patients during executive control tasks.

Compared with HCs, IGD patients exhibited significant hyperactivation in the a: DMN, b: ATN, and c: SMN and hypoactivation in the d: DMN and e: FPN.

Figure 5. Brain response abnormalities in IGD patients during risky decision-making tasks.

Compared with HCs, IGD patients exhibited significant hyperactivation in the a: VN and b: LN and hypoactivation in the c: SMN, d: ATN, e: FPN, and f: DMN.

Table 1 Summary of recent whole brain analysis task study of IGD

TASKS	Contrasts	Active Results	Study	Area	Average age	Sample male/female	Addict Scores	Game time hours /week	Sample	Scores	Scanner	Software	FWHM (mm)	Multiple-comparisons
Caving														
Cue-induced reactivity paradigm	Video game pictures-neutral pictures	IAG>HC	D. H. Han et al., 2010[1]	Korea	21	11	71.2	45.5	8	27.1	Siemens1.5T	BrainVoyager	6	FDR
	B: Game pictures-neutral pictures	IGD>HC	D. H. Han et al., 2012	Korea	14.1	15	75.1	34.5	15	14.2	Philips 3T	BrainVoyager	6	FDR

	Gaming pictures-Neutral pictures	Case>Controls	C. Ko et al., 2009	Taiwan	22	10	77.1a	30	10	22	GE3T	SPM2	8	Uncorr.
	Gaming images-neutral images	IGA[2]>Control	C.-H. Ko et al., 2013a	Taiwan	24.94	16	75.69a	36	16	27.06	GE3T	SPM5	8	FWE[3]
	Gaming images-Neutral images	IGA>Control	C.-H. Ko et al., 2013b	Taiwan	24.57	15	76a	56	15	24.7	GE3T	SPM5	8	Uncorr.
	video game video-neutral video	IGD>HC	J. Liu et al., 2016	China	21.1	11/8	d	49.4	11/8	NA	Siemens3T	BrainVoyager	6	Uncorr.
	(Gaming images-Internet surfing) and rate craving	IGD>HC, IGD<HC	L. Liu et al., 2017a	China	22.8	39	75.59a	18.92	23	45.65	Siemens3T	SPM8	5	FWE
	Gaming pictures-neutral picture	CIA>HC	Sun et al., 2012	China	20.35	10	67.39a	51.3	10	39.8	Philips 3T	SPM5	8	FDR
	(Game videos-control videos) and rate craving	IGD>HC, IGD<HC	J.-T. Zhang et al., 2016b	China	22.25	40	79.88a	27.26	19	42.11	Siemens 3T	spm8	5	GRFT
Go/NoGo task	B: Gaming distracting-original response	Case<Control	G.-C. Liu et al., 2014	Taiwan	22.95	11	75.82a	NA	11	40.63	GE3T	SPM5	NA	Uncorr.
Dot probe paradigm	A_LP: (CGS_WoW>CGS_N) - (IAPS_P>IAPS_N)	PCGP>HC	Lorenz et al., 2013	Germany	24.9	8	2.2e	37.2	9	1	GE3T	SPM8	8	AlphaSim
Wisconsin Card Sorting Test	B: Neutral-Fixation	IGD>HC	**D. H. Han et al., 2016**	Korea	20.2	60	59.1	40.6	42	26.2	Philips 3T	SPM12	6	FDR
Eecutive function														
	Nogo-Go	IGD<Control*	Chen et al., 2015	Taiwan	24.57	15	76a	36	15	26	GE3T	SPM5	8	FWE[3]
	Nogo	IGD>Control, IGD<Control	Ding et al., 2014	China	16.35	14/3	65.82a	27.29	14/3	42.88	GE3T	SPM8	6	AlphaSim
Go/NoGo task	A: correct Nogo-Go；B: incorrect Nogo-correct Nogo	IGD>Control; IGD<Control	C.-H. Ko et al., 2014	Taiwan	24.47	26	84.96a	36	23	39.68	GE3T	SPM5	8	FWE[3]
	A:Nogo-Go	Case>Control	G.-C. Liu et al., 2014	Taiwan	22.95	11	75.82a	NA	11	40.63	GE3T	SPM5	NA	Uncorr.
	A: Correct Nogo-Correct Go C: Incorrect Nogo-Correct GO	Gamer< Control* No differences	Luijten, & Schoenmakers, 2015	Netherlands	21.09	18	3.34g	35	16	1.26	GE3T	SPM8	8	AlphaSim[3]
	B: Incongruent-Congruent	Gamer< Control*												
	Incongruent-Congruent	IAD>Control	Dong et al., 2012	China	23.95	12	>80	42	12	20<	Siemens3T	SPM5	8	FDR
Stroop task	Incorrect responses	IAD>HC, IAD<HC	Dong et al., 2013a	China	23.8	15	84.4	42	15	14.3	Siemens3T	SPM8	8	FDR
	A: Incon_Con-Con_Con; B: Con_Incon-Incon–Incon	IAD>HC; IAD>HC	Dong et al., 2014	China	22	15	>80	42	15	20<	Siemens3T	SPM5	6	AlphaSim
	A: Incongruent-Congruent	IGD>NLFGU	Dong et al., 2017	China	21	18	79.5	24.6	19	26.2	Siemens3T	Neuroelf	6	AlphaSim
Addiction Stroop task	Gaming related words- Neutral words	IGD>HC	Y. Zhang et al., 2016	China	22.2	19	64.35	42	21	28.5	Siemens3T	SPM8	6	AlphaSim
Dot probe paradigm	B_SP: CGS(incon+con)>IAPS(incon+con)	PCGP>HC	Lorenz et al., 2013	Germany	24.9	8	2.2e	37.2	9	1e	GE3T	SPM8	8	AlphaSim
Working memory task	Quiz	EIGP>Control	C. Na et al., , 2010[4]	Korea	NA	7	NA	NA	7	NA	NA	BrainVoyager	NA	NA
	Complex-Rest	AEOP<HC, AEOP>HC	S. M. Kim et al., 2012a	Korea	14.35	13	72.2	34.4	13	41.4	Philips 3T	BrainVoyager	6	FDR
Risk decision														
	A:Win(gain+right) stimuli；B: Loss stimuli	IA>Normal comparison; IA<HC	Dong et al., 2011	China	23.74	14	>80.0	42	13	16.3	Siemens3T	SPM5	8	FDR
Reality-simulated guessing task	A: WIN-CONTROL B: LOSS-CONTROL C: WIN-LOSS	IAD>HC; IAD>HC, IAD<HC; IAD>HC	Dong et al., 2013b	China	21.74	16	>80.0	42	15	16.3	Siemens3T	SPM5	6	AlphaSim
	A:Decision after WIN-CONTROL B: Decision after LOSS-CONTROL	IAD>HC, IAD<HC; IAD>HC, IAD<HC	Dong et al., 2013c	China	21.74	16	>80.0	42	15	16.3	Siemens3T	SPM5	6	AlphaSim
	B:Winning outcomes C: Losing outcomes	IGD>NLFGU；No differenc	Dong et al., 2017	China	21	18	79.5	24.6	19	26.2	Siemens3T	SPM8+Neuroelf	6	AlphaSim

