NEURAL MECHANISMS UNDERLYING INTERNET GAMING DISORDER

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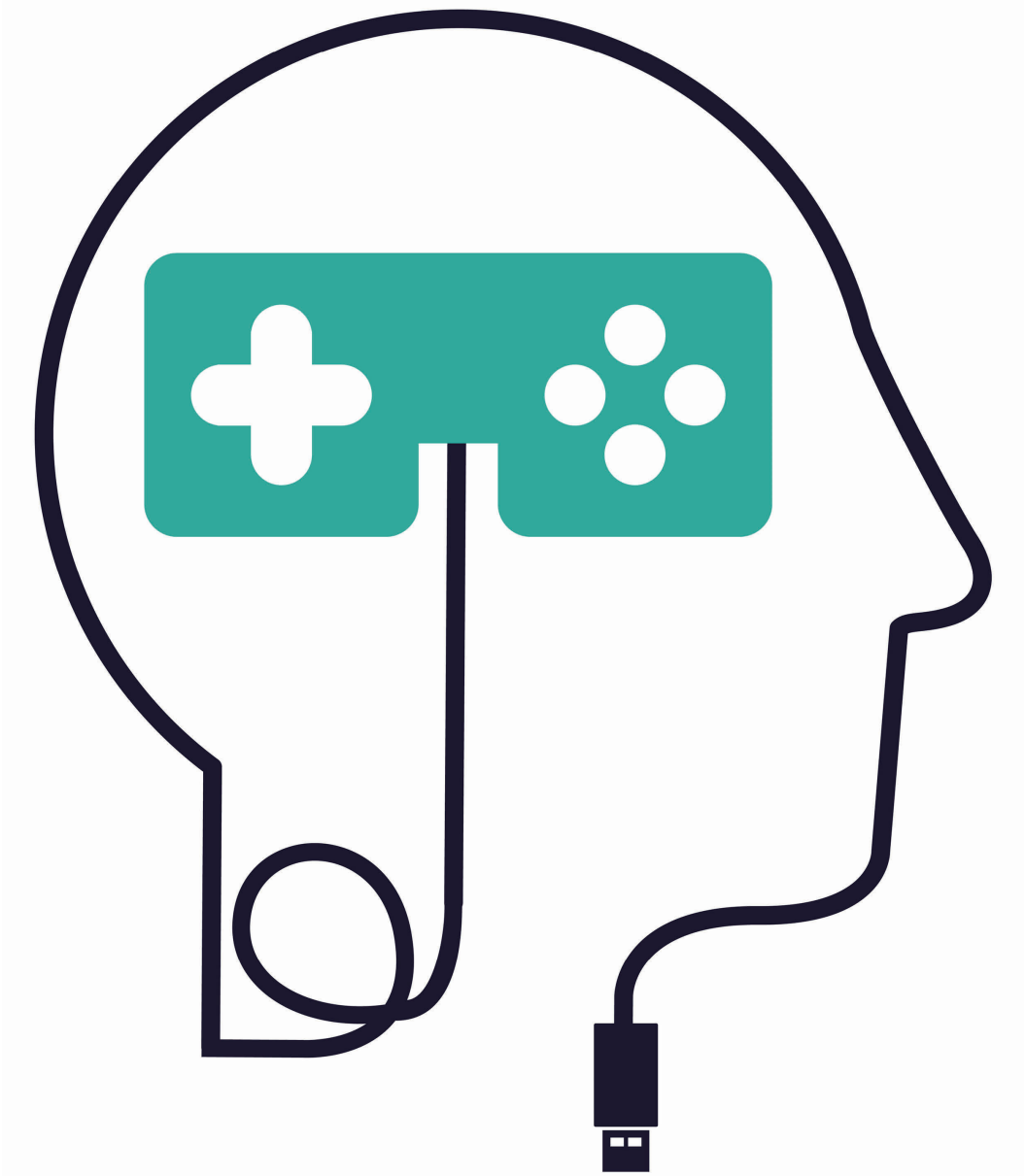

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NEURAL MECHANISMS UNDERLYING INTERNET GAMING DISORDER

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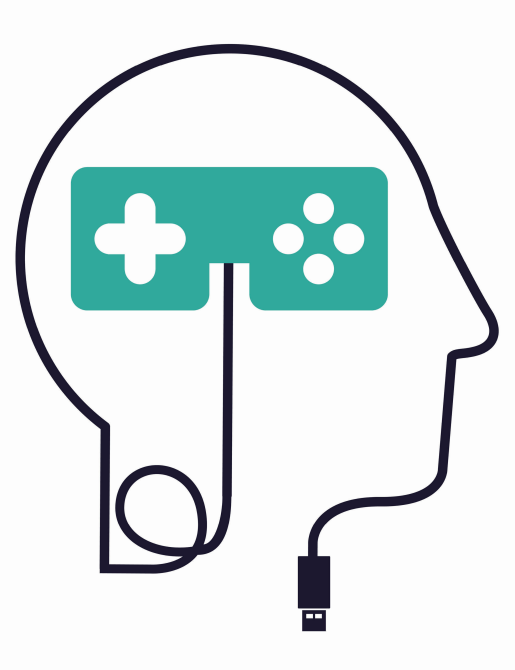

Neural mechanisms of gaming disorder.
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EDITORIAL
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Editorial: Neural Mechanisms Underlying Internet Gaming Disorder

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Editorial on the Research Topic

Neural Mechanisms Underlying Internet Gaming Disorder

Internet Gaming Disorder (IGD), a worldwide mental health issue, has been extensively studied over the last two decades and many studies show that IGD shares characteristics with substance use disorders (SUD) and pathologic gambling in etiology, phenomenology, neurobiological mechanisms, and treatment efficacy. Using Magnetic Resonance Imaging (MRI) techniques along with electroencephalographic and event-related potentials (ERPs) methods, a growing number of studies have emerged exploring neural biomarkers of IGD. Based on neuroscientific empirical studies and considering theories of addictive behaviors, several theoretical models of the development and maintenance of IGD have been proposed. Recently, IGD has been included in the third section of the latest (fifth) edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-5) as a condition that requires additional research. Meanwhile, the World Health Organization (WHO) has included gaming disorder (both predominantly online and predominantly offline) in the ICD 11th revision. This progress dramatically raises academic discussions and public concerns for the importance of studying IGD. The precise neural mechanisms underlying the development, maintenance, and remission of IGD still require further investigations in order to better understand the phenomenon of IGD and to improve treatment outcome.

In this Research Topic, we begin with a review paper by Kimberly Young, a pioneer in the field of Internet addiction research, and Matthias Brand. Young and Brand summarize general aspects of IGD including diagnostic criteria and classification, and they also emphasize the Interaction of Person-Affect-Cognition-Execution (I-PACE) model, a comprehensive model which is based on empirical studies and which aims at inspiring future theory-driven research and new treatment protocols for IGD. Under the framework of Research Domain Criteria (RDoC), advocated by the National Institute of Mental Health, Kuss et al. review brain imaging studies of IGD. They report that gaming addicts have poorer response-inhibition, working memory, decision-making and emotion regulation, which is associated with reduced prefrontal cortex functioning, and conclude that deficiencies in the neural reward system is one key element of IGD, similar to the results found in individuals with substance-related disorders. Based on the recent functional Magnetic Resonance Imaging (fMRI) studies, Weinstein also finds that individuals with IGD show alterations in executive function, decision-making, behavioral inhibition and emotion regulation, which are similar to those reported for SUD. Weinstein also stresses that future studies need to investigate white matter density and functional connectivity in IGD to validate recent findings and to disentangle potential similarities and differences in neuro-chemical and neuro-cognitive brain circuits in IGD and co-morbid conditions such as ADHD and depression. Wei et al. conclude that the interaction of three systems, the impulsive system, the reflective system, and

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the interoceptive-awareness system plays a major role in IGD and argue that the development and maintenance of IGD is associated with a hyperactive "impulsive" system, a hypoactive "reflective" system, and is exacerbated by the interoceptive-awareness system.

Reward processing plays a critical role in adaptive behavior and has been consistently found impaired in SUD. Kim et al. report that individuals with an overuse of Internet games are more likely to fail to choose the response previously reinforced by symbolic (but not monetary) reward, which is accompanied by reduced neural responses to reward in the inferior parietal region and medial orbitofrontal/ventromedial prefrontal cortex. Wang et al. try to control potential effects of cue-familiarity and find that compared to recreational Internet game users, individuals with IGD show enhanced brain activity in the left orbitofrontal cortex and decreased activity in the right anterior cingulate cortex during processing of gaming-related cues. This seems to be linked to the high desire for game playing and the impaired ability in inhibiting the craving for gaming in subjects with IGD. Using ERPs techniques, Peng et al. present data showing that in individuals with IGD amplitudes in ERP component N170 (an index of early face processing) is decreased in response to neutral face expressions compared to happy face expressions, but no group difference during the processing of sad expressions and neutral expressions. They conclude that individuals with IGD may expect more positive emotions in the happy–neutral expressions context. Wang et al. explore impaired decision making using an intertemporal decision-making task among IGD. Compared to control subjects, the IGD group tends to pursuit immediate satisfaction, which is accompanied by reduced brain activations in the dorsolateral prefrontal cortex and bilateral inferior frontal gyrus. These findings indicate a deficiency in the ability of evaluating delayed reward and immediate satisfaction, and an impaired ability in impulse inhibition.

Three studies explore the neural evidence to show negative effects of longtime exposure to violent video game. Pan et al. use the amplitude of low-frequency fluctuations (ALFF) and fractional ALFF (fALFF) to quantify the group difference of spontaneous brain activity between a violent video game group and the control group but didn't find any group difference. Gao et al. further explore whether the exposure to violent video games (VVG) could change players' empathic responses to painful situations, and the results show that the perception of others' pain aren't significantly different in brain regions between violent video game group and non-violent video game group. The study by Szycik et al. did not find group differences in brain responses to emotional cues between excessive users of violent games and control subjects. Given that there are many theoretical and empirical evidence for the negative effect of longtime exposure to violent video game on children and adolescents' development, these results still warrant further investigations and this study inspires future research.

One study in this Research Topic also examines the association between alteration in brain structure and tendency to IGD. Using the index of gray matter volume (GMV), Pan et al. report that GMVs of the bilateral post-central gyri, the left precentral gyri, the left posterior midcingulate cortex, and the right middle frontal gyrus are negatively related to the tendency of IGD symptoms even after controlling for age, years of education and the time spending on online games. These results implicate that the GMVs of brain regions involved in sensorimotor processes and cognitive control are associated to IGD symptoms. Finally, the study by Müller et al. explores the associations between prenatal testosterone and both unspecified Internet addiction disorder and IGD. Digit ratio (2D:4D, digit ratio of the index to the ring finger) marker of the hand was used as a marker of prenatal testosterone. This study reports an association between lower digital ratio (2D:4D, right side, digit ratio of the index to the ring finger, i.e., >1 means lower prenatal testosterone) and higher symptoms of IGD. Moreover, this effect was particularly shown in female participants. These results implied that the 2D:4D marker might be an interesting biomarker for Internet addiction and warrants further studies.

In conclusion, the articles included in this Research Topic focused on several aspects of neurobiological mechanisms underlying IGD. The articles demonstrate that there is already empirical evidence for considering IGD a disorder due to addictive behaviors. However, more systematic and theory-driven studies including different subgroups and in particular longitudinal studies on the brain-behavior association in individuals with symptoms of IGD and other types of Internet-use disorders, are needed to better understand mechanisms of the development and maintenance of this addictive behavior and to optimize intervention techniques.

AUTHOR CONTRIBUTIONS

J-TZ wrote the first draft of the manuscript. J-TZ and MB provided critical revision of the manuscript and important intellectual contributions. Both authors read and approved the submitted version.

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REVIEW
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Merging Theoretical Models and Therapy Approaches in the Context of Internet Gaming Disorder: A Personal Perspective

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Although, it is not yet officially recognized as a clinical entity which is diagnosable, Internet Gaming Disorder (IGD) has been included in section III for further study in the DSM-5 by the American Psychiatric Association (APA, 2013). This is important because there is increasing evidence that people of all ages, in particular teens and young adults, are facing very real and sometimes very severe consequences in daily life resulting from an addictive use of online games. This article summarizes general aspects of IGD including diagnostic criteria and arguments for the classification as an addictive disorder including evidence from neurobiological studies. Based on previous theoretical considerations and empirical findings, this paper examines the use of one recently proposed model, the Interaction of Person-Affect-Cognition-Execution (I-PACE) model, for inspiring future research and for developing new treatment protocols for IGD. The I-PACE model is a theoretical framework that explains symptoms of Internet addiction by looking at interactions between predisposing factors, moderators, and mediators in combination with reduced executive functioning and diminished decision making. Finally, the paper discusses how current treatment protocols focusing on Cognitive-Behavioral Therapy for Internet addiction (CBT-IA) fit with the processes hypothesized in the I-PACE model.

Keywords: internet gaming disorder, internet addiction, I-PACE model, IGD treatment

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INTRODUCTION

Internet addiction was first identified in 1995 based on 600 case studies involving people who suffered from educational, academic, financial, or relationship problems or even job loss because they experienced a loss of control over their Internet use (Young, 1996, 1998a,b). Over the past two decades, Internet addiction research grew very quickly into a rapidly evolving field of study. Other pioneers in the field include psychologists such as Drs. David Greenfield and Marissa Hecht Orzack (Greenfield, 1999; Orzack, 1999) and Dr. Mark Griffiths (e.g., Griffiths and Hunt, 1998; Griffiths, 1999). Empirical studies started to appear with a focus on prevalence rates and psychopathological comorbidities with self-selected samples, multiple case studies, and explorations of several specific psychosocial correlates of Internet addiction, such as personality and social aspects (e.g., Armstrong et al., 2000; Morahan-Martin and Schumacher, 2000; Shapira et al., 2000; Chou, 2001; Kubey et al., 2001; Caplan, 2002). While a debated disorder, these early years of scientific research (1995–2005) created new theoretical and global models on the topic (e.g., Griffiths, 1995, 2005; Davis, 2001),

which aimed at summarizing the main symptoms and potential processes underlying an excessive online activity.

In Asian cultures, the problems with dealing with Internet use are seemingly more significant compared to any other culture (potential reasons are discussed for example in Montag et al., 2016). However, in 2006, the U.S. found through a first national study that more than 10% of Americans meet at least one criterion of problematic Internet use (Aboujaoude et al., 2006). One reason for this could be that in the last 15 years, new Internet applications evolved, for example Facebook, Twitter, and WhatsApp, which make technology a significant part of most people's everyday life (Montag et al., 2015) and blur the differentiation between addictive and functional Internet use.

As early as 2008, professionals discussed the inclusion of Internet addiction in the newest version Diagnostic and Statistical Manual (DSM; Block, 2008). With an increased attention, discussion, and research, the American Psychiatric Association (APA) has recently included Internet Gaming Disorder (IGD) in section III for further study in the DSM-5 (APA, 2013). This has major effects for the research field because by listing IGD in the DSM-5 for further study, the APA hoped to encourage studies on IGD to determine whether this condition is clinically relevant and should therefore be included as a diagnosable disorder in upcoming versions of the DSM. This development was also significant and important because there is increasing evidence that people of all ages, in particular teenagers and young adults, are facing very real and sometimes very severe consequences in daily life resulting from an addictive use of online games (Young, 2004, 2015). The DSM-5 criteria include persistent use of online games, often with other players, resulting in clinically significant impairment or distress as indicated by five (or more) of the following conditions in a 12-month period:

- Preoccupation with Internet games.
- Withdrawal symptoms when Internet gaming is taken away.
- Tolerance as the need to spend increasing amounts of time engaged in Internet games.
- Unsuccessful attempts to control the participation in Internet games.
- Loss of interest in previous hobbies and entertainment as a result of, and with the exception of, Internet games.
- Continued excessive use of Internet games despite knowledge of psychological problems.
- The person has deceived family members, therapist, or others regarding the amount of Internet gaming.
- Use of Internet games to escape or relieve a negative mood (e.g., feelings of helplessness, guilt, anxiety).
- The person has jeopardized or lost a significant relationship, job, or educational or career opportunity because of participation in Internet games.

The DSM-5 notes that only online games without gambling characteristics are relevant in this proposed disorder because online gambling is included in the DSM-5 criteria for gambling disorder. Using the Internet for required activities in an educational, academic, or business context is also not included in the DSM-5 criteria for IGD. In addition, IGD does not include other recreational or social Internet use. Similarly, excessive use of Internet applications with sexual content is excluded. With moving gambling disorder to the category of substance-related and addictive disorders, the DSM-5 emphasizes parallels between substance-use disorders and behavioral addictions. With respect to Internet addiction, however, it is still discussed controversially whether the addiction concept is appropriate for describing the phenomenon. Several authors argue that a more neutral term, which does not directly imply that the behavior is addictive, would be better when referring to an uncontrolled and excessive online behavior (Kardefelt-Winther, 2014, 2017). On the other hand, there are many studies, particularly from a neuroscientific perspective, which find parallels among substance-use disorders and IGD (and also other types of Internet-use disorders) and thus justify the classification as an addiction (Weinstein et al., 2017). On a behavioral level using questionnaires, some studies, however, show that different types of behavioral addictions (i.e., gambling disorder and different types of Internet addiction) have larger overlap among them compared with the overlap among behavioral addictions and substance-use disorders (Sigerson et al., 2017), speaking for a distinct category of behavioral addictions. One has to notice, that there are also significant differences across different types of substance-use disorders (Shmulewitz et al., 2015), and they are nevertheless classified together within one category in the DSM-5. We do not go into a deep discussion of this topic here, but from our perspective, it makes sense to use the addiction concept as one framework for studying IGD and other Interne-use disorders. Naturally, it is important to additionally test alternative frameworks, for example concepts of impulse control disorders or obsessive-compulsive disorders, to better understand the real nature of IGD. Applying different theoretical frameworks to studying IGD is important since some authors argue that one problem of this research field is the lack of a theoretical background in many studies (Billieux et al., 2015; Kardefelt-Winther et al., 2017). We agree with the statement that it is important to conduct theory-driven empirical studies to contribute to a better understanding of the psychological mechanisms underlying the excessive online behavior, and we think that the addiction concept is one important framework, which can inspire theory-driven studies. The addiction concept is also helpful for creating specific treatment protocols based on the experiences within the field of substance-use disorders. We also argue that specific theoretical models of Internet-use disorders already exist (see section below), but they have to be used more intensively in empirical studies to test specific theoretical hypotheses and to increase the validity of these models. As a final note on terminology we would like to comment on the very important difference between "addicted to the Internet" and "addicted on the Internet," which has been pointed out by Starcevic (Starcevic, 2013; Starcevic and Billieux, 2017). We agree with the perspective that the Internet is only a medium that delivers many possibilities for specific online behaviors and that it is crucial to understand the specific mechanisms underlying the different types of behaviors on the Internet. However, given that the term Internet addiction is widely used by many authors in the field, we still use this term when referring to a more general excessive online behavior. Consistent with the DSM-5 terminology, we

also use the term Internet-use disorder, which should then be specified with respect to the specific online behavior (e.g., use of shopping sites, use of pornography etc.).

THE NEUROBIOLOGY OF INTERNET GAMING DISORDER: A BRIEF SUMMARY

As the scientific investigations on Internet addiction in general and IGD in specific have grown rapidly over the past 20 years, it has become very common to address neurobiological correlates of this clinical phenomenon. The knowledge about neurobiological mechanisms of IGD comprises evidence for a genetic contribution, neurochemical alterations, and both structural and functional brain correlates of IGD (Weinstein et al., 2017).

Potential genetic contributions to Internet addiction and IGD are related to the dopamine (Han et al., 2007), the serotonin (Lee et al., 2008), and the cholinergic system (Montag et al., 2012). Studies have revealed that variance of Internet addiction symptoms might be linked to genetic contributions by up to 48%, although there is also a meaningful variance across studies (Deryakulu and Ursavas, 2014; Li et al., 2014; Vink et al., 2016; Hahn et al., 2017). Results are nevertheless comparable with what is known about the genetic contribution to other psychological disorders including substance-use disorders (Egervari et al., 2017) and gambling disorder (Nautiyal et al., 2017). Genetic contributions to Internet addiction most likely interact with other psychological characteristics, such as personality, as has been shown, for example, for self-directedness (Hahn et al., 2017). Self-directedness is one of the most relevant personality traits in the context of Internet-use disorders (Sariyska et al., 2014; Gervasi et al., 2017).

With respect to brain correlates of IGD, the majority of findings show commonalities across IGD and other behavioral addictions (e.g., gambling disorder) and also substance-use disorders. A very recent comprehensive review on neuroimaging findings in IGD by Weinstein et al. (2017) emphasizes that current studies with neuroimaging techniques resemble the results of those studies on substance-use disorder (e.g., the involvement of ventral striatum as neural correlate of craving and dysfunctions in prefrontal brain areas representing deficits in inhibitory control). We here summarize some examples of neuroimaging findings, only. Gray matter density was, for example, studied by Yuan et al. (2011). They reported reduced gray matter volumes in prefrontal regions including the dorsolateral prefrontal cortex and the orbitofrontal cortex in a sample of adolescents suffering from Internet addiction. These prefrontal reductions were correlated with the addiction duration, indicating that these brain changes could reflect the reductions in inhibitory control. Inhibitory and cognitive control dysfunctions have been reported in subjects with IGD/Internet addiction, which are comparable with those found in substance-use disorders (see review in Brand et al., 2014b). Reductions in prefrontal gray matter were also reported by Weng et al. (2013), which were correlated with symptoms severity as measured by the Internet Addiction Test (Young, 1998a). On the other hand, there is also evidence for higher gray matter volume in excessive gamers, for example in the ventral striatum (Kühn et al., 2011). The higher volume of the ventral striatum may reflect a higher reward sensitivity, which has also been shown in individuals with substance-use disorders (cf. Goldstein and Volkow, 2002; Volkow et al., 2012). However, opposite findings of reduced gray matter volume of the ventral striatum have been reported recently in the context of excessive Facebook usage (Montag et al., 2017a). Given that studies in the field are not directly comparable with respect to sample constitution, study design, and analyses, more systematic research comparing different types of Internet-use disorders are necessary.

The commonalities across substance-use disorders, gambling disorder, and IGD become even more obvious when considering functional brain correlates of the disorders. One important example is the greater activity of the ventral striatum when being confronted with game-related cues (Thalemann et al., 2007; Ko et al., 2009; Ahn et al., 2015; Liu et al., 2016). This finding is also comparable with the one observed in patients with alcohol-use disorder when confronted with alcohol-related cues (e.g., Braus et al., 2001; Grüsser et al., 2004). Another example is the prefrontal cortex activity when subjects with IGD perform tasks tapping into executive functions. Prefrontal activity has been shown—dependent upon the task and prefrontal areas included in the analyses—to be both increased and decreased compared to healthy subjects (e.g., Dong et al., 2012, 2013, 2015; Brand et al., 2014b).

In summary, there is some evidence for an involvement of prefrontal and limbic brain regions in the phenomenon of IGD in particular and Internet addiction in general (cf. Kuss and Griffiths, 2012; Meng et al., 2015; Sepede et al., 2016), and—as has been shown very recently—in the addictive use of Social Networking Sites (He et al., 2017). These brain abnormalities correspond with neuropsychological functioning in IGD, especially with reduced performance in executive and cognitive control tasks (cf. Brand et al., 2014b, 2016), which are also comparable with those reported in substance-use disorders, for example in patients with alcohol-use disorder (Zhou et al., 2014). The neuropsychological findings fit with dual-process theories of addiction (cf. Bechara, 2005; Everitt and Robbins, 2016), which have recently been specified for IGD (Schiebener and Brand, 2017) and also for an addictive use of Social Networking Sites (Turel and Qahri-Saremi, 2016). The majority of neurobiological findings support the view of considering IGD as an addictive disorder, which promotes the classification in the DSM-5 category of substance-related and addictive disorders (Weinstein et al., 2017).

The challenge for the next years of neuroscientific research in the field of IGD is to show whether these brain changes are correlated with therapy success, in terms of reversibility, but also in terms of whether these brain abnormalities may predict therapy success.

THEORETICAL MODELS

Since the early case-reports 20 years ago, many studies have investigated the clinical phenomenon of Internet-use disorders, with a particular focus on IGD. As mentioned above, some authors claim that most of the clinical research on IGD and

other behavioral addictions lacks a clear theoretical framework (Billieux et al., 2015; Kardefelt-Winther et al., 2017). As also outlined above, we agree with the impression that many studies that looked at psychiatric co-morbidities or personality correlates of IGD did not consider a clear theoretical background. However, we also argue that theories and theoretical models of Internet addiction already exist, which can be useful for inspiring clear hypotheses on mechanisms underlying the clinical phenomenon of IGD. The early models focused on components of Internet addictions, for example the component model by Griffiths (2005), which has been very influential, for example by inspiring the theory-driven development of assessment tools (Kuss et al., 2013). However, the components model rather summarizes the symptoms and not the psychological processes involved in Internet-use disorders. A couple of years later, two recent models of IGD or Internet addiction in general have been suggested. The model by Dong and Potenza (2014) focuses on cognitive-behavioral mechanisms of IGD and also includes some suggestions for treatment. They argue that searching for immediate reward despite long-term negative consequences plays a central role in IGD. This decision-making style is considered to interact with motivation-seeking (craving), which means both the drive to experience pleasure and the drive to reduce negative affective states. Motivation-seeking is considered to be controlled by monitoring and other executive functions and there are studies showing that inhibitory control is reduced in individuals with IGD (Argyriou et al., 2017). In their model, Dong and Potenza (2014) also included potential options for treatments. Cognitive enhancement therapy and classical cognitive-behavioral therapy are considered useful for changing the dysfunctional decision-making style and for empowering inhibitory control over motivation-seeking. Mindfulness-based stress reduction is considered to contribute to a reduction of motivation-seeking by reducing the motivation to relief from stress and negative affective states. Cognitive bias modification can influence reward sensation, which also contributes to motivation-seeking. In summary, the model by Dong and Potenza (2014) includes the interaction of cognitive (executive) components, decision-making style, and motivational components in explaining IGD, which all can principally be addressed by a combination of different treatment interventions.

Another model of IGD and Internet addiction in general has been introduced by Brand et al. (2014b). This model basically consists of three different parts (or even three different models): The first describes a functional/healthy use of the Internet, the second model aims at describing the development and maintenance of an unspecific/generalized Internet-use disorder and the third part describes potential mechanisms involved in a specific type of Interne-use disorder, for example IGD. The model of a functional use of the Internet highlights that many applications can be used for entertainment, for escaping from reality and for coping with aversive situations in daily life. However, it is argued that the functional/healthy use is characterized by the fact that the Internet is used to satisfy certain needs and goals and is stopped as soon as these goals are achieved. The second part, the model of unspecific/generalized Internet-use disorder, also considers coping mechanisms as important. However, it is assumed that a psychopathological vulnerability (e.g., depression, social anxiety) in interaction with a dysfunctional coping style and certain Internet-use expectancies explains the shift from a functional/healthy use toward an uncontrolled overuse of the Internet, without having a clear first-choice application. This perspective fits with assumptions by other researchers on a problematic use of the Internet or other media with a special focus on the role of using media for coping purposes and for escaping from reality (Kardefelt-Winther, 2014, 2017). The interaction of predisposing factors (depression, social anxiety) with the mediators dysfunctional coping and use expectancies in explaining symptoms of unspecified/generalized Internet-use disorder has been investigated using a large non-clinical sample and structural equation modeling (Brand et al., 2014a). The third part in the work by Brand et al. (2014b) aims at explaining a specific Internet-use disorder, for example IGD. In addition to the aforementioned vulnerability factors as well as dysfunctional coping and expectancies, the model suggests that specific motives for using specific applications contribute to a specific Internet-use disorder. We have additionally argued that within the addiction process, reductions of inhibitory control contribute to dysfunctional decision making with a preference for the short-term rewarding options, which results in an overuse of a specific application (see citations for studies on decision making and executive functions mentioned above).

Two years later, a revised model of specific Internet-use disorders has been suggested. Based on both new theoretical considerations and recent empirical results, the Interaction of Person-Affect-Cognition-Execution (I-PACE) model of specific Internet-use disorders was introduced (Brand et al., 2016). The I-PACE model is a theoretical framework for the hypothesized processes, which underlie the development and maintenance of an addictive use of certain Internet applications, such as gaming, gambling, pornography use, shopping, and communication. The I-PACE model is composed as a process model, including predisposing variables as well as moderator and mediator variables. Understanding the role of (changeable) moderating and mediating variables better could directly inspire therapy (see next section on treatment implications). Specific Internet-use disorders are considered to develop as a consequence of interactions between neurobiological and psychological constitutions (the predisposing variables) and moderating variables, such as coping style and Internet-related cognitive and attentional biases, as well as mediating variables, such as affective and cognitive reactions to situational triggers in combination with reduced inhibitory control. As a result of conditioning processes, these associations become stronger within the addiction process. The main interactions of a person's core characteristics (e.g., personality, psychopathology) with affective aspects (e.g., craving, motivation to experience pleasure, or to reduce negative mood), cognitive aspects (e.g., coping style, implicit positive associations), executive functions, and decision making in the course of the development and maintenance of a specific Internet-use disorder, as summarized in the I-PACE model, are illustrated in **Figure 1**.

The I-PACE model aims at summarizing those processes which are relevant to all types of specific Internet-use disorders.

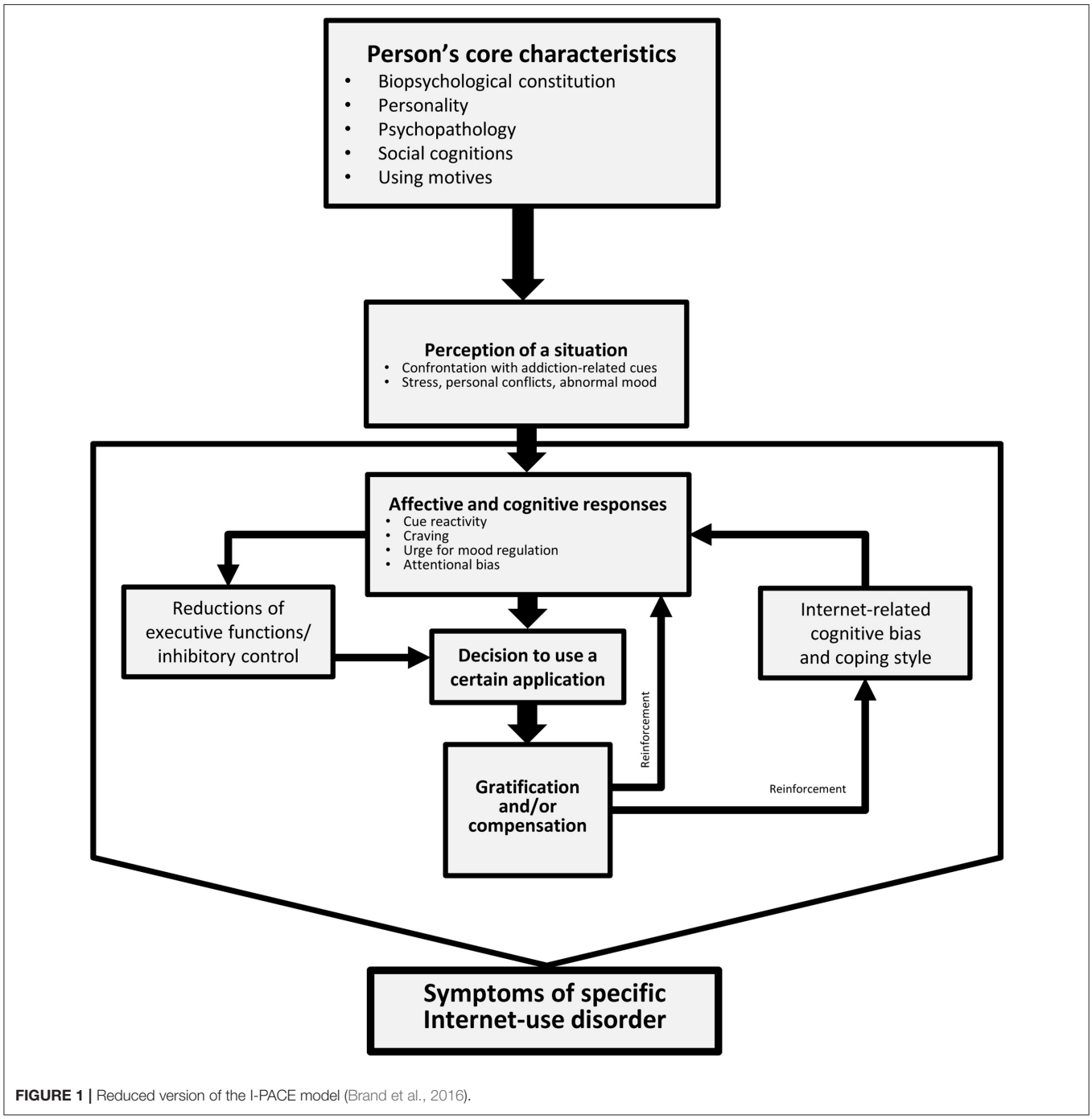

FIGURE 1 | Reduced version of the I-PACE model (Brand et al., 2016).

As a consequence, no gaming-specific elements have been included. Although, this is not the focus of this article, we argue that games deliver many rewards, which contributes to developing IGD on the basis of reward-conditioned cue-reactivity and craving. Many games are designed to be complex enough to be challenging and to allow players to achieve accomplishments, which keeps them playing. Both personal aspects, such as achieving goals, and social interactions, such as communicating with other players, are fundamental ingredients of many games and contribute to an "optimal experience" or feeling of flow while playing (Choi and Kim, 2004). The possibility of achieving a high score is one of the most easily recognizable hook, as players continuously try to beat the high score and this can be done endlessly in most games. In online role-playing games, players try to achieve a higher status ("level-up"), more power, and recognition by other players. Achievement, or in more detail mechanics as a sub-dimension of achievement, together with escapism were indeed clear

predictors of gaming-related problems in the comprehensive study by Kuss et al. (2012). Another hook of online games is that many players create an emotional attachment to their game characters (Young, 2015). Beyond this, an important part of many games is starting or maintaining social relationships (Cole and Griffiths, 2007). Players often make friends with other players and it is these friends who may even request players to continue playing or increase the amount of time spent playing. In fact, even in ego-shooter games, most players report playing in teams. For example, in the study on personality of ego-shooter gamers by Montag et al. (2011), 90% of the 610 participants reported playing regularly as a team player. The relevance of social interactions for many gamers has also been investigated in a longitudinal study by Billieux et al. (2013). They found that discovery in combination with cooperation are the most important predictors of fast progression in online games. These results are consistent with the three-factor model (including 10 sub-factors) proposed by Yee (2006). This model suggests that achievement, social aspects, and immersion are the main components of players' motivation. This model has been examined in many studies and the main assumptions have been validated in most cases. Based on social-cognitive theory, a recent study (De Grove et al., 2016) developed a scale measuring the motivations for playing online games (or in a broader sense digital games). They also found a combination of factors including performance, social aspects, and what they call narrative (which is comparable to the discovery domain) as well as other factors (e.g., escapism, habit) being the main motivations for playing online games (see also Demetrovics et al., 2011). In summary, the most relevant motivations for playing games are achievement (or performance), social interactions, and escapism/discovery. Although, these specific motives have not been included explicitly in the I-PACE model, they represent motives for using a certain application, which is represented by "using motives" in the model and which perhaps can explain why some individuals develop IGD. Also, motives may explain why other individuals develop symptoms of Internet-pornography-use disorder, possibly because they may have a higher sexual excitability or higher trait sexual motivation (Laier et al., 2013; Laier and Brand, 2014; Stark et al., 2015). These using motives are considered person's core characteristics and are therefore important predictors of the development and maintenance of IGD or other Internet-use disorders. However, we also argue that these motives do not influence directly the development of IGD. Although, it is more likely that IGD develops in individuals who have very high gaming-related motives, the gratifications or negative reinforcements which are experienced while playing and which are consistent with the using motives accelerate the development of gaming-related implicit cognitions (e.g., attentional bias, implicit positive associations with games) and also of gaming-specific explicit use expectancies. These cognitive aspects make it more likely to develop cue-reactivity and craving in situations in which an individual is confronted with gaming-related stimuli, or in situations of negative mood or stress in daily life. These interactions of motives, the delivery of gratification feelings when playing, and changes of implicit and explicit cognitive as well as affective reactions in gaming-relevant situations are considered main processes underlying the development and maintenance of IGD (see **Figure 1**).

Although, the I-PACE model is hypothetical and the assumptions regarding the mechanisms which potentially underlie the development and maintenance of specific Internet-use disorders must be investigated in detail, implications for treatment can be prescribed. In the next section, we summarize some recent treatment approaches and relate them to the theoretical assumptions summarized in the I-PACE model. However, the I-PACE model only aims at explaining development and maintenance of symptoms of IGD and other Internet-use disorders. It is important to note that IGD (or generally playing computer and video games, at least if games are played without leaving the home or without physical exercise) is often linked to several further (physiological) implications, such as obesity in children and adolescents, which are related to reductions of sleep quality and overconsumption of sweet drinks (Turel et al., 2017). Such additional problems should not be neglected in therapy of IGD. However, these additional topics are not included in the I-PACE model and are therefore not addressed in the section on treatment implications.

TREATMENT IMPLICATIONS

Although, the nature of IGD and the underlying psychological mechanisms are still debated (see brief discussion in the introduction), the clinical relevance of this phenomenon is obvious. Consequently, it is necessary to provide appropriate treatment interventions to help clients to abstain from gaming or to reduce gaming behavior. In this article, we do not aim to provide a systematic review of clinical interventions of IGD, including both psychotherapy and pharmacological interventions, which can be found elsewhere (Kuss and Lopez-Fernandez, 2016; King et al., 2017; Nakayama et al., 2017).

The majority of studies have examined the use of Cognitive-Behavioral Therapy (CBT) for the treatment of Internet addiction in general or IGD in particular (Dong and Potenza, 2014; King and Delfabbro, 2014), and a first meta-analysis found that CBT outperformed other psychological treatments when referring to the time spent on online behaviors (Winkler et al., 2013).

We here concentrate on one specific type of intervention, CBT for Internet addiction (CBT-IA), and how this treatment approach relates to the I-PACE model. CBT-IA was specifically developed for treating Internet addiction by combining classical CBT elements with specific Internet-related issues (Young, 2011). CBT-IA consists of three phases: (1) Behavior modification, (2) cognitive restructuring, and (3) harm reductions. These three phases are explained in more detail within the next paragraphs. In an outcome study with 128 patients with Internet addiction (Young, 2013), CBT-IA was found to be effective in reducing symptoms, changing maladaptive cognitions, and managing underlying personal and situational factors linked to symptoms of Internet addiction. Most recently, the CBT-IA model can be applied to cases of IGD. In this case, the Internet-related elements of CBT-IA (e.g., maladaptive cognitions about the own Internet use) can be specified with respect to online games (Young, 2013).

Most consistently, treatment should first assess the client's current use of all screens and technology. Although, intake assessments are usually comprehensive and cover most relevant symptoms of psychiatric disorders including addictive behaviors, symptoms of IGD, or other types of Internet-use disorders are often overlooked in a clinical routine interview because of its newness. Some therapists are not familiar with IGD and other types of Internet addiction and may therefore overlook potential signs of this disorder. We argue that it is important that clinicians routinely assess potential symptoms of excessive and uncontrolled use of the Internet in general and IGD in specific.

With the constant availability of all Internet applications it is important to individually develop a clear and structured recovery program with each client regarding the Internet use and the use of other media or screen technology (including video games). Individuals with food addiction or binge-eating behavior evaluate part of their recovery success through objective indicators, such as the amount of caloric intake and weight loss. In analogy to this, treatment of patients with IGD should objectively measure part of the recovery success through reduced online hours, digital dieting, and abstinence from any contact with the problematic online application, which in case of IGD is the specific online game. This is what some authors refer to as digital nutrition, a concept that has been created by Jocelyn Brewer in 2013 (http://www.digitalnutrition.com.au/). Digital nutrition, however, does not mean a full abstinence from all screen technologies or Internet applications, but a healthy and functional, balanced way of using the Internet and media devices.

Digital nutrition is more a kind of preventive strategy for developing a healthy and functional technology use. When individuals suffer from the entire picture of IGD symptoms, therapy should help patients to abstain from gaming and to use the Internet for other purposes only moderately. This is the most difficult step, which is phase 1 of CBT-IA named behavior modification. Therapists need to monitor clients' Internet and technology use and help clients readjust contact with media and screen technology. This also means stimulus and situation control, including guiding clients change situations at home so it will become easier for them not to use the game. This can for example include computer restructuring. Subsequent behaviors become further treatment goals, for example being able to complete daily activities, maintaining a normal routine in everyday life, and spending time outside the Internet with other people (e.g., in sports or clubs) or concentrate on other hobbies. Individuals with IGD need to get re-engaged with activities that they liked prior to the game or find new activities that they can learn to love as part of abstaining from gaming. When merging the I-PACE model and CBT-IA, phase 1 of CBT-IA (behavior modification) mainly addresses the situational aspects and the decision to use a specific application (see **Figure 2**).

Specifically, utilizing the I-PACE model and CBT-IA model, it is important to assess a client's coping styles and Internet-related cognitive biases as well as affective and cognitive responses to the game. This is the main topic of CBT-IA phase 2: Cognitive restructuring. Individuals with IGD suffer from cognitive distortions that keep them addictively engaged in the game. For instance, they may feel lonely, restless, or even depressed but when they are playing an online game, the online character is a great warrior who feels confident and well liked. A client with low self-esteem may perceive himself as undesirable but has the impression that gaming is a way to boost his self-esteem. CBT-IA uses cognitive restructuring to break this pattern of maladaptive cognitions and Internet use expectancies (Young, 2013). "Cognitive restructuring helps put the client's cognitions and feelings "under the microscope" by challenging him or her and, in many cases, re-scripting the negative thinking that lies behind him or her" (Young, 2013, p. 210). CBT-IA can help patients with IGD understand that they are using the online game to avoid negative feelings or to escape from reality and that they are thinking they receive more positive feelings when playing the game compared to any other activity in daily life. This is sometimes hard for the clients, but it is important for therapy success to understand and change these maladaptive thoughts. Again, the focus of both the I-PACE and CBT-IA model is to examine the mechanisms of experiencing gratification by playing the game and also the needs which are not satisfied in real life and which are compensated by playing excessively (Young, 2013; Brand et al., 2016).

Cognitive restructuring with clients is also useful for helping the clients with IGD re-evaluate how rational and valid his or her interpretations of situations and feelings are. For instance, a client who uses online games as a way to feel better about his or her life and to feel strong, powerful, and well recognized will begin to realize that he or she is using the online game to satisfy needs that are unsatisfied in his or her real life. In this context, CBT-IA helps the client to develop more functional and healthy coping strategies to deal with real life stress and negative feelings and to find healthy ways to increase self-esteem and self-efficacy and to build stable interpersonal relationships.

As in many addictions, the most common response in players who do see they have a problem with online gaming is a "guilt-and-purge cycle." True recovery, at least for most gamers, involves looking at the motives and expectancies underlying the game habit. Treatment must also help clients recognize, address, and treat the underlying issues co-occurring with IGD, which is the main aspect of CBT-IA phase 3: Harm reduction. Particularly, underlying depression and social anxiety should be treated.

CBT-IA can be complemented by recently suggested neurocognitive trainings, which have been evaluated positively in the context of substance-use disorders. One example is a retraining of implicit cognitions, which can potentially result in avoidance rather approach tendencies when experiencing craving (Wiers et al., 2011; Eberl et al., 2013a,b). Attentional retraining programs (e.g., Schoenmakers et al., 2010; Christiansen et al., 2015) may be useful to increase clients' inhibitory control (e.g., Houben and Jansen, 2011; Houben et al., 2011; Bowley et al., 2013). This could be done for example by using Go/No-Go Tasks with addiction-related stimuli. However, future studies must demonstrate that these techniques are helpful for increasing inhibitory control in the context of IGD. Cue-exposure therapy (Park et al., 2015) can be useful for reducing the intensity of experienced craving (Pericot-Valverde et al., 2015), which is consistent with current neuroimaging findings in IGD (Zhang et al., 2016).

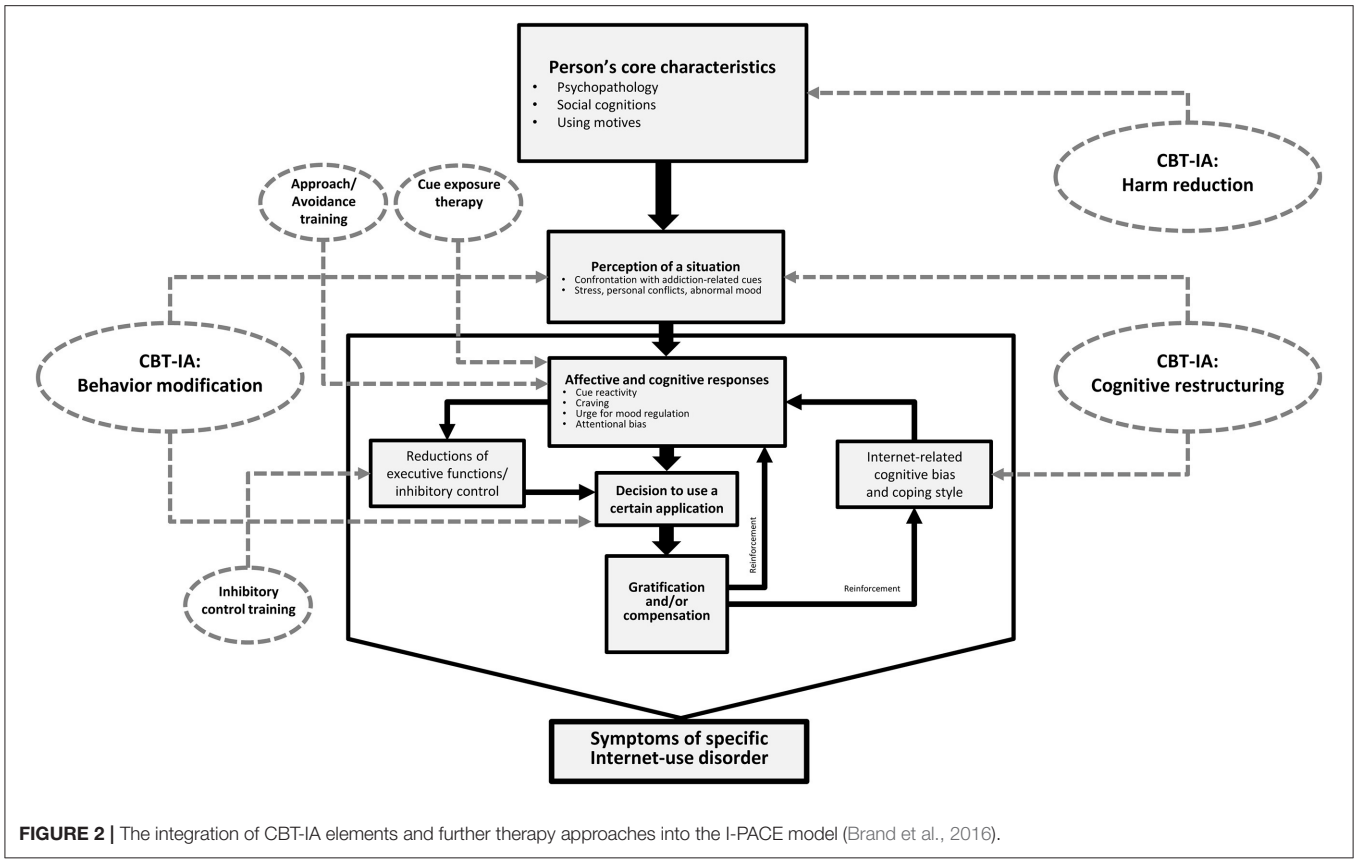

FIGURE 2 | The integration of CBT-IA elements and further therapy approaches into the I-PACE model (Brand et al., 2016).

The synthesis of the I-PACE model's main assumptions about potential processes involved in the development and maintenance of IGD and other Internet-use disorders and some of the most relevant therapy techniques (CBT-IA and additional approaches) is illustrated in **Figure 2**. Although, this figure concentrates on the I-PACE model, it also fits widely with assumptions raised by other authors (Dong and Potenza, 2014). As outlined above, in their model, Dong and Potenza (2014) argued that cognitive behavioral therapy and cognitive enhancement therapy are useful for changing the decision-making style and for increasing inhibitory control over the motivation to use online games. Cognitive bias modification, which is comparable to what is called cognitive restructuring in CBT-IA, is helpful for influencing clients' expectancies to experience reward when playing the game (Zhou et al., 2012). Future studies should also investigate in how far the medium Internet itself is useful for helping clients. Some very recent research focuses on Apps that guide clients through daily life and that help them to reduce stress (e.g., by mindfulness-based stress reduction) or to better deal with negative mood, but such Apps can also track the client's time spent online, which can also be useful for therapy. A recent summary of the contributions of psychoinformatics to the treatment of Internet addiction can be found in Montag et al. (2017b).

Why is it helpful to merge theoretical models of Internet-use disorders (such as the I-PACE) and existing therapy approaches (such as CBT-IA) for both research and clinical practice? We argue that theoretical models have the goal to summarize the main processes underlying both the development and the maintenance of a disorder. These models are useful for specifying research hypotheses on the assumed processes. If we then understand better the core processes involved in the phenomenology of a disorder, we can check whether these processes are addressed by existing therapy approaches, and if not, how current treatment protocols can be complemented by additional specific techniques. On the other hand, studies on the efficacy of treatment approaches can also inspire theoretical models of the disorder. If we see for example that cognitive restructuring is particularly helpful for the clients then obviously cognitive processes (e.g., expectancies) are specifically important in the maintenance of the disorder, and existing models can be checked if they have considered these processes adequately. In summary, the relationship between theoretical models and therapy is bidirectional. This relationship is summarized in **Figure 3**.