		es												
risk-taking and risk decision-making task	A: Risk disadvantageous(RD)-Risk advantageous(RA) B:Decisions after RD-Decisions after RA	IGD<HC; IGD<HC.	Dong & Potenza, 2016	China	21.58	20	NA	42	16	NA	Siemens3T	Neuroelf	6	AlphaSim
Delay-discounting task.	Probabilitistic-fixed	IGD<HC	Lin et al., 2015	China	22.52	19	64.35	42	21	28.5	Siemens3T	SPM5	6	AlphaSim
	A: Delay-no delay; B:Probabilitistic-fixed	IGD>HC; IGD>HC	Y. Wang et al., 2016	China	21.45	20	65.55	42	20	31	Siemens 3T	SPM8	6	AlphaSim
WCST task	A: WCST-Fixation;	IGD>HC	D. H. Han et al., 2016	Korea	20.2	60	59.1	40.6	42	26.2	Philips 3T	SPM12	6	FDR
S-R task associated with feedbacks	A: Outcome Reward(Monetary +Symbolic); B: Outcome Symbolic(correct) C: Outcome Penalty	IGO<Control; IGO<Control ; No difference	J. Kim, Kim, & Kang, 2017	Korea	21.66	18	62.78	24.06	20	29.75	Siemens3T	SPM12	6	FWE
Odd–even-pass task	A: Certain trial(correct 97%); B: Uncertain trial	IGD<HC; IGD<HC	D. Lee et al., 2016	Korea	24.65	24	101.8b/50.9	NA	24	58.1b/27.5	GE3T	SPM8	8	Uncorr.
Cups task	A: Risky-safe choices, Gain domain, Loss domain; B: Win-lose outcomes, Gain domain, Loss domain	No difference, IGD>HC ; IGD>HC, No difference	L. Liu et al., 2017b	China	22.25	41	79.66a	26.94	27	40.22	Siemens 3T	SPM8	5	FWE
Balloon analog risk task	Active>Passive;	IGD<HC;	Qi et al., 2015	China	17.34	23	70.35	28	24	33.42	Siemens3T	SPM8	6	AlphaSim
	Decisions after loss-After win	IGD>HC	Qi et al., 2016	China	17.17	24	70.71	28	24	33.42	Siemens3T	SPM8	6	AlphaSim
Other														
Viewing pictures	Affection-neutral pictures	IGD<HC	D. H. Han et al., 2012	Korea	14.1	15	75.1	34.5	15	14.2	Philips 3T	BrainVoyager	6	FDR
Ball-throwing animations task	(Agency Changing-Location Changing)-(Agency Fixed-Location Changing)	IA>Control	Y.-R. Kim et al., 2012b	Korea	13.49	13+4	62.76c	28.89	17	30.29c	ISOL3T	SPM2	7	Uncorr.
Concepts of self and ideal self task	A: self-unfamiliar person, B: avatar-self	No difference	Lemenager et al., 2014	Germany	26.55	14/2	18.75f	45.78	13/4	2.05	Siemens3T	SPM8	8	FWE'
	Avatar-Ideal	IGD>HC	Dieter et al., 2015	Germany	26.72	13/2	18.53f	44.03	13/4	1.59	Siemens3T	SPM8	NA	FWE
Emotional word task	A:swear-neutral word; B:negative-neutral word	IAD<HC; IAD>HC	Chun et al., 2015	Korea	13.49	16	37.56b	19.44	19	24.68b	Siemens3T	SPM8	8	FDR
Match-to-Sample stroop	Angry Faces-gray square	IGD>HC, IGD<HC	J. Lee et al., 2015	Korea	13.5	18	NAb	NA	18	NA	Siemens3T	SPM8	8	Uncorr.
Emotion regulation task	Neutral Look-Maintain Look-Regulate Decrease	HC increased, IGD blunted	Yip et al., 2017[1]	China	22.07	24	70.13a	>20	23	35.04	Siemens3T	SPM12	6	FWE

[a] Chen Internet Addiction Scale

[b] Korean Internet Addiction Proneness Scale

[c] Korean Adolescent Internet Addiction Scale

[d] Diagnostic Questionnaire for Internet Addiction

[e] World of Warcraft Addiction Inventory

[f] Standardized Clinical Interview to Assess Internet addiction

IGD=Internet gaming disorder; HC=healthy control; IAG, IGD, Case, IGA, CIA, PCGP, Gamer, IAD, EIGP, AEOP and IA are different names for IGD; YIAT=Young's on-line Internet addiction test; FWHM=full width at half maximum; SPM=statistical parametric mapping; FDR=false discovery rate; Uncorr.=uncorrected for multiple comparisons; FWE=family-wise-error; Corr.=corrected for multiple comparisons; GRFT=Gaussian Random Field Theory; AlphaSim= AlphaSim correction; SP=Short-presentation trials, stimulus class(CGS, IAPS)*congruency (congruent, incongruent)>mean; LP=Long-presentation trials, stimulus class (CGS, IAPS)*emotion (CGS-WoW/IAPS-P, CGS-N/IAPS-N)>mean; MCC=Multiple Comparison Correction.

1 F test; 2 Internet gaming addiction with nicotine dependence; 3 Small volume corrected (SVC) analyses, but they meet the statistical threshold used in the rest of the brain, more detail show in supplementary data; 4 Conference abstract; *the contrast based on ROI, was not included in the mean meta-analysis;

Table 2 Activity differences from all studies

Brain regions	Maximum MNI coordinates x, y, z	SDM-Z	p	Cluster Voxels Number	Breakdown
IGD>HC					
Bilateral precuneus; Bilateral median cingulate	-2,-56,42	2.516	~0	3742	
				441	Left precuneus
				374	Left median cingulate / paracingulate gyri
				357	Right precuneus
				347	Right median cingulate / paracingulate gyri, BA 23
	0,-28,34	2.258	0.000002086	331	Left median cingulate / paracingulate gyri, BA 23
				311	Left precuneus, BA 7