When merging the I-PACE and the CBT-IA model, we see that the three main phases of CBT-IA address particularly those variables which are considered moderating and mediating variables in the I-PACE model. We see, however, that most likely CBT-IA can be complemented by additional techniques (smaller ellipses in **Figure 2**). Both the I-PACE and CBT-IA model are also useful for developing new assessment tools for clinical practice. For example, if we see in empirical studies that Internet-use expectancies are critically involved in explaining

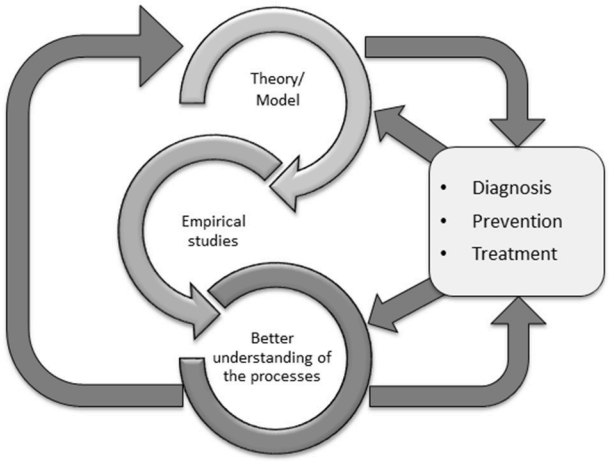

FIGURE 3 | The bidirectional relationship between theoretical models and clinical practice.

symptoms of Internet-use disorders (Brand et al., 2014a) and we see that cognitive restructuring is useful for changing these expectancies (Young, 2013), it would be helpful to have validated tools assessing Internet-use expectancies for clinical practice. It would also be helpful to include this issue in prevention programs. **Figure 3** aims at summarizing the bidirectional relationships between theories (and consequently empirical studies on processes) and clinical practice including diagnosis, prevention, and therapy. Given that both theoretical models and therapy approaches (and also diagnosis and prevention) are never final or perfect, it is important to consider how these two areas can successfully interact and influence each other to increase validity and efficacy.

CONCLUSIONS

This paper reviews the most relevant neurobiological studies associated with the development of IGD, some theoretical models of the development and maintenance of IGD and other specific Internet-use disorders, and treatment implications for addicted clients using the I-PACE and CBT-IA models.

Current neuroimaging studies indicate that IGD and other behavioral addictions (e.g., gambling disorder) as well as substance-use disorders share several similarities. Similarities can be seen on the molecular level (e.g., genetic contribution), neurocircuitry (e.g., the dopamine fronto-striatal loops including ventral striatum and several parts of the prefrontal cortex), and behavioral levels including implicit (e.g., attentional bias) and explicit emotions and cognitions (Brand et al., 2016). As we move forward, the diagnosis of IGD has several implications from the clinical, educational, and cultural contexts.

Clinically, more attention and training should be applied in counseling training, schools, and institutions. Given its newness, symptoms of IGD are still overlooked by some clinicians. Therefore, it is important that clinicians are trained in assessment procedures and routinely check for the presence of excessive and uncontrolled Internet use in their practices. In addition, clinicians should be trained in treatment of IGD and other types of Internet-use disorder. Treatment protocols must be further studied and improved. Indeed, while early outcome data show CBT-IA offers an effective approach to helping clients maintain a healthy online routine, further studies should examine other therapeutic modalities such as group therapy, family therapy, and *in vivo* counseling to look at their combined treatment efficacy.

If indeed IGD is viewed as a disorder this would also have implications for school systems to develop screen smart policies that protect children and adolescents from developing IGD problems. It would be helpful to have educators receive training on how to identify students who are most at-risk for developing IGD. It would be helpful for school administrators to develop policies for technology use by students in the classrooms in order to prevent IGD from occurring, strategies may include limited screen use in the classroom, no gaming policies, and encouragement of social clubs at school.

On the other hand, it makes also sense to note that there are several limitations of the current state-of-the-art in IGD research. There is an ongoing debate about classification, diagnostic criteria and instruments, conceptualization as an addiction or another type of disorder, and many other unsolved problems or challenges for the research aiming at understanding the nature of IGD and other Internet-use disorders. Consequently, it is mandatory not to overpathologize a healthy and balanced use of the Internet in general or games in particular, as long as the use is integrated in daily life without experiencing severe negative consequences.

Theoretical models can inspire empirical studies investigating the nature of IGD and other Internet-use disorders. It is important to use those models for spelling out clear research hypotheses in future studies. Both congruent and divergent validities should be addressed systematically in future studies. Although, the theoretical background for the I-PACE model is the addiction framework, we also have to consider other theoretical approaches within empirical studies to contribute to a better understanding of the underlying mechanisms. Future studies will demonstrate which aspects of the addiction framework and which parts of other theories are valid in explaining IGD. Theoretical models on a disorder can potentially inspire therapy approaches, but only if these theoretical models are valid and have been tested empirically. One of the important challenges for future IGD research is to merge existing theoretical assumptions about the underlying psychological mechanisms of the disorder with therapy and prevention techniques. The inspirations of theory and therapy should be bidirectional and in the best case, research on psychological mechanisms and therapy research interact in concert.

AUTHOR CONTRIBUTIONS

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

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REVIEW
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Neurobiological Correlates in Internet Gaming Disorder: A Systematic Literature Review

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Internet Gaming Disorder (IGD) is a potential mental disorder currently included in the third section of the latest (fifth) edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-5) as a condition that requires additional research to be included in the main manual. Although research efforts in the area have increased, there is a continuing debate about the respective criteria to use as well as the status of the condition as mental health concern. Rather than using diagnostic criteria which are based on subjective symptom experience, the National Institute of Mental Health advocates the use of Research Domain Criteria (RDoC) which may support classifying mental disorders based on dimensions of observable behavior and neurobiological measures because mental disorders are viewed as biological disorders that involve brain circuits that implicate specific domains of cognition, emotion, and behavior. Consequently, IGD should be classified on its underlying neurobiology, as well as its subjective symptom experience. Therefore, the aim of this paper is to review the neurobiological correlates involved in IGD based on the current literature base. Altogether, 853 studies on the neurobiological correlates were identified on ProQuest (in the following scholarly databases: ProQuest Psychology Journals, PsycARTICLES, PsycINFO, Applied Social Sciences Index and Abstracts, and ERIC) and on MEDLINE, with the application of the exclusion criteria resulting in reviewing a total of 27 studies, using fMRI, rsfMRI, VBM, PET, and EEG methods. The results indicate there are significant neurobiological differences between healthy controls and individuals with IGD. The included studies suggest that compared to healthy controls, gaming addicts have poorer response-inhibition and emotion regulation, impaired prefrontal cortex (PFC) functioning and cognitive control, poorer working memory and decision-making capabilities, decreased visual and auditory functioning, and a deficiency in their neuronal reward system, similar to those found in individuals with substance-related addictions. This suggests both substance-related addictions and behavioral addictions share common predisposing factors and may be part of an addiction syndrome. Future research should focus on replicating the reported findings in different cultural contexts, in support of a neurobiological basis of classifying IGD and related disorders.

Keywords: Internet Gaming Disorder, IGD, fMRI, rsfMRI, VBM, PET, EEG, review

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KEY CONCEPTS

Functional Magnetic Resonance Imaging (fMRI) measures changes neuronal activity via levels of blood oxygen (BOLD) in the brain, as blood flow in "active" brain areas increases to transport more glucose, whilst transporting additional oxygenated hemoglobin molecules.

***Resting State Magnetic Resonance Imaging* (*rsfMRI*)** is a subtype of fMRI which measures blood oxygen levels (BOLD) to assess brain activity whilst the subject is in a resting state (i.e., not engaged in a specific activity). The aim is to investigate whether there are differences in brain function in individuals with particular conditions in comparison to healthy controls.

Voxel-based morphometry (VBM) helps characterize subtle structural changes in the brain without the need of prior knowledge. This is especially important given videogame use can affect brain functioning in various ways that may result in changes at the behavioral and cognitive levels.

Positron Emission Tomography (PET) measures metabolic activity in the brain by detecting gamma rays which are emitted through a tracer substance, which are then depicted through computer analysis.

Studies using ***Electroencephalography (EEG)*** are employed to detect neural activity from the underlying cortical areas (anterior, posterior, right, and left) in an individual's cerebral cortex using electrodes attached to the scalp. Using this technique, voltage fluctuations (i.e., current flow produced by excitation of neuronal synapses) are measured between pairs of electrodes.

INTRODUCTION

Internet Gaming Disorder (IGD) is a potential mental disorder currently included in the third section of the latest (fifth) edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-5) as a condition that requires additional research to be included in the main manual (1). Although research efforts in the area have increased, there is a continuing debate about the respective criteria to use as well as the status of the condition as mental health concern [e.g., (2, 3)].

The controversies regarding the proposed classification of IGD in the DSM-5 concern the conceptual, theoretical, as well as methodological issues that have been raised by a number of scholars in the field. Firstly, it has been stated that the addiction framework is restricting because rather than being an addiction, problematic gaming may be the result of maladaptive coping and seeking to satisfy previously unmet needs (4). However, research (5) has also shown that dysfunctional coping and Internet addiction do not have to be mutually exclusive, but that the former predicts the latter, and may therefore suggest that gaming is a form of self-medication, and which is similar to other addictions (6). Secondly, it has been argued that if IGD results from other mental disorders it cannot be considered a bona fide addiction (7). However, from a clinical perspective, it is clear that comorbidity is the norm, not an exception, and this holds not just for Internet and gaming addiction (6, 8), but also for other psychopathology (9) including other addictions (6). Thirdly, previous research on IGD has been criticized for its methodological limitations, given that most research in the area has been conducted using non-clinical populations using psychometric (and therefore subjective) measures (10). However, there are increasing numbers of studies evaluating treatment-seeking clinical patients with IGD [e.g., (11–23)]. Furthermore, methodological limitations of research in the young field of IGD are limiting our understanding and generalization of findings, and therefore it is of utmost importance to continue researching the phenomenon both from a clinical perspective and using methods that can be considered more objective, such as assessing the neurobiological underpinnings of IGD.

Rather than assessing IGD subjectively by relying on diagnostic criteria which are based on subjective symptom experience, the National Institute of Mental Health (24) advocates the use of Research Domain Criteria (RDoC) which may support classifying mental disorders based on dimensions of observable behavior and neurobiological measures because mental disorders are viewed as biological disorders that involve brain circuits that implicate specific domains of cognition, emotion, and behavior. Consequently, IGD should be classified on its underlying neurobiology as well as its subjective symptom experience. Therefore, the aim of this paper is to review the neurobiological correlates in IGD based on the current literature base.

METHODS

Inclusion criteria used for the present review were: (i) assessing neurobiological mechanisms in IGD, (ii) empirical studies, (iii) using neuroimaging techniques, (iv) published in a peer-reviewed journal, (v) written in English, and (vi) published since 2012 as previous reviews have covered the timeframe before then (25). The database ProQuest was searched, including the following databases: Applied Social Sciences Index and Abstracts (ASSIA), ERIC, ProQuest Psychology Journals, PsycARTICLES, and PsycINFO, with another search performed on MEDLINE. The search included the most common types of neuroimaging techniques used in IGD research [i.e., electroencephalogram (EEG), positron emission tomography (PET), single-photon emission computed tomography (SPECT), functional magnetic resonance imaging (fMRI), structural magnetic resonance imaging (sMRI), diffusion-tensor imaging (DTI)] as reported in a previous systematic review [i.e., (25)], leading to the following search strategy: (patholog* OR problem* OR addict* OR compulsive OR dependen* OR disorder*) AND (video OR computer OR internet) gam* AND (neuroimaging OR eeg OR pet OR spect or fmri OR smri OR dti). Each study's title and abstract were screened for eligibility. Full texts of all potentially relevant studies were then retrieved and further examined for eligibility.

RESULTS

A total of 853 studies (ProQuest $n = 745$; MEDLINE $n = 108$) were initially identified, with the search performed on the ProQuest website yielding the following results: ProQuest Psychology Journals $n = 524$; PsycARTICLES $n = 115$; PsycINFO

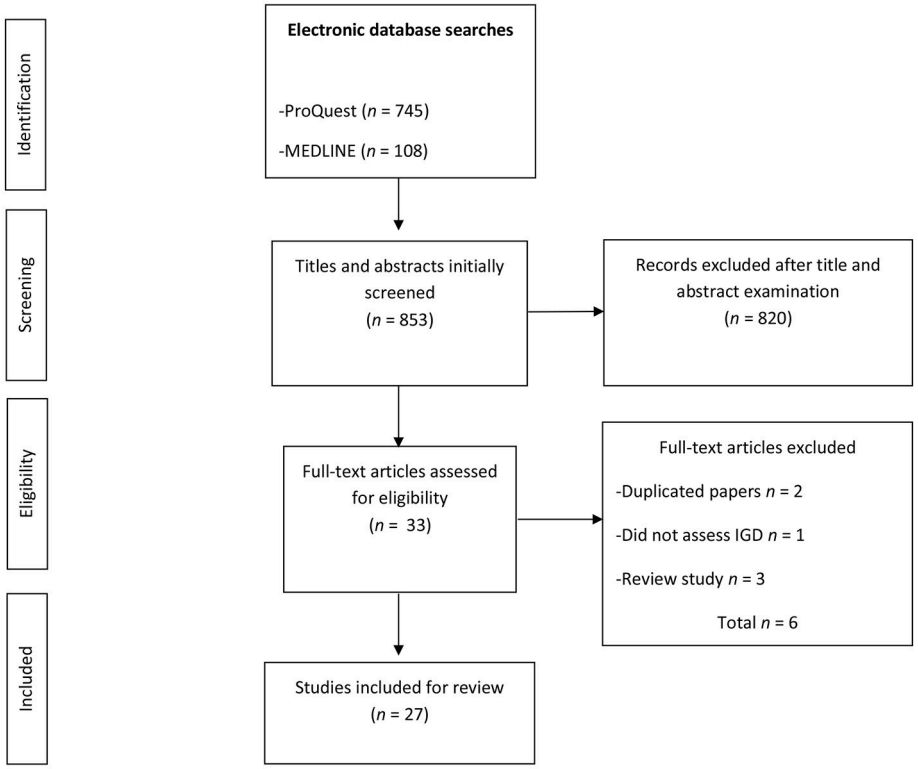

FIGURE 1 | Flow diagram of the study selection process.

$n = 106$; Applied Social Sciences Index and Abstracts $n = 0$; and ERIC $n = 0$. All 853 papers had their titles and abstracts screened, resulting in the exclusion of 820 papers that were of no relevance for the present review, leaving 33 studies which were eligible for further review. Of these, six papers had to be further excluded because they were either duplicates ($n = 2$), did not assess IGD ($n = 1$), or review papers ($n = 3$). A total of 27 studies were deemed eligible for further analysis as they met the inclusion criteria. The selection process is detailed in the flow chart in **Figure 1**.

Functional Magnetic Resonance Imaging (fMRI)

With fMRI, changes in the levels of blood oxygen (BOLD) in the brain are measured because they denote neuronal activity. The ratio of oxyhemoglobin (i.e., hemoglobin which contains oxygen in the blood) to deoxyhemoglobin (i.e., hemoglobin which has released oxygen) in the brain is measured as blood flow in "active" brain areas increases to transport more glucose, whilst transporting additional oxygenated hemoglobin molecules. Measuring this metabolic activity in the brain allows for finer and more detailed imaging of the brain relative to structural MRI. Moreover, the benefits of fMRI comprise the speed of brain imaging, spatial resolution, and no possible health risk in comparison to PET scans (26). A total of four studies were identified that used fMRI in the study of IGD (27–30). The details of these studies are presented in **Table 1** below.

Taken together, the fMRI studies using adolescent samples in China diagnosed with IGD (28, 30) suggested that there were differences between these individuals in comparison to healthy controls with regards to their neurobiology. Specifically, adolescents with IGD were found to have a higher activity in the superior medial frontal gyrus, right anterior cingulate cortex (ACC), right superior and middle frontal gyrus, the left inferior parietal lobule, the left precentral gyrus, and the left precuneus and cuneus, indicating worse response-inhibition and impaired prefrontal cortex (PFC) functioning (28) given previous research as shown that the left frontoparietal network is responsible for response inhibition (31). There was less activity in the bilateral middle and inferior temporal gyri which are responsible for visual processing (such as face recognition), and the right superior parietal lobule (responsible for spatial orientation), suggesting decreased visual and auditory functioning (28). Another fMRI study included in this review included male gamers in the Netherlands (29) and used Go-NoGo and Stroop tasks to assess impulsivity and inhibitory control, finding that problem video game players have lower brain activity in the left inferior frontal gyrus, right inferior parietal lobe in comparison to matched casual gaming controls, indicating that problem gamers have a lower inhibitory control [similar to the results regarding impaired inhibitory control outlined in Ding et al.'s study (28)], with no differences found in attention control and error processing.

TABLE 1 | Functional magnetic resonance imaging (fMRI) studies of Internet Gaming Disorder (IGD).

Author	Sample	Aims	Findings
Ding et al. (28)	$N = 34$ adolescents recruited from a mental health center in China (50 male; mean age = 16.4, $SD = 3.2$ years)	To assess whether sub-facets of trait impulsivity are linked to brain regions associated with impaired impulse inhibition in individuals with IGD	PFC involved in circuit modulating impulsivity. Impaired PFC function related to high impulsivity in adolescents with IGD, and may contribute to IGD process
Sun et al. (30)	$N = 39$ adolescents and adults with IGD recruited form mental health center, and healthy controls in China (83% male; mean age = 20.5, $SD = 3.55$ years)	To investigate whether diffusional kurtosis imaging (DKI) can be used to detect changes in gray matter (GM) in individuals with IGD	DKI can detect subtle differences in GM microstructure between IGD and healthy individuals. DKI model can provide sensitive imaging biomarkers for assessing IGD severity.
Dieter et al. (27)	$N = 32$ adults with IGD recruited in mental health center, and healthy controls in Germany (91% male; mean age = 26.7, $SD = 6.3$ years)	To measure psychological and neurobiological correlates of relationship between avatar and concepts of self and ideal self in individuals with IGD	Disordered gamers identify significantly more with their avatar than non-disordered individuals. Avatar may replace gamers' ideal self-whilst addiction develops.
Luijten et al. (29)	$N = 34$ male gamers in the Netherlands (mean age = 20.8, $SD = 3.1$ years)	To assess cognitive control deficits in individuals with IGD (e.g., inhibitory control, error processing, attention control)	Reduced inhibitory control, but error processing and attention control normal.

Moreover, diffusional kurtosis imaging (measuring water diffusion processes in the brain to assess microstructures) and voxel-based morphometry indicated that adolescents with IGD had lower kurtosis parameters in gray matter (GM) in various neuronal areas, whilst their GM volume in the temporal and parahippocampal gyri was higher, and lower in their left precentral gyrus. Based on the differences found in the assessed mean kurtosis metrics (i.e., water diffusion) between Internet gaming addicts and healthy controls and the brain areas detailed above (30), it appears there are significant differences in the microstructure of the brain between these groups, pointing to a particular IGD pathophysiology (30). [For a detailed representation of the peak MNI coordinates of the voxel and cluster analysis of this study, please refer to the summary provided regarding the MK changes, differences in axial and radial kurtosis between the Internet gaming addiction and the control groups (Sun et al., pp. 48ff.)].

The final fMRI study using adult players of Massively Multiplayer Online Role-Playing Games (MMORPGs) with IGD in Germany (27) showed that they identify with their in-game avatar (i.e., their virtual character), which leads to activation of brain areas associated with self-identification and self-concept-relate processing, i.e., the left angular gyrus, suggesting avatar-identification may be a consequence of compensating for social anxiety, resulting in developing IGD.

Resting State Magnetic Resonance Imaging (rsfMRI)

rsfMRI is a subtype of fMRI which measures blood oxygen levels (BOLD) to assess brain activity whilst the subject is in a resting state (i.e., not engaged in a specific activity). The aim is to investigate whether there are differences in brain function in individuals with particular conditions in comparison to healthy controls (32). In the present review, a total of seven studies used rsMRI to study IGD were included (33–39). Study details are provided in **Table 2**.

Taken together, the rsfMRI studies identified in the present review suggest individuals with IGD have an impaired cognitive control [(34)–(36, 38, 39)], and a deficiency in their ventral striatum reward system (33). Cognitive control in IGD individuals was assessed using a color-word Stroop task, decreased fractional anisotropy (FA) in the right salience network, indicating reduced fiber density, axonal diameter, and myelination in white matter (WM), which may explain problem in regulating the salience network in individuals with IGD that may be associated with impaired cognitive control (36). Decreased WM density in the inferior frontal gyrus, insula, amygdala and anterior cingulate have been demonstrated in individuals with Internet gaming addiction relative to healthy controls, indicating decreased capacities of decision-making, behavioral inhibition and emotion regulation in the IGA group (34). In addition to this, it has been shown that individuals with IGD have decreased fractional amplitudes of low-frequency fluctuation (measuring local brain activity which has been linked to psychiatric disorders) in the cerebellum and increased values in the superior temporal gyrus, suggesting impaired executive function, working memory and decision-making in IGD subjects relative to healthy controls, but also more brain activity that may be associated with increased sensory-motor coordination in IGD (35). Research has also indicated an increased volume of the right caudate and nucleus accumbens (driving the experience of pleasure in the human brain) and reduced strength of resting state functional connectivity in the PFC, tied to decreased cognitive control, similar to these found in substance-related disorders (38). Furthermore, research has found that individuals with IGD have decreased voxel-mirrored homotopic connectivity (measuring the connectivity between brain hemispheres) between the left and right superior frontal gyrus, frontal and middle frontal gyrus, indicating reduced interhemispheric communication in the brain of IGD individuals relative to healthy controls, impacting decision-making, craving and inhibitory errors (39). Moreover, it has been found that individuals who frequently play MMORPGs such as World of Warcraft have a lower physiological responsiveness in the ventral striatum when anticipating monetary rewards with ventral striatum activity differing both with task-based

TABLE 2 | Resting state magnetic resonance imaging (rsfMRI) studies of Internet Gaming Disorder (IGD).

Author	Sample	Aims	Findings
Xing et al. (36)	*N* = 34 adolescents in China (61% male; mean age = 19.1, *SD* = 0.7 years)	To assess the relationship between the salience network and cognitive control in adolescents with IGD	Right salience network associated with impaired executive function. Structural connectivity differences between adolescents with IGD and healthy controls.
Yuan et al. (38)	*N* = 87 adolescents and young adults in China (75% male; mean age = 19, *SD* = 1.4 years, range = 15–23)	To assess differences in striatum volume and resting-state functional connectivity (RSFC) networks between individuals with IGD and healthy controls	Differences in striatum volume and frontostriatal circuits RSFC between individuals with IGD and healthy controls. Cognitive control deficits in IGD correlated with reduced frontostriatal RSFC strength.
Yuan et al. (33)	*N* = 33 young male gamers and non-gamers in Germany (mean age = 25.5, *SD* = 4.2, range = 18–34)	To assess whether World of Warcraft layers have deficient reward system	Evidence for reward system deficiency in frequent online gamers, including significantly decreased neural activation during anticipation of small and large monetary rewards in ventral striatum
Lin et al. (34); Lin et al. (35)	*N* = 52 male young individuals in China (mean age = 22.2, *SD* = 3.1 years)	To assess abnormal spontaneous brain activity in IGD with low-frequency fluctuation (fALFF) at different frequency bands	Individuals with IGD had lower fALFF values in superior temporal gyrus and higher fALFF values in cerebellum
Wang et al. (39)	*N* = 41 adolescents in China (mean age = 16.9, *SD* = 2.7 years; range = 14–17)	To assess interhemispheric resting state functional connectivity of individuals with IGD using voxel-mirrored homotopic connectivity (VMHC)	Individuals with IGD had decreased VMHC between orbital part of left and right superior, middle and inferior frontal gyrus

as well as resting-state fMRI, with the deficient sensitivity to reward predisposing individuals to excessive gaming (rather than reward system deficiency being the result of excessive gaming) (33).

Voxel-Based Morphometry (VBM)

VBM is a useful technique for understanding IGD as it helps characterize subtle structural changes in the brain without the need of prior knowledge (40). This is especially important given videogame use can affect brain functioning in various ways that may result in changes at the behavioral and cognitive levels (41). This subsection will briefly outline some of the key findings obtained from IGD studies using VBM, and more information is provided in **Table 3**.

Lee et al. (42) utilized VBM to investigate the association between GM abnormalities and impulsivity in IGD, and found that IGD subjects exhibited smaller GM volume in brain regions related to executive control, such as the ACC and the supplementary motor area (SMA). It was also found that GM volumes in the ACC and the SMA were negatively associated with impulsiveness, and that IGD subjects exhibited smaller GM volume in the lateral prefrontal and parietal cortices comprising the left ventrolateral PFC and the left inferior parietal lobule when compared to healthy controls. Lee et al. (42) also found that GM volumes in the left ventrolateral PFC were negatively correlated with lifetime usage of videogames. Similarly, further research showed links between GM and impulsivity in IGD individuals. More specifically, Du et al. (43) found that IGD individuals present with higher levels of impulsivity associated with GM volume of the right dorsomedial prefrontal cortex (DMPFC), the bilateral insula and the orbitofrontal cortex (OFC), the right amygdala and decreased left fusiform gyrus. Taken together, these findings suggest GM abnormalities in areas related to executive control may contribute to greater impulsivity in young male adults with IGD, and that dysfunction of these brain areas involved in behavior inhibition, attention and emotion regulation might contribute to impulse control problems in adolescents with IGD (44).

Further research showed that GM density of the bilateral amygdala decreased and the connectivity between the PFC/insula and the amygdala increased in IGD individuals, which suggests emotion dysregulation (44). Furthermore, the altered correlations between impulsivity and GM volume in the DMPFC, OFC, insula, amygdala and the fusiform in IGD adolescents indicate that dysregulation in the brain networks involved in behavior inhibition, attention and emotion regulation might contribute to higher impulsivity levels in adolescents presenting with IGD.

VBM research has helped identifying specific brain regions with GM changes in IGD. Jin et al. (45) found that IGD adolescents showed decreased GM volume in the frontal regions including the bilateral dorsolateral PFC, OFC, ACC, the right SMA and cerebellum after controlling for age and gender effects. These findings are in line with previous studies suggesting GM deficits in the OFC can occur in IGD individuals (46), the involvement of several PFC regions and related PFC –striatal circuits in the process of IGD, and IGD may share similar neural mechanisms with substance dependence at the circuit level.

VBM research has also identified potential detrimental effects of IGD on cognitive control functioning. Wang et al. (39) reported that GM volume of the bilateral ACC, precuneus, SMA, superior parietal cortex, left dorsal lateral PFC, left insula, and bilateral cerebellum decreased significantly in IGD individuals. This study suggests that the alteration of GM volume is associated

TABLE 3 | Voxel-based morphometry (VBM) studies of Internet Gaming Disorder (IGD).

Author	Sample	Aims	Findings
Lee et al. (42)	*N* = 61 adolescents and young adults in South Korea (100% male; mean age = 23.5, *SD* = 2.7 years, range = 18–28 years)	To identify gray matter (GM) changes associated with IGD and assess difficulties in executive control by evaluating impulsivity	IGD subjects showed smaller GM volume in brain areas related to executive control. The GM volume in the anterior cingulate cortex and the supplementary motor area were negative associated to impulsivity
Du et al. (43)	*N* = 52 adolescents and young adults in China (100% male; mean age = 17, *SD* = 3 years)	To investigate potential altered structural correlates of impulsivity in IGD adolescents compared to healthy controls	IGD individuals presented with dysfunction in different brain areas involved in the behavior inhibition, attention and emotion regulation
Ko et al. (44)	*N* = 60 adolescents and young adults in Taiwan (100% male; mean age = 23.6, *SD* = 2.5 years)	To evaluate GM density and functional connectivity (FC) in individuals with IGD	IGD individuals showed altered GM density over the amygdala. Further analysis of the amygdala indicated impaired FC to the frontal lobe
Jin et al. (45)	*N* = 46 young adults in China (65% male; mean age = 19.1, *SD* = 1.1 year)	To assess the abnormal structural resting-state properties of several frontal regions in individuals with IGD	IGD individuals showed significant decreased GM volume in the prefrontal cortex (PFC) regions including the bilateral dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and the right supplementary motor area (SMA)
Weng et al. (46)	*N* = 34 adolescents in China (82% female; mean age = 16.3, *SD* = 3.0 years)	To investigate the differences in the brain morphology between IGD subjects and healthy controls, and to explore the neural possible mechanism of IGD	IGD individuals showed significant GM atrophy in the right OFC, bilateral insula, and right SMA. Overall, microstructure abnormalities of GM and white matter (WM) were found in IGD subjects
Wang et al. (39)	*N* = 56 adolescents in China (67% male; mean age = 18.8, *SD* = 1.3 year)	To investigate cognitive control function and potential alteration of brain GM volume in IGD individuals	GM volume of the bilateral ACC, precuneus, SMA, superior parietal cortex, left DLPFC, left insula, and bilateral cerebellum decreased in IGD individuals in comparison to healthy controls
Lin et al. (34)	*N* = 71 young adults in China (100% male; mean age = 22.2, *SD* = 3.1 years)	To assess if IGD contributes to cerebral structural changes by examining GM and WM density changes in IGD individuals	IGD individuals showed significant lower GM and WM density in several areas of the brain involved in decision-making, behavioral inhibition, and emotional regulation

with performance change of cognitive control in adolescents with IGD, highlighting substantial brain image effects induced by IGD.

Previous VBM research has reported abnormal GM and WM volume in IGD. Lin et al. (34) found that IGD individuals exhibited significantly lower GM density in the bilateral inferior frontal gyrus, left cingulate gyrus, insula, right precuneus, and right hippocampus. It was also found that IGD individuals showed significantly lower WM density in the inferior frontal gyrus, insula, amygdala, and anterior cingulate than healthy controls (34). These findings converge with those reported in earlier studies where IGD subjects were shown to present smaller insular GM density [e.g., (46, 47)], and IGD can negatively affect processes involved in decision-making, behavioral inhibition and emotion.

Overall, VBM research has been helpful in demonstrating potential structural brain changes of IGD individuals. Many of the brain regions found to be altered in IGD individuals have been previously linked to functions contributing to the development of addictive or compulsive behaviors (48). For example, decreased OFC thickness has been identified in individuals with substance-use disorders and behavioral addictions, further implying the development of IGD may involve brain regions similar to those involved in these conditions (49, 50). Although some of the studies reported found changes across different brain regions, these discrepancies help illustrate different ways in which IGD can affect overall brain functioning and the changes it may produce at the behavioral and cognitive level (41), further highlighting the complexity of the phenomenon. Moreover, given that many of the VBM studies reviewed were conducted in adolescent samples and that their brain is still developing, the results reported may not be generalizable across all age groups. One potential avenue to control for this would be to conduct similar studies in samples of children and adults to compare the findings obtained.

Positron Emission Tomography (PET)

PET has been utilized to demonstrate that dopamine is released in the human striatum during videogame play, and that playing videogames can lead to significant changes in brain chemistry similar to pharmacologically induced changes (51). The PET studies are summarised in **Table 4**. Much evidence

TABLE 4 | Positron emission tomography (PET) studies of Internet Gaming Disorder (IGD).

Author	Sample	Aims	Findings
Park et al. (54)	*N* = 20 young adults in South Korea (100% male; mean age = 24.7, *SD* = 2.4 years)	To investigate the differences in regional cerebral glucose metabolism at resting state in IGD individuals	IGD individuals showed greater impulsivity and severity of IGD and impulsiveness were associated. IGD individuals had increased glucose metabolism in the orbitofrontal cortex (OFC), striatum, and sensory regions that are implicated in impulse control, reward processing, and somatic representation of previous experiences
Tian et al. (55)	*N* = 26 adolescents and young adults in China (100% male; mean age = 23.5, *SD* = 2.6 years)	To assess brain dopamine D2 (D_2)/Serotonin 2A (5-HT_{2A}) receptor function and glucose metabolism in IGD individuals	IGD individuals showed decreased glucose metabolism in the prefrontal, temporal, and limbic systems. Further dysregulation of D_2 receptors was found in the striatum and associated to years of IGD

has implicated the dopaminergic system in the regulation of rewarding behaviors and behavioral addictions, such as IGD (52, 53).

In a ^{18}F-fluorodeoxyglucose PET study conducted by Park et al. (54) using a male sample of nine healthy controls and 11 IGD gamers, the authors found greater impulsiveness in IGD players in comparison to healthy controls. Additionally, the imaging data showed IGD gamers had significantly increased glucose metabolism in the right middle orbitofrontal gyrus, left caudate nucleus, and right insula, and decreased metabolism in the bilateral postcentral gyrus, left precentral gyrus, and bilateral occipital regions compared to the control group. In summary, these findings suggest that IGD may share psychological and neural mechanisms with other types of impulse control disorders and substance/nonsubstance-related addiction experiences.

Further research using PET has been carried out in an attempt to shed light on the neurobiological mechanisms of IGD. Tian et al. (55) investigated brain dopamine D_2 (D_2)/Serotonin 2A (5-HT_{2A}) receptor function and glucose metabolism and whether there was an association between D_2 receptor and glucose metabolism in a sample of 12 drug-naïve adult males meeting the criteria for IGD and 14 healthy controls using PET and ^{11}C-N-methylspiperone to assess the availability of D_2/5-HT_{2A} receptors and with ^{18}F-fluorodeoxyglucose to assess regional brain glucose metabolism, a marker of brain function. The findings o suggested IGD individuals presented with significantly decreased glucose metabolism in the prefrontal, temporal, and limbic systems. Additionally, dysregulation of D_2 receptors was observed in the striatum and associated with history of excessive videogame play. Further, low levels of D_2 receptors in the striatum were significantly associated with decreased glucose metabolism in the OFC. Taken together, these findings suggest D_2/5-HT_{2A} receptor-mediated dysregulation of the OFC underlies a mechanism for loss of control and compulsive behavior in IGD individuals.

Although there is a general scarcity of PET studies on IGD, regarding the imaging techniques utilized, fMRI is preferable to PET because it does not require exposing individuals to radiation (56). However, advantages of PET studies may include its usefulness to ascertain the efficacy of pharmacotherapy and predict treatment outcomes (57).

Electroencephalography (EEG)

Studies using EEG are employed to detect neural activity from the underlying cortical areas (anterior, posterior, right, and left) in an individual's cerebral cortex using electrodes attached to the scalp. Using this technique, voltage fluctuations (i.e., current flow produced by excitation of neuronal synapses) are measured between pairs of electrodes (58). More specifically, the relationships between an individual's brain and behavior are assessed via electrophysiological neuronal responses to stimuli (59). However, when compared to other neuroimaging techniques (such as fMRI) the spatial resolution in the subcortical areas is poorer. Up to 2013, most of the published studies utilizing EEG [e.g., (60–64)] assessed young adult males with Internet addiction rather than IGD, although the samples used included gamers. Regarding more recent IGD studies using EEG, the main types of study comprise studies examining (i) excessive and addictive gaming, (ii) gaming addiction and other comorbid disorders, and (iii) gaming addiction (miscellaneous). The included studies are presented in **Table 5**.

Excessive and Addictive Gaming

In the first study to actually include a sample specified as gamers rather than Internet addicts, Littel et al. (65) investigated response inhibition and error-processing. ERPs of 25 excessive gamers were compared to a control group utilizing the Go/NoGo paradigm. Compared to the control group, excessive gamers had poor error-processing (as indicated by reduced fronto-central ERN amplitudes following incorrect trials in the Go/NoGo task). Moreover, the excessive gamers displayed less inhibition on both behavioral and self-report measures, and results were similar to those with impulse control disorders and substance dependence. The authors speculated that poor error processing, trait impulsivity, and diminished behavioral response inhibition may underlie IGD.

TABLE 5 | EEG studies examining gaming addiction/Internet Gaming Disorder.

Author	Sample	Aims	Findings
Littel et al. (65)	25 excessive gamers (mean age 20.52 years; *SD* = 2.95) compared to 27 non-excessive gamers (mean age 21.42 years; *SD* = 2.59) in The Netherlands (100% male)	To investigate response inhibition and error-processing among excessive gamers compared to casual gamers utilizing the Go/NoGo paradigm	Excessive gamers had poorer error-processing and displayed less inhibition compared to controls
Duven et al. (66)	14 pathological gamers (mean age 24.29 years; *SD* = 5.84) compared to 13 casual gamers (mean age 23.31 years; *SD* = 3.01) in Germany (100% male)	To investigate whether there is enhanced motivational attention or tolerance effects in IGD patients compared to casual gamers	An attenuated P300 for IGD patients in response to rewards compared to controls
Park et al. (67)	26 patients with IGD (20 males; mean age 23.04 years; *SD* = 4.15) compared to 23 healthy controls (20 males; mean age 25.04 years; *SD* = 4.29) in South Korea	To examine dysfunctional information processing among individuals with IGD compared to controls	Those with IGD demonstrated a significant reduction in response to the deviant tones in the P300 amplitudes at the midline centro-parietal electrode regions
Kim et al. (68)	20 patients with IGD (mean age 22.71 years; *SD* = 5.47) compared to 29 healthy controls (mean age 23.97 years; *SD* = 4.36) in South Korea (100% male)	To locate bio-markers associated with IGD compared to controls	Those with IGD showed increased resting-state EEG activity at baseline (delta and theta bands)
Kim et al. (69)	27 patients with IGD (24 males; mean age 26.5 years; *SD* = 6.1) compared to 24 with Obsessive-Compulsive Disorder (19 males; mean age 25.0 years; *SD* = 5.7), and 26 healthy controls (18 males; mean age 24.7 years; *SD* = 4.7) in South Korea	To compare the neurophysiological correlates of altered response inhibition among individuals with IGD and obsessive-compulsive disorder (OCD).	The IGD group demonstrated a delayed NoGo-N2 latency at the central electrode site compared to controls.
Son et al. (70)	34 patients with IGD (mean age 22.71 years; *SD* = 5.47) compared to 17 with Alcohol Use Disorder (mean age 29.71 years; *SD* = 4.88), and 29 healthy controls (mean age 23.88 years; *SD* = 4.66) in South Korea (100% male)	To compare the resting-state QEEG patterns among those with IGD, Alcohol Use Disorder, and healthy controls	IGD group had lower absolute beta power than the other two groups. No significant correlations between the IGD severity and QEEG were found.
Park et al. (48)	16 adolescents with IGD+ADHD (mean age 14.6 years; *SD* = 1.9) compared to 15 adolescents with ADHD (mean age 13.7 years; *SD* = 0.8), and 15 adolescent healthy controls (mean age 14.4 years; *SD* = 1.7) in South Korea (100% male)	To compare adolescent males with ADHD and IGD, male ADHD-only, and a male control group using QEEG	Compared to the ADHD-only group, the IGD/ADHD group had lower relative delta power and greater relative beta power in temporal regions
Youh et al. (71)	14 patients with IGD and Major Depressive Disorder (MDD; mean age 20.00 years; *SD* = 5.9) compared to 15 patients with MDD (mean age 20.3 years; *SD* = 5.5) in South Korea (100% male)	To compare the neurobiological differences between IGD+MDD patients and MDD patients using QEEG	Compared to those with MDD-only, inter-hemispheric coherence value for the alpha band between Fp1–Fp2 electrodes was significantly lower in those with IGD+MDD
Peng et al. (72)	16 patients with IGD (13 males; mean age 20.75 years; *SD* = 0.36) compared to 15 healthy controls (12 males; mean age 20.25 years; *SD* = 0.4) in China (100% male)	To examine the unconscious processing of facial expressions among those with IGD compared to controls using EEG	Those with IGD exhibited decreased amplitudes in ERP component N170 in response to neutral expressions compared to happy expressions in the happy–neutral expressions context

A study by Duven et al. (66) examined whether enhanced motivational attention or tolerance effects are present in IGD patients. IGD patients (n = 14) and a control group played a videogame during the recording of ERPs to assess reward processing. The findings demonstrated an attenuated P300 for IGD patients in response to rewards compared to controls. It was also reported that among IGD patients, the latency of N100 was prolonged and the amplitude of N100 was increased. The authors concluded that when playing videogames, tolerance effects are present in IGD patients.

Park et al. (67) used EEG to examine dysfunctional information processing among individuals with IGD. More specifically, they investigated differences in the P300 component of the ERP while participants performed an auditory oddball task. Compared to controls, those with IGD demonstrated a significant reduction in response to the deviant tones in the P300 amplitudes at the midline centro-parietal electrode regions. The authors also reported a negative correlation between IGD severity and P300 amplitudes. It was concluded that the reduced P300 amplitudes may be a neurobiological marker for IGD.

Another study using EEG to try and locate bio-markers associated with IGD was that carried out by Kim et al. (68). The study compared 20 IGD patients with healthy controls over a 6-month period. Using resting-state EEG, participants were

scanned prior to and after treatment. Those with IGD showed increased resting-state EEG activity at baseline (delta and theta bands). After 6 months of treatment, increased delta band activity was normalized and significantly correlated with a reduction in IGD symptoms. It was also reported that higher absolute theta activity at baseline predicted a greater improvement in IGD addiction symptoms following treatment. The authors argued that the increased slow-wave activity represented a state neurophysiological marker for those with IGD.

Gaming Addiction and Other Comorbid Disorders

Kim et al. (69) compared the neurophysiological correlates of altered response inhibition among individuals with IGD and obsessive-compulsive disorder (OCD). A total of 27 IGD patients, 24 OCD patients, and 26 healthy controls participated in a Go/NoGo task while undergoing EEG. The groups were compared on the N2-P3 complexes elicited during Go and NoGo task. The IGD group demonstrated a delayed NoGo-N2 latency at the central electrode site compared to controls. OCD patients had a smaller NoGo-N2 amplitude at the frontal electrode site than those with IGD. The authors concluded that prolonged NoGo-N2 latency may be as a marker of trait impulsivity in IGD and that reduced NoGo-N2 amplitude may be a differential neurophysiological feature between OCD from IGD in regard to compulsivity.

Son et al. (70) compared the resting-state QEEG patterns among those with IGD ($n = 34$), alcohol use disorder (AUD; $n = 17$), and healthy controls ($n = 25$). Results demonstrated that the IGD group had lower absolute beta power than the other two groups. The AUD group had higher absolute delta power than the two other groups. No significant correlations between the IGD severity and QEEG were found. The authors suggested that lower absolute beta power may be a potential trait marker of IGD and that IGD was neurophysiologically distinct from AUD.

In a study by Park et al. (48), the authors noted that IGD is often comorbid with attention deficit hyperactivity disorder (ADHD). Using quantitative electroencephalogram (QEEG) they compared three adolescent groups: males with ADHD and IGD ($n = 16$), male ADHD-only ($n = 15$), and a control group ($n = 15$). Amongst other findings, results showed that compared to the ADHD-only group, the (i) IGD/ADHD group had lower relative delta power and greater relative beta power in temporal regions, (ii) intra-hemispheric coherence values for the bands between P4–O2 electrodes (i.e., delta, theta, alpha, and beta bands) were higher in IGD/ADHD group, and (iii) intra-hemispheric coherence values for the theta band between Fz–Cz and T4–T6 electrodes were higher in IGD/ADHD group. The authors concluded that ADHD adolescents appear to continuously play online videogames to unconsciously enhance attentional ability. They also speculated that *"repetitive activation of brain reward and working memory systems during continuous gaming may result in an increase in neuronal connectivity within the parieto-occipital and temporal regions for the ADHD/IGD group"* (p. 514).

Youh et al. (71) noted that IGD is comorbid with major depressive disorder (MDD). In a study utilizing QEEG, they compared the neurobiological differences between MDD without comorbidity (MDD-only; $n = 15$) and MDD comorbid with IGD (MDD+IGD; $n = 14$). EEG coherences were measured using a 21-channel digital EEG system and computed to assess synchrony in the frequency ranges of alpha and beta between 12 electrode site pairs. The results demonstrated that compared to those with MDD-only (i) inter-hemispheric coherence value for the alpha band between Fp1–Fp2 electrodes was significantly lower in those with IGD, (ii) intra-hemispheric coherence value for the alpha band between P3–O1 electrodes was higher in those with IGD, and (iii) intra-hemispheric coherence values for the beta band between F8–T4, T6–O2, and P4–O2 electrodes were higher in those with IGD. The authors concluded that excessive online gaming may lead to increased intra-hemisphere connectivity in the fronto-temporo-parieto-occipital areas.

Gaming Addiction (Miscellaneous)

One of the more unusual studies examining IGD with EEG is a study by Peng et al. (72) who examined the unconscious processing of facial expressions among those with IGD. The authors claimed that *"IGD is characterized by impairments in social communication and the avoidance of social contact. Facial expression processing is the basis of social communication"* (p. 1). Consequently, they investigated how those with IGD process facial expressions. To examine the differences between the processing of subliminally presented facial expressions (happy, neutral, sad) with ERPs, those with IGD ($n = 16$) and controls participated in a backward masking task. The findings showed those with IGD were slower than controls in response to both sad and neutral expressions in the sad–neutral context. The ERP results demonstrated those with IGD exhibited *"decreased amplitudes in ERP component N170 (an index of early face processing) in response to neutral expressions compared to happy expressions in the happy–neutral expressions context, which might be due to their expectancies for positive emotional content"* (p. 1). Controls exhibited similar N170 amplitudes in response to both sad and neutral expressions in the sad–neutral expressions context, and happy and neutral expressions in the happy–neutral expressions context. The authors concluded those with IGD have different unconscious neutral facial processing patterns compared to normal controls.

Examining the ten EEG studies as a whole, there is little similarity in any of the 10 studies except that they all have small sample sizes and all found significant differences between those with IGD and the control groups concerning the variable(s) under focus. Two studies reported those with IGD had lower inhibition compared to controls (65, 68) but other than this, no other studies compared the same variables so little can be concluded from EEG studies.

DISCUSSION

The research of neurobiological correlates in IGD is relevant particularly in light of the National Institute of Mental Health's (NIMH) support for establishing research domain criteria based on which mental disorders should be classified and may offer a solution to the ongoing debates in the IGD field [e.g., (5)]. IGD neuroimaging is a nascent field that is developing at a fast pace, which has been highlighted by the present review. Taken together,

the fMRI and rsfMRI studies presented indicate that there appear to be significant neurobiological differences between healthy controls and individuals with IGD. The included studies suggest gaming addicts have worse response-inhibition and emotion regulation, impaired PFC functioning and cognitive control, worse working memory and decision-making capabilities, decreased visual and auditory functioning, and a deficiency in their neuronal reward system. These deficiencies are similar to those found in individuals with substance-related addictions, suggesting that both substance-related and behavioral addictions share common predisposing factors and may be part of an addiction syndrome (73, 74). For example, research in the context of alcohol abuse has found that P300 amplitudes are reduced in individuals who have an increased genetic risk for alcoholism (75, 76). This may suggest that similar findings with reduced P300 amplitudes in individuals with IGD have an elevated genetic risk to developing addiction-related problems. Consequently, future research needs to assess possible genetic vulnerability for developing IGD-related problems to verify such conjecture. However, in the fMRI and rsfMRI studies, no differences were found in attention control and error processing between IGD individuals and healthy controls. Moreover, more brain activity was found in gaming addicts relative to healthy controls, suggesting an increased sensory-motor coordination in IGD. Recent research suggests that regular gaming may have therapeutic benefits and gaming can be used to improve a variety of cognitive and motor skills, and is successfully used in the training of professionals, such as soldiers and surgeons (77).

Despite the invaluable contributions offered by neuroimaging studies on IGD, several limitations potentially compromising the generalizability of the results of these studies need to be highlighted. As the majority of these studies are cross-sectional, it is not possible to ascertain the causal relationships between IGD and the altered structures in the brain reported across these studies, particularly the VBM studies. Future research should adopt other research designs that help overcome these shortcomings. For example, further prospective studies are necessary to understand the roles of altered brain structures in the mechanism of IGD. In addition to this, further studies would benefit from larger sample sizes, as the presently reviewed studies were limited with regards to the number of participants that have been included. Another well-known problem in these studies is the use of generalized Internet addiction assessment tools to assess IGD [see (78), for a review on the topic]. Finally, other major psychiatric disorders were excluded from most VBM studies, thus there is some inherent limitation regarding generalizing the results to subjects with IGD with other substance-use or psychiatric disorders.

Moreover, EEG is commonly used in experimental situations because of its generally non-invasive and unobtrusive nature. Another key strength of EEG studies is that they are all strictly controlled laboratory experiments that can identify causal relationships between the variables assessed. Overall, the EEG findings demonstrate that compared to control groups, gaming addicts have decreased P300 amplitudes and an increased P300 latency (reflecting attention allocation). These differences suggest that those with IGD have an impaired attention capacity or they are unable to adequately allocate attention. Findings of these studies also appear to be similar to EEG studies examining other more traditional addictions, such as those to alcohol and cocaine [e.g., (79–81)]. However, one of the key weaknesses in EEG research is that is unable to provide any direct insights into active transmitter systems of the brain when monitoring brain activity.

In a review of electrophysiological correlates of problematic Internet use, D'Hondt et al. (82) noted that problematic internet use which often includes gaming is particularly associated with a reduction of inhibitory control and an increase in cue-reactivity. The EEG literature demonstrates *"that most studies have found that impaired self-control abilities (i.e., inhibition and error monitoring) are associated with underactivated frontal regions in problematic Internet users"* (p. 64). Furthermore, they noted that some EEG studies in the area demonstrate alterations in the processing of emotional stimuli and Internet-related cues, suggesting that *"both reflective (top-down) and automatic/affective (bottom-up) systems, postulated by dual-process models as being determinants in decision making, are impaired among [problematic internet users"* (p. 64). Overall, the present EEG studies agree with these conclusions because EEG studies reviewed in this section indicate that the brains of those with IGD appear to be less efficient in information processing and response inhibition compared to controls. Consequently, such individuals have low impulse control, use increased cognitive resources to complete specific tasks, and appear to have impaired executive control, again demonstrating similarities with other more traditional addictions (79).

In summary, the presented studies suggest that there may be a particular IGD pathophysiology, in support of the NIMH's advocacy of utilizing RDoC criteria for diagnosing mental disorders (24). Future research should focus on replicating the reported findings in different cultural contexts, in support of a neurobiological basis of classifying IGD and related disorders.

AUTHOR CONTRIBUTIONS

DK has reviewed, analyzed and written the sections of fMRI and rsfMRI and written the introduction, methods and discussion. MG has reviewed, analyzed and written the section on EEG and contributed to the full manuscript. HP has reviewed, analyzed and written the sections on VBM and PET and contributed to the full manuscript.

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REVIEW
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A Tripartite Neurocognitive Model of Internet Gaming Disorder

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Playing Internet games has emerged as a growing in prevalence leisure activity. In some cases, excess gaming can lead to addiction-like symptoms and aversive outcomes that may be seen by some as manifestations of a behavioral addiction. Even though agreement regarding the pathologizing of excessive video gaming is not yet achieved and perhaps because the field requires more research, many works have examined the antecedents and outcomes of what is termed internet gaming disorder (IGD). In this article, we aim at summarizing perspectives and findings related to the neurocognitive processes that may underlie IGD and map such findings onto the triadic-system that governs behavior and decision-making, the deficits in which have been shown to be associated with many addictive disorders. This tripartite system model includes the following three brain systems: (1) the impulsive system, which often mediates fast, automatic, unconscious, and habitual behaviors; (2) the reflective system, which mediates deliberating, planning, predicting future outcomes of selected behaviors, and exerting inhibitory control; and (3) the interoceptive awareness system, which generates a state of craving through the translation of somatic signals into a subjective state of drive. We suggest that IGD formation and maintenance can be associated with (1) a hyperactive "impulsive" system; (2) a hypoactive "reflective" system, as exacerbated by (3) an interoceptive awareness system that potentiates the activity of the impulsive system, and/or hijacks the goal-driven cognitive resources needed for the normal operation of the reflective system. Based on this review, we propose ways to improve the therapy and treatment of IGD and reduce the risk of relapse among recovering IGD populations.

Keywords: Internet gaming disorder, insula, decision-making, fMRI, striatum

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INTRODUCTION

The Internet offers a large variety of video games, including First Person or Ego-Shooters (FPS), Massively Multiplayer Online Role Playing Games (MMORPG), Multiplayer Online Battle Arena (MOBA) games, and hybrid forms of online games, such as Overwatch, which include the elements of both MOBA and FPS. MMORPG is the most popular game type among young adults and has been the focus of many IGD studies (1). Regardless of the nature and type of the game, videogames are possibly addictive since they provide strong rewards that are difficult to resist, and which are largely encouraged by videogame developers in order to ensure that gamers keep

on using their games (2). For example, they serve various functional needs of users, such as need for escapism, socialization achievement, and mastery, and are hence appealing to many young adults (3).

Research has shown that given such psychological benefits that stem from the needs served by videogames and the inability of some people to regulate their reward seeking behaviors, some players can present addiction-like symptoms in relation to videogames and that these symptoms can produce a range of aversive effects, on children (2, 4), young-adults (5, 6), and organizational employees (7–9). The concept of internet gaming disorder (IGD) has been suggested as a way to encapsulate such phenomenology and symptoms. IGD is a behavioral addiction on the spectrum of Internet addiction. It can be defined as persistent and recurrent use of the Internet to engage in games, often with other players, leading to clinically significant impairment or distress in a 12-month period (10, 11). Many studies have used adaptations or derivatives of this definition, though there is still a great deal of confusion regarding the boundaries of IGD and its measurement (12). The multiplicity of conceptualizations and measures may contribute to the different prevalence rates estimated in different studies; ranging from 0.1% to over 50% (13).

In 2013, the newly updated version of the Diagnosis and Statistical Manual for Mental Disorders (DSM-5) included IGD in its appendix and suggested nine criteria for characterizing this disorder (10, 11). These criteria are:

- preoccupation with Internet games
- withdrawal symptoms of irritability, anxiety, or sadness
- development of tolerance
- unsuccessful attempts to control the behavior
- loss of interest in other activities
- continued excessive use despite knowledge of psychosocial problems
- deceiving others regarding the amount of time spent gaming
- use of this behavior to escape or relieve a negative mood
- jeopardizing/losing a significant relationship/job/educational opportunity.

These criteria have been traditionally associated with substance-related addiction (14). Subjects should respond with yes/no to questions like "Do you spend a lot of time thinking about games even when you are not playing, or planning when you can play next?"; there is a proposed cut-off point of five criteria in DSM-5 (15). Nevertheless, proposing such criteria and cutoffs have raised a multitude of concerns regarding their ambiguity, reliance on addiction models from other domains, and reliance on prior research, which in many cases used non-clinical samples (12). Hence, many conclude that moving forward we need to conduct more research on IGD and/or better synthesize prior studies (16). Here, we venture to provide a synthesis of prior research on IGD, using a very specific angle, a neuro-cognitive one.

On the basis of recent neuro-cognitive models of addiction (17–20), and possible similarities between IGD and other addictions (13, 21–24), we suggest that the neural substrates involved in IGD development and maintenance can include the key brain systems that govern behavior and decision-making. Deficits in such systems have been shown to be associated with a broad range of addictions, including behavioral ones (17). Adapting this view, we contend that IGD may be associated with an imbalance between several inter-connected neural systems: (1) an hyperactive "impulsive" system, which is fast, automatic, and unconscious; it promotes automatic and habitual actions; (2) a hypoactive "reflective" system, which is slow and deliberative, forecasts the future consequences of a behavior and exerts inhibitory control; and (3) the interoceptive awareness system, which translates bottom-up somatic signals into a subjective state of craving, which in turn potentiates the activity of the impulsive system, and/or hijacks the goal-driven cognitive resources needed for the normal operation of the reflective system (17). In this article, we describe the connection between these three neural systems and IGD and evidence that supports this tripartite model. We use this description for pointing to potential interventions and directions for future studies.

ADDICTIVE PROPERTIES OF INTERNET GAMING

Addiction forms through a sensitization process (25) that changes behaviors from impulsive to compulsive. Similar to other addictive disorders that focus on behaviors (e.g., gambling), IGD cases develop an addictive state without substance intake. This can happen given the rewarding and immersive properties of videogames (26, 27) as well as their ability to address a broad spectrum of human functional needs (3). These include: relationship building, escapism, need for achievement, and mastering the game mechanics. Such motivations increase playtime and desire to play more (3), which in turn sensitizes the brain reward system (28, 29) and can lead to addiction symptoms in vulnerable populations (30).

Not all gamers will present addiction-like symptoms and meet IGD criteria, even if they play for extended periods of time (1). Research has indicates that personality traits such as avoidant traits, schizoid personality, diminished self-control, narcissism, and low self-esteem are significantly related to IGD (31). Hence, people with such traits may be more prone than others to present IGD. In addition, social-environmental factors such as pressure from school (32), which tends to be high especially in East Asia, may propel a higher prevalence rate of IGD cases in Asian countries (33, 34). Males seem to present higher IGD rates compared to women (35); and this changes when the focus is not just on games, but more broadly on Internet use (36). In the absence of prevention and harm reduction strategies that parents and educators can follow, young adults are more prone than others to lose control over online gaming (3).

Here, without discounting the importance of the many addictive features of video games, we emphasize two largely overlooked properties that many videogames have and can drive addictive behavior, if a person has deficits in the brain systems that govern decision-making:

(1) Providing a freedom space for players

A virtual environment means that gamers can fulfill their desires that could not be met in real life and be, at least temporarily,

other people with better qualities [see, for example, the notion of False Online Self in Ref. (37)]. These attributes can be highly rewarding, and present a possible reason for why game players persist in online gaming despite aversive outcomes (38). For instance, during such games, the role acted by a player could easily destroy and damage others in the virtual world and have a strong dominant personality, which may differ from the true-self of the gamer. The game space can be appealing also because it allows levels of violence that are often not afforded in real world. Many Internet games contain elements of violence; this feature may enhance interest in games and make them more rewarding, especially for young adults (39).

In addition to violence features, Internet games also provide an environment to fulfill gamers' desire to build an association, challenge one's abilities, and command others (40, 41). In other words, the virtual world provides a place to escape stress from real life and one's emotional state can be improved by playing online (3). Moreover, many Internet games allow players to pay in order to enhance the ability of the avatar representing them [in-game purchases, see, for example, Ref. (42)]. This process allows fast and easy enhancement compared to real-life attempts to enhance one's image and persona (41). Thus, vulnerable individuals can get sucked into the virtual world and avoid the real world (43). In sum, the virtual world includes many elements that help game players fulfill voids in their real life and provide enjoyable shortcuts for achieving aspirations in a simulation world. This process brings is psychologically rewarding, sometimes more than real life. It can hence motivate consumptions that over time may translate into compulsion.

(2) Anonymity

Anonymity has traditionally been conceived as the inability of others to identify an individual (44). Anonymity is common in many video games in which users use pseudonyms to describe themselves. This gives Internet game players a sense of security (false or not), which makes the virtual environment very appealing. In such environments, people can present abnormal behaviors and be free of direct judgment; for example, vulnerable individuals can show antisocial behaviors in online games (45). These antisocial behaviors may be linked to a loss of inhibition control (46). As such, the perceived-to-be safe environment afforded by anonymity features allows addicted users to engage in antisocial behaviors, which are aligned with their deficits in self-control abilities. When one's true identity is not revealed, anti-social gamers do not need to take responsibility for their in-game behavior, and suspend their enjoyment in the virtual environment (47). This reduced need for self-inhibition is also very appealing, can generate strong psychological rewards, and ultimately, in vulnerable users, lead to transition from habitual gaming to compulsive gaming.

IGD AND THE IMPULSIVE BRAIN SYSTEM (SYSTEM 1)

In the course of addiction, the sensitivity to cues related to the addictive substance or behavior is progressively increased, and responses become more automatic after continuous exposure to addiction stimuli (48). This process could easily shift goal-directed behaviors to compulsive behavior, in which the action becomes independent of the current value of the goal, and result with impulsive behavior (49). Previous research indicates that impulsivity is associated with increased novelty seeking and poor decision-making and can lead to negative consequence such as monetary losses or social failures; thus, it underlies the development and maintenance of state compulsivity (50).

Recent studies found that the striatal-cortical system is a central one for acting prematurely without foresight (51). This system includes the striatum (dopaminergic systems) and the amygdala, which are key structures that form the impulsive system, and mediate reward seeking and compulsion, through sensitization (17). Accordingly, the amygdala has been repeatedly reported to be involved in risk-taking behavior; lower density of gray matter in the amygdala has been found in many substance addiction cases (52, 53) and may be perceived as indicative of making the amygdala-striatal system more efficient (28, 29).

Research has also pointed to the role of the amygdala-striatal system in IGD development and maintenance. The structures of the impulsive system have changed during the transition from goal-directed to compulsive behaviors (54). For instance, excessive play of Internet games was associated with specific aspects of synaptic structure plasticity in both striatal regions. A positron emission tomography study found that, after prolonged Internet use, the level of dopamine D2 receptor and transporters availability in subdivisions of the striatum has been reduced compared with controls (55, 56). Voxel-based morphometry research suggested that frequent Internet game playing is associated with higher volumes in the left striatal and right caudate compared with infrequent game players (57, 58), but the bilateral amygdala had a lower gray matter density in IGD cases compared to controls (59). Moreover, through the repetition of online gaming experience and exposure to gaming-related information, players learn to associate gaming with reward, and progressively become hypersensitive to gaming-related cues (60). This process can establish linkage between gaming-related cues and positive mood, which can increase dopaminergic activity and dopamine levels (61).

Moreover, a person who presents IGD symptoms can become hypersensitive to gaming-related cues; that is, develop attentional bias toward game-related cues (62), which can manifest in issues such as time distortion (63). Human behavior is determined by two aspects of cognition, implicit cognition, which includes memory association and situational circumstance, and explicit cognition, which includes cognitions amenable to introspection and deliberate decision-making (64). According to the implicit association test, which is used to asses implicit associations, players with IGD have a positive motivational implicit response to screenshots of games (65), including in cases of first-person shooter and racing games (66). These findings indicate a strong association between implicit cognition and uncontrolled gaming behavior. Implicit cognition not only represents an automatic appetitive response to a specific substance but can also impact specific behaviors, such as playing online videogames. Because implicit cognitions play an important role in addictive behavior through the generation of automatic approach tendencies, and these cognitions are often

mediated *via* the amygdala–striatal system, the modulation of this system can be associated with addictive behaviors (67, 68), including the presumed-to-be addictive and problematic use of technologies (6, 20, 28, 29, 69, 70, 71).

fMRI studies also point to differences between brain activity of the impulsive system of presumed IGD and non-IGD cases. Both arterial spin-labeling perfusion and functional magnetic resonance imaging found differences during resting state: IGD subjects showed significantly higher global cerebral blood flow in the left parahippocampal and amygdala (72) and revealed reduced functional connectivity with fronto-striatal circuits (73, 74). Studies using the cue-reactivity paradigm indicated higher activation of the striatum among IGD subjects, compared to controls (26, 75). They further suggested functional differences between dorsal and ventral striatal subdivisions. After presenting game-related stimuli and neutral stimuli, the left ventral striatum activity of IGD cases showed negative correlation with cue-induced craving, but dorsal striatal activation was positively associated with duration of IGD. Hence, the transition from ventral to dorsal striatal processing of addiction-related cues may occur among IGD individuals (76).

Overall, continuously playing online can build a strong association between reward and behavior schema, and this association is mainly mediated by the amygdala-striatal system (77); impairment of this system can be associated with addictions in general (17) and specifically IGD (26, 27). The impairment of the impulsive system may be similar across addictions and problematic behaviors (78). Hence, it is not surprising to see structural, functional and connectivity abnormalities in this system in presumed-to-be IGD cases.

IGD AND THE REFLECTIVE BRAIN SYSTEM (SYSTEM 2)

The reflective system can be conceived as a controller of the motivation toward addiction related reward and the impulsive behavior that is produced by impulsive system. The reflective system forecasts the result of current behavior and allows more flexible pursuit of long-term goals. This system consists of two sets of neural systems: a "cool" system (elicited by relatively abstract, decontextualized problems, and refers to basic working memory operations, inhibition of prepotent impulsions, and mental set shifting) and a "hot" system (involved in triggering somatic states from memory, knowledge, cognition, and activates numerous affective/emotional (somatic) response that conflict with each other) (79).

Studies indicated that the cool executive functions are mainly dependent on the lateral inferior and dorsolateral prefrontal cortices, and the anterior cingulate cortex, and that they are involved in several kinds of psychological reaction, such as shifting between multiple tasks and the updating or maintaining of working memory (79). In contrast to the cool executive functions, the orbitofrontal cortex (OFC) and ventromedial prefrontal cortex (VMPFC) form the main structure of hot executive functions. These are involved in the interaction between affective/emotional responses and somatic states that produce overall positive or negative signals related to behavioral choices (79).

IGD and Hot Executive Function

The disruption of hot executive function in addiction has been initially demonstrated in clinical research of patient populations with damage in frontal lobe regions. These studies showed that hot executive function disruption delineates similar result to those obtained in cases of impairment to the frontal cortex (80, 81). The Iowa Gambling Task (IGT) has been typically applied in such addiction studies, to examine decision-making abilities under ambiguity (82). This paradigm was introduced as a tool to measure "risk-anticipation," which involves probabilistic learning *via* monetary rewards and punishments (83). Results of IGT studies demonstrated a reduced decision-making ability compared to controls during the task; they also show that presumed IGD cases made more disadvantageous decisions and performed worse than healthy controls (40, 84, 85). Excessive game playing that results in addiction-like symptoms, therefore, may be associated with deficient ability to integrate previous emotional/affective experiences of rewards or punishments, to motivate and engage in inhibition as well as to trigger somatic responses.

According to the somatic marker hypothesis, somatic response is multidimensional and the emotional experience caused by the reward or punishment under a decision-making situation, would change with the somatic state (86). Adapting this view, one can argue that IGD may be associated with impaired reward and punishment expectation and processing functions. Support for this view has been given in a study on the underlying neural mechanisms of disadvantageous risky decision-making in IGD cases. During the Balloon Analog Risk Task (BART), a significant interaction effect between risk level and activation of the bilateral ventral medial prefrontal cortex (PFC) has been shown (87). Another study, which used a modified delay-discounting task, also suggested that IGD cases prefer the probabilistic or risky options; it also showed that there is a positive correlation between activation of inferior frontal gyrus and probability discounting rates (88).

In contrast, evidence from First Person or Ego-Shooters players suggests that excessive videogame playing may enhance the performance on an IGT compared to controls (89), while experience with First Person or Ego-Shooters games was positively correlated with impulsivity, and experience with strategy games was negatively correlated with impulsivity (85). One reasonable interpretation is that First Person or Ego-Shooters games include many violent elements, which could arouse the impulsive system (90, 91). The most popular type of game, Multiplayer Online Role Playing game, can also contain violent scenes (92). Indeed, studies suggest relation between IGD and aggression (91), which may manifest from deficits in the hot inhibition/control brain system. In other words, after prolonged exposure to violent games, IGD cases may develop higher aggression than healthy subjects, which would promote their risk-taking intentions and behaviors (93).

Several studies have also reported that structural impairment in the orbital frontal cortex in IGD cases. These impairments

include abnormal glucose metabolism, abnormal of cortical thickness, and white matter fiber consistency (94–96). Moreover, compared to the neutral pictures, gaming pictures activated the OFC, right nucleus accumbens and bilateral Anterior Cingulate Cortex (ACC) (26). These results demonstrate that the orbital frontal cortex is involved in the modulation of reactive aggression; simply put the orbital frontal cortex fails to "inhibit" reactive aggression in response to social cues present in the environment (97).

Distinguishing it from other addictive substances and behaviors, video gaming provides different kinds of scenes and environments that can constantly stimulate use, rewards, violence and arousal. This emotional aspect that is apparent especially in violent games can lead to mood changes and disrupt the integration of emotional and cognitive inputs in the orbital frontal cortex (98). This process can also increase impulsivity, tendency for risk-taking and ignoring negative effects while seeking further rewards. The antisocial behavior among IGD cases suggests an association between aggression and excessive play of violent videogames (99). Overall, excessive play of online games can disrupt the hot executive system in two ways. First, the dysfunction of the ventral medial PFC impacts the value evaluation of rewards and punishments (100). Second, game-related cues arouse the mood with aggression, and this can affect the integration of emotional inputs into decision-making. The somatic state would be influenced by the aggression, and as a result, IGD cases develop impulsive tendencies as manifested in impairments to the orbital frontal cortex and the balance mediated by the orbital and ventral medial cortices is infringed upon.

IGD and Cold Executive Function

The ability to suppress automatic and pre-potent response behaviors is critical to the prevention of addictive behaviors. Accordingly, IGD cases showed impairment of inhibition control across many studies (58, 101). Reduction in inhibition of pre-potent responses may essentially make incentive habits more powerful and increase their status to become a "default" automatic habit system (102). This happens because impaired response inhibition could lead to abnormal salience attribution toward gaming-related cues in IGD cases.

Through the paradigms of stop-signal (102) and go/no-go tasks (103), researchers could measure the ability to inhibit advantage response irrelevant to the current task or topic. Subjects were required to withhold response while a particular stop signal (stop-signal task) or stimuli occurs (go/no-go tasks). IGD cases showed impaired inhibition control while they performed relevant go/no-go tasks (such as responding faster to stimuli pictures than to neutral pictures and making more false responses than healthy subjects did) (104–107). A similar picture emerged from studies based on the stop signal task (108, 109). Considering the characteristics of online games, which include many well-designed stimuli (e.g., arousing scenes or pictures), the video-game-special go/no-go task is deemed suitable for videogame addiction research.

Results from recent brain imaging studies suggested that IGD can be associated with a disruption of brain circuits involved in motor response inhibition. Excessive gaming experience is associated with increased gray matter in the right hippocampal formation, dorsolateral PFC, and bilateral cerebellum (110, 111). Resting state studies find decreased functional connectivity in the PFC—striatal circuit in IGD cases (112). Using the go/no-go task, a significantly hyperactive left superior medial frontal and right anterior cingulate cortex during no-go trials was found (105). Using gaming-related picture as cues, healthy controls increased brain activation in the right dorsolateral PFC in comparison with the IGD cases (113). Moreover, 6 months therapy of Bupropion, which is used in the treatment of substance disorders, reduced relevant activations in response to the game-related cues, in IGD cases (114). These results point to possible abnormalities in presumed IGD cases in terms of cold executive function. They show that prolonged playing, sensitizes the impulsive brain systems and when coupled with deficits in executive control (115), it can lead to difficulty to inhibit prepotent game cues and to the emergence of addiction-like symptoms (116).

THE INTEROCEPTIVE PROCESSES (SYSTEM 3)

Previous research has suggested that an interoceptive system can modulate the balance between the impulsive and reflective systems, and that the exacerbated imbalance can help maintaining addictions (20). The main function of interoceptive processes is sensing psychological and physical imbalances and mediating response signals in the form of disgust, craving, urge, etc. as a means to signal the need to restore homeostasis. In the case of addiction, this system mediates anticipation for rewards by translating somatic sensory signals into one's subjectively experience of a desire to engage in the behavior (117–119). This process mainly depends on the structure of bilateral insular cortex (120).

The Insula and IGD

Studies have shown that the insular cortex plays an important role in substance dependence and seeking (121, 122). This happens because the translating of somatic signals into subjective experience of craving increases sensitivity toward addiction-related cues and can reduce inhibition resources availability (118, 120). Indeed, the activation of the insular cortex has been implicated in a wide range of conditions and behaviors, such as anticipating the future results about monetary gains (123) or losses (124). Accordingly, the thickness of insular cortex was negatively associated with cigarette exposure response (125), while damage to the insular cortex could disrupt cigarette smoking; smokers with damage to insula quit smoking easily and show a higher rate of cessation from smoking which is nearly 100 times more than this of smokers without damage to insula (126).

The formation of interoceptive system representation through insular cortex activation is crucial for decision-making regarding prepotent cues (118). Considering the position of the insular cortex in the brain, it can be seen as a bridge between ventromedial and OFC and the impulsive system regions. As such, the insula has been suggested to act as a connector that translates somatic signals and triggers bodily states (118). The co-activation pattern between the insula and the ventromedial frontal cortex has

been revealed during the process of generating somatic markers that involved reference judgments (127). By working in tandem with the vmPFC, the insula could map the relationship between external objects and internal somatic sensory states, and invoke bodily states.

Recent studies also suggest that the insula plays an important role in IGD. They revealed decreased functional connectivity between the insula and the motor/executive cortices (such as dlPFC, OFC, cingulated cortex) in IGD cases (128, 129). This finding revealed weaken connections between the insula and the reflective system among IGD individuals, which might explain loss of control in such cases. As such, in IGD cases the insula can be presumed to have abnormal abilities to communicate with the executive system. While exposed to game-related pictures, the insula has been activated and the activation was positively correlated with self-reported gaming urge stimulated by the pictures (26, 27). This may reveal that the insula is related to the relationship between rewarding cues and the craving level one subjectively experience.

Evidence from co-activation research also suggested strong association between the insula and the impulsive and reflective systems; in the presence of game-related cues, co-activation patterns in orbital frontal cortex, insula, anterior cingulate cortex, and dorsolateral cortex have been observed (26). These findings provide further support to the hypothesis that the key role of the insula is to serve as a hub mediating craving production through communication with impulsive and reflective brain systems.

The insula also plays an important role in the development and maintenance of addiction; it integrates the interoceptive effects of addictive substances or behaviors into conscious awareness, memory, or executive functions (130). In support of this view, research has indicated that deficit in response inhibition is pronounced during periods of heightened motivational state of drug intake (131) or drinking alcohol (132). These deficits are triggered by the high subjective state during the stage of abstinence while the affective stimuli related to the addiction substance consume enormous attentional resources and result in the disruption of inhibitory control. Under such overload of attentional resources, the attraction caused by the stimuli may encourage relapse and make it difficult to overcome tempting addictive behaviors (131, 132). In other words, insula-mediated interoceptive representations have the capacity to "hijack" the cognitive resources necessary for exerting inhibitory control to resist the temptation to smoke, use drugs, or use social media impulsively (20) by disabling activity of the prefrontal (control/reflective) system. The anterior insula has bidirectional connections to the amygdala, ventral striatum, and OFC. The insula integrates the interoceptive state into conscious feelings and into decision-making processes that involve certain risks and rewards; it presents decreased cortical thickness in IGD cases (94, 133). This structural abnormality of the interoceptive system may also hamper self-awareness, which could take the form of failure to recognize an illness (134). Young adults with high levels of IGD often also present depression, anxiety, aggression, or social phobias symptoms (135). Such symptoms may also be associated with dysfunction of the translation of interoceptive signals emerging from somatic and emotional states (136). Moreover, deprivation interoceptive signals (e.g., when one cannot play videogames even if he or she strongly desires to do do) may also hamper metacognitive abilities in addicts (137). This abnormal degree of dissociation in addicted people, between the "object" level and the "meta" level, raises the possibility that poor metacognition lead to action and decision-making monitoring and adjustment (138). Hence, when metacognitive judgment becomes exceedingly disrupted, the repetition of addictive behaviors may be heightened by an underestimation of addiction severity.

The tripartite view that includes three systems of IGD that emerges from this review is presented in **Figure 1**.

DISCUSSION

In this article, we reviewed the neurocognitive processes that may underlie presumed IGD. This is important as many young adults (but not all) lose the ability to resist the reward and pleasure from virtual gaming worlds. That is, for some heavy gamers, an inability to resist unreal rewards emerges, despite mounting monetary, social and performance losses leading to personal, familial, financial, professional, and legal negative consequences. This loss of control that is termed IGD, we argue, may be subserved by a tripartite network of brain systems.

Specifically, the review we provide in this paper suggests that the continuous engagement in videogame playing in IGD cases can be explained by increased automatic motivational response directed at gaming-related behaviors coupled with a lowered efficiency of impulse control and self-reflective processes, and that this imbalance may be further accentuated by abnormal interoceptive awareness processes. This tripartite view of the brain systems involved in addictive disorders (20) as applied to IGD cases here, has received support in various studies; albeit such studies have typically provided a disjointed view regarding the three involved systems. They specifically show that failure to self-control is associated with dysfunction of the impulsive and reflective brain systems (functionally and structurally) and that this dysfunction can be regulated by insular activity, the dysfunction of which can augment the imbalance between reflective and impulsive brain processes. The translation of interoceptive signals in the insula disrupted this balance by changes in somatic states that were aroused by addiction-related stimuli (videogame cues in our case). In addition, impairment in the interoceptive awareness system leads IGD cases to often ignore the negative effects of excessive playing. This increases the probability of relapse in IGD cases. Overall, online gaming provides many rewards to users and can have positive effects on many children (139). However, these same rewards can exploit brain deficits in the impulsive, reflective, and interceptive brain systems and create dysfunctions in learning, motivation, an assessment of the salience of a video game-related stimuli, to such an extent that the vulnerable individual develops addiction-like symptoms in relation to videogame playing.

Previous research has proposed several models of IGD, which are also in line with the framework we present here, but put different emphasis or ignore interoceptive awareness

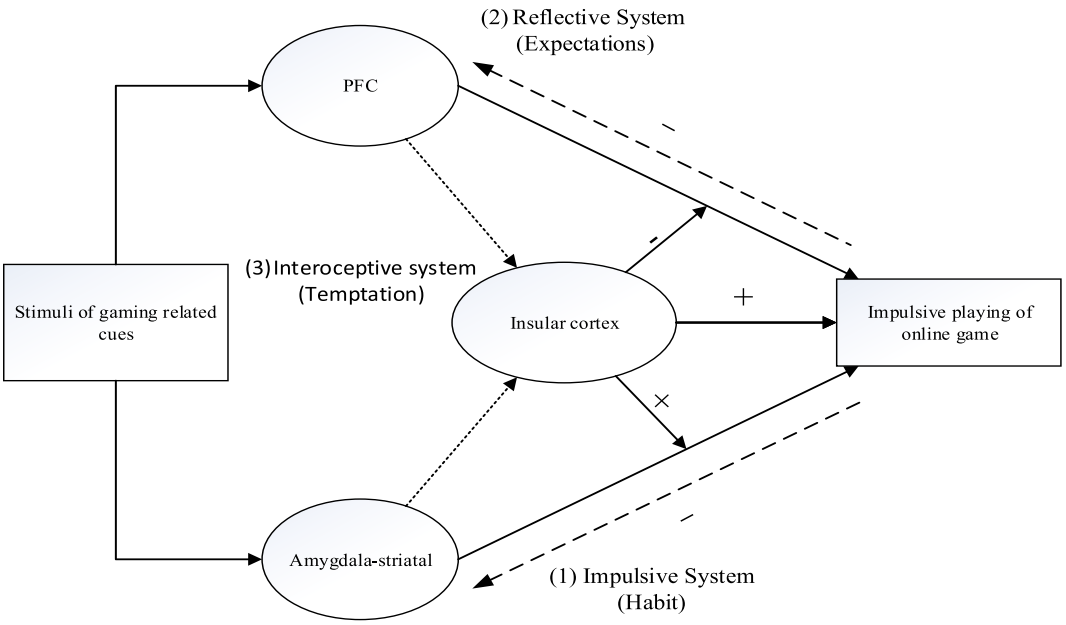

FIGURE 1 | A schematic tripartite neurological model illustrating the key systems that may underlie IGD, (1) gaming related cues excite the impulsive system, which mainly depend on the amygdala and striatum, and activates cue-action links through mental associations, (2) the reflective system mainly depends on the structure of the prefrontal cortex (PFC) and inhibits the impulsions toward an Internet game, (3) the interoceptive awareness systems plays a key role in modulating the equilibrium between system 1 and system 2. Through translating interoceptive signals, the insular cortex maintains craving for an Internet game. The activity of the insular cortex increases the drive to play the Internet game and weakens the inhibition abilities regarding this action. The excessive and problematic play of online games can also invoke changes in the relevant brain regions, and by so doing exacerbate or help expressing other mental health problem.

processes. Davis (140) argued that there are differences between generalized pathological Internet use (GIU) and specific Internet use (SIU) and suggested a cognitive behavior model to explain such differences. According to this model, maladaptive cognition of the external environment drives a series of internal responses such as negative emotions and increases the use of specific rewarding application over the Internet (e.g., online gaming, pornography). This model provides support for the assumptions in our model as both allude to the idea that maladaptive cognitions may underlie IGD; our model points to brain regions that are likely involved in developing and maintaining such cognitions.

On the basis of this research, neurocognitive models have been developed and emphasized the importance of executive function in SIU (18). These overlap with regions we discussed: the VMPFC and dorsolateral lateral PFC are suggested to be most likely involved in development and maintenance of addictive use of Internet applications. Again, this model overlaps some aspects of our model, but our model puts stronger emphasis on interoceptive awareness processes. Similarly, Dong and Potenza (141) proposed a cognitive behavior model for IGD. The model contains three key cognitive domains of IGD: motivational drive and reward-seeking, behavioral control and executive control, and decision-making as related to the long-term negative consequence of current behavioral choices. This model also emphasizes the importance of seeking motivation and the state of craving, and suggests that the state of craving may contribute to the IGD process. This is similar to our model in terms of components but does not specifically focus on the regions involved in craving generation. Similarly, a process model called Person-Affect-Cognition-Execution (I-PACE) suggests that addiction may result from increasing exposure to addiction-related cues and may involve deficits in the personal, affective, cognition, and execution domains. This model is also aligned with our neurocognitive model as personal, affective, cognition and execution domains can be mapped onto the tripartite view we present.

According to our review of neuro-cognitive studies, the dysfunction of brain structure and activations that sub-serves IGD may be similar to this in cases of substance and behavioral addictions. The impairment of the impulsive and reflective processes showed that IGD shares common mechanisms with substance addictions. They showed that prolonged excessive playing can be associated with structural and connectivity abnormalities in relevant brain regions. Importantly, such studies hint at ways through which IGD can be treated; though such approaches should be further examined in future research. First, several studies suggest the bupropion could reduce the craving and urge for video gaming (114, 142). This can be a viable treatment option, but future research should examine its efficacy given different profiles of comorbidity that are plausible in IGD cases.

Second, cognitive behavioral therapy has been most widely used for IGD treatment. It aims at moderating the impulsive processes or at boosting reflective resources such that IGD cases

learn to better cope with their inability to resist gaming. For instance, after recognize the inappropriateness of their behavior, IGD cases may learn to adjust their behavioral patterns and choices (143). Such approaches should also be further studied, especially since they assume relatively intact prefrontal brain regions. This seems to be the case in mild to medium addiction levels (28, 69), but in severe IGD cases, there may be abnormalities in prefrontal regions that will not allow successful cognitive behavioral therapy. This idea merits future research.

AUTHOR CONTRIBUTIONS

LW, OT, AB, and QH were responsible for the study conception and design; LW and SZ wrote the first draft of the paper. SZ, OT, and QH also contributed to the writing of the paper. LW, SZ, OT, AB, and QH made the critical revision of the article. All authors gave the final approval of the article.

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An Update Overview on Brain Imaging Studies of Internet Gaming Disorder

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There are a growing number of studies on structural and functional brain mechanisms underlying Internet gaming disorder (IGD). Recent functional magnetic resonance imaging studies showed that IGD adolescents and adults had reduced gray matter volume in regions associated with attention motor coordination executive function and perception. Adolescents with IGD showed lower white matter (WM) integrity measures in several brain regions that are involved in decision-making, behavioral inhibition, and emotional regulation. IGD adolescents had also disruption in the functional connectivity in areas responsible for learning memory and executive function, processing of auditory, visual, and somatosensory stimuli and relay of sensory and motor signals. IGD adolescents also had decreased functional connectivity of PFC-striatal circuits, increased risk-taking choices, and impaired ability to control their impulses similar to other impulse control disorders. Recent studies indicated that altered executive control mechanisms in attention deficit hyperactivity disorder (ADHD) would be a predisposition for developing IGD. Finally, patients with IGD have also shown an increased functional connectivity of several executive control brain regions that may related to comorbidity with ADHD and depression. The behavioral addiction model argues that IGD shows the features of excessive use despite adverse consequences, withdrawal phenomena, and tolerance that characterize substance use disorders. The evidence supports the behavioral addiction model of IGD by showing structural and functional changes in the mechanisms of reward and craving (but not withdrawal) in IGD. Future studies need to investigate WM density and functional connectivity in IGD in order to validate these findings. Furthermore, more research is required about the similarity in neurochemical and neurocognitive brain circuits in IGD and comorbid conditions such as ADHD and depression.

Keywords: Internet gaming disorder, brain imaging, functional magnetic resonance imaging, dopamine, reward

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INTRODUCTION

The Diagnosis and Brain Imaging of Internet Gaming Disorder (IGD)

Internet gaming disorder involves excessive or poorly controlled preoccupations, urges, or behaviors regarding computer and videogame play that lead to impairment or distress (1). The behavioral addiction model argues that IGD shows the features of excessive use despite adverse consequences, withdrawal phenomena, and tolerance that characterize substance use disorders. There is a debate

whether IGD is the best clinical term for diagnosing Internet addiction, for example, Young argued that IGD is a loss of control over gaming (2, 3) and others have suggested that it is an impulse control disorder (4) or a part of the obsessive-compulsive disorder (5). In the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (6), IGD is identified in Section "Brain Activation" as a condition warranting further clinical research and experience before it might be considered for inclusion as a formal disorder. Previous reviews have described brain-imaging studies in IGD (7–12). In view of the rapid developments in brain research in IGD, particularly in adolescents, this review will summarize these studies and it will describe the gaps in our knowledge on brain imaging of IGD and bring them up to date to April 2017.

In PubMed, a search was conducted using the search terms "Internet addiction," "Internet Gaming Disorder," and "Pathological Internet use," each of which was combined with each of the terms "brain imaging," or "fMRI" or "PET" or "resting state" or "qualitative EEG" using the conjunction "AND." Each term was required to be present in the "Title/Abstract" of the article. The search was further limited by "English" as the publication language and Publication Date from 2008 to April 2017. The only studies that were selected for the review were original research articles that were published in peer-reviewed journals. The search has yielded eligible 98 studies of which 76 were selected including 23 studies of the resting state, 18 studies of functional connectivity, 27 activation studies, and 8 studies of pharmacology. As a general caution, throughout this review, in making group comparisons, there are reported differences between IGD group and control groups but these differences do not imply a causal role of IGD. Group differences may reflect predisposing factors rather than decreases due to IGD.

Brain Imaging Studies of the Resting State in IGD

Excessive Internet game use was associated with abnormal resting state activity in the brain regions that are responsible for impulse control, reward processing, and somatic representation of previous experiences (13). Adolescents with IGD also showed higher global cerebral blood flow in areas that are important for learning and memory (amygdala/hippocampus), conscious urges to use drugs (insula) executive function and inhibition (14). Individuals with IGD showed enhanced regional homogeneity (ReHo) in brain regions that relate with sensory-motor coordination (15, 16) and decreased ReHo in brain regions that are responsible for visual and auditory functions (15). The synchronization among these regions and the frontal lobe supports the evidence for enhancement of reward pathways (17). Both IGD and alcohol use disorder (AUD) patients had increased ReHo in the posterior cingulate cortex (PCC) an area associated with attention, future plans, and retrieval of autobiographical memories, whereas only IGD patients had decreased ReHo in the superior temporal gyrus an area associated with auditory processing and language (18). Scores on Internet addiction severity positively correlated with ReHo in the medial frontal cortex, precuneus/PCC, and left inferior temporal cortex (ITC) among participants with IGD (18). A further clarification as to the difference between IGD and AUD is provided by a recent study on resting-state quantitative electroencephalography (QEEG) patterns associated with IGD and AUD (19). The study showed that lower absolute beta power can be used as a potential trait marker of IGD whereas higher absolute power in the delta band may be a susceptibility marker for AUD. This study clarifies the unique characteristics of IGD as a behavioral addiction, which is distinct from AUD, by providing neurophysiological evidence. In conclusion, studies of the resting state provide preliminary evidence for cognitive function in IGD but apart from a single study (18) they cannot provide evidence as to the development of IGD. The structural changes to brain regions that are involved in the function and maintenance of IGD need further corroboration before any conclusions are drawn.

Studies on the Brain's Gray Matter Volume and White Matter (WM) Density

Early studies showed higher left striatal gray matter volume in IGD participants in functional magnetic resonance imaging (fMRI) and these measures negatively correlated with deliberation time on the Cambridge Gambling Task (20). This study has used a decision-making task that can help clarify the relationships between brain function, i.e., decision-making and structural changes in reward centers in the brain. Participants with IGD had also lower gray matter density (GMD) in areas involved in urges and the regulation of emotional behavior but no causality can be inferred from the results of this study (21). Progamers showed increased gray matter volumes of areas associated with attention and sensory-motor coordination (22). Studies also found lower WM density measures in several brain regions [orbitofrontal cortex (OFC), corpus callosum, cingulate, inferior frontal-occipital fasciculus, and corona radiation, internal, and external capsules] in adolescents with IGD (23). Participants with IGD also showed higher WM density in the thalamus and left PCC and higher WM density in the thalamus was associated with greater severity of IGD (24). Participants with IGD showed decreased gray matter volume in frontal brain regions and reduced WM in the parahippocampal gyrus and the limb of the internal capsule (25). This study showed an association between gray matter atrophy and WM density with length of time of play enabling to assess effects of play on the brain's WM atrophy. Gray matter atrophy was reported in areas involved in cognitive and motor control and reduced WM density in areas involved in cognitive planning and control in IGD (26). Finally, IGD participants had lower GMD in brain regions that are involved in decision-making, behavioral inhibition and emotional regulation and reduced WM density in the inferior frontal gyrus, insula, amygdala, and anterior cingulate (27). In conclusion, these studies indicate preliminary findings of structural changes in gray matter volume and WM density in IGD. Regions consistently shown gray matter volume changes in IGD include the anterior cingulate, supplementary motor areas, cerebellum, insula, and the inferior temporal gyrus (12). There are few studies showing several brain regions that were associated with changes in WM density in IGD and therefore there is a need for studies that will select those regions that were repeatedly associated with structural changes in IGD. Except for a single study

(25) that found an association between gray and WM changes and length of play, no inferences on causality can be drawn.

Recent Studies in Young Adults and Adolescents

Recent studies showed that adolescents with IGD had lower diffusion measures in the areas are associated with attention and control, impulse control, motor function and emotional regulation (28). IGD adolescents also showed reduced gray matter volume in regions associated with attention motor coordination working memory and perception (29) findings that are compatible with studies on gray matter volume in IGD (21, 25, 26). Moreover, gray matter volume of the anterior cingulate cortex (ACC) negatively correlated with response errors on the Stroop task (29). IGD adolescents had reduced gray matter volume in prefrontal cortex and the amygdala that correlated with Barratt Impulsivity Scale hence enabling to make an association between function (impulsivity) and structure (gray matter in the OFC and the amygdala) (27). IGD participants also showed reduced WM density in the ACC and right dorsolateral–prefrontal cortex, regions associated with executive function such as the Stroop task (30). Increased videogame play was associated with delayed development of the OCF, pallidum, putamen, hippocampus, caudate/putamen insula, and the thalamus. Furthermore, higher mean diffusivity measures in the areas of the thalamus, hippocampus, putamen, and the insula was associated with lower intelligence (31). These measures indicate an association between videogame play, intelligence, and brain development but cannot enable any causal inferences. There is also evidence for reduced WM efficiency in the frontal cortex, ACC and pallidum in IGD (32). IGD subjects had also increased WM density and decreased diffusivity in frontal fiber tracts (33). In conclusion, the studies reviewed so far present structural changes in adolescents and young adults with IGD that require replication and validation. Furthermore, these are cross-sectional studies precluding any inference on causality.

See **Table 1** for resting state and structural studies of Internet and gaming disorder.

Cortical Thickness

Studies that measured cortical thickness in fMRI revealed conflicting results of increased and decreased cortical thickness in several brain regions in adolescents with IGD (34, 35). The cortical thickness of the OCF correlated with impaired performance on the color-word Stroop task (35). The apparent contradiction between the two studies showing increased and decreased cortical thickness seems to suggest that the changes are not robust and merit further studies.

FUNCTIONAL CONNECTIVITY

Functional Connectivity at a Resting State

Early studies in participants with IGD showed increased functional connectivity between regions that are associated with cognitive regulation, signal processing, and storage of relevant auditory-verbal memory processes (36). These findings are consistent with current models emphasizing the role of cortical-subcortical pathology in addiction (37). Disruption in functional connectivity in IGD may also affect motivation and reward. Smokers with IGD exhibited decreased functional connectivity with brain regions that are involved in the evaluation and expectancy of reward (38). IGD participants showed reduced connectivity in areas responsible for executive function and increased connectivity in sensory-motor brain networks (39). Lower functional connectivity in IGD affected executive control networks (40). IGD participants also showed increased volume of the caudate and nucleus accumbens as well as reduced resting state functional connectivity of dorsal prefrontal cortex (DLPFC)-caudate and OCF and the nucleus accumbens, regions associated with reward (41). Impulsivity also correlated negatively with functional connectivity between the amygdala, dorsolateral prefrontal cortex, and the OCF (42) and it was associated with alterations over the frontal-limbic connections (43). In conclusion, these are few studies with several regions that have been specifically related to drug addiction but also others that are associated with general cognitive function so more studies need to be conducted in order to select related from unrelated brain regions.

Recent Studies in Adolescents

Consistent with recent models emphasizing the role of cortical–subcortical pathology in addiction, adolescents with IGD showed reduced functional connectivity in cortical–subcortical circuits (44). IGD adolescents had also disruption in the functional connectivity in areas responsible for learning memory and executive function, processing of auditory, visual, and somatosensory stimuli and relay of sensory and motor signals (45). IGD adolescents showed decreased functional connectivity of PFC and striatal circuits areas associated with reward (46). Adolescents with IGD also showed reduced dorsal putamen functional connectivity with the posterior insula-parietal operculum (47). IGD participants had increased volumes of dorsal striatum (caudate) and ventral striatum (nucleus accumbens) (48). IGD participants also exhibited enhanced resting state functional connectivity between the anterior insula and areas that are involved in salience, craving, self-monitoring, and attention (49). Furthermore, IGD participants had stronger functional connectivity between left posterior insula and brain regions indicating reduced ability to inhibit motor responses and control over craving for Internet gaming (49). IGD participants had decreased connectivity measures between parts of the frontal cortex (50). Finally, IGD adolescents demonstrated increased functional connectivity in brain regions involved in working memory, spatial orientation and attention processing (51). In conclusion, participants with IGD showed reduced connectivity in several areas that are responsible for executive function, cognitive control, sensory processing motivation and reward. Some of these regions are common to IGD and substance use disorders but others are associated with general mechanisms of learning, memory and information processing that are not specific to IGD and substance use disorder, so a better selection is required and no inferences on causality can be drawn from present studies. See **Table 2** for studies on functional connectivity in Internet and gaming disorder.

TABLE 1 | Resting state and structural studies of Internet and gaming disorder.[a]

Reference	Methods	Participants	Main findings and evaluations
Park et al. (13)	Regional cerebral metabolic rates of glucose (rCMRglu) in positron-emission tomography (PET)	Eleven Internet and gaming over users and nine control participants	Increased activity in the OFC, striatum, and sensory regions Evaluation—a cross-sectional study with a small number of participants
Liu et al. (16)	Regional homogeneity (ReHo) measure in MRI	Nineteen IGD college students (11 males 8 females) and 19 control participants	Enhanced ReHo in the cerebellum, brainstem, right cingulate gyrus, bilateral parahippocampus, right frontal lobe (rectal gyrus, inferior frontal gyrus and middle frontal gyrus), left superior frontal gyrus, left precuneus, right postcentral gyrus, right middle occipital gyrus, right inferior temporal gyrus, left superior temporal gyrus, and middle temporal gyrus Evaluation—a cross-sectional study—preliminary results
Kuhn et al. (20)	Gray matter volume measure in MRI	Seventy-six frequent compared with 78 infrequent adolescent video game players (14 years old)	Higher left striatal gray matter volume negatively correlated with deliberation time on Cambridge Gambling Task Activity on the Monetary Incentive Delay task was enhanced during feedback of loss compared with no loss Evaluation—a cross-sectional study enables to assess relationships between a cognitive task and brain's GMD
Zhou et al. (21)	Gray matter volume measure in MRI	Eighteen Internet addicted adolescents (16 males 2 females) and 15 control participants (13 males)	Lower gray matter density (GMD) in the left ACC, left PCC, left insula, and left lingual gyrus Evaluation—a cross-sectional study—preliminary results of gray matter in IGD
Yuan et al. (25)	White matter (WM) fractional anisotropy (FA) changes using the diffusion tensor imaging (DTI) in MRI	Eighteen adolescents with IGD (12 males) and 18 control participants	Decreased gray matter volume in the bilateral DLPFC, the SMA, the OFC, the cerebellum and the left rostral ACC. Enhanced FA value of the left PLIC and reduced FA value in the WM within the right PHG Gray matter volumes of the DLPFC, rACC, SMA, and WM FA changes of the PLIC correlated with the duration of Internet addiction Evaluation—a cross-sectional study that enables evaluation of GM and WM changes over time of play
Dong et al. (12)	Regional homogeneity (ReHo) measure in MRI	Fifteen Internet and gaming disorder and 14 control participants	Enhanced regional homogeneity (ReHo) in the brainstem, inferior parietal lobule, left posterior cerebellum, and left middle frontal gyrus, decreased ReHo in temporal, occipital and parietal cortex Evaluation—a cross-sectional study—preliminary findings of ReHo
Han et al. (22)	Gray matter volume measure in MRI	Twenty IGD participants, 18 male control participants and 17 progammers	Increased impulsiveness and perseverative errors, and volume in left thalamus gray matter, but decreased gray matter volume in inferior temporal gyri, right middle occipital gyrus, and left inferior occipital gyrus Evaluation—a cross-sectional study preliminary findings of GM changes
Lin et al. (23)	Brain WM integrity measured by diffusion tensor imaging (DTI) in MRI. Whole brain voxel-wise analysis of fractional anisotropy (FA) was performed by tract-based spatial statistics (TBSS)	Seventeen Internet addiction disorder (14 males) and 16 control adolescents	Lower FA in the OFC, corpus callosum, cingulate, inferior frontal–occipital fasciculus, and corona radiation, internal and external capsules, FA values in the left genu of the corpus callosum negatively correlated with scores on the screen for child anxiety related emotional disorders, and between FA values in the left external capsule and Young's Internet addiction scale Evaluation—a cross-sectional study enables assessment of WM changes in relation to Internet addiction and anxiety severity
Dong et al. (64)	WM integrity using diffusion tensor imaging (DTI) in MRI	Sixteen Internet gaming addicted participants and 15 control participants	Higher fractional anisotropy (FA), in the thalamus and left PCC. Higher FA in the thalamus was associated with greater severity of Internet addiction Evaluation—a cross-sectional study enables evaluation of changes in WM in relation to IGD severity
Weng et al. (26)	GMD and WM density changes using Voxel-based morphometry (VBM) analysis and tract-based spatial statistics (TBSS) was reported	Seventeen IGD participants (13 females and 4 males) and 17 control participants (15 females 2 males)	Gray matter atrophy in the right OFC, bilateral insula, and right supplementary motor area Reduced FA in the right genu of corpus callosum, bilateral frontal lobe WM, and right external capsule. Gray matter volumes of the right OFC, bilateral insula and FA values of the right external capsule positively correlated with Young's Internet addiction scores Evaluation—a cross-sectional study that enables evaluation of GM changes in relation to IGD severity

(*Continued*)

TABLE 1 | Continued

Reference	Methods	Participants	Main findings and evaluations
Hong et al. (35)	Cortical thickness in MRI	Fifteen male adolescents diagnosed with Internet addiction and 15 male control participants	Decreased cortical thickness in the right lateral OFC Evaluation—a cross-sectional study with preliminary results of cortical thickness
Yuan et al. (34)	Cortical thickness in MRI	Eighteen adolescents with Internet gaming disorder and 18 control participants	Increased cortical thickness in the left precentral cortex, precuneus, inferior middle frontal cortex temporal and middle temporal cortices Decreased cortical thicknesses of the left lateral OFC, insula, lingual gyrus, the right postcentral gyrus, entorhinal cortex and inferior parietal cortex Cortical thicknesses of the left precentral cortex, precuneus, and lingual gyrus correlated with duration of online gaming addiction and the cortical thickness of the OCF correlated with the impaired task performance during the color-word Stroop task Evaluation—a cross-sectional study that enables the evaluation of the relationship between cortical thickness and duration of online gaming and also with cognitive performance
Sun et al. (28)	Diffusional kurtosis imaging (DKI) in the detection of gray matter diffusion	Eighteen participants with Internet gaming disorder and 21 control participants	Lower gray matter diffusion in the right anterolateral cerebellum, right inferior and superior temporal gyri, right SMA, middle occipital gyrus, right precuneus, postcentral gyrus, right inferior frontal gyrus, left lateral lingual gyrus, left paracentral lobule, left ACC, and median cingulate cortex, bilateral fusiform gyrus, insula, PCC, and thalamus Higher GM volume in the right inferior and middle temporal gyri, and right PHG, and lower volume in the left precentral gyrus Evaluation—a cross-sectional study that measures GM diffusion—preliminary findings
Son et al. (19)	Resting-state quantitative electroencephalography (QEEG)	Thirty-four participants with IGD, 17 with AUD, and 25 healthy control participants	IGD participants had lower absolute beta power than AUD and the healthy control group. The AUD group showed higher absolute delta power than IGD and the healthy control group. No significant correlations between the severity of IGD and QEEG activities in patients with IGD Evaluation—a cross-sectional study—enables evaluation of EEG in relation to IGD severity
Wang et al. (24)	Gray matter volume measure in MRI	Twenty-eight Internet participants with Internet gaming disorder and 28 control participants	Gray matter volume of the bilateral ACC, precuneus, SMA, SPL, left DLPFC, left insula, and bilateral cerebellum decreased in IGD participants compared with healthy control participants Gray matter volume of the ACC negatively correlated with the incongruent response errors on the Stroop Evaluation—a cross-sectional study that enabled assessment of relationship between GM changes with cognitive performance
Kim et al. (18)	Regional homogeneity (ReHo) measure in MRI	Sixteen patients with Internet gaming addiction (IGD), 14 alcohol use disorder (AUD), and 15 control participants	IGD and AUD participants had increased ReHo in the PCC. IGD participants showed decreased ReHo in the right superior temporal gyrus compared with AUD and control participants. Patients with AUD showed decreased ReHo in the ACC Scores on Internet addiction severity positively correlated with ReHo in the medial frontal cortex, precuneus/PCC, and left inferior temporal cortex (ITC) among participants with IGD Evaluation—a cross-sectional study that enabled a comparison of ReHo measures between IGD and AUD. The study enabled assessment of relationship between ReHo measures with IGD severity
Lin et al. (27)	GMD and WM density changes using voxel-based morphometric analysis in MRI	Thirty-five participants with Internet gaming disorder and 36 control participants	Lower GMD in the bilateral inferior frontal gyrus, left cingulate gyrus, insula, right precuneus, and right hippocampus. Lower WM density in the inferior frontal gyrus, insula, amygdala, and anterior cingulate Evaluation—a cross-sectional study with a large number of participants enables GM and WM analysis in IGD
Takeuchi et al. (32)	Diffusion tensor imaging mean diffusivity (MD)	A hundred and fourteen boys and 126 girls	The amount of videogame play was associated with increased MD in the left middle, inferior, and orbital frontal cortex; left pallidum; left putamen; left hippocampus; left caudate; right putamen; right insula; and thalamus in both cross-sectional and longitudinal analyses Higher MD in the areas of the left thalamus, left hippocampus, left putamen, left insula, and left Heschl gyrus was associated with lower intelligence Evaluation—a cross-sectional study with a very large sample enables cross-sectional and longitudinal assessment of diffusion in the brain

(*Continued*)

TABLE 1 | Continued

Reference	Methods	Participants	Main findings and evaluations
Yuan et al. (30)	White matter (WM) integrity and connectivity	Twenty-eight IGD adolescents and 25 control participants	Reduced FA in the ACC-right dorsolateral prefrontal cortex pathways in IGD Evaluation—a cross-sectional study assessing WM integrity
Zhai et al. (32)	WM integrity measured with diffusion tensor imaging (DTI)	Sixteen right-handed adolescents with IGD and 16 control participants	Reduced nodal efficiency in frontal cortex, ACC, and pallidium in IGD. The global efficiency of WM network correlated with the IAT scores in IGD Evaluation—a cross-sectional study assessing WM integrity and also enabled assessment of the relationships between WM changes and IGD severity
Jeong et al. (33)	WM integrity and connectivity	A hundred and eighty-one male patients including 58 of IGD subjects without psychiatric comorbidity and 26 male control subjects	Increased FA values within forceps minor right anterior thalamic radiation, right corticospinal tract, right inferior longitudinal fasciculus, right cingulum to hippocampus and right inferior fronto-occipital fasciculus (IFOF) decreases in RD value within forceps minor, right anterior thalamic radiation, and IFOF relative to control subjects Evaluation—a cross-sectional study assessing WM integrity and connectivity
Park et al. (92)	Qualitative EEG	Sixteen adolescent males with ADHD and IGD, 15 adolescent males with ADHD-only, and 15 healthy adolescent males	Compared to the ADHD-only group, the ADHD + IGD group showed lower relative delta power and greater relative beta power in temporal regions. The relative theta power in frontal regions was higher in ADHD-only group compared to HC group. Increased neuronal connectivity within the parieto-occipital and temporal regions for the ADHD + IGD group Evaluation—a cross-sectional study assessing qualitative EEG—low localization
Youh et al. (95)	Qualitative EEG	Fourteen males with MDD and IGD and 15 male with MDD-only	An association between decreased interhemispheric connectivity in the frontal region and vulnerability to attention problems in patients with MDD and IGD Interhemispheric and intrahemispheric coherence value for the alpha band was significantly lower in MDD + IGD than MDD-only patients. Intrahemispheric coherence values for the beta band were higher in MDD + IGD than MDD-only patients. Increased intrahemisphere connectivity in the frontal–temporal–parietal–occipital areas may result from excessive online gaming Evaluation—a cross-sectional study assessing qualitative EEG—low localization

[a]*Studies arranged chronologically.*

DLPFC, dorsolateral prefrontal cortex; SMA, supplementary motor area; OFC, orbitofrontal cortex; ACC, anterior cingulate cortex; PLIC, posterior limb of the internal capsule; PHG, parahippocampal gyrus; PCC, posterior cingulate cortex; STG, superior temporal gyrus; MPFC, medial prefrontal cortex; AG, angular gyrus; SPL, superior parietal lobule.