				284	Right median cingulate / paracingulate gyri
				240	Left median network, cingulum
				193	Corpus callosum
				134	Right precuneus, BA 7
				133	Right median network, cingulum
				111	Left posterior cingulate gyrus, BA 23
	-4,10,26	1.597	0.000603795	55	Left anterior cingulate / paracingulate gyri
Left precentral gyrus, BA 44	-46,8,36	2.079	0.000020623	645	
				253	Left precentral gyrus, BA 6
				160	Left precentral gyrus, BA 44
				92	Left inferior frontal gyrus, opercular part, BA 44
Right inferior frontal gyrus, BA 48	54,16,20	1.855	0.000119746	753	
				272	Right inferior frontal gyrus, opercular part, BA 44
	48,16,28	1.790	0.000171363	103	Right inferior frontal gyrus, opercular part, BA 48
				98	Right inferior frontal gyrus, triangular part, BA 48
Left frontal orbito-polar tract	-30,24,-16	1.323	0.003239930	20	
IGD<HC					
Left inferior network, BA45，BA 47	-40,38,2	-1.541	0.000007212	983	
	-48,32,6	-1.358	0.000027895	507	Left inferior frontal gyrus, triangular part, BA 45
	-32,40,-6	-0.961	0.000928938	90	Left inferior network, inferior fronto-occipital fasciculus
				68	Left anterior thalamic projections
				62	Left inferior frontal gyrus, triangular part, BA 47

The surviving clusters which p < 0.05 or voxels number > 50 were reported in this table

Table 3 Activity differences from cue reactivity task

Brain regions	Maximum MNI coordinates x, y, z	SDM-Z	*p*	Cluster Voxels Number	Breakdown
IGD>HC					
Bilateral precuneus BA7; Bilateral median cingulate	-4, -68, 46	3.622	~0	3637	
	-2, -48, 36	3.277	~0	493	Left precuneus
	4, -56, 32	2.933	0.000022709	422	Right precuneus
	-4, -68, 42	3.606	~0	411	Left precuneus, BA 7
	2, -16, 32	2.141	0.001684487	284	Right median cingulate / paracingulate gyri, BA 23
	4, -68, 36	2.950	0.000019610	246	Right precuneus, BA 7
	-2, -46, 48	3.194	0.000001013	240	Left median cingulate / paracingulate gyri
	0, -10, 40	2.127	0.001826942	221	Left median cingulate / paracingulate gyri, BA 23
				139	Corpus callosum
	8, -62, 24	2.236	0.001087904	123	Right median cingulate / paracingulate gyri
				120	Left median network, cingulum
				98	Left posterior cingulate gyrus, BA 23
				97	Left anterior cingulate / paracingulate gyri, BA 24
				92	Right median network, cingulum
	0, 20, 28	2.335	0.000656426	73	Left anterior cingulate / paracingulate gyri
				62	Left precuneus, BA 5
				57	Right precuneus, BA 23
				55	Left superior parietal gyrus, BA 7
				53	Right precuneus, BA 5

Left precentral gyus, BA 6	-52, 0, 32	2.821	0.000044405	1112	
				394	Left precentral gyrus, BA 6
				165	Left precentral gyrus, BA 44
				143	Left inferior frontal gyrus, opercular part, BA 44
				103	Corpus callosum
				70	Left middle frontal gyrus, BA 44
				62	Left inferior frontal gyrus, triangular part, BA 48
Right frontal	46, 16, 16	2.091	0.002192318	166	
aslant tract	52, 26, 22	2.076	0.002392530	89	Right inferior frontal gyrus, triangular part, BA 45
	50, 24, 18	2.067	0.002497852		Right inferior frontal gyrus, triangular part, BA 45
	48, 26, 22	2.046	0.002762079		Right inferior frontal gyrus, triangular part, BA 48
	46, 16, 16	2.091	0.002192318	31	Right frontal aslant tract
IGD<HC					
Right superior	44, -14, 22	-1.760	0.000008285	1417	
longitudinal	-50, 30, 6	-1.566		390	Right rolandic operculum, BA 48
fasciculus III；	34, -22, 8	-1.698	0.000016510	316	Right insula, BA 48
insula, BA 48	-32, 40, -6	-0.961		137	Right heschl gyrus, BA 48
				110	Right superior temporal gyrus, BA 48
	42, -20, 6	-1.606	0.000033021	100	Corpus callosum
	40, -22, 24	-1.699	0.000016510	93	Right superior longitudinal fasciculus III
				88	Right fronto-insular tract 5
Right	26, -26, 60	-1.034	0.002323389	94	
postcentral	26, -26, 60	-1.034	0.002323389	29	Right postcentral gyrus, BA 6
gyrus, BA 6	28, -24, 54	-1.029	0.002377093	20	Right hand superior U tract
	28, -32, 54	-0.918	0.004225671	6	Right superior longitudinal fasciculus II