BRAIN ACTIVATION

Cue-Exposure Activation Studies of Videogame Urges

Males with IGD had greater activation in the meso-cortico-limbic system compared with females while playing a space-infringement game (52). Several frontal striatal and limbic brain regions were activated in IGD participants in fMRI (53). A longitudinal study of cue-reactivity found activation in the ACC and OCF of IGD participants over 6 weeks in fMRI (54). Gaming cues also activated regions that are associated with urges to play games (55). Furthermore, Gaming and smoking cues shared similar mechanisms of cue-induced reactivity of the frontal-limbic network (56). Exposure to World of Warcraft game figures activated brain regions that were associated with cognitive, emotion and motivation-related function in IGD participants (57). IGD participants had increased activation in regions that are associated with visuospatial orientation, space, attention, mental imagery and executive function (58). IGD participants also showed attention bias to short presentations of game pictures and enhanced brain responses in the medial prefrontal cortex and the ACC (59). IGD adolescents showed activation of areas associated with visual–spatial attention and body self-awareness during ball-throwing animations simulating the experience of "disembodied state" in cyberspace (60, 61). In conclusion, several studies have shown a consistent pattern of brain regions that were activated in response to video playing stimuli in IGD. Secondly, studies that use tasks that simulate reward (15) enable to assess the effects of cue exposure on the brain. Finally, only a single brain-imaging study (54) followed cue-activation over time enabling an assessment of causality.

Recent Activation Studies in IGD

Internet gaming disorder participants exhibited higher cue-induced activations within the ventral and dorsal striatum compared with healthy control participants (62). There was a positive correlation between dorsal striatum activation and duration of IGD indicating a transition from ventral to dorsal striatal processing among individuals with IGD (60). Second, Internet gaming addiction appears to be associated with increased

TABLE 2 | Studies of functional connectivity in fMRI.[a]

Reference	Method	Participants	Main findings and evaluation
Ding et al. (36)	Functional connectivity in fMRI	Seventeen adolescents with Internet gaming disorder and 24 control adolescents	Increased functional connectivity in the bilateral cerebellum posterior lobe and middle temporal gyrus. Decreased connectivity in the bilateral inferior parietal lobule and right inferior temporal gyrus. Connectivity with the PCC positively correlated with Internet Addiction Scores in the right precuneus, PCC, thalamus, caudate, nucleus accumbens, SMA, and lingual gyrus. It negatively correlated with the right cerebellum, anterior lobe and left SPL Evaluation—a cross-sectional study assessing functional connectivity. Enables assessment of the relationship between connectivity and IGD severity
Hong et al. (47)	Functional connectivity in fMRI	Twelve adolescents with Internet addiction and 11 control participants	Reduced functional connectivity in corticosubcortical circuits (~24% with prefrontal and ~27% with parietal cortex). Bilateral putamen was the most extensively involved subcortical brain region Evaluation—a cross-sectional study assessing functional connectivity
Feng et al. (14)	Arterial spin-labeling (ASL) perfusion in fMRI	Fifteen adolescents with IGA and 18 control adolescents	Higher global cerebral blood flow (CBF) in the left inferior temporal lobe/fusiform gyrus, left PHG/amygdala, right medial frontal lobe/ACC, left and right insula, right middle temporal gyrus, right pre-central gyrus, left SMA, left cingulate gyrus, and right inferior parietal lobe. Lower CBF in the left middle temporal gyrus, left middle occipital gyrus, and right cingulate gyrus Evaluation—a cross-sectional study assessing perfusion. Preliminary findings
Wee et al. (45)	Functional connectivity in fMRI	Seventeen adolescents with IGD and 16 control participants	Disruption in the functional connectivity with the frontal, occipital, and parietal lobes Functional connectivity with the frontal, occipital, and parietal lobes correlated with the IAD severity Evaluation—a cross-sectional study assessing functional connectivity. Enables assessment of the relationship between connectivity and IGD severity
Chen et al. (38)	Functional connectivity in fMRI	Twenty-nine smokers with IGD, 22 non-smokers with IGD, and 30 control participants	Decreased resting state functional connectivity with posterior cingulate cortex in the right rectus gyrus. Increased resting state functional connectivity with the left middle frontal gyrus in smokers with IGA compared with non-smokers with IGA Evaluation—a cross-sectional study assessing functional connectivity. Enables assessment of the relationship between connectivity and IGD severity.
Dong et al. (40)	Functional connectivity in fMRI	Thirty-five IGD and 36 control participants	Lower functional connectivity in executive control networks. 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 Evaluation—a cross-sectional study assessing functional connectivity. Enables assessment of the relationship between connectivity and cognitive function
Ko et al. (42)	GMD and functional connectivity in fMRI	Thirty males with IGD and 30 control participants	Lower GMD in the bilateral amygdala and higher impulsivity. Lower functional connectivity with the left amygdala over the left DLPFC and with the right amygdala over the left DLPFC and OFC. Higher functional connectivity with the bilateral amygdala over the contralateral insula The functional connectivity between the left amygdala and DLPFC negatively correlated with impulsivity. The functional connectivity of the right amygdala to the left DLPFC and OFC also negatively correlated with impulsivity Evaluation—a cross-sectional study assessing functional connectivity. Enables assessment of the relationship between connectivity and impulsivity
Hong et al. (47)	Functional connectivity in fMRI in subdivisions of striatum	Twelve male adolescents with Internet gaming disorder and 11 male control participants	Reduced dorsal putamen functional connectivity with the posterior insula-parietal operculum. Time spent playing online games predicted significantly greater functional connectivity between the dorsal putamen and bilateral primary somatosensory cortices Lower functional connectivity between the dorsal putamen and bilateral sensorimotor cortices in healthy control participants Evaluation—a cross-sectional study assessing functional connectivity. Enables assessment of the relationship between connectivity and time spent playing online
Wang et al. (50)	Functional connectivity and voxel-mirrored homotopic connectivity (VMHC) method	Seventeen participants with IGD and 24 healthy control participants	Decreased VMHC between the left and right superior frontal gyrus (orbital part), inferior frontal gyrus (orbital part), middle frontal gyrus, and superior frontal gyrus Evaluation—a cross-sectional study assessing functional connectivity
Zhang et al. (49)	Functional connectivity of the insula in fMRI	Seventy-four young adults with Internet gaming disorder (IGD) and 41 control participants	Enhanced functional connectivity between the anterior insula and a network of regions including ACC, putamen, angular gyrus, and precuneous. Stronger functional connectivity between the posterior insula and postcentral gyrus, pre-central gyrus, SMA, STG. IGD severity was positively associated with connectivity between the anterior insula and AG, and STG, and with connectivity between the posterior insula and STG. Duration of Internet gaming was positively associated with connectivity between the anterior insula and ACC Evaluation—a cross-sectional study assessing functional connectivity. Enables assessment of the relationship between connectivity and duration of Internet gaming

(*Continued*)

TABLE 2 | Continued

Reference	Method	Participants	Main findings and evaluation
Cai et al. (48)	Functional connectivity in fMRI in striatal nuclei (caudate, putamen, and nucleus accumbens) volumes	Twenty-seven adolescents with IGD and 30 control participants	Increased volumes of dorsal striatum (caudate) and ventral striatum (nucleus accumbens) and more errors on the Stroop task. Caudate volume correlated with Stroop task performance and nucleus accumbens (NAc) volume was associated with the Internet addiction test (IAT) score in the IGD group Evaluation—a cross-sectional study assessing functional connectivity with the striatum. Enables assessment of the relationship between volume of the striatum with cognitive performance and IGD severity
Du et al. (51)	Functional connectivity density (rsFCD) in fMRI	Twenty-seven male IGD adolescents and 35 healthy control participants	IGD adolescents exhibited higher global/long-range rsFCD in the bilateral dorsal lateral prefrontal cortex (DLPFC) and the right inferior temporal cortex (ITC)/fusiform compared with healthy control participants Evaluation—a cross-sectional study assessing functional connectivity
Jin et al. (46)	Functional connectivity	Twenty-five adolescents with IGD and 21 age- and gender-matched control participants	Decreased functional connectivity between the insula, and temporal and occipital cortices and dorsal striatum, pallidum, and thalamus in IGD. Some of those changes were associated with the severity of IGD Evaluation—a cross-sectional study assessing functional connectivity. Enables assessment of the relationship between connectivity and IGD severity
Wang et al. (39)	Functional connectivity	Thirty-seven IGD subjects and 35 matched control subjects	Reduced connectivity in the prefrontal cortex, left posterior cingulate cortex, right amygdala, and bilateral lingual gyrus, and increased functional connectivity in sensory-motor-related brain networks in IGD Evaluation—a cross-sectional study assessing functional connectivity
Zhang et al. (49)	Functional connectivity of insula-based network	Seventy-four young adults with IGD and 41 age- and gender-matched control subjects	Enhanced functional connectivity between the anterior insula and the ACC, putamen, angular gyrus, and precuneous. Stronger functional connectivity between the posterior insula and postcentral gyrus, precentral gyrus, supplemental motor area, and superior temporal gyrus (STG). IGD severity was positively associated with connectivity between the anterior insula and angular gyrus, and STG, and with connectivity between the posterior insula and STG. Duration of Internet gaming was positively associated with connectivity between the anterior insula and ACC Evaluation—a cross-sectional study assessing functional connectivity. Enables assessment of the relationship between connectivity and duration of Internet gaming
Du et al. (51)	Functional connectivity	Twenty-seven male IGD adolescents and 35 control participants	Enhanced functional connectivity in the bilateral dorsal lateral prefrontal cortex (DLPFC) and the right inferior temporal cortex (ITC)/fusiform Evaluation—a cross-sectional study assessing functional connectivity
Park et al. (10, 43, 92)	Functional connectivity in fMRI	Nineteen Internet gaming disorder adolescents and 20 age-matched control participants	Higher impulsiveness and higher global efficiency and lower local efficiency pathological states. Topological alterations were specifically attributable to inter-regional connections incident on the frontal region, and the degree of impulsiveness was associated with the topological alterations over the frontal-limbic connections Evaluation—a cross-sectional study assessing functional connectivity
Yuan et al. (41)	Functional connectivity in fMRI	Twenty-eight IGD adolescents and 25 control participants	Reduced FA in salience network, right central executive network tracts, and between-network (the ACC-right DLPFC tracts). Correlation between the effective and structural connection from salience network to central executive network and the number of errors during incongruent condition in Stroop task in both IGD and control participants Evaluation—a cross-sectional study assessing functional connectivity. Enables assessment of the relationship between connectivity and cognitive performance

[a]*Studies arranged chronologically.*

DLPFC, dorsolateral prefrontal cortex; SMA, supplementary motor area; OFC, orbitofrontal cortex; ACC, anterior cingulate cortex; PLIC, posterior limb of the internal capsule; PHG, parahippocampal gyrus; PCC, posterior cingulate cortex; STG, superior temporal gyrus; MPFC, medial prefrontal cortex; AG, angular gyrus; SPL, superior parietal lobule.

identification with one's avatar, indicated by high left Angular Gyrus activations in pathological Internet gamers (63). This experimental manipulation can suggest how self-identification during videogame play can affect brain mechanisms responsible for processing of auditory, visual and somatosensory modalities. Addiction to social networks was characterized by emotion regulation deficits reflected by reduced striatal activation during self-reflection compared to during ideal reflection in IGD players (63). This is an experimental manipulation of self-reflection which is related to brain activation and possibly can imply how the two interact. In conclusion, several studies have shown a consistent pattern of brain activation in response to video playing stimuli that is similar to activation of drug cues. Regions consistently activated by cue-exposure were the caudate nucleus, OCF, dorsolateral prefrontal cortex, inferior frontal cortex, anterior cingulate, PCC, para-hippocampus, and the precuneus (12). A single study (62) found an association between parts of the striatum and duration of IGD indicating long-term changes as result of play. These studies show how cue exposure can affect the brain's reward, processing of sensory information and self-reflection.

Inhibitory Control Mechanisms

Individuals with IGD display faulty inhibitory control mechanism such as impaired response inhibition on the Stroop task and

related activity in the anterior and PCC (64). IGD participants also committed more commission errors on Go/No Go tasks and impaired response inhibition under gaming cue distraction (65). Impulsivity and response inhibition were associated with impaired function in the insula and greater activation of the frontal–striatal network in IGD (66). IGD participants also showed greater impulsivity and lower activity of motor areas while performing the Go/No Go task (67). In adolescents with IGD, there was increased activity in attention, and motor areas during No-Go trials (68). IGD participants failed to recruit frontal–basal ganglia pathway and inhibit unwanted actions on the Go-Stop paradigm (69). Furthermore, IGD participants showed higher activations when processing Internet gaming-related stimuli on a modified Stroop task in brain areas that are involved in selective attention, visual processing, working memory, and cognitive control (70).

Recent Studies in IGD

A recent study found decreased left middle and superior temporal gyrus activation during interference of socially anxious words in IGD, possibly indicating social anxiety (71). A meta-analysis concluded that individuals with IGD are more likely to exhibit impaired response inhibition (72). In conclusion, these are consistent findings that the impairment in performance of response inhibition tasks is followed by failure to recruit frontal–basal ganglia pathways and use of other brain areas during inhibition in both adolescents and adults with IGD.

Reward

Internet gaming disorder is associated with faulty decision-making and preference for immediate reward to long-term gains. IGD individuals subjectively experienced monetary gain and loss during the performance of a guessing task (73). IGD participants also showed increased activation in OCF in gain trials and decreased activation in the ACC during loss trials implicating enhanced reward sensitivity and decreased loss sensitivity. IGD participants also showed increased brain activity in other regions (the inferior frontal cortex, insula, ACC) and decreased activation in the caudate and PCC after continuous wins during performance on a continuous wins-and-losses task in fMRI (74). Finally, IGD participants preferred the probabilistic options to fixed ones and were faster to respond compared with control participants while performing on a probability-discounting task in fMRI (75). They also showed decreased activation in the inferior frontal gyrus and the precentral gyrus when choosing the probabilistic options than control participants. IGD participants also showed selection of risk-disadvantageous choices, and they make risky decisions more hastily and with less recruitment of regions implicated in impulse control (76). IGD adolescents had decreased reward sensitivity and they have been only sensitive to error monitoring regardless of positive feelings, such as sense of satisfaction (77). These finding imply impaired decision-making together with enhanced compensatory brain mechanisms that are consistent with impulsive decision-making.

Recent Studies in IGD Participants

A recent study showed that negative outcomes affected the covariance between risk level and activation of brain regions related to value estimation (prefrontal cortex), anticipation of rewards (Ventral Striatum), and emotional-related learning (hippocampus) which may be one of the underlying neural mechanisms of disadvantageous risky decision-making in adolescents with IGD (78). IGD participants exhibited stronger functional connectivity when selecting small and immediate gains on a delay-discounting task (79). The results indicated that IGD participants have enhanced sensitivity to reward and decreased ability to control their impulsivity effectively, which leads to suboptimal decision-making (79). Males with IGD showed decision-making deficits indicating an imbalance between hypersensitivity for reward and weaker risk experience and self-control for loss (62). A recent review has suggested that both patients with IGD and those with pathological gambling exhibit decreased loss sensitivity; enhanced reactivity to gaming and gambling cues, enhanced impulsive choice behavior aberrant reward-based learning; and no changes in cognitive flexibility (80). In conclusion, IGD adolescents showed disadvantaged increased risk-taking choices and impaired ability to control their impulses similar to other impulse control disorders. The advantage of these studies is the use of simulated decision-making tasks to assess the effects of faulty decision-making processes on brain mechanisms responsible for reward.

BRAIN IMAGING STUDIES ON DOPAMINE, 5-HT AND COMORBID PSYCHIATRIC DISORDERS

Neurotransmitters such as DA, serotonin (5-HT) play an important role in drug and alcohol dependence, mainly by mediating dopamine reward and withdrawal mechanisms (81, 82). Consistent with evidence in drug and AUDs which are associated with deficient dopamine reward activity (83–86) IGD participants showed reduced levels of dopamine D_2 receptor availability in the striatum (87) and reduced striatal dopamine transporter (DAT) availability (88). Finally, male IGD participants showed a significant decrease in glucose metabolism in the prefrontal, temporal, and limbic regions and lower levels of D_2 receptor availability in the striatum (89). The results indicate that D_2 receptor-mediated dysregulation of the OCF could underlie a mechanism for loss of control and compulsive behavior in IGD. Since there is no baseline measure of dopamine levels before the addiction it is not possible to determine whether dopamine deficiency is a predisposing factor for drug and AUD disorders or IGD. Magnetic resonance spectroscopy studies showed lower levels of N-acetylaspartate in the right frontal cortex and of choline in the medial temporal cortex in IGD participants that are similar to those of patients with attention deficit hyperactivity disorder (ADHD) and clinical depression (90). The studies so far support the evidence for deficient dopaminergic reward activity that classifies IGD as a behavioral addiction. The association between IGD and impaired self-regulation is also compatible with the model of IGD as an impulse control disorder lying within the impulsive–compulsive spectrum (1).

Recent Studies on Comorbidity of IGD with ADHD and Depression

A recent study found that individuals with IGD showed altered PCC functional connectivity that might be dependent upon history of childhood ADHD (91). These findings suggest that altered neural networks for executive control in ADHD would be a predisposition for developing IGD. Furthermore, a study that used qualitative EGG to compare adolescents with IGD with or without ADHD found that Adolescents who show greater vulnerability to ADHD seem to continuously play Internet games to enhance attentional ability (92). Second, repetitive activation of brain reward and working memory systems during continuous gaming may result in an increase in neuronal connectivity within the parieto-occipital and temporal regions for the comorbid ADHD and IGD participants (92). Finally, a study that investigated the comorbidity of IGD with depression found that IGD participants with comorbid major depressive disorder (MDD) who performed on the Wisconsin card sorting task showed failure to suppress activity in the hippocampus during an attention demanding task, possibly as a consequence of depression (93). Patients with IGD have also shown an increased functional connectivity of several executive control brain regions that may relate to psychiatric comorbidity with ADHD and depression (94). Comorbidity of IGD with MDD was also indicated by decreased inter-hemispheric connectivity in the frontal region and vulnerability to attention problems in a study that used qualitative EEG (95). Furthermore, increased intrahemisphere connectivity in the fronto-temporo-parieto-occipital areas may result from excessive online gaming. The comorbidity with depression and ADHD may also associated with dopamine deficiency in IGD. Further studies need to investigate the similarity in neurochemical and neurocognitive brain circuits in IGD and comorbid conditions such as ADHD and depression.

DISCUSSION

The studies reviewed so far show consistent findings demonstrating the resemblance between the neural mechanisms underlying substance use disorder and IGD. The behavioral addiction model argues that IGD shows the features of excessive use despite adverse consequences, withdrawal phenomena, and tolerance that characterize substance use disorders. The evidence supports the behavioral addiction model of IGD by showing structural and functional changes in the mechanisms of reward and craving (but not withdrawal) in IGD. A recent meta-analysis found a significant activation of brain regions that mediate reward (the bilateral medial frontal gyrus and the left cingulate gyrus) in IGD (96). These studies support the notion that IGD is associated with changes to the brain's reward system and mechanisms of loss of control and inhibition. There is also longitudinal evidence that pharmacological treatment with medication such as bupropion can attenuate cue reactivity in IGD (97) similar to the attenuation that occurs in nicotine-dependent users (98). IGD is associated with reduced brain's DAT density and lower dopamine D_2 receptor occupancy. It seems that excessive use of the brain's dopamine reward system resembles the downregulation seen in case of drug and alcohol abuse, although in both disorder there are no baseline measures prior to the addiction precluding any inferences about causality. Finally, there is pharmacogenetic evidence that dopaminergic genes (Taq1A1 variation of dopamine D_2 receptor and low activity Val158Met in the catecholamine-O-methyltransferase alleles) (99) and serotonergic genes (SS-5HTTLPR) together with personality factors may play a role in the vulnerability to IGD (100). The evidence for genetic dopaminergic vulnerability is compatible with the behavioral addiction model of IGD and consequently, IGD may be classified as a reward deficiency syndrome (101, 102). The evidence of genetic serotonergic vulnerability and brain imaging studies support the evidence of comorbidity of IGD with anxiety OCD and depression. Finally, playing games may be actually good for you and recent studies showed that playing computer game could improve the brain's plasticity and thus be advantageous to certain conditions such as posttraumatic stress disorder, schizophrenia, and neurodegenerative disease (103).

One of the major limitations in brain imaging studies of IGD is they are mainly cross-sectional studies without baseline measures that rely on associations between structural and functional brain changes in the brain and Internet and videogame characteristics. These associations do not provide any proof that IGD activity plays a causal role in the development of the adolescent or adult brain. There are factors that may mediate such associations such as educational, cognitive, emotional and social factors. There are methodological considerations of age (use of adolescents and students), culture (most studies were done in the Far East), and lack of comparison groups with substance use disorders and these are major limitations of the studies that were reviewed so far. Finally, very few studies looked at sex differences in cognitive and brain function in IGD.

CONCLUSION

There is an emerging evidence that IGD is associated with similar brain mechanisms responsible for substance use disorders. The brain imaging studies in IGD show similarity in brain mechanisms between IGD and substance use disorder and therefore support the classification of IGD as a behavioral addiction.

AUTHOR CONTRIBUTIONS

AW contributed substantially to the conception and design of the review.

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Impaired Feedback Processing for Symbolic Reward in Individuals with Internet Game Overuse

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Reward processing, which plays a critical role in adaptive behavior, is impaired in addiction disorders, which are accompanied by functional abnormalities in brain reward circuits. Internet gaming disorder, like substance addiction, is thought to be associated with impaired reward processing, but little is known about how it affects learning, especially when feedback is conveyed by less-salient motivational events. Here, using both monetary (±500 KRW) and symbolic (Chinese characters "right" or "wrong") rewards and penalties, we investigated whether behavioral performance and feedback-related neural responses are altered in Internet game overuse (IGO) group. Using functional MRI, brain responses for these two types of reward/penalty feedback were compared between young males with problems of IGO (IGOs, n = 18, mean age = 22.2 ± 2.0 years) and age-matched control subjects (Controls, n = 20, mean age = 21.2 ± 2.1) during a visuomotor association task where associations were learned between English letters and one of four responses. No group difference was found in adjustment of error responses following the penalty or in brain responses to penalty, for either monetary or symbolic penalties. The IGO individuals, however, were more likely to fail to choose the response previously reinforced by symbolic (but not monetary) reward. A whole brain two-way ANOVA analysis for reward revealed reduced activations in the IGO group in the rostral anterior cingulate cortex/ventromedial prefrontal cortex (vmPFC) in response to both reward types, suggesting impaired reward processing. However, the responses to reward in the inferior parietal region and medial orbitofrontal cortex/vmPFC were affected by the types of reward in the IGO group. Unlike the control group, in the IGO group the reward response was reduced only for symbolic reward, suggesting lower attentional and value processing specific to symbolic reward. Furthermore, the more severe the Internet gaming overuse symptoms in the IGO group, the greater the activations of the ventral striatum for monetary relative to symbolic reward. These findings suggest that IGO is associated with bias toward motivationally salient reward, which would lead to poor goal-directed behavior in everyday life.

Keywords: Internet gaming disorder, feedback learning, reward value, ventromedial prefrontal cortex, ventral striatum

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INTRODUCTION

Excessive Internet gaming in adolescents and young adults has been a growing public health concern due to its negative psychological and social consequences, including sleep abnormalities, lower well-being, depression, low academic achievement, and job loss [for reviews, see Ref. (1)]. Like pathological gambling disorder, the behavioral and neurological characteristics of this behavioral problem, which is often called Internet gaming disorder (IGD), seem to include the intolerance, craving, and withdrawal symptoms associated with substance abuse (2).

In all addiction, disruption of the dopaminergic mesolimbic system is known to underlie a pathologically persistence that is driven by positive outcomes, despite possible negative consequences (3, 4). Just as those with cocaine addiction show distorted sensitivity to positive and negative outcomes (5, 6), individuals with IGD also fail to utilize either positive or negative outcome during a guessing task (7–9). Relative to normal healthy individuals, those with IGD also show enhanced activation in the orbitofrontal cortex for positive outcomes and decreased activation in anterior cingulate for negative outcomes (7). Reduced activations were also reported for individuals with IGD in various subcortical regions, depending on reward types (e.g., monetary reward, social reward, and performance feedback) for a simple left/right discrimination task (10).

The dopaminergic mesolimbic system is known to be involved in the experience of hedonic feelings (10), reward prediction (11), and reinforcement learning based on reward-prediction errors (12–14). Increases of neural response have been reported in the ventral striatum (VS) and ventromedial prefrontal cortex (vmPFC) in response to cues associated with addictions, such as nicotine (15) or cocaine (16) addiction. Greater responses in orbitofrontal cortex were also observed in individuals with IGD (7, 17) and pathological gambling (18, 19), which is in line with the "incentive sensitivity hypothesis" (20). Addiction, however, has also been associated with deficits in the dopaminergic reward system, leading to the "reward deficiency hypothesis" (21) in which problems of substance addiction are viewed as compensatory behavior for deficiencies in the reward system (22). Consistent with this view, IGD individuals showed reduced levels of dopamine D_2 receptor availability and dopamine transporter (23, 24), as well as reduced striatum activation for cues predicting monetary reward during Internet games (25, 26). Both views may explain the poor academic achievement often observed in adolescents and young adults with IGD (27). For example, the selective sensitivity to positive feedback may be related to problems in school or everyday life, where appreciation of reward is based on internal motivation (recognition or awareness of one's progress), not on external incentive (e.g., monetary gain or loss). Alternatively, the deficits in reward processing associated with reduced brain responses may impair feedback processing in learning, including both reward processing for positive outcomes and error processing for negative outcomes.

In human learning, the ability to adjust or maintain one's future behavior involves various cognitive functions, ranging from forming stimulus-response associations based on the repetitive experience of the outcome, to evaluating the value of the outcome itself, to exerting attentional control for remembering the stimulus-response-outcome sequence. The efficiency of feedback processing is often affected by the value of the outcome (such as its saliency), as well as by individual differences in the capacity of attention or memory control. Given that there is a bias in value processing (e.g., overvaluation of game-rewards) in IGD individuals (28), several learning deficits may be predicted for feedback/reinforcement learning. However, impairments in learning from rewards are not easily separated from those involving penalty, since both reward and penalty serve independently as feedback in reinforcement learning (29). One approach to examining how a deficit or bias in reward processing in IGD influences feedback learning may be to isolate the results of information processing of reward from those of penalty in terms of the rate of behavioral adjustments in future response selection.

In this study, in order to understand the effect of IGD on feedback learning, young male adults at high risk for IGD [i.e., problematic Internet game overuse (IGO)] were examined during a visuomotor association learning task. Identification of the neural mechanisms and behavioral features associated with feedback learning in individuals with IGO should provide further understanding of the reward-related problematic behaviors observed in IGD. We hypothesize that feedback processing during learning would be altered, which, therefore, would result in differences in behavioral performance and neuronal responses in individuals with IGO relative to controls. A primary goal, therefore, was to determine whether and to what extent different types of feedback result in differences in learning and brain responses between IGO individual and controls. In order to separate the effects of reward from penalty feedback on learning, we analyzed the rates of staying with the same response after each reward and the rate of switching to a different choice after penalty. As well as impaired reward processing, abnormal insular and anterior cingulate cortex responses associated with response inhibition or error processing have been reported in IGD individuals (8, 30). Thus, it is conceivable that alterations in feedback processing of reward and/or penalty would be reflected in the responses of brain regions related to reward and/or penalty, respectively. In order to assess feedbacks of different motivational saliency, we compared the effects of monetary and symbolic feedback. If IGO is associated with greater bias toward externally salient incentive relative to less-salient ones, we would predict that the effect of saliency on learning would be greater for those with IGO than those without IGO. We would also predict that these differences in feedback saliency would result in different patterns of activation of the reward network between IGO individuals and controls. Of particular interest are the vmPFC, which is known to be involved in evaluation of the subjective value of objects or events (31), and the VS, which has been suggested to encode hedonic experience (32).

In addition to evaluating the hypothesis and related predictions outlined above, we also wished to determine if the severity of IGO symptoms is associated with greater bias in hedonic responses of VS, as was previously found for gambling disorder (19). To achieve this, we examined the relationship between IGO severity measured in questionnaires and the difference in VS responses to monetary relative to symbolic reward.

MATERIALS AND METHODS

Participants

The participants consisted of 18 young males with IGO (IGOs; age 22.2 ± 2.0, males) and 20 Control males (Controls; age: 21.2 ± 2.1), recruited through advertisements in the university community in Kangwon province, South Korea. All were right-handed, and none reported a history of neurological or psychiatric disorders. Written consent was obtained from each participant after the study objectives and methods were fully explained. Participants received the incentives earned during the learning task after finishing the experiment. The study was carried out in accordance with the recommendations of the principles of Declaration of Helsinki, with written informed consent obtained from all subjects. The protocol was approved by the institutional review board of Kangwon National University.

As a part of the recruitment procedures, all volunteers were prescreened with the Internet Game Addiction Diagnostic Scale (IGADS) (33) and asked about their type of Internet usage (e.g., shopping, social networking, or game). Only those who reported gaming as their main use of the Internet and showed high scores on the IGADS (higher than the upper 20% of the distribution, i.e., 67) were classified as potential participants of the IGO group, while those who reported no Internet game activity and had low IGADS scores (lower than the mean, i.e., 47) were provisionally placed in the Control group of the fMRI study. Then, the modified Korean version of the Young's Internet Addiction Test (IAT) (34, 35), which consists of 20 items associated with problematic online Internet use, such as withdrawal and intolerance, was administered for those prescreened for the fMRI study. It is scored on a 100-point scale. A value of 50 or higher has been suggested to indicate occasional or frequent problematic Internet use and one over 80 to indicate significant pathological use (36). In this study, only those who showed a criterion score of 50 or higher on the IAT questionnaire were finally placed in the IGO group. Among the potential members of Controls, those who did not reach the criterion score of 50 for the IAT questionnaire, and were of comparable age to the IGO group, were placed in the final Control group.

To characterize the IGO group, the participants were given a clinical assessment and a personality evaluation relevant to the phenomenon of IGD (37). We assessed depression symptoms with the Beck Depression Inventory (BDI) (38), impulsivity with the Barratt Impulsiveness Scale-11 (BIS-11)-Revised (39), and personality traits (novelty seeking, harm avoidance, reward dependence, and persistence) with the Temperament and Character Inventory (TCI) (40). In addition, working memory (WM) capacity was evaluated with digit span forward and digit span backward using a subtest of the Wechsler Adult Intelligence Scale-IV (41).

Stimuli and fMRI Paradigm

Participants underwent an fMRI scan session of four runs, for which participants were told to learn S-R associations in a trial and error fashion (**Figure 1A**). For each letter (learning stimulus), one of four alternative keys (response) was to be pressed. Both monetary and symbolic feedbacks were employed to indicate whether the response was correct or an error (**Figure 1B**). A correct choice was followed by positive feedback, either a monetary gain or *via* a symbolic signal. Likewise, any erroneous response was followed by negative feedback, either a monetary loss or a symbolic signal. Monetary gain (monetary reward) and loss (monetary penalty) were indicated by "+500" or "−500," respectively, appearing in the center of a circle on the display. The Chinese symbols right [正] (symbolic reward) or wrong [不] (symbolic penalty) appeared in this circle to represent symbolic feedback (educated Koreans are familiar with basic Chinese characters). In order to minimize visual confusion, positive feedbacks were presented in green and negative feedbacks in red.

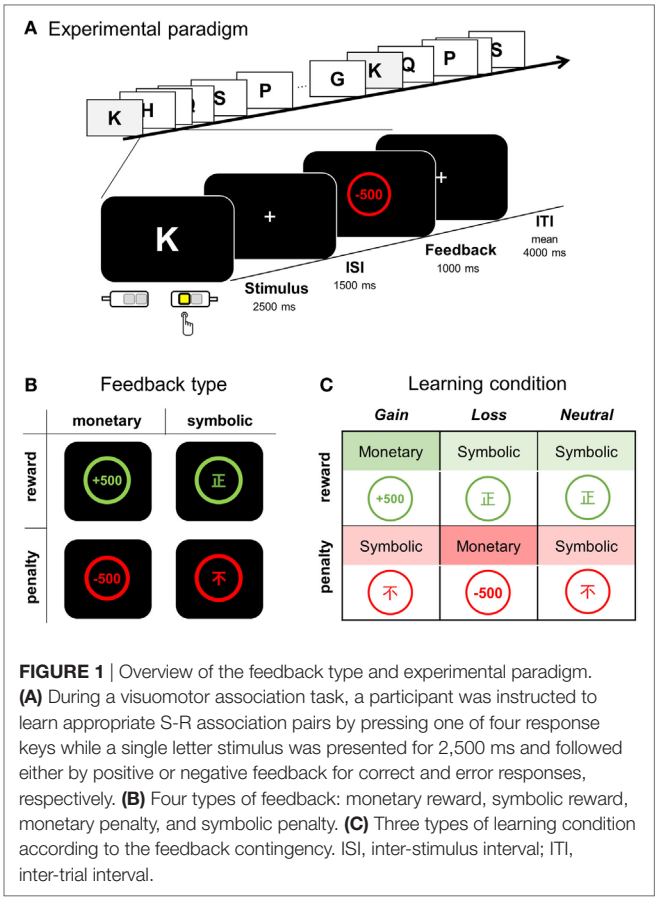

FIGURE 1 | Overview of the feedback type and experimental paradigm. **(A)** During a visuomotor association task, a participant was instructed to learn appropriate S-R association pairs by pressing one of four response keys while a single letter stimulus was presented for 2,500 ms and followed either by positive or negative feedback for correct and error responses, respectively. **(B)** Four types of feedback: monetary reward, symbolic reward, monetary penalty, and symbolic penalty. **(C)** Three types of learning condition according to the feedback contingency. ISI, inter-stimulus interval; ITI, inter-trial interval.

We compared three learning conditions (i.e., *gain*, *loss*, and *neutral* conditions), each of which differed in the nature of positive and negative feedbacks (**Figure 1C**). For the association assigned to the *gain* condition, monetary reward followed a correct response (CR), whereas symbolic penalty followed an error response. For the *loss* condition, a monetary penalty served as negative feedback, whereas a symbolic reward was used for positive feedback. For the *neutral* condition, no monetary gain or loss occurred, and only symbolic reward or penalty followed correct and error responses, respectively.

The learning list was composed of 24 English letters; two letters, O and X were excluded to avoid associations with pre-existing meanings of correctness (to Koreans, X is associated with "incorrect" and O with "correct"). Eight letters were assigned

to each learning condition, and eight associations (2 × 4 runs) were to be learned for each learning condition. Only six association pairs (two for each condition) were introduced for each run, during which the associations were repeated eight times (a total of 48 trials per run). Participants were informed that the association contingency between a letter and a target response was fixed for all stimuli and that choosing the CR arbitrarily assigned to each alphabetic character would be always followed by a reward. For each trial, the choice of response was required to be made while a learning stimulus (an English character) was displayed for 2.5 s; feedback was display for 1.0 s, following a 1.5 s inter-stimulus interval (ISI, display of "+") (**Figure 1A**). Trials were separated by jittered inter-trial intervals (ITI, display of "+", mean jitter = 4 s, range = 2.5 to 6.5 s). Responses were made by pressing one of four keys: two keys either with an index or middle finger for each hand. Stimuli and feedback display were presented with an MR-compatible NordicNeurolab Visual system (SVGA, resolution: 800 × 600), and the behavioral response was recorded using a response button box (4-button box HHSC-2 × 4-c, Current Designs Inc., Philadelphia, PA, USA). Responses faster than 100 ms were excluded from the analysis of reaction time (RT).

To determine if the valence and arousal for each feedback type differed between two groups, subjective ratings were obtained using a post-experiment questionnaire after the fMRI scan. Emotional valence ("how positive/negative" it was to them: from 1 = extremely pleasant to 9 = extremely unpleasant) and arousal ("how relaxing/exciting" it was: from 1 = not at all aroused to 9 = extremely aroused) were rated with a self-assessment manikin (42).

MRI Acquisition

MRI data were collected on a 3-T SIEMENS TRIO scanner with a 12-channel radio frequency coil while participants performed the learning task. T2*-weighted echo planar images were obtained using a gradient echo planar imaging sequence with the following parameters: repetition time (TR) = 2,000 ms, echo time (TE) = 30 ms, flip angle = 90°, slice thickness = 3.0 with 1 mm gap, field of view = 240 mm^2, matrix size = 80 × 80, voxel size = 3.0 mm × 3.0 mm × 3.0 mm, 36 slices, descending sequential, 223 volumes per run. T1-weighted structural data for anatomical localization were acquired using a 3D fast-field echo sequence (TR = 1,900 ms, TE = 2.52 ms, flip angle = 9°, field of view = 256 mm × 256 mm, matrix size = 256 × 256 × 192, voxel size = 1.0 mm × 1.0 mm × 1.0 mm). Stimulus presentation and behavioral data collection were implemented using E-prime 2.0 software (Psychology Software Tools, Inc., Pittsburgh, PA, USA).

Behavioral Data Analyses

Conventional behavioral analyses were performed both on the average percentage of CRs and on RT obtained for three conditions of four runs (192 trials), using a two-way mixed ANOVA with two levels of between-subject group factor (IGOs vs. Controls) and three levels of within-subject condition factor (*gain*, *loss*, and *neutral*). Behavioral responses were sorted *post hoc*, based on the choice of response of the current trial in relationship to the feedback type of the previous trial with the same stimulus. Here we define four types of response: choosing the same response as the one that had been followed by a reward for the previous presentation of the same stimulus (referred to as a "correct-stay response"), or choosing a different response (a "correct-change response"); choosing a different response from the one that had been followed by a penalty for the previous presentation of the same stimulus (an "incorrect-change response"), or choosing the same response (an "incorrect-stay response"). The rate of correct-stay (incorrect-change) responses was computed by dividing the total number of correct-stay (incorrect-change) responses by the sum of correct-stay and correct-change responses (incorrect-stay and incorrect-change) responses and subjected to a between group analysis (*two sample t-test*) for each feedback type. Statistical analyses were performed using IBM SPSS statistics 20.0 (IBM Corp., Armonk, NY, USA), and a threshold for statistical significance of $p < 0.05$.

fMRI Data Analyses

Image Preprocessing

Preprocessing and statistical analysis of the fMRI data were performed using Statistical Parametric Mapping software[1] (SPM12; Wellcome Trust Centre for Neuroimaging, London, UK) implemented in MATLAB R2013b (The MathWorks, Inc., Natick, MA, USA). First, the origin of each individual anatomical image (*x*, *y*, *z* = 0, 0, 0 mm coordinates) was set to the anterior commissure. Functional data were realigned to the first volume to correct for subject movements, slice-time corrected to the middle of the image acquisition, segmented to white matter, gray matter and CSF using Tissue Probability Map template, spatially transformed to match the MNI template, and spatially smoothed with a 6-mm Gaussian kernel. fMRI data for each individual were high-pass filtered with a cutoff period of 120-s.

Statistical analyses were performed with a two-stage mixed effect model. In the first individual analysis, a general linear model was used to generate voxel-wise statistical parametric maps from the functional data. For each participant, the following regressors were modeled for the four feedback events based on combinations of two feedback valences (positive or negative) and three learning condition trials (*gain*, *loss*, or *neutral*): positive feedback (i.e., monetary reward) and negative feedback (symbolic penalty) for trials of *gain* condition, positive feedback (symbolic reward) and negative feedback (monetary penalty) at *loss* condition trials, and positive feedback (symbolic reward) and negative feedback (symbolic penalty) at *neutral* condition trials, using a stick function time-locked with the presentation of feedback. The regressors were convolved with a canonical hemodynamic response function. Additional regressors of no interest were also included, such as the realignment parameters from the preprocessing step, for correcting for head movement and outlier scans. Outliers based on the global mean signal (>5 *z*-score) and movement (>2 mm) were detected using Artifact Detection Tools (ART[2]). The number of outliers did not differ between groups (IGO: mean [M] = 18.2, SD = 17.9; Control: M = 10.7, SD = 11.9, $t = 1.53$,

[1] http://www.fil.ion.ucl.ac.uk/spm.

[2] http://www.nitrc.org/projects/artifact_detect.

$p = 0.13$). To test whether movements differed between groups, we calculated the mean frame-by-frame movement (43): there are no significant differences between IGO and Control groups (IGO: M = 0.145, SD = 0.04; Control: M = 0.143, SD = 0.06, $t = 0.12$, $p = 0.90$).

Feedback-Related fMRI Group Analysis

Individual contrast images for monetary reward, symbolic reward, monetary penalty, and symbolic penalty obtained from the first level analyses were entered to three separated second level group analysis using a random effects model. First, we examined the difference between feedback valence by comparing reward (positive feedback) and penalty (negative feedback). A paired *t*-test was performed with the contrast of [$\text{Reward}_{(\text{monetary + symbolic})}$ vs. $\text{Penalty}_{(\text{monetary + symbolic})}$]. Brain regions for which significantly greater activations were specific to reward or penalty were used as functional masks for further group analyses. Then a two-way factorial ANOVA was performed to identify brain regions showing a group difference specific to the monetary effect using a between factor (group: IGO vs. Control) and a within factor (feedback type: monetary vs. symbolic). These ANOVAs were separately performed for reward and penalty. Examples of reward analysis follow: the main effect of group using the contrast of [$\text{IGO}_{(\text{monetary reward + symbolic reward})}$ vs. $\text{Control}_{(\text{monetary reward + symbolic reward})}$]; the main effect of feedback type using the contrast of [$\text{monetary reward}_{(\text{IGO + Control})}$ vs. $\text{symbolic reward}_{(\text{IGO + Control})}$]; and the interaction of group × feedback type using the contrast of [($\text{IGO}_{\text{monetary reward}} > \text{IGO}_{\text{symbolic reward}}$) vs. ($\text{Control}_{\text{monetary reward}} > \text{Control}_{\text{symbolic reward}}$)]. The findings for the main effect of feedback type are listed in Tables S4 and S5 in Supplementary Material for reward and penalty, respectively.

For these whole brain voxel-wise analyses, statistical parametric maps were primarily thresholded at a voxel-level *p*-value of 0.001 and corrected for multiple-comparisons using cluster-extent based thresholding, in which a cluster size exceeding 184 mm^3 ($k > 23$) was considered significant, which resulting in a cluster-level family-wise error (FWE) corrected *p*-value of 0.05. The cluster-extent estimation was based on a Monte Carlo simulation, using a MATLAB script (cluster_threshold_beta.m obtained from https://www2.bc.edu/sd-slotnick/scripts.htm) with the following parameters: acquisition matrix = 80 × 80; original voxel dimensions = 3 × 3 × 3; number of slices = 36; FWHM = 6; resampled voxel resolution = 2 × 2 × 2; corrected *p*-value = 0.05; voxel-based *p*-value = 0.001; iterations = 1,000.

From brain regions showing significant responses in the whole brain voxel-wise analyses, the mean percent signal changes were calculated from the first level contrast images for each participant using MarsBar (0.41[3]). To reveal patterns of significant interaction, these percent signal changes were also used in simple effect tests using SPSS statistics 20.0. In addition, any possible relationship between the feedback-related brain response and subject's personality, or between the brain response and behavioral measurements, were examined using the Pearson correlation analysis test.

[3]http://marsbar.sourceforge.net.

Correlation Analysis with IGO Symptom Severity for the VS

Based on our *a priori* hypothesis for the VS region, we examined the relationship between the incentive-related response of the VS and degree of IGO symptoms, as measured by IAT. The incentive associated brain contrast images (monetary reward > symbolic reward) were subjected to correlation analysis using IAT score as the covariates. Using a small volume correction approach, significance was determined with multiple-comparisons correction (FWE *p*-value of 0.05) within *a priori* VS mask ($k = 384$, volumes = 3,072 mm^3). The VS mask was made by combining the caudate head ROI (WFU-PickAtlas[4] with human-atlas TD Brodmann's areas +) and the nucleus accumbens ROI (Harvard–Oxford Subcortical Structural Atlas[5]). The same analysis was also performed with IGADS score for IGO severity.

RESULTS

Demographic and Clinical Results

The demographic, clinical assessment, and personality measurement data were summarized in **Table 1**. The IGADS, IAT, and game playing time of the IGO group were significantly higher than those of the controls ($t = 22.11$, 12.30, 7.66, respectively, all $p < 0.0001$). There was no group difference in WM capacity ($t = 0.13$, $p = 0.90$). As expected, the IGO group had significantly higher depression (BDI: $t = 3.39$, $p = 0.001$) and impulsivity scores (BIS-11: $t = 4.7$, $p < 0.001$), relative to the Control group. We also found IGO-associated group differences in personality traits: higher novelty seeking ($t = 2.58$, $p = 0.014$), harm avoidance ($t = 3.55$, $p = 0.001$), and lower persistence ($t = -3.15$, $p = 0.003$).

[4]https://www.nitrc.org/projects/wfu_pickatlas.
[5]http://www.cma.mgh.harvard.edu/.

TABLE 1 | Demographic characteristics of participants.

	IGO ($n = 18$)	Controls ($n = 20$)	*t*	*p*
Age (years)	22.17 (2.0)	21.20 (2.2)	1.40	$p = 0.169$
IGADS	75.61 (6.4)	31.05 (6.0)	22.11	$p < 0.001$**
IAT	62.78 (10.3)	29.75 (5.9)	12.30	$p < 0.001$**
Reported time being spent for Game (h)	24.06 (11.5)	0.91 (3.3)	7.66	$p < 0.001$**
WM (forward)	10.7 (1.6)	10.6 (1.9)	0.13	$p = 0.900$
Depression (BDI)	14.17 (8.8)	6.45 (4.9)	3.39	$p = 0.001$*
Impulsivity (BIS-11)	72.56 (9.6)	59.20 (7.8)	4.70	$p < 0.001$**
Temperament (TCI)				
Novelty seeking	44.06 (6.8)	38.10 (7.4)	2.58	$p = 0.014$*
Harm avoidance	48.50 (10.7)	37.30 (8.8)	3.55	$p = 0.001$*
Reward dependence	48.33 (8.9)	48.15 (12.5)	0.05	$p = 0.959$
Persistence	39.39 (7.4)	48.85 (10.6)	−3.15	$p = 0.003$*

Mean values are displayed with SDs in parentheses.
IGO group, Internet game overuse group; IGADS, Internet Game Addiction Diagnostic Scale; IAT, Internet addiction test; BDI, Beck depression inventory; BIS-11, Barret Impulsivity Scale-11; TCI, temperament and character inventory, WM, working memory.
**Statistical significant at p < 0.05 (two-tailed).*
***p < 0.001 (two-tailed).*

However, there was no group difference in reward dependence ($t = 0.05$, $p = 0.959$).

Behavioral Results

Behavioral Effects of Monetary Incentive and Loss

In general, the CR rate of the *gain* condition (M = 68.7%, SD = 7.1) was higher relative to the *loss* (M = 64.2%, SD = 10.7) or *neutral* conditions (M = 60.4%, SD = 13.4) [$F_{(2, 72)} = 12.28$, $p < 0.001$, **Figure 2A**]. The same learning condition effect was observed in RT: shorter RT of the *gain* condition (M = 899.9, SD = 175.2 ms) relative to the *loss* (M = 972.7, SD = 176.6 ms) or *neutral* conditions (M = 985.0, SD = 179.9 ms) [$F_{(2, 72)} = 12.6$, $p < 0.001$]. There was no significant difference between the groups (IGO: M = 62.0%, SD = 10.8; Control: M = 66.6%, SD = 6.5) [$F_{(1, 36)} = 2.62$, $p = 0.11$] or interaction between group by condition. Like CR, there was no significant group difference in RT [$F_{(1, 36)} = 1.16$, $p = 0.29$] or interaction between group and condition [$F_{(2, 72)} = 1.85$, $p = 0.16$].

For the correct-stay rate, there was no group difference following monetary reward, $t = -0.57$, $p = 0.57$ (**Figure 2B**). After symbolic rewards, however, the correct-stay rate of the IGO group (M = 0.82, SD = 0.18) was significantly lower than that of the Control group (M = 0.91, SD = 0.07), $t = -2.17$, $p = 0.036$, indicating a deficit of positive feedback processing in the IGO group only when no incentive was involved. For the incorrect-change rate, no group difference was found either after monetary [IGO: M = 0.87, SD = 0.09; Control: M = 0.86, SD = 0.09, $t = 0.22$, $p = 0.82$] or symbolic penalty [IGO: M = 0.82, SD = 0.12; Control: M = 0.85, SD = 0.07, $t = -0.94$, $p = 0.35$] (**Figure 2C**). Detailed information for the behavioral results are listed in Table S1 in Supplementary Material.

Individual Differences Associated with Learning Performance

None of personality or clinical measures was found to be associated with feedback learning performance. However, WM capacity was associated with learning performance in the individuals with IGO. For example, only for the IGO group, both the correct-stay rate following monetary reward ($r = 0.57$, $p = 0.013$) and the incorrect-change rate following monetary penalty ($r = 0.62$, $p = 0.006$) were positively correlated with individual WM capacity. Performance following symbolic feedback was not associated with WM capacity for the IGO group (correct-stay rate following symbolic reward: $r = 0.38$, $p = 0.13$; incorrect-change rate following symbolic penalty: $r = 0.30$, $p = 0.24$). For the Control group, no relationship was found with WM capacity for any feedback type (the correct-stay rates following monetary reward, $r = 0.05$, $p = 0.85$, or symbol reward, $r = 0.41$, $p = 0.07$; the incorrect-change rates following monetary penalty, $r = 0.14$ $p = 0.56$ or symbol penalty, $r = -0.10$, $p = 0.67$).

Subjective Rating of Feedback

Different valence and arousal ratings for monetary effects (monetary–symbolic) were compared between groups for each feedback valence (Figure S1 and Table S2 in Supplementary Material). Analysis of emotional valence ratings on positive feedback showed that, relative to the Control group, the IGO group exhibited a marginally increased arousal for monetary reward relative to symbolic reward (IGO: 2.11 ± 2.4, Control: 0.8 ± 2.2, $t = 1.75$, $p = 0.09$), whereas the two groups did not differ on emotional valence ratings (IGO: 1.78 ± 1.6, Control: 1.1 ± 1.2, $t = 1.47$, $p = 0.15$). Interestingly, compared to the Control group, the IGO group rated monetary penalty more negative (IGO: 1.94 ± 1.6, Control: 0.85 ± 1.1, $t = 2.43$, $p = 0.020$) and more arousing (IGO: 3.11 ± 2.3, Control: 1.3 ± 1.4, $t = 2.91$ $p = 0.006$) than symbolic penalty.

Imaging Results

Feedback Valence-Specific Brain Activation: Reward vs. Penalty

Brain regions showing feedback valence effects are summarized in Table S3 and Figure S2 in Supplementary Material. As expected, various regions (shown in yellow in **Figure 3**), including vmPFC and VS, showed greater activation for positive relative to negative feedback, while the anterior insula, right DLPFC, and dmPFC, showed greater activations for negative relative to positive feedback. Those valence-specific maps were used for further analysis of group comparison for positive and negative feedback.

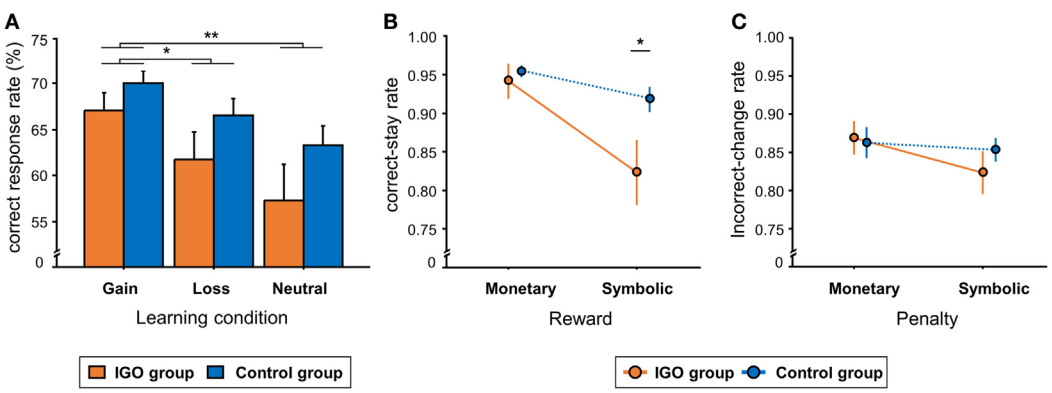

FIGURE 2 | Behavioral results. **(A)** The mean percent of correct response (CR) in the three learning conditions. **(B)** The group means of correct-stay rate, i.e., the rate of choosing the same CR, following either monetary or symbolic reward. **(C)** The group means of incorrect-change rate, i.e., the rate of choosing a different response, following either monetary or symbolic penalty. IGO: Internet game overuse; $^{*}p < 0.05$, $^{**}p < 0.01$.

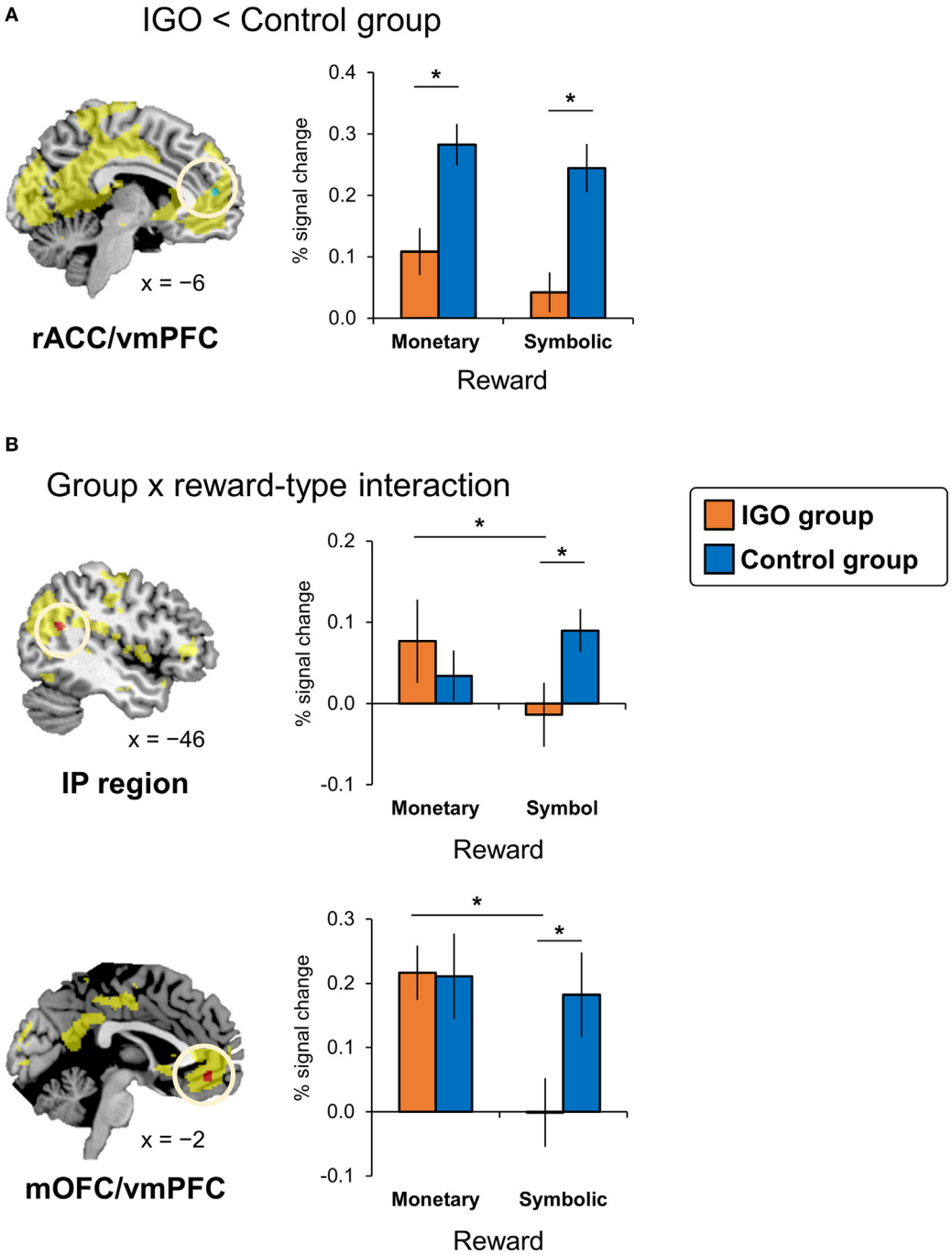

FIGURE 3 | Internet game overuse (IGO) associated differences in brain activations during reward processing. **(A)** The IGO group showed reduced activations for reward in the left rostral anterior cingulate cortex/ventromedial prefrontal cortex (rACC/vmPFC) region (shown in green) indicated by a significant group main effect [$IGO_{(monetary\ reward\ +\ symbolic\ reward)}$ vs. $Control_{(monetary\ reward\ +\ symbolic\ reward)}$]. **(B)** The left inferior parietal (IP) region and medial orbitofrontal cortex/ventromedial prefrontal cortex (mOFC/vmPFC) showing a significant interaction effect between group and reward types (shown in red) [($IGO_{monetary\ reward}$ > $IGO_{symbolic\ reward}$) vs. ($Control_{monetary\ reward}$ > $Control_{symbolic\ reward}$)]. The regions shown in yellow indicate areas whose activations were greater for reward relative to penalty in the voxel-wise analysis of all participants.

Group Differences in Brain Responses to Reward

According to the two-way factorial ANOVA analysis with the factors group (IGO vs. Control) and positive feedback type (monetary reward vs. symbol reward) (**Table 2**; Table S4 in Supplementary Material), an anterior dorsal part of vmPFC near the rostral anterior cingulate cortex (rACC/vmPFC) was the only brain region showing a significant reduction of activation of IGO relative to the Control group (**Figure 3A**, cluster-level FWE

$p < 0.05$). Furthermore, we found a significant group and feedback interaction in the more posterior ventral part of vmPFC near the medial orbitofrontal cortex (mOFC/vmPFC) and the left inferior parietal (IP) region, in which the IGO group showed reduced activation for symbolic relative to monetary reward, whereas the Control group showed no such reward type difference (**Figure 3B**, cluster-level FWE $p < 0.05$).

In particular, for the *neutral* condition (IGO: $r = 0.54$, $p < 0.05$; Control: $r = 0.21$, $p = 0.38$), for which no monetary incentive or loss was involved in learning, only in the IGO group was the individual difference in the level of activity in the mOFC/vmPFC region significantly positively correlated with the CR (**Figure 4**). A trend of positive correlation was found in the IGO group also with the correct-stay rate (following the symbolic reward) of the *neutral* condition (IGO: $r = 0.47$, $p = 0.051$; Control: $r = 0.32$, $p = 0.17$). These findings are in contrast to the observation that the level of mOFC/vmPFC activity in IGO group individuals had no relationship with the incorrect-change rate of the *neutral* condition ($r = 0.30$, $p = 0.23$). For the IGO group, no such relationship was observed in the rACC/vmPFC region that was defined by a significant group difference (IGO: monetary, $r = -0.13$ $p = 0.62$; symbol, $r = 0.13$ $p = 0.61$; Control: monetary, $r = -0.23$, $p = 0.34$; symbol, $r = -0.17$, $p = 0.47$) or the IP region defined by a significant group by feedback type interaction (IGO: monetary, $r = 0.12$ $p = 0.65$; symbol, $r = 0.31$ $p = 0.22$; Control: monetary, $r = -0.26$, $p = 0.27$; symbol, $r = -0.22$, $p = 0.36$).

TABLE 2 | Brain regions showing group differences in response to reward.

Region	R/L/M	BA	MNI coordinate			Stats	
			x	*y*	*z*	*T*	Size[a]
Group difference							
IGO < Control							
rACC/vmPFC	L	32	−6	50	12	18.8	29
IGO > Control							
NS							
Group × reward-type interaction							
IP region	L	39	−46	−56	20	20.5	26
mOFC/vmPFC	M	11	−2	44	−10	19.8	24

Inclusively masked with contrast of [reward–penalty].
IGO group, Internet game overuse group; IP region, inferior parietal region; rACC, rostral anterior cingulate cortex; mOFC, medial orbitofrontal cortex; vmPFC, ventromedial prefrontal cortex.
[a]*Cluster-level corrected p < 0.05.*

Group Differences in Brain Responses to Penalty

There were no IGO-associated differences in brain response for penalty: there was no group difference or interaction between group and feedback type (cluster-level FWE $p < 0.05$). However, the penalty type itself (monetary penalty vs. symbolic penalty) affected brain responses in several regions, as listed in Table S5 in Supplementary Material.

The Relationship between Incentive-Related VS Responses and Severity of IGO Symptoms

In a VS region defined *a priori* based on a previous finding for gambling disorder (19), a significant positive relationship was found in the IGO group between the IAT score and the size of the incentive effect of the regional activity (monetary reward > symbolic reward) (MNI *x*, *y*, *z* = 12, 20, −2, $k = 22$, $T = 5.65$, small volume corrected FWE $p < 0.05$; $r = 0.87$, $p < 0.001$), but not the Control group ($r = -0.02$, $p = 0.87$) (**Figure 5**). Similar results were found with IGADS scores (IGO: $r = 0.71$ $p < 0.001$; Control: $r = -0.24$, $p = 0.31$). This relationship was also confirmed with the IGADS score for the right VS (MNI *x*, *y*, *z* = 12, 14, 0, $k = 12$, $T = 4.7$, small volume corrected FWE $p < 0.05$). Other brain regions showing the same relationship either with IAT or IGADS are reported in Table S6 in Supplementary Material.

DISCUSSION

Here we investigated whether and how behavioral performance and feedback-related neural responses during learning are altered in IGO group. Our main interest was to see if IGO is associated with abnormally high sensitivity for motivational salient feedback, or abnormally low sensitivity for non-salient feedback. Within a simple association learning task, participants

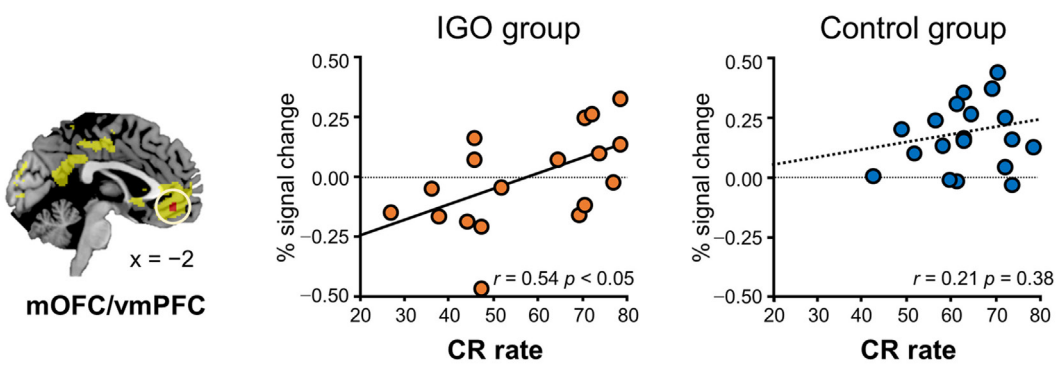

FIGURE 4 | Relationship between level of medial orbitofrontal cortex/ventromedial prefrontal cortex (mOFC/vmPFC) response for symbolic reward and learning. Only for the Internet game overuse (IGO) group, the percent correct response (CR) rate of the *neutral* condition was positively correlated with the level of brain response for symbolic reward. The regions shown in yellow indicate areas whose activations were greater for reward relative to penalty in the voxel-wise analysis of all participants.

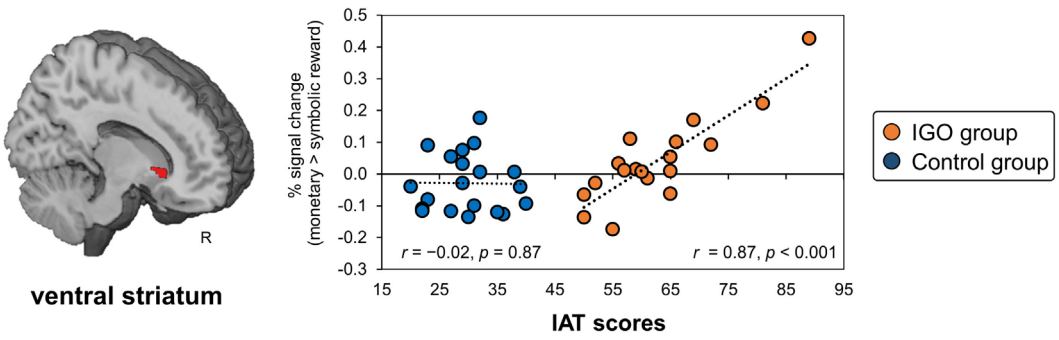

FIGURE 5 | The relationship between ventral striatum (VS) response bias for monetary reward and severity of Internet game overuse (IGO) symptoms. The greater differential activation in the right VS region for monetary relative to symbolic reward [for the contrast of (monetary reward > symbolic reward)] was associated with higher IAT scores in the IGO group, but not the Control group. IAT: Young's internet addiction test.

experienced various types of feedback that differed in motivational saliency (i.e., monetary reward/penalty vs. non-monetary symbolic reward/penalty). In comparison to the Control group, we observed several behavioral and neural response differences in the IGO group. First, individuals with IGO exhibited reduced learning efficiency for non-monetary (i.e., symbolic) positive feedback, whereas they did not differ in learning from monetary-positive feedback or from negative feedback (i.e., monetary or symbolic penalty). Second, the brain response for symbolic reward was blunted in the vmPFC region, unlike for monetary reward. Lastly, the level of bias observed in the VS activation for monetary reward, relative to symbolic reward, was associated with severity of IGO symptoms.

Internet Gaming Overuse and Learning Efficiency

It is well-known that monetary incentives improve performance (44–46). This incentive effect was clearly observed for learning in the current study, where the CR of the *gain* condition was greater than that of the *loss* or *neutral* condition across all participants of both groups. However, the learning impairment with symbolic reward, but not monetary reward, was detected in the IGO group only when the effect of positive feedback was distinguished from that of negative feedback. This is contrast to the absence of a group difference in the incorrect-change rate, indicating that the IGO group had no problem in error processing from negative feedback, whether monetary or symbolic. Given that symbolic reward provides as much learning-relevant information as monetary reward, indicating the previously chosen response as the target response, the internal motivation derived from the symbolic reward seems to have been greater for individuals without IGO than for those with IGO. For the Control group, both types of positive feedback were equally useful for repeating the same response in the future. These findings can be viewed as consistent with "incentive sensitivity hypothesis," since individuals with IGO did not process symbolic as efficiently as monetary reward, either due to impaired learning or reduced motivation. If they failed to attend or encode an event followed by the lesser motivationally salient feedback (i.e., symbolic reward), then the individuals with IGO may have not often been able to repeat the same response in the subsequent trial. At the least, the current study indicates that this is not associated with their inability to process symbolic/social feedback, since the IGO individuals successfully avoided repeating the same error response after symbolic penalty as often as after monetary penalty.

To further understand how the IGO group performed as well as the Control group in terms of correct-stay rate following monetary reward, we examined the relationship between individual differences in efficiency of reward processing and other psychological measures and found this to be associated with WM capacity, but only for the IGO group, and only for monetary reward. It is reasonable to suppose that WM individual differences will influence performance when a WM strategy is employed. The positive correlation between WM and the learning performance for monetary feedbacks in the IGO group suggests the use of a WM strategy when high motivation is triggered by monetary incentive. We also observed a similar relationship for monetary penalty in the IGOs, suggesting higher motivation IGO individuals, for both monetary incentive and loss. The self-reported arousal data are consistent with this conclusion. The difference in arousal levels for the two feedback types (monetary > symbolic), was significantly greater in the IGO group than the Controls (more so for penalty than reward). Given that high arousal associated with stronger motivation is known to improve performance (47, 48), the greater arousal measured by self-report in the current study indicates that unlike the Controls, the IGO group had greater motivation for monetary feedback relative to the symbolic feedback, which resulted in recruiting a WM strategy.

Reduced Activation for Positive Feedback Processing: rACC/vmPFC

The rACC/vmPFC is known to be anatomically connected with the striatum and associated with reward processing (49). It is viewed as a part of a reward circuit (50, 51) that is sensitive to feedback valence (positive > negative) (52, 53). In the current study, reduced responses of rACC/vmPFC were found in the IGO group, both for monetary and symbolic rewards. Recent imaging studies of IGD revealed reductions in glucose metabolism (54)

and gray matter volume (55) in the rACC/vmPFC region. The reduction of reward-associated activations has been well documented in individuals with substance addiction, such as cocaine addiction (56), as well as its correlation with the level of substance pursuit behavior (57). The current findings suggest that impaired reward processing is associated with IGO, which shares neuropathologies with other types of addiction, including substance abuse. We speculate that the probable impairments of reward processing by rACC/vmPFC must have been compensated for with a cognitive strategy, such as WM, as described above, when a monetary incentive was at stake.

Reduced Activations for Symbolic Reward: OFC/vmPFC and IP Region

Both in the mOFC/vmPFC and IP regions, reduced activations specific for symbolic reward were observed only in the IGO group. These patterns of differential activation were in parallel with the behavioral data. For example, the correct-stay rate, especially following symbolic reward, was lower in the IGO group. The vmPFC region near the medial OFC has been suggested to be involved in value representation (58–60), especially for the subjective value of reward (e.g., reward magnitude) (31, 61) or preference information (62). Therefore, the reduced activations for the symbolic reward relative to the monetary reward in the mOFC/vmPFC of IGOs may reflect lower value representation for the non-monetary feedback, resulting in a weak motivational modification in goal-directed behavior (60, 63). This is in contrast to the Controls, who did not show any significant differences in activation or behavioral performance between two types of reward, suggesting that the symbolic feedback was comparable to the monetary incentive in terms of reward value as positive feedback. This interpretation is relevant to a well-known clinical feature of addiction, namely, losing interest in social and recreational activities other than the addicted behavior, such as hobbies and entertainment (e.g., Internet gaming) (64). For monetary reward, we did not find any difference in brain activations of these regions between the IGO and Control groups, in contrast to the findings of Dong et al. (7), who reported an increased OFC activation for monetary reward in individuals with IGO, relative to Controls.

It is worth noting that we found group differences in reward-associated activations in two focal regions of vmPFC: the more dorsal anterior region referred as rACC/vmPFC and the more ventral posterior region called mOFC/vmPFC. In contrast to decreases in activation in the dorsal anterior region of vmPFC (rACC/vmPFC) for both types of reward, in the more ventral posterior region (mOFC/vmPFC) the IGO-associated reduction was found only for symbolic reward. A functional dissociation has been suggested by a recent neuroimaging study (50): the more dorsal part of vmPFC (corresponding the rACC/vmPFC in our study) for positive prediction error; the more ventral part of vmPFC (mOFC/vmPFC in our study) for value processing. According to this dissociation, IGO seems to be associated not only with impairment of positive prediction error processing (rACC/vmPFC), which should be required for all reward type, but also with impairment of value processing (mOFC/vmPFC), which affects only for the non-monetary reward.

Like the vmPFC, reduced activation for the symbolic relative to monetary reward was found in the left IP region of the IGO group, whereas there was no reward type difference in the Control group. Activity of the IP region is known to be involved in directing attention (65) or reward-related decision making as a part of cognitive control (66). The IP activation level has been shown to be modulated by motivation (67, 68) or reward (69). Therefore, the reduced response for symbolic reward, relative to monetary reward, in the IP region of IGO group can be interpreted as a lower level of attentional control for symbolic reward, resulting in poorer learning in these individuals.

Note that no relationship was found in the IP region between individual differences in the activation level for symbolic reward and the CR rate of the *neutral* condition in the IGO group, unlike the mOFC/vmPFC region. This might be related to a characteristic of our task, in which the behavioral adjustments for next response involved long-term delayed period across many trials. Unlike the value processing of the mOFC/vmPFC region, the attentional processing mediated by the IP region may not be long lasting across inter-trials during learning, at least not long enough to translate into the average learning performance. The representations of reward encoded by the mOFC/vmPFC (31, 59), on the contrary, have been shown to involve a long-term motivational setup of the individual (70). This may explain our finding of an association between individual differences at the neural level of the mOFC/vmPFC and average performance level. The absence of such a relationship in our Control group may be related to the very small inter-individual variations of behavioral performance in this group, due to the high (above 90%) average correct-stay rate for symbolic reward (as well as for monetary reward in both groups). Thus, we could not determine if there was a relationship between behavioral performance and mOFC/vmPFC activation for monetary reward in either group, or for symbolic reward in the Control group.

Incentive Effects in the VS Associated with Severity of IGO Symptoms

As predicted, individual differences in VS bias for monetary reward were directly related to IGO severity. This finding is similar to that from pathological gamblers, in whom the differential VS activation for monetary reward relative to a non-addictive reward (i.e., an erotic reward) was associated with gambling severity (19). In summary, our results for IGOs support the notion that addiction is associated not with increased sensitivity (e.g., greater VS activation to all addiction-related stimuli relative to normal healthy individuals), but with an imbalance of sensitivity (i.e., greater VS activation for the addiction-related stimulus relative to non-addictive stimuli) (15, 19).

Note that VS biases were, in fact, observed in both groups: some showed a bias toward monetary reward and others toward symbolic feedback (shown in **Figure 5**). Unlike the mOFC/vmPFC, the VS bias toward monetary relative to symbolic reward was not exclusively observed in the IGO group. In addition, half of the IGO group (as well as half of Controls)

showed a VS bias in the opposite direction, i.e., a greater response toward symbolic, rather than monetary reward. The greater bias toward monetary relative to symbolic reward in individuals with severe IGO symptoms suggests that this could be a risk factor for IGD.

Penalty Processing in Individuals with IGO

Unlike the case for reward processing, we did not find any behavioral or neuronal evidence in individuals with IGO of impaired penalty processing. This may seem surprising in light of past findings. For example, it has been reported that IGD individuals show reduced insular brain activation accompanying response inhibition difficulties (30), or hyperactivation of the ACC during error processing (8), results that are consistent with those from substance use disorder individuals, who showed impaired response inhibition or error processing (71). One possibility for the discrepancy between these and our results is the nature of error processing following penalty. The efficient penalty feedback processing in our study, measured as incorrect-change rate, is not associated with how well one inhibits a previously punished response, but is related to how well one switches to another response choice (three options) after penalty. Another possibility is that penalty feedback processing, even including response inhibition and error processing, may not be affected or impaired in individuals at high risk for IGD.

Limitations

We did not find any IGO-related hypersensitivity for monetary reward, except for an indication of using a WM strategy. We cannot rule out the possibility that hypersensitivity would have been observed if a sufficiently larger incentive was used than 20% of the accumulated earning of 500 KRW (less than 0.5 USD), like the 10 USD used by Dong et al. (7), or the video gaming items used by King and Delfabbro (28). However, we had no problem in finding differential responses for a specific reward type in the IGO group, both in brain activations and in behavior. Due to the practical difficulty in separating the effects of IGD from other personality issues, we cannot exclude the possibility that the high level of depression and impulsivity associated with abnormal reward processing (72, 73) influenced our results. Note that we focused on feedback-related brain activity using a fixed contingency between a stimulus and a type of positive (or negative) feedback. This classical learning paradigm was methodologically useful for measuring the level of learning-related behavioral performance. However, this deterministic reward paradigm did not afford the opportunity to observe abnormal reward-anticipatory processing in the Internet gamer (25). Lastly, the current findings were obtained from individuals with IGO who were identified via screening with the criteria of Young' IAT, which has been the dominant screening method in previous research. In future research, the methodological procedures might be improved (74, 75) using a more reliable and valid tool, such as the DSM-5 criteria (76).

CONCLUSION

In summary, IGOs was found to impair selectively learning from non-incentive symbolic reward, while not induced the normal level of brain responses in the mOFC/vmPFC and IP regions, indicating deficits in reward evaluation and attentional control processing, respectively. Also, the level of bias in the VS response toward monetary reward was associated with addiction severity, indicating a risk factor for IGD. These results provide clues for effective treatment and prevention of IGD. Considering formal educational settings where symbolic rewards are used rather than monetary reward, they suggest that individuals with IGO would suffer from poor learning performance in class, in addition to not allocating enough study time outside of school. The same problem would reoccur in normal daily life, where goal-directed behavior is often driven by internal motivation, not by external incentives. In particular, for individuals who combine a greater VS bias for external incentive (e.g., monetary reward) relative to internal incentive (e.g., symbolic feedback), with a personality of high depression and/or impulsivity, Internet games should be approached with great caution and care, rather than sought out as harmless entertainment.

ETHICS STATEMENT

The study was carried out in accordance with the recommendations of the principles of Declaration of Helsinki, with written informed consent obtained from all subjects. The protocol was approved by the institutional review board of Kangwon National University.

AUTHOR CONTRIBUTIONS

JK, HK, and EK made substantial contributions to the conception and design of this work. JK recruited the subjects and collected and analyzed the fMRI data. All authors contributed to the interpretation of data. JK and EK drafted the manuscript, which all authors critically revised for important intellectual content. All authors approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://journal.frontiersin.org/article/10.3389/fpsyt.2017.00195/full#supplementary-material.

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Altered Brain Activities Associated with Craving and Cue Reactivity in People with Internet Gaming Disorder: Evidence from the Comparison with Recreational Internet Game Users

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Although the neural substrates of cue reactivity in Internet gaming disorder (IGD) have been examined in previous studies, most of these studies focused on the comparison between IGD subjects and healthy controls, which cannot exclude a potential effect of cue-familiarity. To overcome this limitation, the current study focuses on the comparison between IGD subjects and recreational Internet game users (RGU) who play online games recreationally but do not develop dependence. Data from 40 RGU and 30 IGD subjects were collected while they were performing an event-related cue reactivity task in the fMRI scanner. The results showed that the IGD subjects were associated with enhanced activation in the left orbitofrontal cortex (OFC) and decreased activation in the right anterior cingulate cortex (ACC), right precuneus, left precentral gyrus and right postcentral gyrus in comparison with the RGU subjects. OFC is involved in reward evaluation and ACC is implicated in executive control function based on previous researches. Moreover, the activation of OFC were correlated with the desire for game-playing. Thus, the higher activation in OFC might suggests high desire for game playing, and the lower activation in ACC might indicates impaired ability in inhibiting the urge to gaming-related stimuli in IGD subjects. Additionally, decreased activation in the precuneus, the precentral and postcentral gyrus may suggest the deficit in disentangling from game-playing stimuli. These findings explain why IGD subjects develop dependence on game-playing while RGU subjects can play online games recreationally and prevent the transition from voluntary game-playing to eventually IGD.

Keywords: recreational Internet game users, Internet gaming disorder, cue-reactivity, impulse inhibition, intense desire

INTRODUCTION

Internet gaming disorder (IGD), the most prevalent (57.5 percent) subtype of Internet addiction disorder (IAD) (Han et al., 2012; Ko et al., 2013; Chen et al., 2015), is defined as the incapacity to control the desire for obsessive online game playing, which leads to various functional impairments, such as social, financial, occupational, and behavioral difficulties (Young, 1998; Achab et al., 2011; Dong et al., 2012b,c, 2013b, 2014a; Ko, 2014; Ko et al., 2014; Petry et al., 2014). It has been regarded as a type of non-financial pathologic gambling (Griffiths, 2005; Han et al., 2012), a form of behavior addiction (Holden, 2001), or a type of impulse control disorder (Sadock and Sadock, 2007). Based on the similarities among IGD, substance disorder, and pathologic gambling, the DSM-5 proposed the diagnostic criteria for IGD in conditions for further study (American Psychiatric Association, 2013).

Craving is defined as the intense desire for the experience of a psychoactive substance or behavior (Blumenthal and Gold, 2009). It has been considered as the central feature of pathologic gambling and substance disorder (Ko et al., 2008). The degree of craving can be increased by addiction-related cues (Blumenthal and Gold, 2009), which is thought to play a critical role in developing and maintaining addictive behaviors (Carter and Tiffany, 1999; Tong et al., 2007; Goudriaan et al., 2010), as well as relapse to addictive behaviors (Cooney et al., 1997; Kosten et al., 2005; Marissen et al., 2006). Previous neuroimaging researches on substance dependence and pathological gambling have revealed abnormal brain activity in the orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), amygdala, hippocampus, and precuneus in response to addiction-relevant cues (Maas et al., 1998; Tremblay and Schultz, 1999; George et al., 2001; Wrase et al., 2002; Crockford et al., 2005; Filbey et al., 2008). Similarly, studies on the IGD have reported that compared to healthy controls (HC), subjects with IGD showed aberrant activation in OFC, DLPFC, ACC, precuneus, caudate nucleus in response to gaming pictures (Ko et al., 2008; Han et al., 2010; Sun et al., 2012; Liu et al., 2016; Zhang et al., 2016).

However, all these studies on the cue-reactivity of IGD focused on the contrast between IGD subjects and HC (Ko et al., 2008; Han et al., 2010; Sun et al., 2012; Liu et al., 2016). This method has some limitations. First, it failed to control the game familiarities between IGD and HC, as IGD subjects are more familiar with the gaming cues than the HC; Second, IGD subjects played online games a lot, however, the HC subjects are low-frequent/none game players, they have limited experience with online gaming. To overcome these limitations, it is important to include a specific group of game players—the recreational Internet game users (RGU) as the control group. RGU are individuals who play online games recreationally but do not develop transition to addiction (Viriyavejakul, 2008; Kuss and Griffiths, 2012). They do not show the core symptoms of addiction, such as loss of control, withdrawal, and conflict (Ko, 2014). More importantly, they do not meet the diagnostic criteria for IGD by DSM-5 and do not need treatment (Petry et al., 2014). Thus, the present study focused on the differences in neural activity of craving and cue-reactivity between IGD and RGU to expand the understanding of specific features of IGD, and explore risk factors and effective interventions for IGD.

As reviewed above, previous studies have demonstrated that IGD subjects reported stronger craving for game-playing and showed aberrant brain activities in regions responsible for reward evaluation, such as DLPFC, OFC (Ko et al., 2008; Han et al., 2010; Sun et al., 2012; Dong et al., 2017a) as compared to HC subjects. Accordingly, we expected similar brain activities to game relevant cues in IGD subjects as compared to RGU subjects. In addition, it has been noted that IGD subjects are associated with failures in controlling the desire for playing online games (Lin et al., 2015a). Numerous imaging studies have found impaired executive control ability in IGD subjects (Dong and Zhou, 2010; Dong et al., 2010, 2011b, 2012a, 2014b, 2015, 2017b; Dong and Potenza, 2014; Weinstein and Lejoyeux, 2015; Wang L. et al., 2016a,b; Wang Y. et al., 2016b; Weinstein et al., 2017), yet, the direct evidence for the impaired executive control ability in inhibiting craving for game-playing in the context of online gaming cues are still lacking (Ko et al., 2008, 2013; Han et al., 2010; Sun et al., 2012). Thus, the present study filled in the gap. We expected that IGD subjects would show dysfunctional brain activities in the executive-control-related regions.

MATERIALS AND METHODS

Participants

The present study was approved by the Human Investigations Committee of Zhejiang Normal University. Forty RGU and 30 individuals with IGD were recruited in this study. All participants were right-handed and provided written informed content in accordance with the Declaration of Helsinki. Participants were screened according to their scores on Young's online Internet addiction test (IAT) (Young, 2009), the nine-item diagnostic criteria of IGD proposed by the DSM-5 committee (Petry et al., 2014), and their weekly Internet gaming time. Young's IAT consists of 20 items. Previous studies have testified the reliability and validity of IAT in classifying IAD (Widyanto and Mcmurran, 2004; Widyanto et al., 2011). Each item of Young's IAT assesses the degree of Internet use-related problems (i.e., psychological dependence, withdrawal, and related problems in sleep, school, or work) on a 5-point-scale. Individuals who scored between 31 and 49 points are regarded as average online users who maintain control of Internet use, though sometimes they may spent a bit too long in surfing the Internet. Scores between 50 and 80 points reveal occasional or frequent Internet use-related problems as a result of uncontrolled Internet usage[1].

Inclusion criteria for the IGD group were the following: (1) scored larger than 50 on Young's IAT (Lin et al., 2015a,b; Wang L. et al., 2016a,b); (2) met at least 5 DSM-5 criteria; (3) play online games is their major Internet activity; (4) play online games more than 14 h per week, for a minimum of 2 years;

[1]http://netaddiction.com/internet-addiction-test/

(5) endorsement of League of Legends (a popular online game in China) as the only source of Internet online games. The inclusion of RGU is the key step of the current study. The inclusion criteria for the RGU group were used previously (Wang Y. et al., 2016a) and described briefly as follows: (1) scored less than 50 on Young's IAT; (2) met fewer than 5 DSM-5 criteria; (3) play online games more than 14 h per week, for a minimum of 2 years; (4) endorsement of League of Legends as the only source of Internet online games; (5) reported no feeling of remorse or guilt about playing online games and stated that their regular use did not interfere with school, family, work, or social obligations. Exclusion criteria for all participants included (1) historical records of or current psychiatric/neurological disorders (e.g., depression, anxiety, schizophrenia and substance dependence) assessed by a structured psychiatric interviews (MINI) (Lecrubier et al., 1997); (2) previous or current use of gambling and illegal drugs (i.e., heroin, marijuana) or any other types of addictions (e.g., alcohol). Participants were required to not take any medicine or substances including tea and coffee on the day of scanning.

Table 1 shows the demographic information of the two groups. There was no significant difference in age, BDI score, education level and the Internet gaming time between the IGD and RGU group, while the IAT scores and DSM-5 scores of the IGD group were significantly higher than those of the RGU group.

Task and Procedure

An event-related cue reactivity task was applied in this study. It contains two types of cue pictures: 30 gaming-related pictures and 30 typing-related pictures (neutral baseline). And in each type, half of the 30 pictures contained a face and the half contained a hand. As shown in **Figure 1A**, gaming-related pictures describe a person who is playing the online game (LOL) on a computer, with half pictures showing faces and the other half showing hands. In typing-related pictures, the same person is typing an article on keyboard in front of a computer. The task of participants was to answer whether there was a face in the picture. They had to press the button '1' (refer to 'yes') on the keyboard when a face was present and press '2' (refer to 'no') when there was no face presented.

Figure 1B shows the timeline of a sample trial in the task. Firstly, a fixed 500 ms of cross was presented, followed by a cue picture as stated above. All pictures were presented in a randomized order. Each picture was presented for up to 3000 ms, during which participants had to make a response. The screen turned to black after button pressing and lasted for (3000 – response time)ms. Then, in the craving evaluation stage, participants were asked to evaluate the level of their craving for the corresponding stimuli on a 5-point scale, 1 (no craving) to 5 (extremely high craving). This stage lasted for up to 3000 ms and was terminated by a button-press. Finally, a 1500–3500 ms blank screen was presented between each trial. The whole task contained 60 trials and took almost 9 min. The task was presented and behavioral data was collected by the E-prime software (Psychology Software Tools, Inc.). All participants were asked to fill out a 10-item gaming urge questionnaire, range from 1 to 10 to assess the gaming craving prior to the fMRI (functional magnetic resonance imaging) scan (Cox et al., 2001).

Behavioral Data Analysis

The performance parameters for the cue reactivity task were mean reaction time (RT) and mean scores of craving (gaming-related minus typing-related), named as induced craving scores. In addition, the scores of craving prior to the fMRI scan, named as initial craving scores, were also analyzed. In order to examine the difference between the IGD and RGU group, we performed an independent sample *t*-test on these three parameters.

Image Acquisition and Pre-processing

Functional MRI data were collected by a 3T MR system (Siemens Trio) with a gradient-echo EPI T2* sensitive pulse sequence in 33 slices, interleaved sequence, 3 mm thickness, 30 ms echo time (TE), 2000 ms repetition time (TR), 220 mm × 220 mm of field of view, 90° flip angle and 64 × 64 for matrix. All trials were presented using Invivo synchronous system (Invivo Company[2]) via a monitor in the head coil, which allowed participants to view the trials presented on the screen.

The fMRI data were analyzed using SPM8 (Statistical Parametric Mapping[3]). Images were sliced-timed, reoriented and realigned to the first volume. And then T1-co-registered volumes were normalized to an SPM T1 template and smoothed using a 6 mm FWHM Gaussian Kernel spatially. No participant was

[2]http://www.invivocorp.com/

[3]http://www.fil.ion.ucl.ac.uk/spm

TABLE 1 | Demographic information and group differences.

	IGD *N* = 30	RGU *N* = 40	*T*	*p*
Age (Mean ± SD)	21.07 ± 1.34	21.45 ± 1.32	−1.20	0.236
BDI score (Mean ± SD)	2.23 ± 0.82	2.05 ± 0.85	0.91	0.366
Years of education (Mean ± SD)	15.23 ± 2.33	15.78 ± 1.37	−1.14	0.262
IAT score (Mean ± SD)	65.30 ± 11.68	41.35 ± 10.19	9.14	0.000***
DSM-5 score (Mean ± SD)	5.80 ± 1.10	2.63 ± 1.37	10.42	0.000***
Years playing online games (Mean ± SD)	3.50 ± 1.07	3.34 ± 0.96	0.67	0.509
Game playing per week (Hours; Mean ± SD)	18.90 ± 9.13	20.13 ± 9.57	−0.97	0.334

*IGD, Internet gaming disorder; RGU, recreational Internet game users; BDI, Beck Depression Inventory; IAT, Internet addiction test; ***$p < 0.001$.*

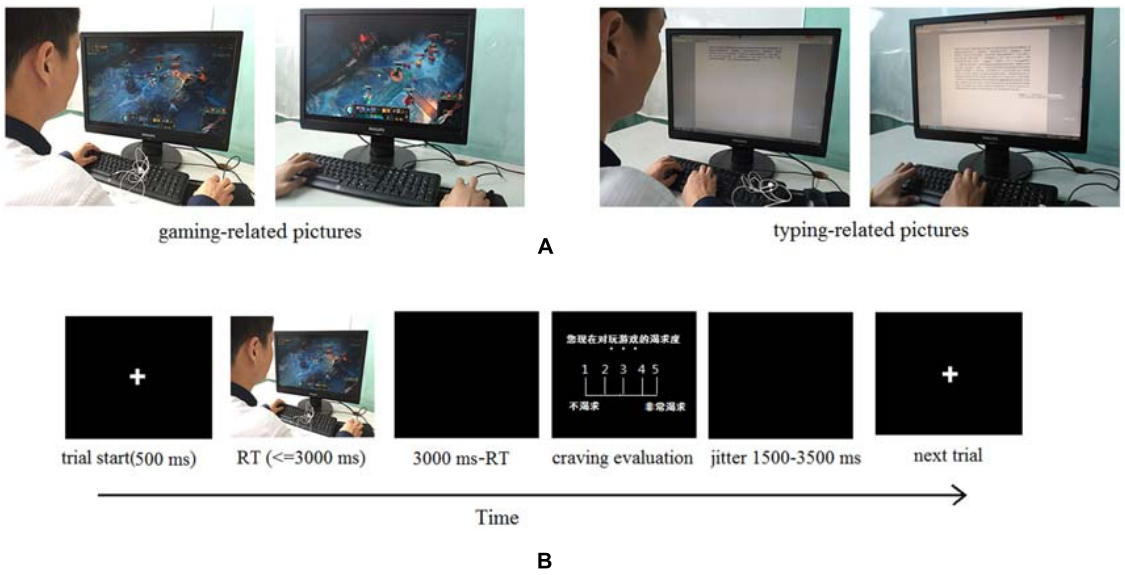

FIGURE 1 | (A) Examples of gaming-related stimuli (left) and typing-related stimuli (right). **(B)** The timeline of one trial in the event-related cue-reactivity task. The test version of the task is in Chinese. "您现在对玩游戏的渴求度" means "The degree of your craving for game-playing right now"; "不渴求" means "no craving"; "非常渴求" means "extremely high craving."

excluded due to large head motion coefficients based on the criteria (head motion < 2.5 mm and 2.5 degree).

First-Level FMRI Analysis

In the present study, we applied a general linear model (GLM) to examine blood oxygen level dependence (BLOD) signal related to the two event types (gaming-related trials, typing-related trials) and others (missed or error response). GLM built a design matric to represent a combination of the experimental onsets convolved with a canonical haemodynamic response function (HRF), which included all trial conditions (gaming-related trials, typing-related trials, and missed trials) and six head motion parameters. Then, to improve the signal-to-noise ratio, a high pass filter (cut-off period was 128 s) was used to filter out low frequency noise.

Second-Level Group FMRI Analysis

Second-level analysis was conducted at the group level. At first, we identified voxels that showed a main effect in the gaming-related trials versus the typing-related trials among each group (IGD, RGU). Secondly, we determined voxels that were significantly different in BOLD signal between the two groups [$(IGD_{gaming} - IGD_{typing}) - (RGU_{gaming} - RGU_{typing})$]. We then identified clusters of contiguous significantly different voxels at an uncorrected threshold $p < 0.005$. Finally, these clusters were tested for cluster-level FWE (family-wise-error) correction $p < 0.05$. Specially, the AlphaSim estimation indicated that clusters extent of 15 adjoining voxels would achieve the FEW threshold $p < 0.05$ effectively. The smoothing kernel applied in simulating false-positive (noise) maps using AlphaSim software was 6.0 mm and was estimated from residual fields of the contrast maps being pooled into the one-sample *t*-test.

Regression Analysis

To identify the correlation between brain activities and behavioral performances, we first extracted the BOLD signal from the mean value of the remaining clusters that showed between-group differences. Then the BOLD data for all subjects were submitted to robust regression analyses with the RT, the induced craving scores, the initial craving scores, and the IAT and DSM scores. Note, robust regression analysis was used here to eliminate the effect of outliers, which represents the correlations between brain activations and behavioral performances.

RESULTS

Behavioral Performance

The behavioral results showed significantly higher induced craving scores (IGD: 1.98 ± 1.10, RGU: 1.21 ± 0.78, $t(1,69) = 3.25$, $p = 0.002$) and initial craving scores (IGD: 53.10 ± 15.36, RGU: 39.13 ± 15.71, $t(1,69) = 3.72$, $p = 0.000$) in the IGD group as compared to the RGU group. No significant group-difference was found in the RT to cue pictures. Additionally, we found a significantly positive correlation between the IAT, DSM scores and the initial craving scores for all subjects (**Figures 2A,B**) and for the IGD group (**Figures 2C,D**). And the induced craving scores showed positively correlation with the IAT, DSM scores for all participants, respectively (**Figures 2E,F**).