Table 4 Activity differences from Executive function tasks

Brain regions	Maximum			Cluster	
	MNI coordinates x, y, z	SDM-Z	*p*	Voxels Number	Breakdown
IGD>HC					
Right superior temporal gyrus	46, -4, -10	1.716	0.000055730	1241	
				275	Right insula, BA 48
				109	Right middle temporal gyrus, BA 21
				103	Right superior temporal gyrus, BA 48
				100	Corpus callosum
				84	Right superior temporal gyrus, BA 22
				83	Right inferior network, inferior longitudinal fasciculus
				61	Right temporal pole, superior temporal gyrus, BA 38
				59	Right superior temporal gyrus, BA 21
Bilateral precuneus, Bilateral cingulate	-4, 0, 28	1.428	0.000519156	1176	
				207	Right median cingulate / paracingulate gyri, BA 23
	0, -8, 34	1.393	0.000663698	181	Left median cingulate / paracingulate gyri, BA 23
	-2, -56, 36	1.295	0.001279891	172	Left precuneus
				92	Corpus callosum
				88	Left median network, cingulum
	-2, -34, 30	1.203	0.002219141	62	Left posterior cingulate gyrus, BA 23
				56	Left median cingulate /

				52	paracingulate gyri Right precuneus
Right caudate nucleus, BA 25	8, 18, 8	1.299	0.001245797	108	
Left superior longitudinal fasciculus II	-40, -62, 34	1.216	0.002051950	28	
IGD<HC					
Left inferior frontal gyrus, triangular part, BA 48	-56, 20, 14	-1.587	0.000005186	975	
				423	Left inferior frontal gyrus, triangular part, BA 45
				164	Left inferior frontal gyrus, triangular part, BA 48
				114	Left inferior frontal gyrus, opercular part, BA 48
				79	Left inferior frontal gyrus, opercular part, BA 44
	-36, 26, 20	-0.696	0.003133655	63	Corpus callosum

Table 5 Activity differences from Risky decision-making tasks

Brain regions	Maximum MNI coordinates x, y, z	SDM-Z	*p*	Voxels Number	Cluster Breakdown
IGD>HC					
Left striatum	-16, 20, -10	1.666	0.000011325	1046	
				263	Left striatum
				108	Left inferior frontal gyrus, orbital part, BA 11
				99	Corpus callosum
				77	Left inferior network, uncinate fasciculus
				65	Left frontal orbito-polar tract
				60	Left olfactory cortex, BA 25
				55	Left caudate nucleus, BA 25
				50	Left insula, BA 48
Right inferior frontal gyrus, orbital part, BA 11	24, 22, -18	1.131	0.000322044	417	
				80	Right inferior frontal gyrus, orbital part, BA 11
				60	Right frontal orbito-polar tract
Right inferior network, inferior longitudinal fasciculus	36, -60, -10	1.173	0.000242531	288	
				152	Right inferior network, inferior longitudinal fasciculus
				113	Right fusiform gyrus, BA 37
IGD<HC					
Left superior frontal gyrus, medial, BA 32	-2, 54, 14	-1.403	0.000060916	1025	
				250	Left superior frontal gyrus, medial, BA 10
				214	Right superior frontal gyrus, medial, BA 10
				105	Right anterior cingulate / paracingulate gyri, BA 32
				101	Left superior frontal gyrus, medial, BA 32
				76	Left anterior cingulate / paracingulate gyri, BA 32
				60	Left superior frontal gyrus, medial
				51	Left anterior cingulate / paracingulate gyri, BA 10
Left inferior frontal gyrus, triangular part, BA 45	-50, 30, 8	-1.501	0.000021696	959	
				610	Left inferior frontal gyrus, triangular part, BA 45
				80	Left inferior frontal gyrus, triangular part, BA 47
Right precentral gyrus, BA	40, -12, 46	-1.308	0.000122845	762	

6				348	Right precentral gyrus, BA 6
				165	Right precentral gyrus, BA 4
				78	Right superior longitudinal fasciculus II
				68	Right postcentral gyrus, BA 4
Left median network, cingulum	-16, -46, 30	-1.070	0.000826776	67	

Highlights

- IGD is associated with alterations in default mode, frontoparietal control and attention networks
- The insula is the brain region that consistently showed abnormalities across different paradigms in IGD
- No brain regions involved in the reward network were found abnormal activated during this process of cue-reactivity task for IGD