Imaging Results

We examined the brain activities in the cue-reactivity task between the IGD and RGU group (**Figure 3** and **Table 2**). The IGD group showed increased BOLD signal activation in the left

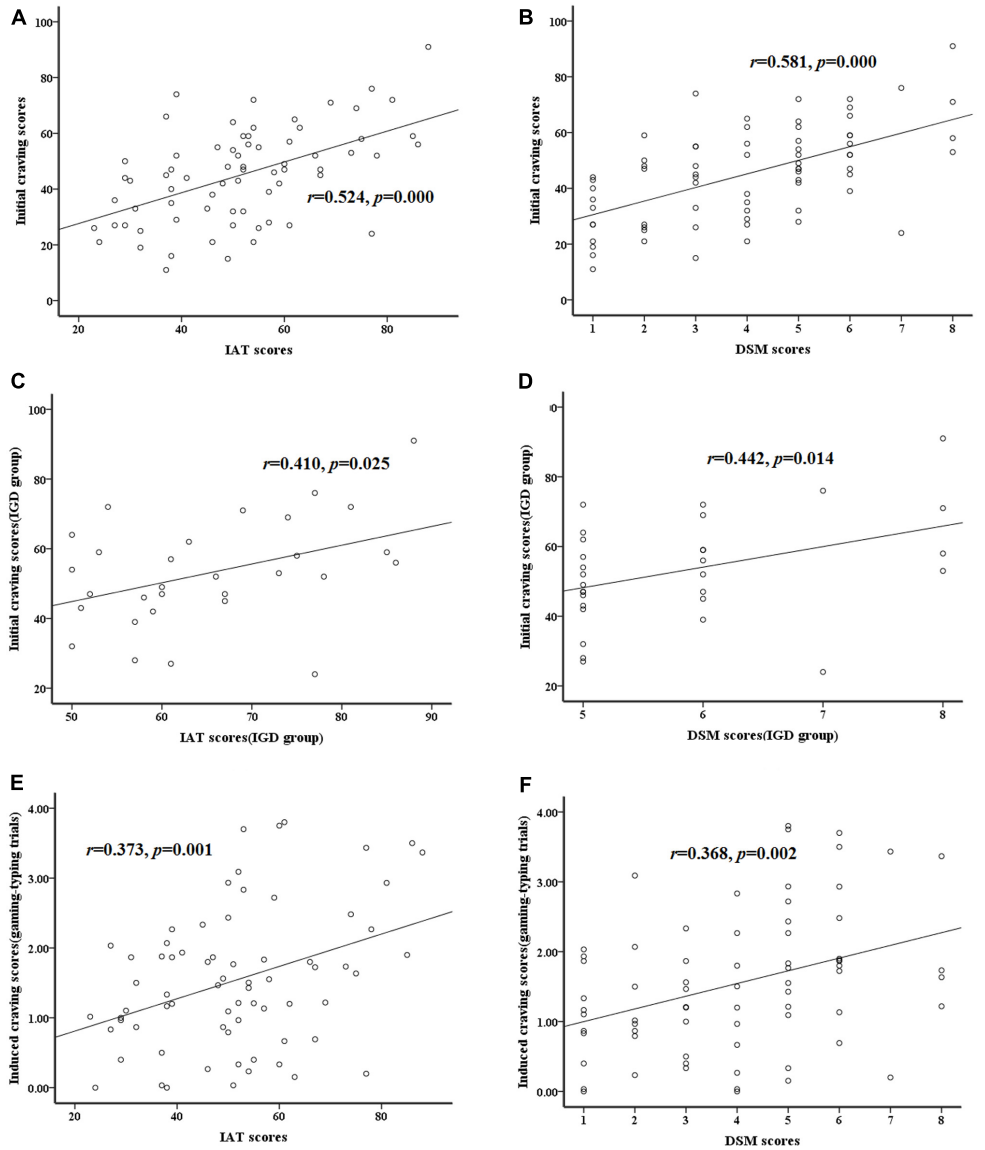

FIGURE 2 | Correlations between the severity and the craving scores. **(A,B)** The initial craving scores show significantly positive correlation with the IAT scores, DSM scores for all subjects, respectively. **(C,D)** The initial craving scores show significantly positive correlation with the IAT scores, DSM scores for only IGD subjects, respectively. **(E,F)** The induced craving scores show significantly positive correlation with the IAT scores, DSM scores for all subjects, respectively.

OFC compared to the RGU group, and decreased brain activities in the right ACC, right precuneus, left precentral gyrus and right postcentral gyrus in the IGD group when comparing to the RGU group.

Regression Analysis Results

As the robust regression lines in the **Figure 4**, there were significant regression correlations between brain activations in the OFC, ACC, precuneus, left precentral gyrus and right postcentral gyrus and the IAT, DSM scores, which means brain activations in the these regions were correlated positively or negatively with the IAT, DSM scores for all participants. At the same time, the regression correlations between brain activation in these regions (except ACC) and the initial craving scores were significant or marginally significant. Also, we put the results of linear regression in the figure to show the differences between linear regression and robust regression.

DISCUSSIONS

As far as we know, this is the first study comparing the neural activities associated with gaming-cues evoked craving between subjects with IGD and RGU. The IGD subjects reported higher scores of craving for game-playing and showed dysfunctional

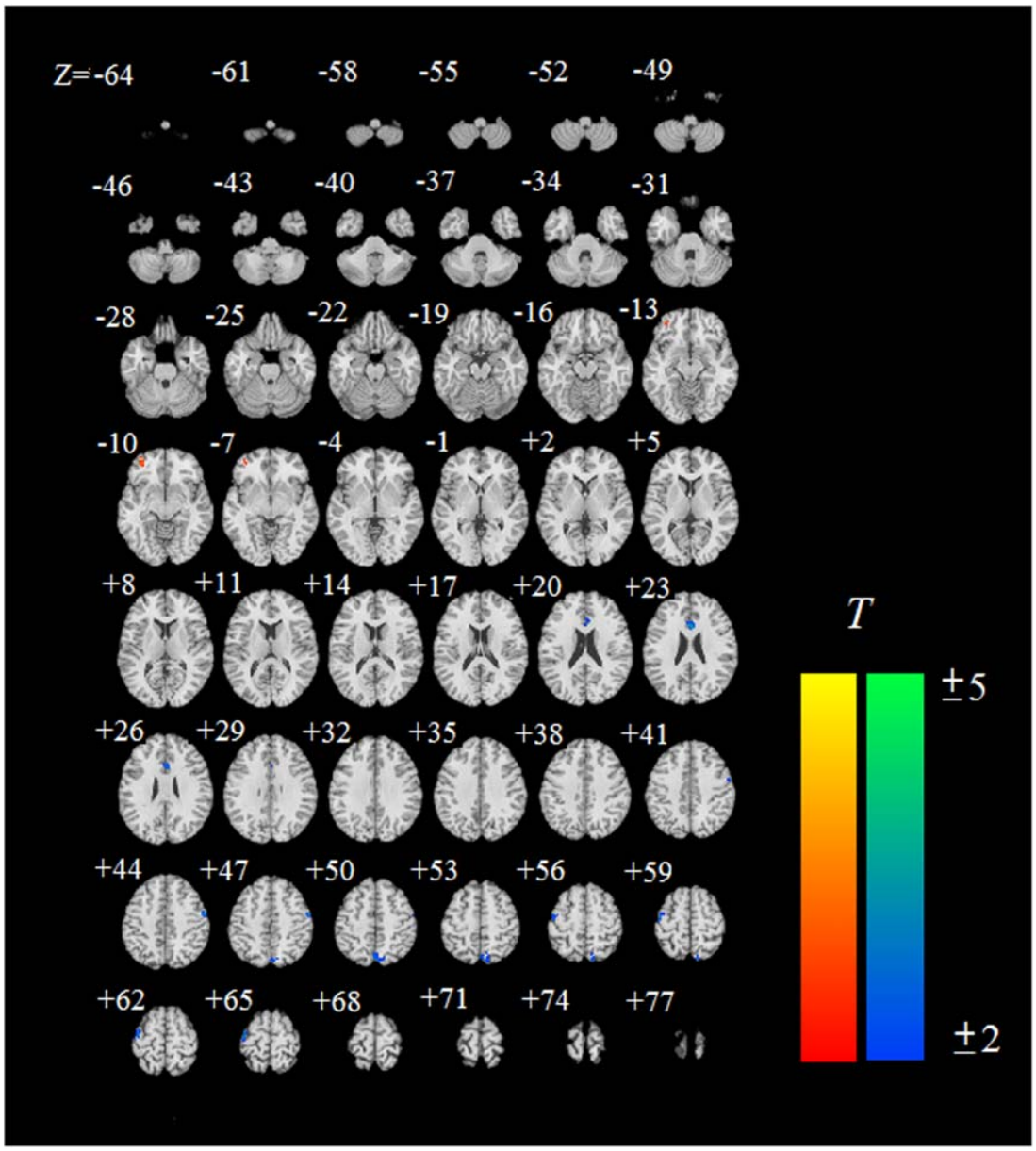

FIGURE 3 | Brain regions showing significant difference in IGD subjects compared with RGU subjects. The IGD subjects showed enhanced activation (shown in red) in the left orbitofrontal cortex (OFC), and decreased activation (shown in blue) in the right anterior cingulate cortex (ACC), right precuneus, left precentral gyrus and right postcentral gyrus when comparing to the RGU group. 'Z = ' is the z coordinate of the slice in MNI space.

brain activation in the left OFC, the right ACC, right precuneus, left precentral gyrus and right postcentral gyrus as compared to the RGU group.

Higher Desire for Game-Playing in IGD

The present imaging results demonstrated that the IGD subjects showed higher brain activity in the left OFC than the RGU group when exposed to the gaming-related cues. The OFC is widely thought to be involved in goal-directed behavior through assessing the significant stimuli and selecting appropriate behavior to achieve desired outcomes (Rolls, 2000). The similar feature has been reported in subjects with substance disorders, pathologic gambling, and online games addiction (Wrase et al., 2002; Myrick et al., 2004; Kosten et al., 2005; Franklin et al., 2007; Filbey et al., 2008). The OFC was found to be activated by expectations and delivery of reward (Elliott et al., 2000; Rolls, 2000; Schultz et al., 2000). It generates and maintains expectations for potential reward associated with reinforcement by integrating experiential history with current events (Bonson et al., 2002). These findings may reveal the important role of OFC in the craving for game-playing in IGD.

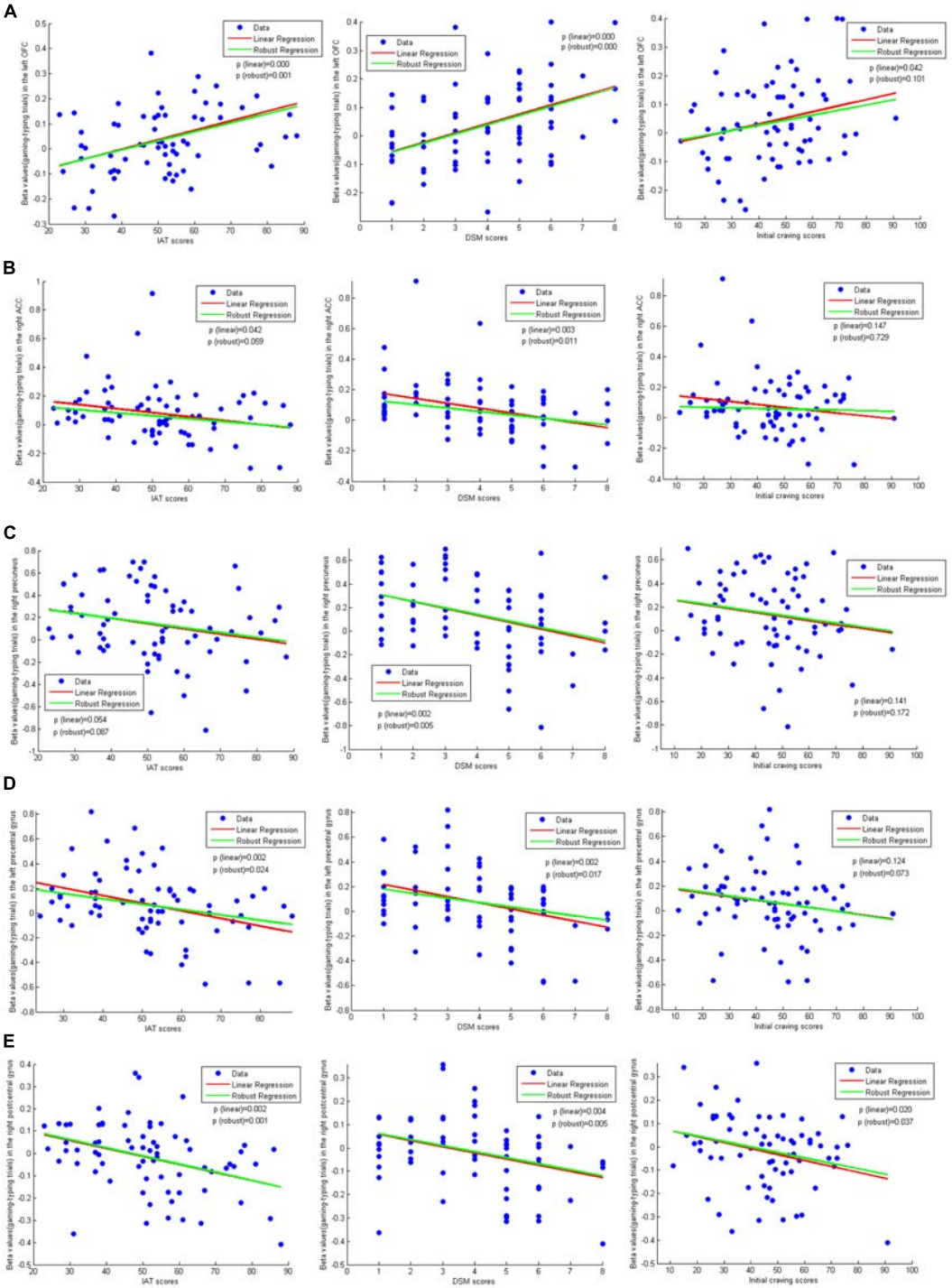

FIGURE 4 | Regression relationship between brain activities and behavioral performances. p(linear) in each figure refers to the *p*-value of linear regression coefficient. p(robust) in each figure refers to the *p*-value of robust regression coefficient. **(A)** Shows the regression correlation between brain activation in the left OFC and the IAT scores, DSM scores and the initial craving scores, respectively. **(B)** Shows the regression correlation between brain activation in the right ACC and the IAT scores, DSM scores and the initial craving scores, respectively. **(C)** Shows the regression correlation between brain activation in the right precuneus and the IAT scores, DSM scores and the initial craving scores, respectively. **(D)** Shows the regression correlation between brain activation in the left precentral gyrus and the IAT scores, DSM scores and the initial craving scores, respectively. **(E)** Shows the regression correlation between brain activation in the right postcentral gyrus and the IAT scores, DSM scores and the initial craving scores, respectively.

TABLE 2 | Brain regions showing significant group-difference in BOLD signal.

Regions	*x*	*y*	*z*	Size	BA	Max *t*
IGD > RGU subjects						
Orbitofrontal frontal gyrus (L)	−38	44	−9	17	11	3.54
IGD < RGU subjects						
Anterior cingulate cortex (R)	3	15	23	27	24	−4.14
Precuneus (R)	3	−75	43	34	7	−3.50
Precentral gyrus (L)	−40	−8	57	32	6	−3.76
Postcentral gyrus (R)	57	−12	42	15	3	−4.10

We list significant clusters of increased (IGD > RGU subjects) or decreased (IGD < RGU subjects) activation to the gaming-related cues > typing-related cues. Shown are the coordinates of the local maxima in MNI space, the size of the clusters, the Brodmann Area, and the maximal T-statistic. Coordinates represent the local maxima in the gaming-related cues > typing-related cues contrast. BLOD, blood oxygen level dependence; IGD, Internet gaming disorder; RGU, recreational Internet gaming users; L, left; R, right.

In current study, the IGD group reported significantly higher craving for online games than the RGU group both during and before fMRI scan. There was a positive association between the BOLD signal of the OFC, the initial craving scores, and the severity values of IGD (the IAT scores, DSM scores) among all participants. Thus, the larger the IGD values are, the stronger craving for gaming-playing and higher activation in the OFC would be observed. Taking all, we suggest that subjects with IGD generate expectations for game-playing through assessing the reward value of gaming behavior (which was induced by gaming-related cues) in the OFC. Therefore, they show stronger desire for game-playing than the RGU group, in line with the intense desire for drug-taking in drug addictions (Arthur et al., 2001; Goldstein and Volkow, 2002). Alternatively, the OFC might be involved in other functions, such as the inhibition and so on. Further studies are warranted to investigate this possibility.

Impaired Control Ability in IGD

In the current study, decreased brain activity were detected in the right ACC in the IGD group comparing to the RGU group in response to gaming-related cues. Also, negative trends between the activities of ACC, the DSM and IAT scores were found among all participants, which suggest that the lower activation in the ACC is accompanied with higher severity of IGD. These results indicate that the ACC plays an essential role in the cue-reactivity of IGD, in accordance with prior researches on the cue-reactivity of IGD and other addictions (Ko et al., 2008; Goudriaan et al., 2010; Engelmann et al., 2012; Sun et al., 2012; Liu et al., 2016).

Convergent evidences have demonstrated that the ACC is involved in executive control function (Kerns et al., 2004; Dong et al., 2011a; Goldstein and Volkow, 2011; Wheelock et al., 2014). Executive control refers to one's ability to direct or stop behaviors and thoughts, particularly when the behaviors (or thoughts) may not be advantageous or are regarded as improper (Goldstein and Volkow, 2011). Several neuroimaging researches have examined the impaired executive control ability indexed by dysfunction or structural abnormalities in ACC in people with IGD (Dong et al., 2011a, 2013a; Zhou et al., 2011; Wang et al., 2015; Dong and Potenza, 2016), as well as in drug addiction and pathologic gambling (Ruiter et al., 2011; Moeller et al., 2013; Santangelo et al., 2013; Schmidt et al., 2014; Feng et al., 2015). Better control ability in recreational online game users than online game addicts are associated with enhanced activation in ACC in a decision-making task (Wang Y. et al., 2016b). Combined with these findings, the present result may reveal a deficient executive control ability in IGD subjects, accompanied with comparably better control ability in RGU subjects. Additionally, subjects with IGD have been reported to link with deficit in executive control ability in cognitive tasks (Hester et al., 2010; Dong et al., 2011b; Wang et al., 2017) and are characterized by diminished control ability in Internet game-playing (Lin et al., 2015a). Besides, they showed higher scores in impulsivity (Lee et al., 2012) and thus are labeled as impulse control disorder (Sadock and Sadock, 2007). These behavioral phenomena of IGD are compatible with our results. Alternatively, the ACC is also implicated in attention processes (Bush et al., 1999; Seidman et al., 2006), thus, the lower activation in ACC might also suggest reduced attentional capacity in IGD subjects. However, considering the feature of the current event-related cue-reactivity task, which requires participants to suppress their strong craving for game-playing and focus on the task (pressing the correct button), and taking the findings above together, we speculated that IGD subjects show deficit in controlling their intensive desire for game-playing (provoked by gaming-related cues) as compared to RGU subjects, which is consistent with the impaired control ability to inhibit the craving for drug intake in drug addiction (Arthur et al., 2001; Goldstein and Volkow, 2002; Sinha and Li, 2007). Further studies are needed to investigate this issue. Notably, a cognitive-behavioral model of IGD proposed by Dong and Potenza (2014) have revealed enhanced desires for game-playing and poor control over such desires determined by the impairments of executive control function in individuals with IGD. The present result may contribute to certify the generalizability and availability of the model.

The Roles of Precuneus, Precentral, and Postcentral Gyrus

Decreased brain activation in the right precuneus, left precentral and right postcentral gyrus were detected in subjects with IGD as compared to RGU subjects in response to gaming-related cues. In correlation analysis results, we found negative trends between the BOLD signal of the precuneus, the precentral, postcentral gyrus and the initial craving scores. Altered activities in these regions

have been reported in previous studies about the cue-reactivity of IGD (Han et al., 2010; Sun et al., 2012; Liu et al., 2016). These results may indicate that the precuneus, the precentral and postcentral gyrus have a strong relationship with the cue reactivity in IGD.

A review about neural substrates of smoking cue reactivity has argued that the precuneus play an important role in cue reactivity (Engelmann et al., 2012). The precuneus has been proposed to contribute to attentional tracking of stimuli and the preparation of motor behaviors (Cavanna and Trimble, 2006). And it is involved in shifting attention between motor targets and motor imagery (Cavanna and Trimble, 2006). The precentral gyrus located in the Brodmann area 6 (pre-motor and supplementary motor cortex) is implicated in motor planning and execution. And the postcentral gyrus, as the primary somatosensory cortex, are the main sensory receptive region for the sense of touch. Besides, we found that the IGD subjects showed lower accuracy and longer RT than the RGU subjects, which demonstrated bad behavioral performance in subjects with IGD. On the aspect of our experimental task, participants were required to press buttons by observing if there was a face in the cue pictures with the background of game-playing. The lower activation in precuneus, precentral and postcentral gyrus in IGD may suggest the deficit in integrating visual and motor information from the cue-pictures and shifting attention from the stimuli of game-playing to the experimental task (pressing correct buttons). So far, the precuneus, precentral and postcentral gyrus received little attention in previous studies on the cue-reactivity of IGD. Thus, the present intriguing speculation may suggest that these three areas could be important areas of interest for further researches of cue reactivity in IGD.

Limitations

There are some limitations of the present study to be noted. First, the causal relationship between IGD and the abnormal activity in the regions stated above could not be confirmed in the present study. It will be interesting to explore this relationship in future studies. Second, only seven female subjects were recruited for this study due to the higher popularity of online gaming in men than in women. Although they were balanced in the two groups (3 female IGD, 4 female RGU), the results may be biased. Further researches are needed to explore the gender effect in IGD. Third, several other variables, e.g., IQ, self-efficiency and socioeconomic status of the subjects, were not measured in the current study. The potential subgroup-difference in these variables may bias the results. Future studies should take these aspects into consideration. Finally, as the diagnostic criteria of IGD were still under consideration, the findings based on this criteria might be affected by it. A better diagnostic criterion of IGD might bring new insight into this issue.

CONCLUSION

The present study examined different brain activation pattern between subjects with IGD and RGU using an event-related cue reactivity task. Hyperactive OFC indicates higher desire for game-playing and lower activation in ACC suggests impaired control ability in inhibiting the craving for game-playing in IGD subjects. Additionally, we infer that the decreased activation in the precuneus, precentral and postcentral gyrus may be associated with the difficulty in shifting attention from stimuli of game-playing to face-detection task in the IGD subjects. These findings explain why IGD subjects failed in preventing the transition from voluntary game-playing to eventual IGD, while as a contrast, RGU subjects can play online games recreationally without developing online-gaming dependence.

AUTHOR CONTRIBUTIONS

LxW analyzed the data and wrote the first draft of the manuscript. LxW, YW, HL, and XL contributed to experimental programming, data preprocessing. XD contributed to fMRI data collection. GD designed this research. GD and LdW revised and improved the manuscript. All authors contributed to and have approved the final manuscript.

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Unconscious Processing of Facial Expressions in Individuals with Internet Gaming Disorder

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Internet Gaming Disorder (IGD) is characterized by impairments in social communication and the avoidance of social contact. Facial expression processing is the basis of social communication. However, few studies have investigated how individuals with IGD process facial expressions, and whether they have deficits in emotional facial processing remains unclear. The aim of the present study was to explore these two issues by investigating the time course of emotional facial processing in individuals with IGD. A backward masking task was used to investigate the differences between individuals with IGD and normal controls (NC) in the processing of subliminally presented facial expressions (sad, happy, and neutral) with event-related potentials (ERPs). The behavioral results showed that individuals with IGD are slower than NC in response to both sad and neutral expressions in the sad–neutral context. The ERP results showed that individuals with IGD exhibit decreased amplitudes in ERP component N170 (an index of early face processing) in response to neutral expressions compared to happy expressions in the happy–neutral expressions context, which might be due to their expectancies for positive emotional content. The NC, on the other hand, exhibited comparable N170 amplitudes in response to both happy and neutral expressions in the happy–neutral expressions context, as well as sad and neutral expressions in the sad–neutral expressions context. Both individuals with IGD and NC showed comparable ERP amplitudes during the processing of sad expressions and neutral expressions. The present study revealed that individuals with IGD have different unconscious neutral facial processing patterns compared with normal individuals and suggested that individuals with IGD may expect more positive emotion in the happy–neutral expressions context.

Highlights:

- The present study investigated whether the unconscious processing of facial expressions is influenced by excessive online gaming. A validated backward masking paradigm was used to investigate whether individuals with Internet Gaming Disorder (IGD) and normal controls (NC) exhibit different patterns in facial expression processing.
- The results demonstrated that individuals with IGD respond differently to facial expressions compared with NC on a preattentive level. Behaviorally, individuals with IGD are slower than NC in response to both sad and neutral expressions in the sad–neutral context. The ERP results further showed (1) decreased amplitudes in the N170 component (an index of early face processing) in individuals with IGD when they process neutral expressions compared with happy expressions in the happy–neutral expressions

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context, whereas the NC exhibited comparable N170 amplitudes in response to these two expressions; (2) both the IGD and NC group demonstrated similar N170 amplitudes in response to sad and neutral faces in the sad–neutral expressions context.

• The decreased amplitudes of N170 to neutral faces than happy faces in individuals with IGD might due to their less expectancies for neutral content in the happy–neutral expressions context, while individuals with IGD may have no different expectancies for neutral and sad faces in the sad–neutral expressions context.

Keywords: Internet Gaming Disorder, backward masking, unconscious facial processing, ERPs, N170

INTRODUCTION

Excessive computer game playing can be both addictive and pathological (D'Hondt et al., 2015; Lemmens et al., 2015). As a behavioral addiction, Internet Gaming Disorder (IGD) is characterized by compulsive gaming behaviors with harmful personal or social consequences, such as impairments in individuals' academic, occupational, or social functioning (Brady, 1996; Young, 1998; DSM-V, American Psychiatric Association, 2013; Tam and Walter, 2013; Spada, 2014; Van Rooij and Prause, 2014; D'Hondt et al., 2015; Kuss and Lopez-Fernandez, 2016). Research has found that Internet addiction (including online gaming activities and other forms of Internet use) shares essential features with other addictions, including decreased executive control abilities and excessive emotional processing of addiction-related stimuli (Ng and Wiemer-Hastings, 2005; He et al., 2011; D'Hondt et al., 2015). Accordingly, previous studies of IGD focused predominantly on impairments in inhibitory control or executive control among individuals with IGD (Dong et al., 2010, 2011; Wang et al., 2013; D'Hondt et al., 2015; Zhang et al., 2016). The deficits of individuals with IGD in social interactions and social skills such as emotional and interpersonal communication have also received considerable attention (Young, 1998; Engelberg and Sjöberg, 2004; D'Hondt et al., 2015), but so far, there have been limited experimental studies on the processing of real-world socioemotional stimuli among individuals with IGD. Thus, the underlying mechanisms behind these deficits remain unclear.

Social communication has been suggested to depend largely on the capacity for expression recognition (Blair, 2005; He et al., 2011). Facial expressions are important socioemotional stimuli, as they can convey information about the identities, emotions, and intentions of other people, and thus represent a primary element of non-verbal communication in everyday life (Batty and Taylor, 2003; Itier and Taylor, 2004). Previous studies indirectly related to facial processing in IGD found that action video game players or violent media users had a reduced attention to happy faces in emotion recognition tasks (Kirsh et al., 2006; Kirsh and Mounts, 2007; Bailey and West, 2013). For example, Kirsh et al. (2006) found that compared with participants low in violent media consumption, participants high in violent media consumption were slower to identify happy expressions and faster to identify anger expressions. However, IGD-afflicted individuals' processing of facial expressions remains unclear. Furthermore, studies on normal participants have revealed that emotional cues can be extracted from facial expressions in the preattentive or unconscious stage of face processing (Öhman, 1999; Dimberg et al., 2000; Vuilleumier and Schwartz, 2001; Vuilleumier, 2002). However, although deficits in conscious neutral-face processing were found in excessive Internet users (He et al., 2011), whether individuals with IGD had unique unconscious emotional facial processing patterns remained unclear. We therefore aimed to explore this issue in the present study.

To further investigate unconscious facial processing in individuals with IGD, the present study employed a visual backward masking paradigm. Visual backward masking is an "empirically rich and theoretically interesting phenomenon" that indicates the attenuation of the visibility of a target stimulus by a mask stimulus presented after the target (Breitmeyer, 1984; Breitmeyer and Ogmen, 2000, p. 1572). In this paradigm, a target stimulus is presented briefly (usually for 1–100 ms) and followed by a mask stimulus, which is a meaningless or scrambled picture that overlaps with the target stimulus spatially or structurally (Esteves and Öhman, 1993). The mask stimulus impairs the explicit awareness or perception of the target stimulus (Morris et al., 1999; Breitmeyer and Ogmen, 2000). This paradigm has been widely used to investigate recognition thresholds as well as to examine emotional and visual information processing, which are partially independent of awareness, in a variety of specific subject populations, such as people with affective disorders (Esteves and Öhman, 1993; Breitmeyer and Ogmen, 2000; Axelrod et al., 2015; Zhang et al., 2016). For example, Zhang et al. (2016) found deficits of unconscious facial processing in patients with major depression using the visual backward masking paradigm with event-related potentials (ERPs).

To gain a better understanding of unconscious facial processing, we used ERPs, which have high temporal resolution, in the present study. To our knowledge, there was only one published ERP study focusing on the facial processing of excessive Internet users (He et al., 2011). He et al. (2011) found deficits in early face processing among excessive Internet users by asking participants to passively view upright and inverted faces and non-face stimuli presented above the conscious threshold. Specifically, excessive Internet users were found to be impaired in social stimulus processing but intact in holistic configural face processing, which were represented as a smaller N170 face effect (i.e., the difference in the amplitudes of the N170 for neutral-face vs. non-face stimuli) and similar N170 inversion effect (i.e., the difference in the amplitudes of the N170 component of ERP in response to upright vs. inverted neutral faces) in excessive Internet users compared with normal controls

(NC; He et al., 2011). N170 is widely acknowledged to be a face-sensitive ERP component, typically occurring 140 to 200 ms after stimulus onset and responding maximally to face stimuli, reflecting automatic processing in the early stage of face perception (Rossion et al., 2000; Itier and Taylor, 2004). The N170 component has been found to be not only associated with the structural encoding of faces (e.g., Dimberg et al., 2000; Sato et al., 2001; Eimer et al., 2003; Holmes et al., 2003; Schupp et al., 2004), but also modulated by emotional facial expressions (e.g., Blau et al., 2007; Pegna et al., 2008; for review, see Rellecke et al., 2013). Third, N170 was found to be associated with unconscious face processing in normal subjects (e.g., Pegna et al., 2008; Carlson and Reinke, 2010). For example, using the backward masking paradigm, Carlson and Reinke (2010) found that a masked fearful face enhanced the contralateral N170. Thus, in the present study, the N170 amplitude was taken as the index which indicated unconscious emotional facial perception in the early stage of face processing. Furthermore, expectancies for emotional content were suggested to influence the recognition of facial expressions (Leppänen et al., 2003; Hugenberg, 2005). For example, facilitation of the processing was observed when the stimuli were congruent with participants' expectancies, and the opposite effect was observed when the stimuli were incongruent with participants' expectancies (Leppänen et al., 2003; Hugenberg, 2005). Besides, according to a cognitive-behavioral model of problematic Internet use, pathological involvement in gaming results from problematic cognitions coupled with behaviors maintaining maladaptive responses (Davis, 2001). For example, individuals who have negative views of themselves may use gaming to achieve positive social interactions, social acceptance, or positive social feedback (King and Delfabbro, 2014). Besides, previous study found that individuals with Internet addiction had higher scores on the Behavior Inhibition System and Behavior Approach System Scale (BIS/BAS scale) fun-seeking subscales, suggesting that these individuals had higher sensitivity to the stimuli with reward, and were more likely to engage in approach behavior for the rewarding stimuli (Yen et al., 2009). Based on these previous findings which indicated the influence of expectancy on facial expression recognition (Leppänen et al., 2003; Hugenberg, 2005), together with the association between problematic gaming behavior with individuals with IGD and their aforementioned social needs (King and Delfabbro, 2014), and IGD's higher sensitivity to rewarding stimuli (Yen et al., 2009), we speculate that to individuals with IGD, neutral faces are comparatively less rewarded than happy faces; accordingly, individuals with IGD may have less expectancy for neutral stimuli than for positive stimuli, and this incongruence would subsequently led to the lower activation for neutral expressions than happy expressions. Thus, we expected to observe that IGD show reduced N170 amplitudes in response to neutral expressions in the happy–neutral context, while NC group show comparable N170 to happy and neutral expressions in the happy–neutral context, which may represent different patterns in emotional facial processing between individuals with IGD and NC. Whereas this effect would not present in the sad–neutral context since individuals in both groups have no expectancy for sad or neutral expressions.

MATERIALS AND METHODS

Participants

Sixteen participants with IGD and 16 NC were recruited from local universities in Shenzhen, China. Descriptions of participants' demographics are presented in **Table 1**. There were no significant differences between the two groups in terms of age, handedness, or education. The proposed diagnostic cutpoint of the DSM-5 was suggested to be conservative (e.g., Lemmens et al., 2015); thus, Young's Internet Addiction Test (IAT) was used to screen people for IGD in the present study. IAT is a reliable instrument and widely used in studies investigating Internet addiction disorders, including IGD (e.g., Khazaal et al., 2008). Young (1998) suggested that a score between 40 and 69 signifies problems due to Internet use. However, IAT relies on subjective ratings and is therefore susceptible to participants' concealment or underestimation. Additionally, previous studies used "experience in playing video games of 10 or more hours a week" (Weinreich et al., 2015, p. 61) or "at least 4 years and for at least 2 h daily" (Szycik et al., 2017, p. 2) as the inclusion criterion for the expert/excessive users of violent video games. Thus, the present study also included the length of time that the participants spent on online gaming as a criterion. Individuals were asked to provide the number of hours per day and per week they spent online gaming. Individuals with score $\geq$40 on the IAT and who spent $\geq$4 h per day and $\geq$30 h per week on Internet gaming were included in our IGD cohort. Moreover, to control for comorbidities such as depression and anxiety (Sanders et al., 2000; Yen et al., 2007; Wei et al., 2012; Lai et al., 2015), we excluded individuals with IGD who scored more than 40 points on either the Zung Self-Rating Depression Scale (SDS) (Zung, 1965) or the Zung Self-Rating Anxiety Scale (SAS) (Zung, 1971). None of the participants had a history of head injury, neurological disorders, substance abuse or dependence over the past 6 months. All research procedures were approved by the Medical Ethical Committee of Shenzhen University Medical School according to the Declaration of Helsinki. All the participants provided written informed consent indicating that they fully understood the study.

Stimuli

We used the backward masking task program (see Procedure) and stimuli employed in Zhang et al.'s (2016) study. The target face stimuli, including 20 happy expressions, 20 sad

TABLE 1 | Participants' demographics for the normal controls and individuals with IGD.

Characteristics	Control (n = 16)	IGD (n = 16)	t	p
Mean age (years)	20.25 ± 0.4	20.75 ± 0.36	−1.14	0.27
Gender (female/male)	4/12	3/13		
IAT	33.63 ± 1.3	58.13 ± 2.81	−7.33	0.00
SAS	27 ± 1.14	30.63 ± 1.31	−1.22	0.09
SDS	32.31 ± 0.98	33.94 ± 0.94	−1.18	0.26

Descriptive data are presented as mean ± standard error. IAT, Internet Addiction Test (Young, 1998); SAS, Self-Rating Anxiety Scale (Zung, 1971); SDS, Self-Rating Depression Scale (Zung, 1965). Df is 15 in the statistics.

expressions, and 40 neutral expressions, were selected from the native Chinese Facial Affective Picture System (CFAPS), which includes pictures assessed by Chinese participants in a previous study (Gong et al., 2011). The above-mentioned study found significant differences in nine-point-scale ratings for both emotional valence and arousal among the three categories of expressions. The study reported the following for valence ratings: "(2,77) = 143, $p < 0.001$, = 0.787, happy = 5.92 ± 0.13; sad = 2.78 ± 0.13; neutral = 4.22 ± 0.09; pairwise comparisons: *ps* < 0.001; for arousal ratings, (2,77) = 30.2, $p < 0.001$, = 0.439, happy = 5.13 ± 0.22; sad = 5.83 ± 0.22; neutral = 3.82 ± 0.16; for pairwise comparisons, emotional vs. neutral: $p < 0.001$, happy vs. sad: $p < 0.087$" (Zhang et al., 2016, p. 15). The stimulus display and behavioral data acquisition were conducted using E-Prime software (version 2.0, Psychology Software Tools, Inc., Boston, MA, United States).

Procedure

The procedure consisted of a happy block and a sad block. At the beginning of each trial, a central fixation cross was presented for 500 ms, followed by a 400-600 ms blank screen. Then, a target (happy/sad or neutral) face was presented for 17 ms, followed immediately by a scrambled face as a mask, which lasted for 150 ms (Zhang et al., 2016). Previous studies set the duration of the mask stimulus at 100 to 300 ms or other durations above the awareness threshold (e.g., Rolls and Tovee, 1994; Whalen et al., 1998; Fisch et al., 2009; for review, see Pessoa, 2005). Here, we used 150 ms according to the parameter in Zhang et al.'s (2016) study. The participants were required to discriminate the target faces by pressing two buttons on the computer keyboard with their left or right index fingers as soon as possible (Zhang et al., 2016). Each block included 160 trials with 80 emotional expressions and 80 neutral expressions that were randomized and presented as target stimuli—that is, 20 happy and 20 neutral faces were presented a total of four times in the happy block; 20 sad and 20 neutral faces were presented a total of four times in the sad block. The assignment of keys to each valence of expressions, and the sequence of blocks was counterbalanced across the participants (Zhang et al., 2016).

ERP Recording

Brain electrical activity was recorded through a 64-electrode scalp cap using the 10–20 system (Brain Products, Munich, Germany). The TP10 channel was used as the reference during the recordings (Kaufmann et al., 2009; Ferrante et al., 2015; Cui et al., 2017). Two electrodes were used to measure the electrooculogram (EOG). EEG and EOG activity were amplified at 0.01–100 Hz passband and sampled at 500 Hz. The EEG data were recorded with all electrode impedances maintained below 5 kΩ. The EEG data from each electrode were re-referenced to the average of the left and right mastoids prior to further analysis.

The EEG data were pre-processed and analyzed using BrainVision Analyzer 2.1 (Brain Products, Munich, Germany). Pre-processing included bad channel detection and removal, epoching, and eyeblink removal. Then, the signal was passed through a 0.01–30 Hz band-pass filter. The epochs consisted of the 200 ms before and 1000 ms after the onset of the target stimuli. EOG artifacts were corrected using independent component analysis (ICA) (Jung et al., 2001). Epochs with amplitude values exceeding ±80 μV at any electrode were excluded before the application of the EEG averaging procedure. The ERPs were independently computed for each participant and each experimental condition.

The ERP was time-locked to the presentation of the target face. Based on previous research on face processing (Luo et al., 2010; Frühholz et al., 2011; Zhang et al., 2016) and the topographical distribution of the grand-averaged ERP activity in the current study, the average amplitudes at the P8 and PO8 electrode sites were selected for the statistical analysis of the N170 component (time window: 150–230 ms). For each component, mean amplitudes were obtained within the corresponding time window and averaged from the electrodes.

Data Analysis

Further statistical analyses were conducted using IBM SPSS Statistics 22 (IBM Corp., Armonk, NY, United States). Because the happy and sad blocks were different emotional contexts, separate analyses of variance (ANOVAs) of the interaction of emotional valence (happy vs. neutral, sad vs. neutral, or happy vs. sad) × group (IGD vs. control) were conducted for the behavioral data and each ERP component. Both the behavioral data and the ERP amplitudes were analyzed with repeated measures ANOVAs using Greenhouse–Geisser adjusted degrees of freedom. The between-subject factor was the study group (IGD vs. control), and the within-subject factor was emotional valence of expression (happy vs. neutral, sad vs. neutral, or happy vs. sad). The *post hoc* analysis used Bonferroni corrections for multiple comparisons.

RESULTS

The numbers of trials included in the experimental conditions are listed in **Table 2**. For the following results, the descriptive data are presented as mean ± standard error unless noted otherwise.

Behavioral Data

Regarding reaction time, in the sad block, the main effect of valence was significant, $F(1,30) = 4.86$, $p < 0.05$, = 0.14; reaction time was shorter for sad expressions (618.87 ± 31.48 ms) than for neutral expressions (663.39 ± 34.77 ms); the main effect of group

TABLE 2 | Number of trials included in each condition.

Condition	Control ($n = 16$)	IGD ($n = 16$)	*t*	*p*
Happy expressions	62.44 ± 3.29	55.44 ± 4.20	1.40	0.18
Neutral expressions in happy block	52.88 ± 4.78	54.5 ± 4.12	−0.36	0.73
Sad expressions	59.5 ± 2.60	51.2 ± 4.79	1.72	0.10
Neutral expressions in sad block	52.38 ± 3.74	46.75 ± 3.95	1.42	0.18

Df is 15 in the statistics.

was significant, $F(1,30) = 5.09$, $p < 0.05$, $= 0.15$; and reaction time was shorter for the NC group (569.84 ± 44.68 ms) than for the IGD group (712.42 ± 44.68 ms). The interaction was not significant, $p > 0.5$. In the happy block, the main effect of valence was significant, $F(1,30) = 6.63$, $p < 0.05$, $= 0.18$; reaction time was shorter for happy expressions (583.97 ± 39.33 ms) than for neutral expressions (648.08 ± 36.6 ms); no other main and interaction effects reached significance, all ps > 0.1; reaction time for the NC group (577.25 ± 50.76 ms) was comparable with that for the IGD group (654.81 ± 50.76 ms). When the happy and sad trials were directly compared, the main effect and the interaction were not significant, all ps > 0.05.

In terms of accuracy, in the sad–neutral block, in the happy–neutral block, and when the happy and sad trials were directly compared, no main effect and interaction effect reached significance.

ERP Data

N170

A 2 (group) × 2 (happy vs. neutral) ANOVA revealed that the main effect of valence was not significant, $(1,30) = 3.47$, $p = 0.07$, $= 0.10$, and the main effect of group was not significant, $(1,30) = 0.01$, $p = 0.92$, < 0.001. However, the interaction of valence by group was significant, $(1,30) = 4.25$, $p = 0.048$, $= 0.124$ (**Figure 1**). The *post hoc* analysis revealed that for the IGD group, happy expressions elicited a comparatively more negative-directed N170 component (3.02 ± 1.12 μV) than neutral faces (4.18 ± 1.09 μV), $(1,30) = 7.70$, $p = 0.009$, $= 0.20$, Bonferroni corrected. However, for the control group, happy and neutral expressions elicited similar N170 components (happy: 3.79 ± 1.12 μV, neutral: 3.73 ± 1.09 μV), $(1,30) = 0.02$, $p = 0.89$, $= 0.001$, Bonferroni corrected.

However, the amplitudes in the sad–neutral context did not show significant main or interaction effects in the sad–neutral condition (**Figure 2**). A 2 (group) × 2 (sad vs. neutral) ANOVA revealed that the main effects of valence [$F(1,30] = 0.39$, $p = 0.54$, $= 0.01$], group [$F(1,30) = 0.02$, $p = 0.88$, $= 0.001$], and the interaction [$F(1,30) = 0.02$, $p = 0.88$, $= 0.001$] were not significant and that the N170 components elicited by happy and neutral expressions in the IGD group (sad: 3.79 ± 1.21 μV, neutral: 3.65 ± 1.15 μV) were similar to those elicited in the control group (sad: 3.57 ± 1.21 μV, neutral: 3.35 ± 1.15 μV).

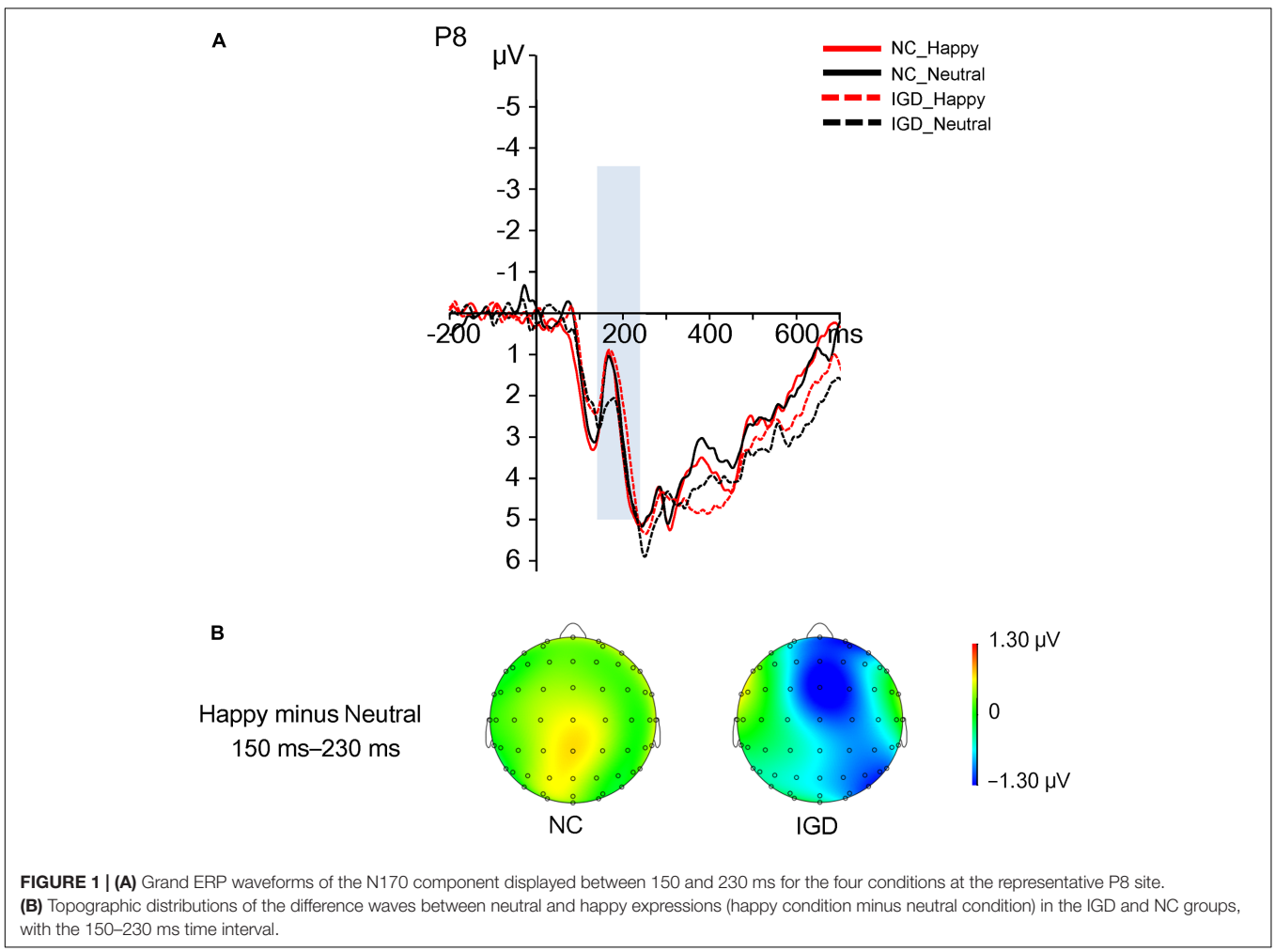

FIGURE 1 | (A) Grand ERP waveforms of the N170 component displayed between 150 and 230 ms for the four conditions at the representative P8 site. **(B)** Topographic distributions of the difference waves between neutral and happy expressions (happy condition minus neutral condition) in the IGD and NC groups, with the 150–230 ms time interval.

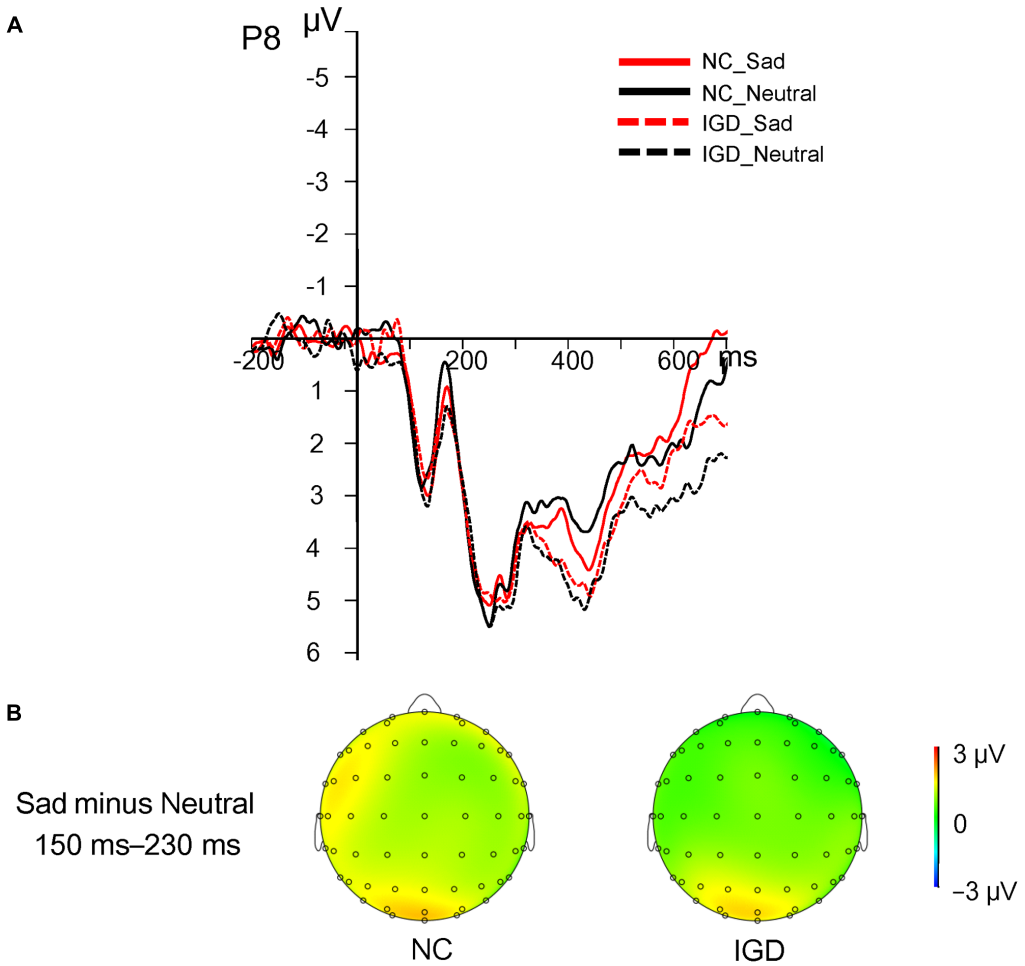

FIGURE 2 | (A) Grand ERP waveforms of the N170 component displayed between 150 and 230 ms for the four conditions at the representative P8 site. **(B)** Topographic distributions of the difference waves between neutral and happy expressions (sad condition minus neutral condition) in the IGD and control groups, with the 150–230 ms time interval.

When directly comparing N170 amplitudes in response to sad and happy expressions, a 2 (IGD vs. NC group) × 2 (sad vs. happy) ANOVA demonstrated that the main effects of valence, group, and the interaction were not significant, all *p*s > 0.05.

DISCUSSION

As a perceptual basis for social interaction, emotional expression processing is an important component of interpersonal communication. Although a wealth of studies have investigated executive functions in individuals with IGD, studies on the emotional expression processing of individuals with IGD have been limited; in particular, to our knowledge, there have been no published studies investigating unconscious processing of emotional expressions in IGD. The behavioral data of the present study revealed that both the IGD and NC groups responded faster to unconscious emotional expressions (happy and sad expressions) than to neutral expressions, suggesting that individuals with IGD have normal ability to extract emotional signals from facial expressions in the preattentive stage. This result was consistent with a previous finding which demonstrated a shorter reaction time to emotional expressions than to neutral expression in normal participants (Calder et al., 1997; Eimer et al., 2003) and extended this finding to individuals with IGD. Besides, compared with IGD, NC group showed shorter reaction time to both sad and neutral expressions in the sad block. However, there was no similar effect on happy and neutral expressions in the happy block. Prototypical happy faces were suggested to be more easily recognized and more distinguishable from neutral than sad faces (Calder et al., 1997; Surguladze et al., 2003). Based on this suggestion, in the happy block, happy expressions might be more distinguishable than neutral expressions for both NC and IGD group, thus facilitate the recognition task for the two expressions in both NC and IGD group. While there was no facilitation of recognition in the sad block since the sad expressions are not much distinguishable from neutral expressions as happy expressions. These results suggest that regarding the reaction

time, the sad block condition/sad–neutral context might be more sensitive in distinguishing IGD and NC in unconscious facial recognition.

More importantly, the present study explored the time course of unconscious emotional facial processing in individuals with IGD. The ERP results showed reduced N170 amplitude in individuals with IGD when they processed unconscious neutral faces compared with happy faces, while NC showed similar N170 amplitudes when they processed neutral and happy faces in the happy–neutral context. Both individuals with IGD and NC showed similar N170 amplitudes to sad faces and neutral faces in the sad–neutral context. The decreased N170 amplitude for neutral expressions compared to happy expressions in the IGD group support our hypothesis, which suggested that participants' different expectancies in processing positive and negative stimuli would influence their facial recognition, and lead to different facial processing in IGD and NC. Participants' expectancies were previously suggested to influence implicit evaluation by affecting the valence of the prime stimuli in the affective priming task (Leppänen et al., 2003; Hugenberg, 2005). In the present study, neutral expressions were less rewarded than happy expressions in individuals with IGD, and IGD might have less expectancy for neutral expressions than for happy expressions, resulting in decreased N170 amplitudes for neutral expressions than happy expressions. However, in the sad–neutral condition, individuals may not have more expectancy for sad faces or less expectancy for neutral faces, leading to similar responses to sad and neutral faces. It should be noted that we cannot conclude that individuals with IGD have deficits in emotional facial recognition, since they showed similar N170 amplitudes to those of NC in response to happy and sad expressions. On the other hand, this result implies that individuals with IGD may have normal ability to extract emotional information from emotional expressions. Furthermore, the present ERP data showed differences between IGD and NC group in happy block condition, while the behavioral data showed differences of two groups in sad block condition. We suggest that N170 represent the distinct unconscious face processing of IGD in early stage, whereas the reaction time might reflect the facial expressions recognition in the late stage. However, considering that behavioral data often does not align to ERP data for easy explanations, more studies are needed for this issue.

In summary, the present results extended the previous findings on the face processing of excessive Internet users and demonstrated distinct mechanisms for facial expression processing in different facial contexts among individuals with IGD. Specifically, compared with NC, individuals with IGD have lower N170 amplitudes in response to neutral faces than in response to happy faces in the happy–neutral expression context, which may arise from their lower expectancy for neutral expressions. This effect was not observed in the sad–neutral expression context for either IGD or NC individuals.

Limitations and Future Studies

There are two limitations in the present study. First, more males than females were recruited due to the relative scarcity of females with excessive use of Internet game playing. Second, although previous studies found that substantial amounts of time in the virtual world (e.g., playing video games) were associated with individuals' decreased interpersonal relationships in the real world and suggested that the lower frequency of social-emotional communication may alter how individuals with IGD process facial expressions in the real world (Lo et al., 2005; Weinreich et al., 2015), we cannot draw any conclusions about the causality of IGD subjects' distinct facial expression processing pattern or the their impairments in social communication. More studies are needed to investigate the emotional facial processing mechanisms of individuals with IGD.

AUTHOR CONTRIBUTIONS

XP, FC, and CJ developed the concepts for the study. TW collected the data. XP and TW analyzed the data. XP, CJ, and FC wrote the manuscript. All authors contributed to the manuscript and approved the final version of the manuscript for submission.

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Dysfunctional Prefrontal Function Is Associated with Impulsivity in People with Internet Gaming Disorder during a Delay Discounting Task

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Internet gaming disorder (IGD), defined as the persistent use of online games with ignorance of adverse consequences, has increasingly raised widespread public concerns. This study aimed at elucidating the precise mechanisms underlying IGD by comparing intertemporal decision-making process between 18 IGD participants and 21 matched healthy controls (HCs). Both behavioral and fMRI data were recorded from a delay discounting task. At the behavioral level, the IGD showed a higher discount rate *k* than HC; and in IGD group, both the reaction time (delay – immediate) and the discount rate *k* were significantly positively correlated with the severity of IGD. At the neural level, the IGD exhibited reduced brain activations in the dorsolateral prefrontal cortex and bilateral inferior frontal gyrus compared to HC during performing delay trials relative to immediate ones. Taken together, the results suggested that IGD showed deficits in making decisions and tended to pursuit immediate satisfaction. The underlying mechanism arises from the deficient ability in evaluating between delayed reward and immediate satisfaction, and the impaired ability in impulse inhibition, which may be associated with the dysfunction of the prefrontal activation. These might be the reason why IGD continue playing online games in spite of facing severe negative consequences.

Keywords: Internet gaming disorder, decision-making, delay discounting task, dorsolateral prefrontal cortex, inferior frontal gyrus

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INTRODUCTION

Internet gaming disorder (IGD) has increasingly raised widespread public concerns. It is defined as recurrent and persistent use of online games, which lead to a variety of negative consequences in terms of daily life and mental health, such as maladaptive coping, ill interpersonal relationship, and decreased academic achievements (1, 2). Experimental studies and questionnaire surveys have indicated that individuals with IGD show great behavioral and neuronal similarities to those with drug addictions, substance abuse, and gambling disorder in many aspects, involving comorbid psychiatric symptoms, behavior control, and decision-making (3–5). Nevertheless, compared with substance-related and addictive disorders (e.g., alcohol abuse disorder), a significant feature for IGD

is no substance or chemical intake. In May 2013, IGD has been listed in Section "Results" of the DSM-5 as a condition warranting further studies (6–8).

Intertemporal decision-making refers to situations where people need to choose between two options: an immediate but smaller reward and a delayed but larger one (9). Delay discounting task (DDT) is a widely used paradigm in exploring intertemporal decision-making and measuring impulsive choices (10), but rarely used to detect the decision-making and planning of IGD. When the delay is shorter, people generally prefer the larger reward rather than the smaller one; but with gradually increased delay, people will shift their preference to the smaller reward rather than the larger one. Individuals who shift their preferences to smaller rewards after shorter delays would be regarded as more impulsive than individuals who shift their preferences after longer delays (11). Studies using DDT have found that delayed rewards tend to be more steeply discounted in substance addicts in relation to alcohol (12), heroin (13), cocaine (14), methamphetamine (15), and pathological gamblers (16) when compared to healthy controls (HCs). Furthermore, there is evidence that individuals with IGD are more impulsive than recreational Internet gaming users and HC (17–20). These findings raise the possibility that the IGD, in accordance with drug and gambling addicts, show myopia for the future, i.e., preference for short-term rewards (e.g., Internet games) and ignorance for long-term losses (e.g., social relationship).

Previous works with the DDT established the neural correlates of brain regions in intertemporal decision-making and then proposed a dual-valuation model, which assumed that there were two separate systems contributing to such decisions (21, 22). One system (called the "β system") included mesolimbic dopamine projection regions and weighed the immediate rewards (i.e., nucleus accumbens and medial prefrontal cortex); the other system (called the "δ system") included the lateral prefrontal cortical areas and weighed the delayed rewards. Human imaging studies also explored brain activations during delay discounting process in behavioral addiction and substance dependence samples. Pathological gamblers showed elevated brain activities in the dorsolateral prefrontal cortex (DLPFC) and amygdala when selecting delayed rewards compared with HC (23). Alcoholics were reported to show increased activities in the inferior frontal gyrus (IFG), insula, and supplementary motor area along with steeper discounting of delayed rewards (24). Smokers also exhibited dysfunctional brain activations in the IFG, DLPFC, and insula during the inhibition of immediate smaller rewards to gain the delayed larger ones (25). The DLPFC has been proved to be involved in behavioral inhibition, reward processing, and decision-making; the IFG is also critical for inhibition and risky decision-making; besides, the insula plays a part in cognitive function and motor control (26–28). Specifically, the altered functional connectivity in the bilateral prefrontal lobe has been detected in IGD (29).

Although previous researches have revealed decision-making deficits in IGD, the underlying mechanism of impaired ability to control their behaviors remains unclear. To explore the reasons why individuals with IGD pursue instantaneous rewarding experience regardless of long-term benefits, 21 HCs and 18 IGD were recruited to perform the DDT, which comprised a series of selections between immediate smaller monetary rewards and delayed larger monetary rewards.

Our previous study has found that the participants with IGD were prone to take risks and exhibited less activation in the IFG and superior temporal gyri when making risky choices in comparison to HC (30). A study that used Go/No-Go paradigm with gaming cue distraction found that the IGD showed impaired response inhibition and decreased brain activities in the right DLPFC (31). In individuals with IGD, viewing Internet gaming-related stimuli significantly induced increased brain activations in the prefrontal cortex, inferior parietal lobule, and striatum (19, 20, 32). These findings suggest that the brain regions associated with cognitive control, craving, decision-making, and reward induce dysfunctional effects by virtue of the frequent use of Internet games in IGD. Therefore, we hypothesized that the IGD group may show similar behavioral tendency (myopia for the future) and brain activation patterns parallel with findings in other addiction disorders. At the behavioral level, we expected to observe steeper discounting of delayed rewards in IGD compared to HC and a modulation of delayed reward representations by the severity of IGD. At the neural level, we expected IGD to show less brain activations in those brain regions (i.e., DLPFC, IFG), which are related to the evaluation of delayed rewards, and to impulse inhibition. We also expected that brain activations would be correlated with behavioral performances in IGD group.

MATERIALS AND METHODS

Participants

The experiment conforms to the Code of Ethics of the World Medical Association (Declaration of Helsinki). The Human Investigations Committee of Zhejiang Normal University approved this research. All participants signed the informed consent forms before the experiment. Participants were right-handed male students (18 IGD and 21 HC) recruited through advertisements in Shanghai, PR China. Only males were included due to higher IGD prevalence in men than that in women. There were several exclusion criteria for selecting participants, including history or current neurological or mental disorders as measured by MINI international neuropsychiatric interview and the mood states scale, history or current psychiatric disease (e.g., depression, schizophrenia), and history of drug abuse (e.g., cocaine, alcohol) or any other type of behavioral addictions as measured by standard interviews and self-report instruments. All participants did not report a history of behavioral addiction, substance abuses, and mental disorders. Importantly, none of them reported brain injuries, brain surgeries, and any attention problems such as attention deficit hyperactivity disorder. In addition, all participants were told to not take any addictive substances 3 h before the experiment began, including coffee, cigarette, and alcohol.

The diagnosis of IGD was determined based on (1) a modified Young's online Internet Addiction Test (33), which emphasized on IGD (IAT, see Supplementary Material), (2) the proposed nine-item IGD diagnostic scale based on DSM-5 (34), and (3) the criteria for time and frequency of gaming playing. Both the questionnaire and criteria were precisely translated into

Chinese for the suitability of participants. To critically assess gaming behaviors and IGD symptoms, we then replaced all the statements of online activities in the original questionnaire with specific items, such as game playing or online games. The validity of the modified IAT was tested, and the Cronbach's alpha coefficient of reliability index was an acceptable 0.90. The modified IAT consists of 20 items associated with online games including psychological dependence, compulsive use, withdrawal, related problems in school or work, sleep, family, and time management. For each item, participants were instructed to choose a number from the following scale: 1 = "Rarely" to 5 = "Always," or "Does not Apply." The score of the modified IAT is ranged from 20 to 100, which represents the severity of IGD. Scores over 50 indicate occasional or frequent Internet addiction problems, and scores over 80 indicate severe Internet addiction problems (35).

The demographic characteristics for both groups were shown in **Table 1**. The IGD and HC did not significantly differ in age and education years. In this study, the IGD group was composed of individuals who (1) scored over 50 on the modified IAT, (2) met at least five of the nine DSM-5 criteria, (3) spent at least 2 h on online games per day during the last 2 years, and (4) spent most of their online time playing online games (>80%). However, the HC group did not satisfy any above-mentioned criteria.

Task and Procedure

The whole time of the task lasted about 15 min for each participant. Participants first practiced 20 trials to be familiar with the task before completed the DDT task in the scanner. During the task, participants need to make choices between an immediate reward and a larger amount of money with a specified delayed time (e.g., now 10 Yuan versus 7 days later 12 Yuan, $1 is equal to about 6.6 Yuan). The monetary amounts varied from 12 to 15, 20, 30, 40, and 50 Yuan, and the delay time ranged from 6 h to 1, 3, 7, 30, and 90 days. Thus, there were 36 trials in 1 block, and the task consisted 2 blocks in total. The trials in this study were presented randomly in E-prime (version 2.0, Psychology Software Tool, **Figure 1**).

TABLE 1 | Demographic characteristics for HC and IGD participants.

	HC (M ± SD)	IGD (M ± SD)	*t*	*p*
Age	23.1 ± 2.0	22.1 ± 3.2	1.2	0.25
Years of education	14.6 ± 1.4	14.4 ± 1.6	0.8	0.42
IAT	31.5 ± 11.9	64.0 ± 10.1	9.1	0.00**
DSM	1.3 ± 0.9	5.2 ± 0.8	12.1	0.00**
Time spent on games per day (in hours)	0.5 ± 0.2	2.9 ± 0.4	23.6	0.00**

HC, healthy control; IGD, Internet gaming disorder.
*** p < 0.01.*

All participants were paid a guaranteed 40 Yuan (≈$6) for the participation and an extra reward (ranged from 12 to 50 Yuan) that depended on their selections in DDT task. To elicit participants' motivation to response properly, they were informed that they would receive additional payments according to their performances during the task. For example, if they selected the fixed money on the trial, then they would gain 10 Yuan in cash; if they selected the delayed option, they would gain that amount of money in cash after the corresponding delay.

Behavioral Data Analysis

Delay discounting rate was estimated for each participant by the following hyperbolic model (36):

$$V = \frac{A}{(1+kD)}. \quad (1)$$

The V represents the subjective value of the delayed reward; A is the amount of the delayed reward; D is the length of delay to its delivery; and k is a free parameter that indicates the steepness of the discount curve. Higher k values indicate more rapid discounting and greater impulsivity (37–39). An important procedure for estimating k value was to determine the indifference points, which were the points that the fixed reward and the delayed reward were of equal subjective value for an individual. The indifference points were calculated across a series of different delay lengths and monetary amounts and were fitted into the Eq. 1. There were two steps of the behavior data analyses for DDT. In the first step, a non-linear curve-fitting program (Origin 7.0) was used to determine each participant's best-fit values of k. The second step was to perform a log 10 transformation of the k values. The log transformation was required for these data due to their non-normal distribution (40, 41). To examine the different discount rate k of IGD and HC, an independent sample t test was performed.

Image Acquisition and Pre-Processing

fMRI data were collected using a 3T scanner (Siemens Trio) with a gradient-echo EPI T2 sensitive pulse sequence in 33

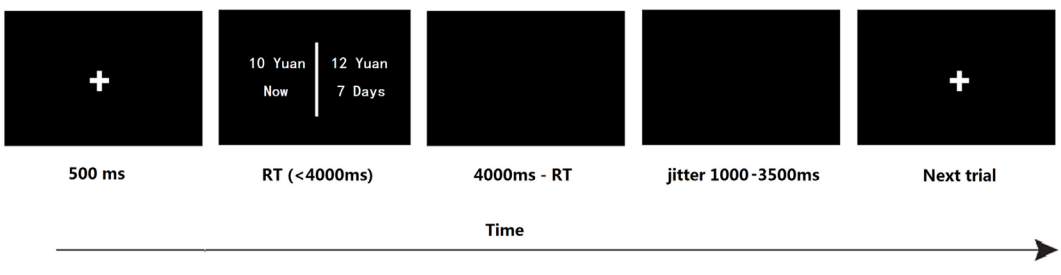

FIGURE 1 | The timeline of one trial in the delay discounting task. The immediate but smaller option is fixed on 10 Yuan; in the delayed but larger options, monetary amounts ranged from 12 to 15, 20, 30, 40, and 50 Yuan, and the delay time ranged from 6 h to 1, 3, 7, 30, and 90 days. "Yuan" is the basic unit of money in China.

slices (interleaved sequence, 3-mm thickness, repetition time = 2,000 ms, echo time (TE) = 30 ms, flip angle 90°, field of view 220 × 220 mm^2, matrix 64 × 64). Stimuli were presented by *Invivo* synchronous system (*Invivo* Company)[1] through a monitor in the head coil. Structural images covering the whole brain were collected using a T1-weighted three-dimensional spoiled gradient-recalled sequence (176 slices, flip angle = 15°, TE = 3.93 ms, slice thickness = 1.0 mm, skip = 0 mm, inversion time = 1100 ms, field of view = 240 × 240 mm, and in-plane resolution = 256 × 256).

The pre-processing of imaging analysis was conducted through Statistical Parametric Mapping (SPM) software package, SPM5.[2] Images were slice-timed, reoriented, and realigned to the first volume. T1-co-registered volumes were then normalized to an SPM T1 template and spatially smoothed using a 6-mm full-at-half-maximum Gaussian kernel.

First-Level Regression Analysis

A general linear model (GLM) was applied to identify blood oxygen level dependence (BOLD) signal in relation to two conditions: choice of immediate smaller reward and choice of delayed larger reward. Error trials were excluded. The GLM was independently applied to each voxel to identify voxels that were significantly activated for the event types of interest. A high pass filter (cut-off period = 128 s) was applied to improve the signal-to-noise ratio by filtering out low frequency noise.

Second-Level Group Analysis

Second-level analysis was performed at the group level. First, we determined which voxels showed a main effect of delayed trials versus immediate trials within each group (IGD, HC). Second, we tested which voxels significantly differed in BOLD signal between IGD and HC [$(IGD_{delay} - IGD_{immediate}) - (HC_{delay} - HC_{immediate})$]. Third, we identified clusters of contiguously significant voxels at an uncorrected threshold $p < 0.05$. Finally, we tested these clusters for cluster-level FWE correction $p < 0.05$, and the AlphaSim estimation indicated that clusters with 102 contiguous voxels would achieve an effective FWE threshold $p < 0.05$. The smoothing kernel was 6.0 mm, which was used during simulating false-positive (noise) maps through AlphaSim and was estimated from the residual fields of the contrast maps used in the one-sample *t*-test.

Correlation Analysis

Correlation analysis was calculated between brain activities and the behavioral performances to test our hypothesis. We further carried out ROI analyses with seed regions from contrast delay trials versus immediate trials. For each ROI, a representative beta value was obtained by averaging the signal of all the voxels within the ROI. The correlations among the severity of IGD, log *k* values, reaction time (RT), and the beta values were calculated. The RT stands for the difference between the response to delayed options and the response to immediate options (delay – immediate).

RESULTS

Behavioral Performance

The result of independent sample *t*-test suggested that the *k* value of IGD was higher than that of HC at a marginal significant level ($t = 2.01$, $p = 0.05$, $d = 0.53$). The mean discounting rate *k* values and corresponding SDs for IGD and HC were 0.19 ± 0.16 and 0.11 ± 0.14, respectively (**Figure 2A**), and this indicated the IGD discounted the rewards more steeply than HC (**Figure 2B**). The R^2 value for discounting function (0.88 for IGD and 0.71 for HC) denoted the variance accounted for by the Eq. 1. The

[1]http://www.invivocorp.com/.

[2]http://www.fil.ion.ucl.ac.uk/spm/.

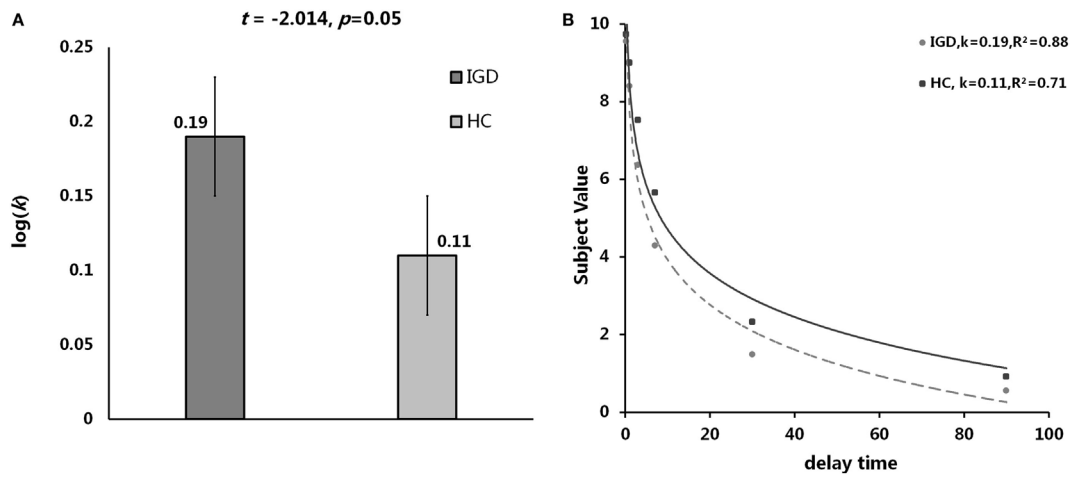

FIGURE 2 | Delay discounting value differences between Internet gaming disorder (IGD) and healthy control (HC). **(A)** The IGD showed higher *k* value than HC. **(B)** Delay discount functions for HC and IGD. Points show mean indifferent points for monetary rewards as a function of delay time. R^2 represents how close the fitted curve is from the actual data points. First, the variation between data points and the mean values is calculated. In least-squares fitting, the total sum of squares (TSS) includes two parts: the variation explained by regression and that not explained by regression [the residual sum of square (RSS)]. Then the $R^2 = 1 - RSS/TSS$.

RT (delay − immediate) of IGD was longer than HC, but it did not reach statistical significance (HC: −86 ± 213 ms, IGD: −56 ± 194 ms, $t(1, 37) = 1.43$, $p = 0.11$). In addition, the severity of IGD was significantly positively correlated with the log *k* values ($r = 0.552$, $p = 0.027$; **Figure 3A**) and RT ($r = 0.530$, $p = 0.035$; **Figure 3B**) in IGD group. But the correlations among these variables did not reach a significant level in HC group.

Imaging Results

We compared the two groups in terms of BOLD signal differences between delayed choices and immediate choices. Group comparison suggested that the IGD showed smaller BOLD signal differences, between delayed and immediate choice, over the left DLPFC and bilateral IFG than HC (**Figure 4** and **Table 2**), which was consistent with our hypothesis. Nevertheless, the IGD did not show any greater BOLD signals in the whole brain compared to HC. In each group, the IGD showed greater brain activations in the anterior cingulate gyrus and lower brain activations in the left IFG and medial frontal gyrus for delayed choices than immediate choices; the HC showed greater brain activations in the right IFG, orbital gyrus, and middle frontal gyrus for delayed choices than immediate choices (**Figure 5** and **Table 3**).

Correlation Results

The correlations between beta values and behavioral performance were analyzed within each group. The brain activations in the DLPFC and bilateral IFG were all significantly positively correlated with the log *k* values in both groups (see the results in **Figure 6**), and the correlation between beta value in the DLPFC and log *k* in the two groups was significantly different by a Fisher's *Z* test ($z = 2.44$, $p < 0.05$). In IGD group, the brain activations in the bilateral IFG (delay − immediate) were positively correlated with the severity of IGD, but it did not reach the significant level (left IFG: $r = 0.478$, $p = 0.061$; right IFG: $r = 0.480$, $p = 0.060$; **Figure 7**); no significant correlations were found between brain activations and the severity of IGD in HC group ($p > 0.1$). In addition, there were no significant correlations between the brain activations and RT in each group ($p > 0.1$).

DISCUSSION

Consistent with our hypotheses, the IGD showed higher discounting rate *k* and less brain activations than HC. The foregoing results indicated that the IGD group were more impulsive and might have deficient decision-making ability, which was in line with our previous study (42). In particular, we found that the left DLPFC and bilateral IFG were more deactivated in trials in which the IGD selected the delayed rewards compared to HC, which may provide evidences to further understand the mechanisms underlying IGD.

Deficient Ability in Evaluating the Delayed Reward in IGD

Compared with HC, IGD showed lower brain activations in the left DLPFC when choosing the delayed options. Consistent with this finding, Hoffman et al.'s study found that methamphetamine-dependent individuals exhibited lower activation in the DLPFC than that of HC in delayed decisions (43). According to the dual-system mode, the δ system, which included the DLPFC, was mainly used for weighting the delayed rewards (21, 22). Researchers have also found that the DLPFC primarily responds to the delays of delayed rewards, and the activation in the DLPFC is negatively related to increasing delay time (44). Specifically, there is evidence that the DLPFC plays a vital role in encoding the attributes of multiple reward predictions into an integrated value (45).

Thus, the relatively reduced brain activities in the DLPFC observed in IGD may indicate that IGD had potential deficits

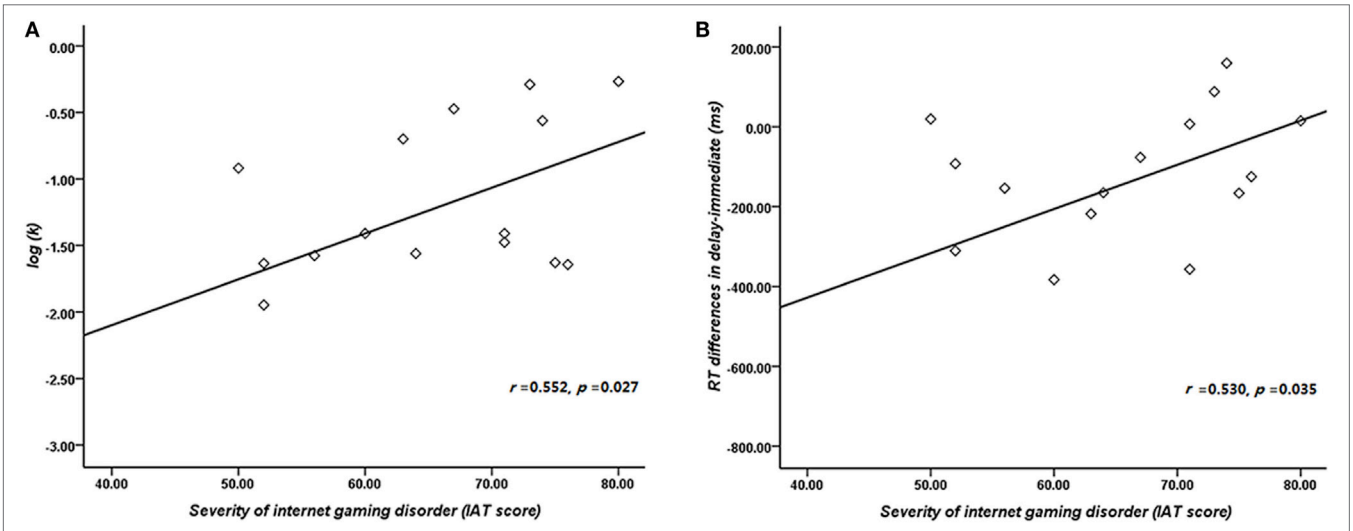

FIGURE 3 | Correlation between the severity of Internet gaming disorder (IGD) and behavioral performance. **(A)** Correlation between the severity of IGD and log *k*. **(B)** Correlation between the severity of IGD and reaction time (delay − immediate). (Scores greater than 3 SDs were regarded as outliers and were excluded from further analysis.)

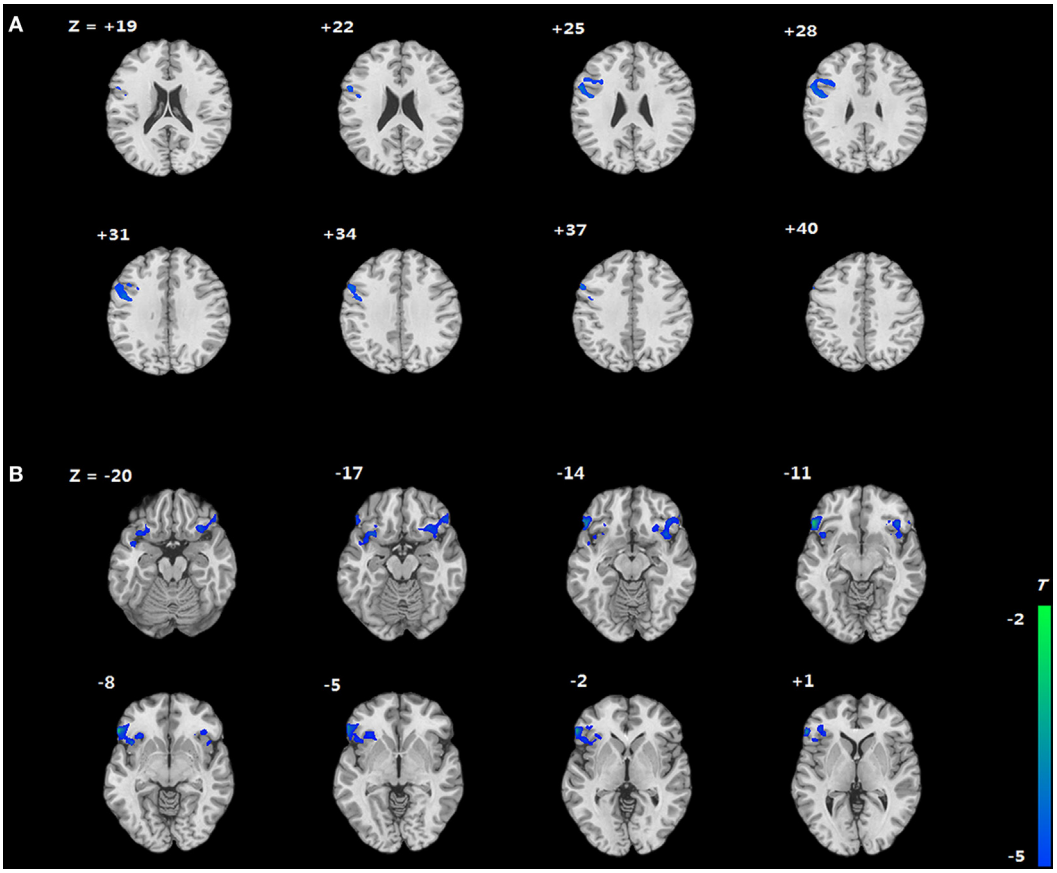

FIGURE 4 | Brain areas showing differences in Internet gaming disorder (IGD) when comparing to healthy control (HC) [(IGD_{delay} – $IGD_{immediate}$) – (HC_{delay} – $HC_{immediate}$)]. **(A)** IGD show lower brain activation in left dorsolateral prefrontal cortex than HC. **(B)** IGD show lower brain activation in bilateral IFG than HC.

TABLE 2 | Brain activations change between IGD and HC (delay – immediate).

Region[a]	BA	*x*, *y*, *z*[b]	Max *t*	Number of voxels[c]	H
Inferior frontal gyrus	47	–54, 27, –12	–3.93	257	L
Dorsolateral prefrontal cortex	9	–57, 9, 24	–3.23	113	L
Inferior frontal gyrus	47	39, 27, –12	–3.02	109	R

[a]*The brain regions with maximal t score were selected to be shown.*
[b]*Peak Montreal Neurological Institute coordinates.*
[c]*Coordinates represent the local maxima in the delay > immediate contrast. If multiple local maxima existed in the same region, only the maximum with the highest t score is shown. Voxel size = 3 × 3 × 3.*
HC, healthy control; IGD, Internet gaming disorder.

in evaluating the magnitudes and delays of rewards. They could not fully integrate all the information of choices, which would lead to a lower capability in decision-making, even with longer decision-making time. Furthermore, a resting-state study has identified that the individuals with IGD show reduced functional connectivity strength between the DLPFC and caudate, suggesting impaired effective modulation of the DLPFC on rewards (46), which are also observed in substance abuse populations (47). Another explanation for the results is that there may be a minimum activation threshold of the DLPFC for individuals to choose the delayed reward. The activation below the minimum threshold would connect with the decisions for the immediate reward rather than the delayed one. Because the IGD have a lower activation of the DLPFC, they reach the minimum threshold at shorter delays than HC.

In addition, the RT was positively correlated with the severity of IGD, indicating that the more serious the IGD was, the longer time they needed to make choices. The correlation findings supported the explanation that the IGD showed deficient evaluating ability of the delayed features to some extent. To sum up, we inferred that the IGD unconsciously focused on the short-term gains, which might be associated with the poor reward evaluation ability.

Impaired Impulse Inhibition in Decision-Making in IGD

Apart from for the known role in reward processing, the DLPFC, as the highest-order association area, is also responsible for executive functions such as response inhibition and multi-attribute decision-making (48, 49). Especially, studies have proved that the activity in the DLPFC will enhance when individuals exercise self-control (50). Moreover, reduced brain activation of the IFG was also observed in IGD during the

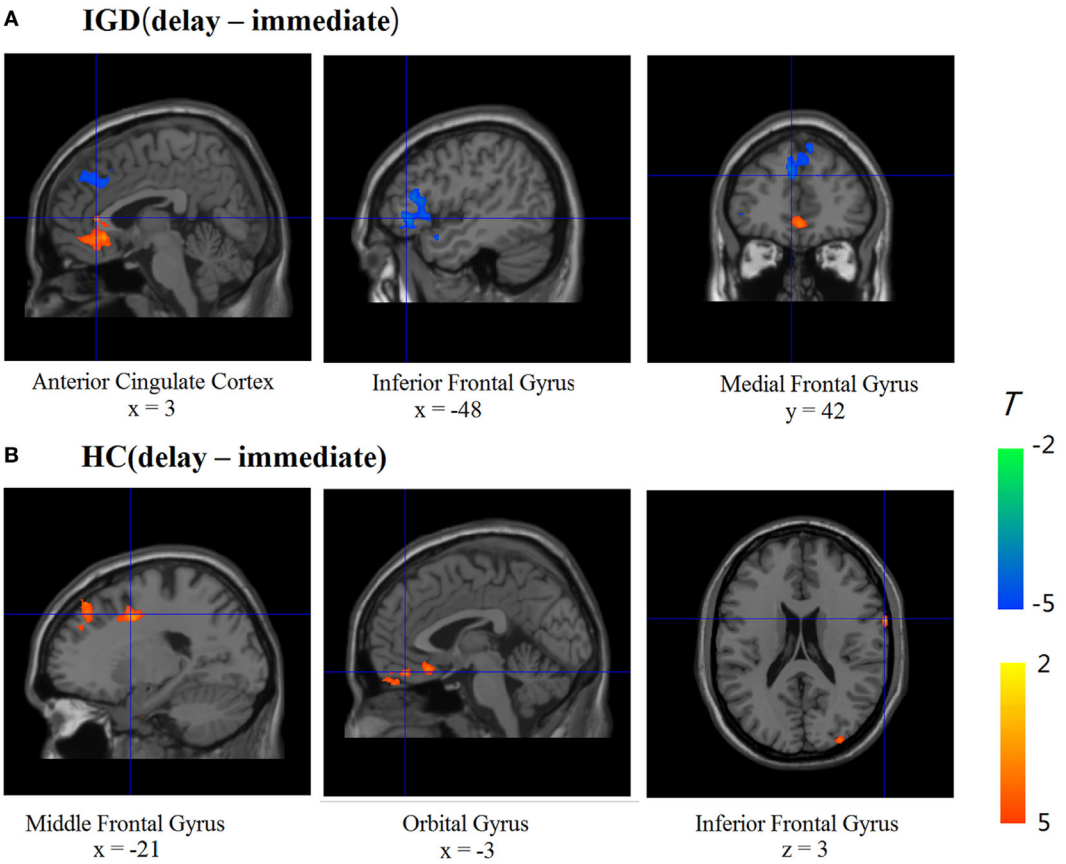

FIGURE 5 | Brain activations change between different conditions in Internet gaming disorder (IGD) and healthy control (HC) (delay – immediate). **(A)** The IGD showed greater brain activation in the ACC and lower brain activations in the left inferior frontal gyrus (IFG) and medial frontal gyrus (delay > immediate). **(B)** The HC showed greater brain activations in the right IFG, orbital gyrus, and middle frontal gyrus (delay > immediate).

TABLE 3 | Brain activations change between different conditions in IGD and HC.

Region[a]	BA	*x*, *y*, *z*[b]	Max *t*	Number of voxels[c]	H
IGD(delay – immediate)					
Anterior cingulate cortex	24	3, 33, 6	5.74	198	R
Medial frontal gyrus	9	–6, 42, 27	–4.21	149	L
Inferior frontal gyrus	47	–48, 33, –6	–4.20	268	L
HC(delay – immediate)					
Inferior frontal gyrus	44	66, 21, 3	5.16	195	R
Orbital gyrus	11	–3, 42, –21	4.50	510	L
Middle frontal gyrus	6	–21, 3, 42	4.30	254	L

[a]*The brain regions with maximal t score were selected to be shown.*
[b]*Peak Montreal Neurological Institute coordinates.*
[c]*Coordinates represent the local maxima in the delay > immediate contrast. If multiple local maxima existed in the same region, only the maximum with the highest t score is shown. Voxel size = 3 × 3 × 3.*
HC, healthy control; IGD, Internet gaming disorder.

inhibition processing in the present research. It has been noted that the IFG is involved in cognitive control and impulse inhibition (51, 52). Moreover, the IFG is responsible for self-control and inhibition of prepotent responses for giving up immediate gratification and seeking for long-term interests (53–55). Critically, the IFG has also been identified as a crucial structure in the process of establishing flexible association between outcomes and advantageous actions (56). In general, the DLPFC and IFG play essential roles in the deployment of self-control and impulse inhibition. In this study, the lower BOLD signal in the bilateral IFG and DLPFC may reflect that the impaired ability for the IGD to control their behaviors and inhibit their impulse.

The altered brain activities in the DLPFC and IFG have been reported in previous researches, which reveal the low capacity of impulse inhibition in response to immediate rewards in IGD. Probabilistic discounting task have detected that the IGD exhibited high level of impulsivity and diminished BOLD signal in the IFG than both HC and recreational gaming users (18, 57). During risky decision-making, the IGD showed altered modulation of the bilateral DLPFC when taking risky choices (58). Moreover, we also found that the brain activations in the DLPFC and bilateral IFG were positively correlated with the log *k* values, suggesting that the IGD with greater activation local to the DLPFC and IFG was more impulsive. Although attributed to extracognitive endeavor by the prefrontal activation, the IGD cannot effectively

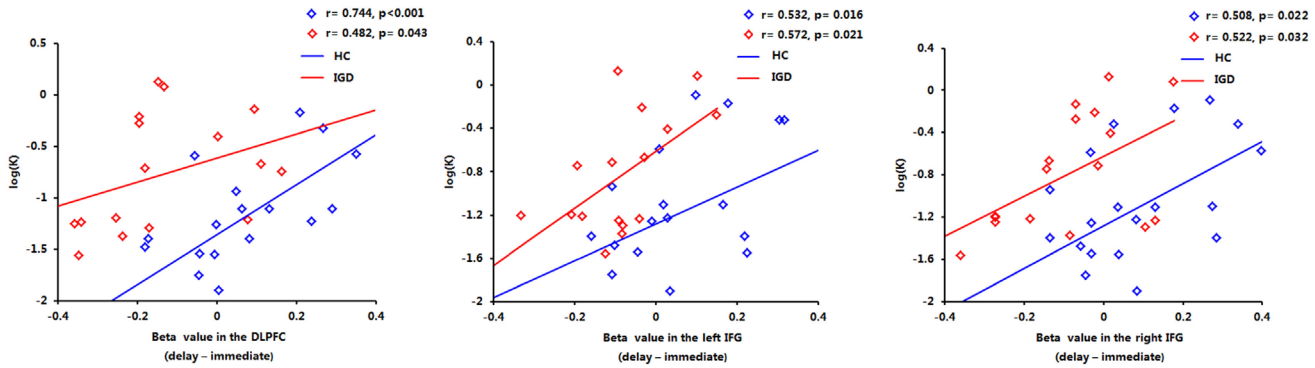

FIGURE 6 | Positive correlations between the brain activations in the dorsolateral prefrontal cortex (DLPFC) and bilateral inferior frontal gyrus (IFG) and log *k* in both groups.

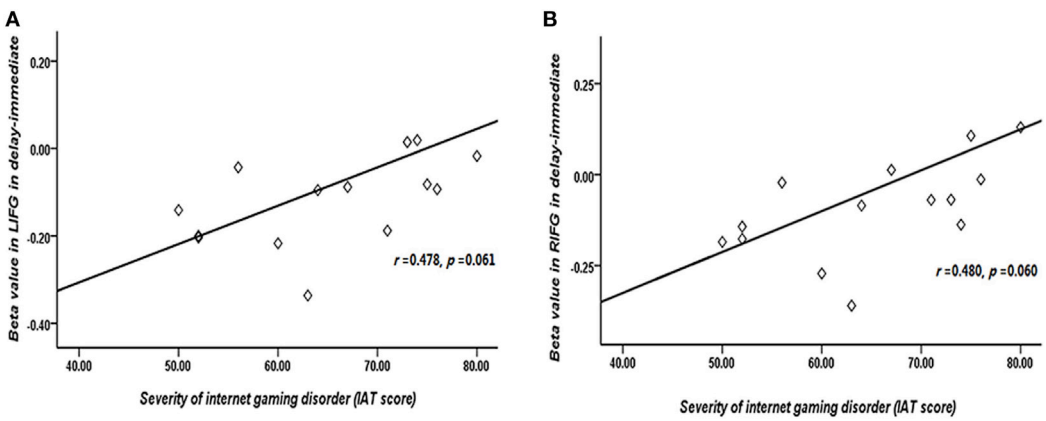

FIGURE 7 | Correlation between the severity of Internet gaming disorder (IGD) and brain activations in the bilateral inferior frontal gyrus (IFG). **(A)** Correlation between peak left IFG activation (delay – immediate) and the severity of IGD. **(B)** Correlation between peak right IFG activation (delay – immediate) and the severity of IGD. (Scores that greater than 3 SDs were regarded as outliers and were excluded from further analysis.)

control themselves to choose the delayed reward in the selection process.

In addition, positive correlation was found between the severity of IGD and the log *k* values, suggesting individuals with IGD who showed more severe IGD symptoms were also more impulsive. Another positive correlation between the severity of IGD and brain activation in the bilateral IFG might indicate that the more severe the IGD was, the more endeavors they needed to engage in selecting delayed decisions. What's more, impaired executive control and reward circuit have been detected in IGD (42), which is parallel with our findings. Taken all into consideration, the results suggested that the IGD demonstrated deficient ability in reward evaluation and impulse inhibition, which might be associated with the dysfunction of the prefrontal activation. These findings are consistent with a prior meta-analysis of fMRI studies, implicating that dysfunctional prefrontal activation plays an important role of in the neurobiological mechanism of IGD (59).

Limitations

There were several limitations ought to be noted. First, only male participants were recruited in this study, thus further studies should shed light on female participants. Second, to ease the difficulty of the tasks and let participants concentrate on the decision-making process, we did not balance the positions of the immediate options and delayed options, which might potentially bias the results.

CONCLUSION

In summary, this study suggested that IGD showed steeper discounting rate and altered brain activities in the DLPFC and IFG. The mechanism might lie in their impairment in both evaluating the delayed reward and impulse inhibition ability in decision-making, which was associated with the dysfunction of prefrontal function. This could be a reason why they prefer immediate satisfaction to larger delayed rewards. More broadly,

our research findings also provide insights into the reason why IGD continue playing online games even when they are faced with severe negative consequences caused by excessive engagement in Internet games.

ETHICS STATEMENT

The experiment conforms to The Code of Ethics of the World Medical Association (Declaration of Helsinki). The Human Investigations Committee of Zhejiang Normal University approved this research. All subjects signed the informed consent forms before the experiment.

AUTHOR CONTRIBUTIONS

YW contributed to experimental programming, data collection and data analyses and wrote the first draft of the manuscript. GD designed this research. YH and GD revised and improved the manuscript. JX, HZ, XL, and XD contributed to experimental programming, and data collection. All authors contributed to and have approved the final manuscript.

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Spontaneous Brain Activity Did Not Show the Effect of Violent Video Games on Aggression: A Resting-State fMRI Study

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A great many of empirical researches have proved that longtime exposure to violent video game can lead to a series of negative effects. Although research has focused on the neural basis of the correlation between violent video game and aggression, little is known whether the spontaneous brain activity is associated with violent video game exposure. To address this question, we measured the spontaneous brain activity using resting-state functional magnetic resonance imaging (fMRI). We used the amplitude of low-frequency fluctuations (ALFF) and fractional ALFF (fALFF) to quantify spontaneous brain activity. The results showed there is no significant difference in ALFF, or fALFF, between violent video game group and the control part, indicating that long time exposure to violent video games won't significantly influence spontaneous brain activity, especially the core brain regions such as execution control, moral judgment and short-term memory. This implies the adverse impact of violent video games is exaggerated.

Keywords: violent video game, aggression, resting state fMRI, amplitude of low-frequency fluctuations (ALFF), fractional ALFF

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INTRODUCTION

With the rapid development of video game industry, video game plays an important part in our daily life. According to CNNIC (China Internet network information center), until June 2017, there are 751 million cyber citizens in China, one fifth of the world cyber citizens, and the amount of cyber citizens who play online video games is 421.64 million in China, and still keep increasing. It should be noted that most video games contain violent content (Yoon and Somers, 2003). Moreover, violent crimes associated with violent video game happened from time to time, which leads to a heated discussion among violent video games and aggression.

Many behavioral researches have proved that long time exposure to violent video games is associated with aggression. Violent video games contains lots of shooting, stabbing, boxing and kicking actions to hurt other game characters to avoid being killed or to achieve the goal (Anderson et al., 2010), which prompts the increasing of aggressive attitudes, beliefs and personality (Anderson and Dill, 2000) and leads to low level of helping behavior and prosocial behavior (Bushman and Anderson, 2009; Gentile et al., 2009; Anderson et al., 2010). Specifically, Engelhardt et al. (2011) using event-related potential technique and found that, compared to

playing non-violent video game, the same duration of playing violent video game for 25 min leaded to desensitization to real life violence, and higher level of aggression in the competitive reaction time (CRT) task. Arriaga et al. (2014) measured the involuntary pupil dilation responses (PDR) after playing the game, and it turned out that participants in the violent video game conditions showed lower PDR to the victims of violence than participants in the non-violent game condition, which indicated violent video game players were not sensitive to violent scene. In addition, Anderson and Dill (2000) found that compared to non-violent video game, violent video game triggered players's aggressive cognition, resulting in higher aggression level in the CRT task. Study launched by Bartholow and Anderson (2002) proved that only 10 min of violent video game play could result in more aggressive behavior than non-violent video game play. According to General Aggression Model (Anderson and Bushman, 2002), excessive violent video game use can cause long time effect, that is, repeatedly exposure to violent video game for months or years will reinforce individuals' aggressive opponent in their believes and personality, transferring the state aggression to trait aggression. This indicates that long time exposure to violent video game may lead to permanent changes embodied in their brain changes of violent video gamers.

Neuroimaging studies have deepened our understanding of violent video game effects. There are many task-functional magnetic resonance imaging (fMRI) researches about violent video games and aggression. According to Gentile et al. (2016), there are three types task-fMRI researches. First, two or more groups of participants with different violent video game experiences are recruited to complete the cognitive or affective tasks, while their fMRI data is collected. Specifically, Mathews et al. (2005) found that high media violence participants displayed lower anterior cingulate activation during the stroop task than low media violence participants. Second, participants are required to play violent video games, and their brain activation in the different part of game play (e.g., violent vs. non-violent) are compared. Moreover, Weber et al. (2006) found an active suppression of emotional areas [rostral anterior cingulate cortex (ACC) and amygdala] as well as increased activity in planning and control areas (dorsal anterior cingulate cortex), specifically around the time of firing a weapon. Third, participants are randomly assigned to play the violent or non-violent video game for around 25 min, and then perform some cognition or affective tasks while fMRI data is recorded. Wang et al. (2009) examined brain activity during a Counting Stroop task and during an Emotional Stroop task and found that participants who had just played a violent game displayed relatively lower functional connectivity between the left dorsolateral prefrontal cortex and the ACC during the Counting Stroop task. Similarly, Hummer et al. (2010) found that playing a violent video game decreased activity in prefrontal cortex regions during a Go-No Go task.

In addition, quite a few fMRI researches about video games used to focus on the addiction aspect. Animal electrophysiological researches and human functional imaging researches have all proved that there existed a reward system, i.e., the dopamine neural circuit (O'Doherty, 2004; Bressan and Crippa, 2005; Knutson and Cooper, 2005; Schultz, 2006; Delgado, 2007; Hikosaka et al., 2008; Haber and Knutson, 2010). Plenty of researches have repeated this statement. For example, Ko et al. (2013) found that there was an overlap between brain activities of default mode network (DMN) and game addiction in game addiction group. Hoeft et al. (2008) found that males showed greater activation and functional connectivity compared to females in the mesocorticolimbic system, which may be attributable to higher motivational states in males, as well as gender differences in reward prediction, learning reward values and cognitive state during computer video games. It is suggested that long time exposure to violent video games could also reinforce this system, as rewarding is quite the inherent nature of game (Koepp et al., 1998; Mathiak et al., 2013).

In conclusion, abundant researches have showed that long time exposure to violent video games is highly associated with certain brain changes in many perspectives. Still, it should be noted that findings in behavioral researches can be confounded by subjects' consciousness, task fMRI researches used to focus on one aspect of brain changes (i.e., brain changes related to the cognition or emotion), and concerning addiction researches are still quite few (Kim and Kim, 2010; Van Rooij et al., 2011; Zhu et al., 2015). Besides, spontaneous brain activity associated with violent video game exposure has not yet been well understood. Thus the resting-state fMRI study could be employed to investigate the long time effect of violent video games. To sum up, the hypothesis in this research is long time exposure to violent video games is associated with abnormal spontaneous brain activities.

Resting-state fMRI technique refines to measure the BOLD signal in the resting mood, the spontaneous brain activities without information import or export (i.e., performing any task). The spontaneous fluctuations that occur during the resting state reveal the intrinsic functional architecture of the brain and are related to extrinsic behavior performance (Fox and Raichle, 2007). What's more, the task-free condition makes it more straightforward to investigate spontaneous brain activities that are related to behavioral performances (Bing et al., 2013). Thus, the resting state blood oxygen level-dependent signal has an edge in identifying the underlying neural basis of long time exposure to violent video games. The amplitude of spontaneous low-frequency fluctuation (ALFF) is widely used in indicating the extent of spontaneous neuronal activity (Zang et al., 2007), with high test–retest reliability (Zuo and Xing, 2014). Fractional ALFF is the ratio of power spectrum of low-frequency to that of entire frequency range, which is thought to be more robust with higher sensibility and higher specificity (Zou et al., 2008). The intention of selecting two indicator is to maintain the reliability of our results. In this way, it is applicable in identifying the potential neural circuit of long time effects of violent video games. Using these methods, the present study examined the spontaneous brain activity affected by violent video game exposure.

MATERIALS AND METHODS

Participants

Fifty-two right-handed males (21.08 years, $SD = 1.76$, range: $17 \sim 27$ years) were recruited in this study, who played violent video games (i.e., games contain shooting, killing, slashing, and wrestling, like League of Legends, Counter-Strike, Grand Theft Auto, Warcraft, Cross Fire) more than 10 h a week in recent 3 months, while the non-violent video game group refers to participants who did not play violent video game at all. They were recruited through flyers posted across the campus of Southwest University, China. All of them had normal or corrected-to-normal vision and had no history of psychiatric or neurological disorders based on self-report. Before the experiments, all participants were informed of their right to privacy, and that they could quit the experiments anytime. After the experiments, each of them was paid $10 for their participation. Written informed consent was obtained from each participant, and this study was approved by the Administration Committee of Psychological Research at Southwest University. Three participants were removed from the sample due to excessive head motion during data preprocessing, and the remaining 49 participants were included in the formal data analysis.

Video Game Questionnaire

Video game questionnaire (Anderson and Dill, 2000) is used to select participants with different video game experience. Participants were asked to list three favorite video games, the number of hours they played each game in a week, and then rate the violence of their content and graphics (from 1 = not at all to 7 = extremely). High score indicates high video game experience. The questionnaire showed good reliability with internal consistency coefficient 0.91. This is to make sure the two groups, violent video game group and the control group are selected correctly.

Buss-Perry Aggression Questionaire (BPAQ)

This questionaire was used to measure trait aggression, which was compiled by Buss and Perry (1992). BPAQ consists of 29 items and four subscales: physical aggression; verbal aggression; anger and hostility. Participants rate themselves on each statement, on a scale of 1, extremely uncharacteristic of me, to 5, extremely characteristic of me. The higher the score, the higher the level of aggression. Among young adults, internal consistency alpha coefficients of BPAQ range from 0.55 to 0.94 in China. Additionally, the BPAQ has test–retest reliability coefficients around 0.81. Its construct validity is supported by other self-report methods of personality traits. In our study, the internal consistency alpha coefficients of BPAQ was 0.832. This questionaire is to investigate whether there exists significant difference in trait aggression between violent video game group and the control group.

Image Acquisition

Participants were scanned in a 3.0 Tesla Siemens Trio scanner (Siemens Medical, Erlangen, Germany). First, high-resolution T1-weighted structural images were acquired sagittally. The scanning parameters were as follows: 1900/2.52 ms (repetition time/echo time), 1 mm (thickness), 176 slices; 256 mm × 256 mm (field of view), 900 ms (inversion time), 9° (flip angle) and 1 mm × 1 mm × 1 mm (voxel size). Then, functional images were obtained using a T2-weighted gradient recalled echo planar imaging sequence with the following parameters: 25 axial slices; slice thickness = 5 mm; repetition time = 1500 ms; echo time = 29 ms; image matrix = 64 × 64; field of view = 192 mm × 192 mm; flip angle = 90°; voxel size = 3 mm × 3 mm × 3 mm; volumes = 200. During the resting state scanning, participants were instructed to stay awake with their eyes closed and not think about anything in particular.

Data Preprocessing

The preprocessing of resting state fMRI images was performed using a toolbox for Acquired Data were preprocessed using Data Processing Assistant for Resting-State fMRI (DPARSFA[1]) based on SPM8[2], which was run on the matlab R 2009a software[3] (MathWorks Inc.). The preprocessing steps were as follows: (1) Images from the first 10 volumes at the beginning of the resting state scanning were discarded to eliminate magnetic saturation effects; (2) the remaining 190 images were corrected for slice timing and head motion correction to adjust the time series of the images (head motion was <2.5 mm of translation along any axis and <2.5° of angular rotation along any axis). 27 violent video gamers and 22 non-violent video game participants were valid in the present study; (3) the structural images were coregistered to the mean functional image and were subsequently segmented as gray matter, white matter and cerebrospinal fluid employing the new segment method; (4) each functional image was normalized to the standard Montreal Neurological Institute (MNI) space with the application of DARTEL (diffeomorphic anatomical registration through exponentiated Lie algebra) (3 mm × 3 mm × 3 mm resampling); (5) after normalization, spatial smoothing was performed with an 8 mm full-width-half-maximum Gaussian kernel; (6) nuisance linear regression was performed with the white matter, cerebrospinal fluid and 6 rigid body head motion parameters; (7) the linear trends were removed, and finally, the images were temporally band-pass filtered (0.01–0.08 Hz) to reduce low-frequency drift and high-frequency noise (Biswal et al., 1995).

Data Analysis

ALFF, fALFF Calculation

Amplitude of low-frequency fluctuations calculations were performed using the Resting-State fMRI Data Analysis Toolkit (version 1.8; Song et al., 2011). The ALFF is defined as the strength of regional spontaneous fluctuations of a given brain region. According to the methods proposed by Zang et al. (2007), time series in each voxel was transformed to a frequency domain with a fast Fourier transformation, and the power spectrum was obtained. Area under the peak point can be considered

[1]http://restfmri.net/forum/DPARSF

[2]http://www.fil.ion.ucl.ac.uk/spm/software/spm8/

[3]http://www.mathworks.com

as the energy of signals. Then, the square root of the power spectrum was calculated and each voxel in 0.01–0.08 Hz was averaged. This averaged square root was considered to be the ALFF. For standardization purposes, the ALFF value of each voxel was divided by the global mean ALFF value to normalize the global volume effects (Zang et al., 2007). Because low-frequency fluctuations in the gray matter are higher than those in the white matter (Biswal et al., 1995; Wei et al., 2012), only ALFFs in the gray mask were calculated.

Fractional ALFF is the standardized value of ALFF, it is a ratio of the power of each frequency at the low-frequency range (0.01–0.08 Hz) to that of the entire frequency range (0–0.25 Hz). Same as ALFF, the Z scores of fALFF were calculated by using the fALFF value to minus the mean value of global mean value and then divided by the standard deviation (Zou et al., 2008).

Statistical Analysis

First of all, to see whether our grouping is correct or not, we examined difference of violent video game experience between violent video game experience group and the control group by performing an independent sample T-test.

To compare the results of spontaneous brain activity during resting-state fMRI and trait aggression measured by BPAQ and better understand our results, we also conducted the independent samples T-test between the BPAQ score of violent video game group and that of control group.

To investigate the differences in spontaneous brain activation between groups, we performed two samples T-test on both ALFF and fALFF. AlphaSim correction was conducted for multiple comparison correction.

RESULTS

Independent samples T-test based on violent video game experience showed that there were significant difference ($t = 4.00$, $p < 0.001$) between violent video game group (41.40 ± 20.85) and the control group (18.53 ± 18.66).

Independent samples T-test based on BPAQ score showed that there were no significant difference ($t = 0.73$, $p = 0.47$) between violent video game group (68.89 ± 12.07) and the control group (66.42 ± 12.41), and there were no significant difference on physical aggression ($t = 1.01$, $p = 0.31$); anger ($t = 0.07$, $p = 0.94$) and hostility ($t = -0.76$, $p = 0.47$). However, there were significant difference on verbal aggression ($t = 2.01$, $p = 0.045$) between violent video game group (14.36 ± 3.48) and the control group (12.21 ± 3.97).

Group Differences in ALFF Data

To examine the spontaneous brain activities between group of violent video games and group of non-violent video game, we performed two samples T-test. The results showed that there was no significant difference between violent video gamers and their counterparts in ALFF, AlphaSim correction was performed with voxel size $p < 0.001$, and cluster size $p < 0.05$, voxel = 13, see **Figure 1**. There was no significant difference between violent video game group and the control group in fALFF, either.

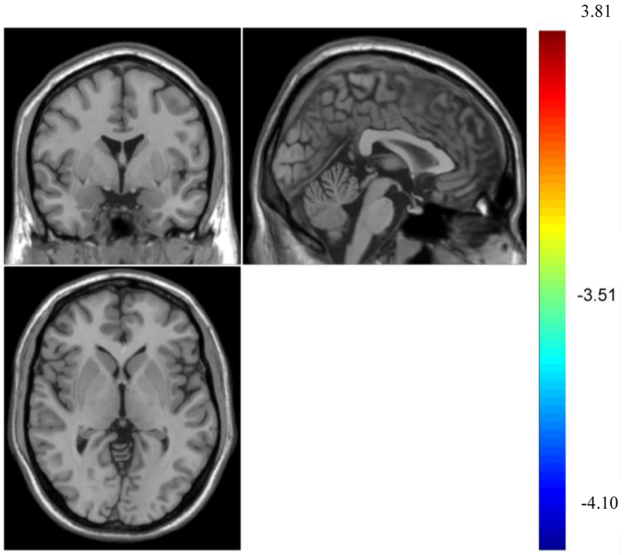

FIGURE 1 | Result of amplitude of low-frequency fluctuation (ALFF) after Alphasim correction, with voxel size $p < 0.001$, cluster size = 13, $p < 0.05$. No clusters were found.

DISCUSSION

Resting-state fMRI were employed to investigate whether long time exposure to violent video games is related to abnormal spontaneous brain activities.

First, two samples T-test on violent video game experience showed that there were significant difference between violent video game group and the control group. The violent video game experience of former group is significantly higher than that of the control group, which proved that our grouping is correct and effective. This is the premise of further analysis.

For ALFF and fALFF, there were no significant difference between violent video game group and the control group, which is consistent with the result of two samples T-test on BPAQ total score. The two group are not remarkably different on spontaneous activities or trait aggression. This is against our former hypothesis.

As mentioned in former fMRI researches (Young et al., 2010; Molenberghs et al., 2015; Gentile et al., 2016), ACC, orbitofrontal cortex (OFC), temporo-parietal junction (TPJ) are the core regions related to aggression and moral judgement.

It should also be noted that ACC, OFC, and TPJ are the significant part in the DMN (the default mode network). DMN is distinctly important in emotion-processing, monitoring environment changes, self-introspection, maintaining self-awareness, and also extracting episodic memories (Immordino-Yang et al., 2012). Previous researchers have found that aggression is highly associated with misfunction in ACC (van Meel et al., 2007; Olvet and Hajcak, 2008). ACC can predict aggressive behavior, and people with injured ACC also behave in an aggressive way (Boes et al., 2008; Ducharme et al., 2011). As a crucial part in limbic system,

ACC has rich functional connectivities with many regions, like prefrontal gyrus, hippocampal gyrus, parietal cortex, and hypothalamus. Specifically, ACC plays an important part in executive control (Awh and Gehring, 1999). Our findings suggested that individuals long-time exposed to violent video games did not show neuropsychological evidence of weak self-monitoring and self-control. OFC is one of the vital regions in moral sensitivity, which is quite important in judging the moral attributes of certain behaviors as morally justified or morally unjustified (Moll et al., 2007; Decety and Porges, 2011). OFC will be activated when individuals try hard to restrain the feeling of disgust and pain to adjust their feelings (Hooker and Knight, 2006). It is also a core node in moral sensitivity. Our results illustrate that there is no misfunction of moral sensitivity in this area after long time exposure to violent video games. TPJ, a brain area where the temporal and parietal lobes meet, at the posterior end of the Sylvian fissure (Abu-Akel and Shamay-Tsoory, 2011), was involved in the process of the sense of agency and higher level social cognition, such as empathy, moral reasoning and theory of mind (Saxe and Wexler, 2005; Decety and Lamm, 2007; Young and Dungan, 2011). When the activity in TPJ was restrained by transcranial magnetic stimulation (TMS) technique. Individuals tended to consider the intentional hurting behavior as morally justified (Young et al., 2010). This illustrated that TPJ is quite important in moral judgement. Specifically, right TPJ is in the lime light and received more and more attention recently. It has been proved that right TPJ plays a vital part in reasoning other individuals' mental status during moral judgement, then estimate their judgment as morally appropriate or inappropriate. Taken together, no spontaneous brain activities in these areas suggested that long time exposure to violent video games neither influence the function in DMN, nor results in inappropriate moral sensitivity, impaired ability to feel others' pain and violence desensitization and violent behaviors, aggressive personality, subsequently.

What's more, our research findings is supported by increasing number of literatures claiming that the severe effect of violent video games is overstated (Ferguson et al., 2008, 2017a,b; Decety et al., 2009; Ferguson, 2010; Collins and Freeman, 2013; DeCamp and Ferguson, 2017; Gao et al., 2017; Hilgard et al., 2017; Szycik et al., 2017a,b). Ferguson et al. (2017b) allocated young adult players randomly to either play violent game, non-violent game, or to be given the choice between several violent and non-violent games, and then the ice water task was performed on each individuals to measure the aggression level, as well as stress levels and hostility. Results showed that there were no difference between different game conditions on hostility, stress, or aggression, indicating no evidence that violent video games can contribute to aggression. Gao et al. (2017) found that the perception of others' pain were not significantly different in brain regions between VG (violent video gamers group) and NG (non-violent video gamers group), the desensitization effect of VVGs was overrated. Another research (Szycik et al., 2017b) also proved that there were no significant differences in brain responses when viewing pictures depicting emotional and neutral situations with and without social interaction, 15 excessive users of violent games and control subjects matched for age and education included. They suggested that the impact of violent video games on emotional processing may acute and short-lived. In another research conducted by Szycik et al. (2017a), 28 male adult subjects were screened with excessive long time use of violent video games. They were examined in two experiments using standardized emotional pictures of positive, negative and neutral valence. No group differences were found even at reduced statistical thresholds which speaks against desensitization of emotion sensitive brain regions as a result of excessive use of violent video games.

Meta-analyses investigating the potential correlates between violent video games and violent behaviors were positive but with small effect size ranging between 1 and 4% (Anderson and Bushman, 2001; Sherry, 2001; Anderson et al., 2010) and has been challenged the existence of publication bias (Ferguson, 2007). What's more, a recent meta-analysis (Hilgard et al., 2017) re-examined another meta-analysis with the opinion of associations between violent video games and aggression (Anderson et al., 2010), in this present meta-analysis, a developed techniques was employed to detect the publication and analytic bias, as well as adjusting effect sizes. The results are quite different from the latter, with very little effect size. Our former research examining the difference in empathy for pain between violent video game group and non-violent video game group also showed evidence against the idea that long time exposure to violent video games will cause desensitization effect.

One can speculate from the above findings that there is no causal link between violent video games and aggression. This is mainly because, firstly the cause of aggression cannot be simply illuminated. Many environmental factors, such as childhood trauma, family background, contribute to aggression, mutually. For instance, research conducted by DeCamp and Ferguson (2017) found that the relationships between violent video games and aggressive behavior reduced to trivial effect size when controlled factors like parental attachment, youth disclosure, home yelling, home violence. Secondly, individuals are not the "blank slate" players. All the influence exerted by violent video games, or other outside forces is moderated by the characteristics of the player (e.g., cognitive styles, gender, different criteria of moral judgement). It has been proved that different motivations for choosing the same violent video game could resulting in different consequences, some of individuals may choose one violent video game as a way to release their stress, while others may choose the same violent games as a way to be able to conduct violent behavior and enjoy violence. As a result, the former one will probably be able to adjust himself to a better mood while the latter one is more likely to ruminate into violent content and causing serious consequences (Bowman and Tamborini, 2015; Ferguson et al., 2017a).

In China, the risk factors are mainly biological causes like gene defect, IQ, and gender; family causes like family structure, parent–child relationship, parental supervision; social factors, especially the function of peer pressure and bullying. These factors will influence juvenile delinquency, more in a combined way than solely. Violent video games is not the primary cause of aggression. According to General Aggressive Model (GAM),

after gameplay, the oppression, provocation and clues about aggression will affect individuals' mental process, impelling the development of aggressive cognition, emotion and behavior. Moreover, repeated exposure to violent video games could reinforce this loop and the aggressive personality is developed. However, this theory doesn't fully explained the relationship between violent video games and aggression, players are seen as passive, negative receiver to what are put on them. It failed to pay enough attention to the subjective initiative of players. Our research emphasis the necessity to develop more sophisticated model, as well as advanced methodologies, to better explain the possible factors and pathways will lead to aggression.

There were also deficiencies in our study. First of all, our participants are all selected from college, whether our findings can apply to different groups remains uncertain. What's more, given the fact that female violent video game players are quite few, our research target mainly focused on the males. The resting state brain activities in females and in male–female comparison worth further investigation. And further researches should also pay more attention to other potential aspects relating to aggression in more specific and sophisticated way.

CONCLUSION

On the whole, our results suggested that there is no strong link between long time exposure to violent video games and spontaneous brain activity, didn't show any neuropsychological evidence of aggression, enhanced our understanding to the relationship between long time exposure to violent video games and aggression.

ETHICS STATEMENT

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Written informed consent was obtained after detailed explanation of the study protocol, which was approved by the Ethics Committee of Southwest University. The Institutional Review Board at Southwest University (SWU) in Chongqing, China approved this consent procedure. Written informed consent was obtained from all participants. The Institutional Review Board at SWU approved all procedures.

Informed consent: Informed consent was obtained from all individual participants included in the study.

AUTHOR CONTRIBUTIONS

Conceived and designed the experiments: XG and WP. Performed the experiments: WP, XG, SS, FL, and CL. Analyzed the data: WP, SS, FL, and CL. Wrote the paper: WP and XG.

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Long-Time Exposure to Violent Video Games Does Not Show Desensitization on Empathy for Pain: An fMRI Study

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As a typical form of empathy, empathy for pain refers to the perception and appraisal of others' pain, as well as the corresponding affective responses. Numerous studies investigated the factors affecting the empathy for pain, in which the exposure to violent video games (VVGs) could change players' empathic responses to painful situations. However, it remains unclear whether exposure to VVG influences the empathy for pain. In the present study, in terms of the exposure experience to VVG, two groups of participants (18 in VVG group, VG; 17 in non-VVG group, NG) were screened from nearly 200 video game experience questionnaires. And then, the functional magnetic resonance imaging data were recorded when they were viewing painful and non-painful stimuli. The results showed that the perception of others' pain were not significantly different in brain regions between groups, from which we could infer that the desensitization effect of VVGs was overrated.

Keywords: violent video games, violence, empathy, empathy for pain, fMRI

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INTRODUCTION

Recently, the society has witnessed the rapidly development in video game industry. A non-negligible issue is that most of the video games contain violent content (Yoon and Somers, 2003), which could be harmful to the players, even jeopardize the public safety. The relationship between exposure to media violence and its potential negative effects has been the subject of social, political, and scientific attention for decades. Playing violent games may heighten aggressive behavior, cognition, and affection; increase physiological arousal and hostility; and decrease the probability of helping others (e.g., Anderson and Bushman, 2001, 2002; Bushman and Anderson, 2001, 2009; Anderson et al., 2004, 2008; Gentile et al., 2004; Bartholow et al., 2005; Bushman and Huesmann, 2006). Playing violent video games (VVGs) also has a desensitizing physiological effect (Carnagey et al., 2007), and may also be associated with non-violent delinquent behaviors (Anderson and Dill, 2000; Ferguson and Kilburn, 2009; Desai et al., 2010; Gunter and Daly, 2012), such as cheating, skipping school, stealing, and substance abuse. Previous researches have investigated the relationship between empathy and exposure to video game violence. It has been suggested that exposure to VVG was associated with lower empathy (Funk et al., 2004; Anderson et al., 2010). However, the existing researches concerning desensitization effects of VVG are not inconsistent. For example, Ferguson and Kilburn (2010) conducted a meta-analysis and the results suggested that VVGs were not significantly associated with aggression, neither with prosocial behavior

(Jerabeck and Ferguson, 2013; Elson and Ferguson, 2014; Tear and Nielsen, 2014). Instead, some of the VVGs could even increase the cognition abilities such as object tracing, spatial discrimination, and central attention (Green and Bavelier, 2006, 2007). Even the inconsistent researches are not quite much, given the publication bias and the validity of behavioral investigations, the null results of previous researches should also pay attention to. These indicated that the long-time effect of VVGs should be carefully examined further.

Empathy is a crucial component of human emotional experience and social interaction (Bernhardt and Singer, 2012), which is vital to our everyday communication and survival in a social environment (Fan et al., 2011). Usually, empathy refers to the capacity to understand and share the emotional and affective states of another person in relation to oneself (Decety and Jackson, 2004; Singer et al., 2006; Hein and Singer, 2008; Guo et al., 2012, 2013). The capacity for empathy allows us to understand others' emotions, motivations, and behaviors, which help us to decide what we can do. Empathy for pain is a typical form of empathy. When witnessing other people suffering in pain, the observers often show compassion, sympathy and care-giving to them (Goubert et al., 2005). The empathy for pain is attracting increasing attention because of its survival value embodied in the capacity that positively correlates to prosocial behavior and behaviors conforming to our social norms (Hoffman, 2008).

There are a growing number of functional magnetic resonance imaging (fMRI) studies that focus on empathy for pain. Research demonstrates that the first-hand experience of pain and the observation of others in pain activate similar neural circuits. These neural circuits consist of areas encoding different dimensions of pain perception. The primary and secondary somatosensory cortex mainly subserve the sensory-discriminative dimension of pain (e.g., Bushnell et al., 1999; Avenanti et al., 2005; Valeriani et al., 2008; Akitsuki and Decety, 2009), whereas the supplementary motor area (SMA), cerebellum, insula, anterior cingulate cortex (ACC), and the anterior mid-cingulate cortex (aMCC) mainly subserve the affective-motivational dimension of pain (e.g., Singer et al., 2004; Danziger et al., 2006; Gu and Han, 2007; Lamm et al., 2007; Akitsuki and Decety, 2009). These two dimensions are highly correlated (Decety, 2011). There are also brain regions encoding the cognitive-evaluative dimension of pain, such as the temporoparietal junction (TPJ) and the orbitofrontal cortex (OFC), which are involved in social interaction, intention, and belief (e.g., Walter et al., 2004; Amodio and Frith, 2006; Moll and de Oliveira-Souza, 2007). Other regions, like the amygdala, thalamus, and periaqueductal gray (PAG) may also be activated when watching others in pain (e.g., Phelps et al., 2001; Adolphs, 2002; Winston et al., 2003). Furthermore, empathy or empathy-related neural networks may interact with (and be modulated by) the activity of other neural networks relevant for social cognition, such as mentalizing, cognitive control, and emotion regulation (Bufalari and Ionta, 2013). Based on these findings, it is apparent that pain empathy is associated with cognitive and emotional regions such as TPJ, OFC, and ACC, which were vital in cognitive control and moral judgment (Molenberghs et al., 2015). We could speculate that lack of empathy for pain in others may lead to terrible consequences, not only to the individuals themselves, but also the whole society.

Long-time exposure to VVGs may blunt this capacity and result in undesirable consequences. In this research, we mainly focused on the relationship between long-term exposure to video game violence and empathy to investigate the negative effects of media violence on empathy, especially empathy for pain for others. According to former researches, desensitization to video game violence may be a core factor to low capacity of empathy for pain in others. It has been repeatedly proved that longtime exposure to video game violence leads to desensitization, which refers to impaired emotional response to negative feelings coupling with aggressive consequences. This may cause numb senses of knowing the pain and suffering of others which may result in low empathy for others' pain. A negative correlation was confirmed between long-term video game violence exposure and empathy (Funk et al., 2004; Bartholow et al., 2005; Krahé and Möller, 2010). There are also neuropsychological evidences to support this argument. Playing VVGs can affect some regions or neural circuits of the frontal lobe (e.g., Davidson et al., 2000; Mathiak and Weber, 2006; Wang et al., 2009), and this may affect the response of gamers to emotional stimuli (Kühn et al., 2011). Similar results were found by Gentile et al. (2016) that long time exposure to VVGs may lead to suppression in regions relating to emotional response regions and cognitive regions and abnormal activities in cognitive control regions (Gentile et al., 2016). Moreover, Montag et al. (2012) assumed that due to a frequent confrontation with violent scenes, the first-person-shooter-video-gamers might have habituated to the effects of unpleasant stimuli, resulting in lower brain activation. Coincidentally, Guo et al. (2013) explored participants' empathic responses after short-term exposure to violent videos, using fMRI. They found that short-term exposure to media violence reduced the activation of the aMCC and insula, and proposed that exposure to media violence had a desensitizing effect. These indicated that longtime exposure to media violence is associated with empathy for pain in others. In addition, it also should be noted that extant literature still exist some inconsistency between VVGs and desensitization effect, which needs further exploration.

What's more, there currently is few fMRI research exploring the relationship between exposure to video game violence and pain empathy. This kind of research can help us to understand the neural mechanism of empathy and to identify the influence of violent games on the brain. Based on past research on empathy among healthy participants (e.g., Akitsuki and Decety, 2009; Fan et al., 2011, 2014; Lamm et al., 2011) and certain types of groups (e.g., Mathews and MacLeod, 2005; Decety et al., 2009), as well as research on the affective processing and empathy among violent video gamers (e.g., Anderson et al., 2010; Barlett and Anderson, 2011; Zhen et al., 2011; Guo et al., 2013), the present study aimed to identify whether video game violence can affect the capacity of empathy for pain, if so, how video game violence can affect the capacity of empathy for pain.

MATERIALS AND METHODS

Participants

All the participants were recruited from the community of Southwest University (Chongqing, China). Participants were selected from approximately 200 undergraduates who completed a video game questionnaire (Anderson and Dill, 2000) that examined their previous game experience. We calculated a score representing their previous game experience and then randomly selected 20 individuals scoring above the 75th percentile and 20 individuals scoring below the 25th percentile, to comprise high and low previous-exposure groups (VG and NGs), respectively. All the participants were males aged 18 to 27 ($M = 21.17$, $SD = 2.065$). All the participants were right-handed and had normal or corrected-to-normal vision. None of them had a history of neurological or psychiatric disorders. All participants gave informed consent before scanning. After the experiment, they were paid for their participation.

Materials

Video Game Questionnaire

The video game questionnaire (Anderson and Dill, 2000) was used to select participants. Participants were asked to list three their favorite video games, indicate the number of hours they played each game in a week, and then rate the violence of their content and graphics (from 1 = not at all to 7 = extremely). Previous game experience was measured by summing the content and graphics ratings for each game, multiplying the sum of the number of hours the game was played each week, and then averaging across the three games. The questionnaire showed good reliability and validity. The internal consistency coefficient was 0.89–0.91, and the Q factor of each factor reached 0.7 (attractive factor: 0.77; violence factor: 0.90; time factor: 0.73).

Interpersonal Reactivity Index-China (IRI-C)

Interpersonal Reactivity Index-China (IRI-C) is a 22-item questionnaire for measuring trait empathy. The IRI-C is the Chinese version of IRI (Zhang et al., 2010), and four dimensions were included in this questionnaire: perspective taking, fantasy, empathic concern, and personal distress. IRI-C has been demonstrated to have satisfactory reliability and validity (Zhang et al., 2010; Jiang et al., 2014).

Stimuli in the Experiment

Eighty digital color pictures showing people's hands, forearms, or feet in painful or non-painful situations (40 pictures each) were used as stimuli. All situations depicted familiar events that occasionally happen in our everyday life; the stimuli were similar to those used by Meng et al. (2012). Examples of painful situations depicted a hand cut by a knife and a foot stabbed by pins (**Figure 1**). Non-painful situations were paired with painful situations, without any nociceptive components, such as using a knife to cut cucumbers and a foot touched by an eraser. All pictures were shot from first-person perspectives and edited to the same size. Luminance, contrast, and color were matched between painful and non-painful pictures (Meng et al., 2012).

Procedure

First, participants were scanned to acquire high-resolution structural images. Then functional images were acquired, while the participants viewing the stimuli displayed on a gray background. The E-prime software (Psychology Software Tools, Inc., Pittsburgh, PA, USA) and a back-projection system were used for presenting the stimuli. All the pictures were randomly presented on the screen and the procedure in each run was exactly the same. Participants were asked to watch each picture carefully and to try to experience the feelings of the persons whose body parts were shown in the pictures. The oddball paradigm was used to ensure that participants viewed the pictures carefully and did not close their eyes. This entailed two kinds of trials: stimulus-only trials and stimulus–response trials.

In stimulus-only trials, each picture was presented for 2,000 ms with jittered inter-stimulus intervals (ISI, lasted for 2,000, 4,000, or 6,000ms), during which a black fixation point was presented against the gray background. Participants were instructed to view the picture carefully and just wait for the next trial. In stimulus–response trials, each picture was presented for 2,000 ms, followed by a response screen showing the following message: "painful picture: 1; non-painful picture: 4." Participants were instructed to press "1" if they thought the picture was painful, and to press "4" if they thought the picture was non-painful. This screen remained for 2,000 ms. Jittered ISI were used as they were in the stimulus-only trials. Stimulus–response trials made up about 20 percent of all trials (16 trials) in the experiment. The two kinds of trials were randomly presented during the experiment (see **Figure 2**).

All the participants responded in all 17 stimulus–response trials. The mean number of correct answers of all participants was 14.64 ($SD = 2.13$). Participants in the two groups did not differ significantly in their mean number of correct answers ($M_{VG} = 14.57$, $SD = 2.31$; $M_{NG} = 14.71$, $SD = 2.02$). Therefore, both groups viewed the presented pictures equally.

fMRI Image Acquisition and Analysis

Scanning was performed with a whole-body 3T Siemens scanner (Siemens Magnetom Trio Tim, Southwest University, Chongqing, China). Functional images were acquired using an echo-planar imaging (EPI) sequence and the following parameters: slice number = 32, TR = 2000 ms, TE = 30 ms, flip angle = 90°, matrix size = 64 × 64, slice thickness = 3 mm. Images were acquired using an ascending interleaved sequence with no temporal gap between consecutive image acquisitions. There was one run of functional scanning that was approximately 9 min (270 EPI volumes). A high-resolution structural image was acquired using a T1-weighted, multiplanar reconstruction (MPR) sequence and the following parameters: TR = 1900 ms, TE = 2.52 ms, slice thickness = 1 mm, flip angle = 9°, matrix size = 256 × 256, voxel size = 3 mm × 3 mm × 3 mm.

Data preprocessing was carried out with SPM8 (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, London, UK) implemented in MATLAB 7.0 (The Math Works, Inc., Sherborn, MA, USA). The first five volumes were discarded to allow for T1 equilibration effects.

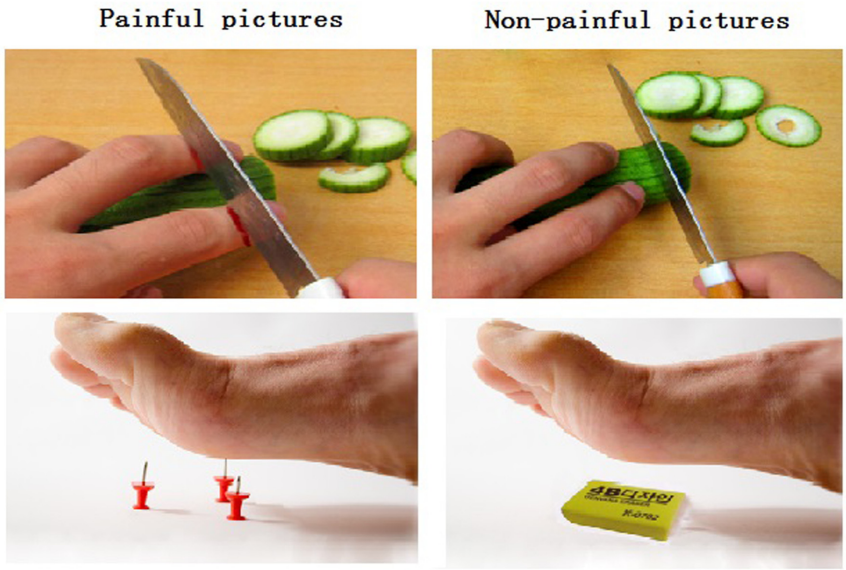

FIGURE 1 | Illustration of the painful and non-painful pictures. (Left) The left panel shows examples of non-painful pictures. **(Right)** The right panel shows examples of painful pictures.

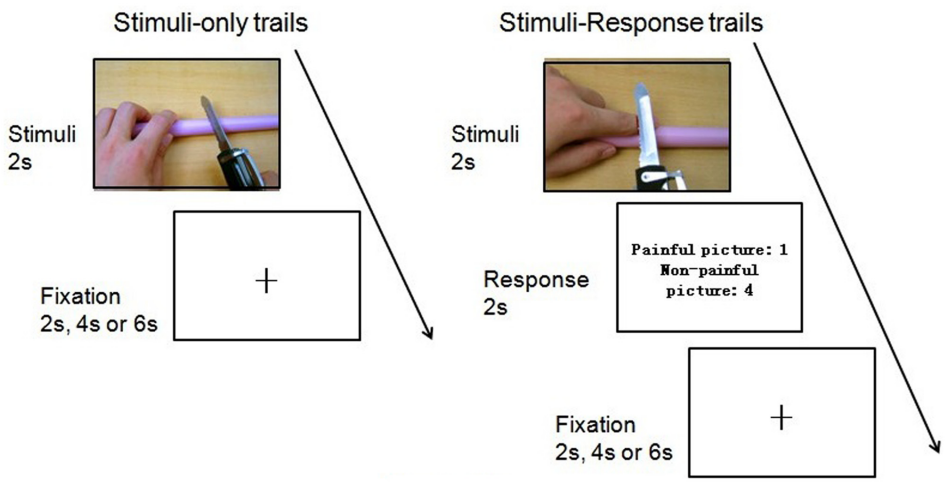

FIGURE 2 | Flow paradigm of the experiment.

Data preprocessing included slice-timing correction, correction for head motion (realigned to the first volume), normalization, and smoothing using a 6-mm full-width half-maximum isotropic Gaussian kernel. It should be noted that head motions in all participants were corrected and met the criteria with head motion < 3 mm. In this case, three participants were deleted from the analysis.

We then analyzed the neural responses to painful and non-painful stimuli in the VG (PVG and NVG) and in the NG (PNG and NNG). Statistical analyses were performed using the general linear model (GLM) implemented in SPM8. GLMs were estimated using a hemodynamic response function and a high pass filter of 128 Hz, as well as correction for autocorrelations. For the analysis, the six movement regressors of each subject were also included in the design matrix as covariates. The simple main effects of each subject for two types of events (P and NP) were computed by applying '1 −1' contrasts. The four first-level individual contrast images (PVG, NVG, PNG, and NNG) were then analyzed at the second group level adopting the methods of independent samples *t*-test.

Brain activation representing the perception of painful stimuli was defined using the (PVG + PNG) – (NVG + NNG) contrast. The full factorial model was established to identify different brain regions between NG and VG [(PNG − NNG) − (PVG − NVG), (PVG − NVG) − (PNG − NNG)].

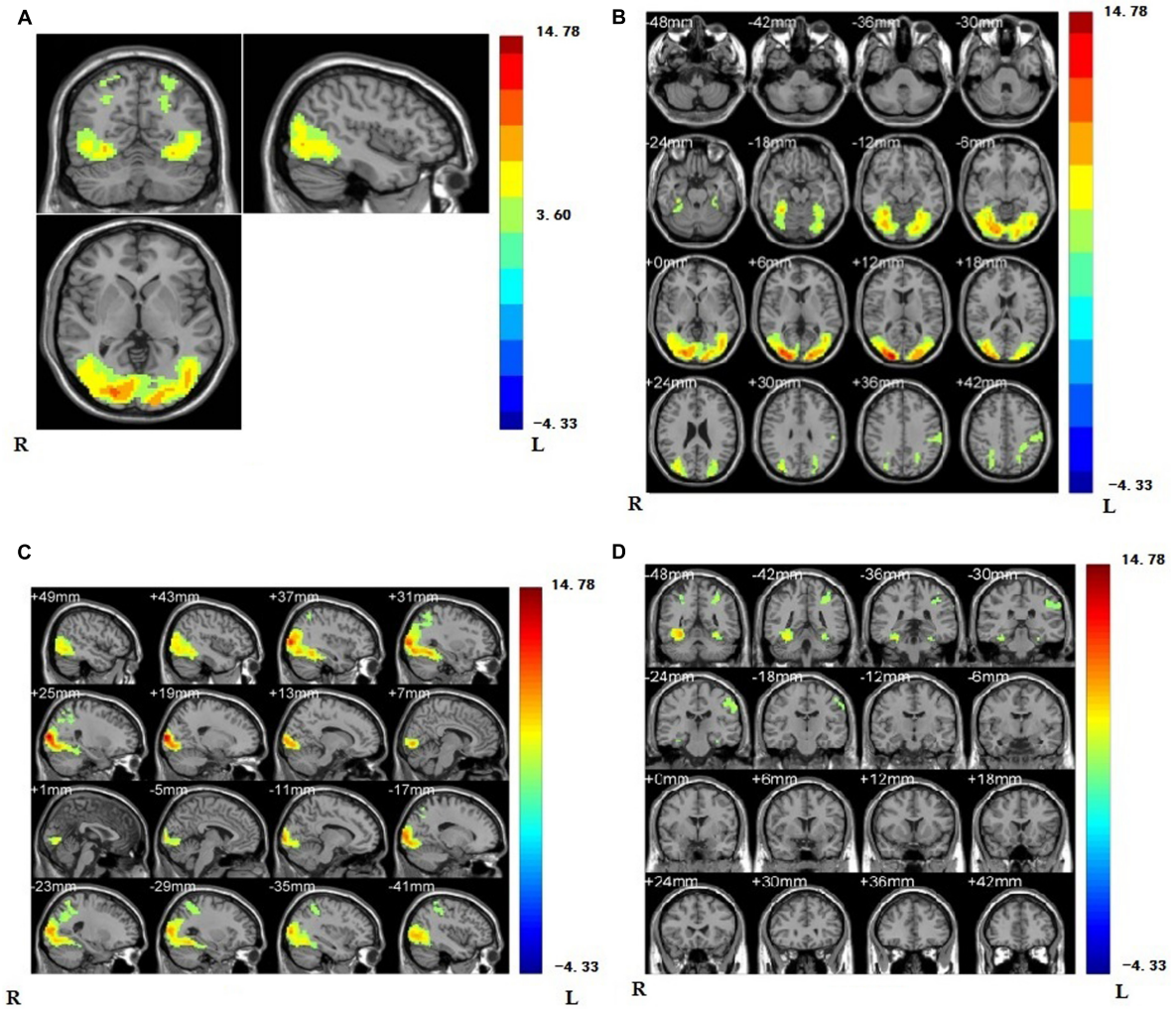

FIGURE 3 | (A) Regions showing higher activation are the regions of supramarginal gyrus, lateral middle occipital gyrus, lateral fusiform gyrus, right inferior occipital gyrus, inferior parietal gyrus, middle temporal gyrus, and visual related regions such as V2 compared with non-painful stimuli ($p < 0.001$, Alphasim corrected; $k > 1361$). We have separately MR imaging at the position of oblique-axial **(B)** plane, oblique coronal; **(C)** and sagittalia; **(D)** in regions activated.

RESULTS

Two participants in the NG did not complete our study so their data were deleted. The data of two participants in the NG and one in the VG were deleted either because of excessive head movements. Hence, the data in our final analysis were collected from 35 participants, including 18 participants in the VG and 17 participants in the NG.

Behavioral Data

An independent-sample *t*-test of VVG exposure in two conditions was conducted and results were found the difference of familiarity with the VG ($M = 142.39$, $SD = 18.66$) and NG ($M = 25.62$, $SD = 6.44$), $t(33) = 5.78$, $p < 0.05$, suggesting significant difference between VG and NG.

No significant difference between VG ($M = 49.38$, $SD = 8.57$), and NG ($M = 47.52$, $SD = 10.79$) in IRI-C total score, $t(33) = 0.57$, $p > 0.05$, either in each dimension [$t(33) = 0.11$, 0.26, 1.09, and 0.68, $p > 0.05$].

No significant difference between VG ($M = 72.12$, $SD = 17.49$), and NG ($M = 72.66$, $SD = 25.19$) in BPAQ total score, $t(33) = -0.077$, $p > 0.05$, either in each dimension [$t(33) = -0.034$, 0.365, −0.065, and −0.397, $p > 0.05$].

fMRI Data

As a first step, we contrasted the brain activity of the painful conditions with the non-painful conditions for all the subjects. The results of (PVG + PNG) − (NVG + NNG) showed that when viewing others in pain, regions were activated in the right supramarginal gyrus (rSMG), lateral middle occipital gyrus, lateral fusiform gyrus, right inferior occipital gyrus, inferior parietal gyrus, middle temporal gyrus, and visual related regions such as V2 (see **Figure 3** and **Table 1**).

TABLE 1 | Brain regions showing significant activation in lateral middle occipital gyrus, lateral fusiform gyrus, right inferior occipital gyrus, right supramarginal gyrus, inferior parietal gyrus, middle temporal gyrus, and visual related regions such as V2 while viewing painful stimuli compared with non-painful stimuli ($p < 0.001$, Alphasim corrected; $k > 1361$).

Region of activation	Lat.	MNI			*t*-value	*k*
		x	*y*	*z*		
Middle occipital gyrus	R	21	−96	12	14.78	483
Middle occipital gyrus	L	−24	−87	12	9.04	683
Fusiform gyrus	R	30	−51	−12	9.90	427
Inferior occipital gyrus	R	33	−75	−9	9.06	216
Fusiform gyrus	L	−30	−63	−12	7.68	357
Supramarginal gyrus	R	33	−54	57	5.18	130
Inferior parietal gyrus	L	−27	−51	48	4.76	187
Secondary visual cortex (V2)	R	36	−87	9	11.75	369

And one sample *t*-test in VG and NG was separately conducted and the results showed that, in both groups, regions in lateral occipital gyrus, lateral fusiform gyrus, right middle temporal gyrus, and the Secondary visual cortex (V2) were significantly activated (see **Figures 4A,B** and **Table 2**).

Since the focus of our study was to explore how previous exposure to video game violence influenced participants' empathic responses, we examined the activation of brain regions showing differences between the two groups. There is no significant difference between VG and NG ($p < 0.001$, Alphasim corrected).

DISCUSSION

The goal of our study was to explore the influence of previous exposure to video game violence on neural empathic responses to the pain of others. fMRI results showed that there is significant difference between viewing painful pictures of others and viewing non-painful pictures, which has also been proved separately in VG and NG. While further examination didn't show that the empathic neural pattern is different between groups.

Consistent with previous fMRI studies on empathy for pain (e.g., Jackson et al., 2005; Cheng et al., 2008; Nummenmaa et al., 2008; Akitsuki and Decety, 2009; Guo et al., 2012, 2013), the present study found that viewing painful pictures activated many empathy-related regions in the (PVG + PNG) − (NVG + NNG) contrast.

Unlike the linguistic function that has been generally hitherto acknowledged, the supramarginal gyrus is also closely linked to empathy. The supramarginal gyrus is part of the somatosensory association cortex, which is involved in perception of space and limbs location and a part of the mirror neuron system (Carlson, 2012). It has been proved that supramarginal gyrus, especially the right supramarginal gyrus (rSMG) is significantly associated with self-other distinction, the crucial part of the theory of mind (ToM), attributing to the self-other distinction during empathy (Hoffmann et al., 2015). Empathy involves sharing the emotional state of others and being aware of the state both of self and others (Singer and Lamm, 2009). Failure of self-other distinction during empathy results in egocentric emotional responses and deficits in ToM (Hoffmann et al., 2015). Silani et al. (2013) found that overcoming emotional egocentricity bias in empathic judgment is associated with increased activation in the rSMG. What's more, a research conducted by Lang et al. (2011) found the same rSMG activation to emotional exclamations of others' pain. This is consistent with what we had expected, as viewing others in pain will activate the regions related to empathy. The occipital gyrus are mainly associated with visual processing (Berlucchi, 2014). It has been proved that the inferior occipital gyrus plays an important part in identifying emotionally important visual clues, and viewing unpleasant pictures can significantly activate the left inferior occipital gyrus compared to the neutral situations (Geday et al., 2003). What's more, the posterior fusiform and inferior occipital gyrus were assumed as the core regions in identifying emotionally important visual clues (Geday et al., 2003). The present study also found that participants viewing painful pictures had stronger activation in the inferior parietal lobule than those viewing non-painful pictures. The inferior parietal lobule has a critical function in distinguishing between self-produced actions and actions generated by others (Decety and Jackson, 2004; Lamm et al., 2008). A previous fMRI study demonstrated that higher activation of this region reflects less self-other overlap, which leads to greater accuracy during social perception (Lawrence et al., 2006). Another significantly activated region is the lateral fusiform, which is known as a key region related to facial perception. However, it has been proved that fusiform gyrus is associated with the processing of "ToM" and so is empathy (Castelli et al., 2000; Gallagher et al., 2000; Moll et al., 2002). It can be modulated by emotional valence, and it has been proved that right fusiform gyrus was more active than the left during emotional processing (Geday et al., 2003). This is consistent with our findings, which suggest that exposure to painful pictures will induce the emotional response and the unpleasant pictures are more arousing.

It should be noted that there are no significant difference in the full factorial design in [(PVG − NVG) − (PNG − NNG)]. This may suggest that there is no deficit in the neural responses of empathy for pain in individuals with VVG experience, being inconsistent with some extant studies (e.g., Funk et al., 2004; Anderson et al., 2010; Strenziok et al., 2011; Zhen et al., 2011; Montag et al., 2012; Guo et al., 2013), which all suggest that long-term exposure to media violence has a desensitization effect. However, Decety et al. (2009) showed that youth with aggressive conduct disorder do not have a deficit in empathy and may have an atypical pattern of neural response while viewing others in pain. Similarly, a survey conducted by Collins and Freeman (2013) found no difference in empathy between gamers and non-gamers. This can be seen from the painful pictures and non-painful pictures contrast both in VG and NG. The brain activation in both VG and NG showed similar pattern when viewing painful pictures compared to viewing non-painful pictures. The lateral fusiform gyrus was activated in both groups, which is important during empathy.

This may indicate that long-time exposure to VVGs is not strongly associated with desensitization to violence, especially pain empathy to others. This is supported by researches

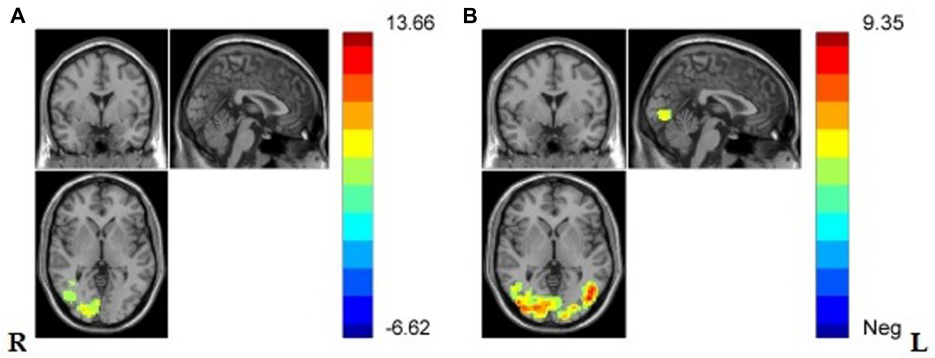

FIGURE 4 | (A) Brain regions showing significant activation while viewing painful stimuli compared with non-painful stimuli in NG in lateral middle occipital gyrus, lateral V2, right middle temporal gyrus, lateral fusiform gyrus. ($p < 0.001$, Alphasim corrected; $k > 1138$). **(B)** Brain regions showing significant activation while viewing painful stimuli compared with non-painful stimuli in VG in lateral occipital gyrus, lateral fusiform gyrus, left V2, and right middle temporal gyrus ($p < 0.001$, Alphasim corrected; $k > 1132$).

TABLE 2 | Brain regions showing significant activation in lateral occipital gyrus, lateral fusiform gyrus, left V2, and right middle temporal gyrus in VG, and significant activation in lateral occipital gyrus, lateral fusiform gyrus, right lingual gyrus, left V2, and right middle temporal gyrus while viewing painful stimuli compared with non-painful stimuli ($p < 0.001$, Alphasim corrected; $k > 1132$ in VG and $k > 1138$ in NG).

Conditions	Region of activation	Lat.	MNI			*t*-value	*k*
			x	*y*	*z*		
NG	Middle occipital gyrus	R	21	−96	12	13.66	367
	Middle occipital gyrus	L	−42	−87	0	6.32	476
	Secondary visual cortex (V2)	R	36	−87	9	8.26	102
	Secondary visual cortex (V2)	L	−36	−9	0	5.92	116
	Middle temporal gyrus	R	51	−69	12	4.67	99
	Fusiform gyrus	R	36	−48	−15	6.28	249
	Fusiform gyrus	L	−27	−60	−15	7.53	199
VG	Middle occipital gyrus	L	−45	−75	0	7.89	442
	Middle occipital gyrus	R	45	−81	0	7.53	365
	Fusiform gyrus	L	−48	−66	0	8.30	195
	Fusiform gyrus	R	30	−66	−12	7.66	362
	Secondary visual cortex (V2)	L	−12	−78	−9	7.09	268
	Middle temporal gyrus	R	48	−63	−3	6.21	93

conducted by Szycik et al. (2016, 2017). In their researches, the positive, negative, and neutral pictures were displayed and the fMRI data was collected. Repeated experiments proved that there was no evidence for a neural desensitization in the processing of emotionally salient stimuli, same as our research findings. Taking all the findings together, it is necessary for us to rethink the desensitization hypothesis. The catalyst model proposed by Ferguson et al. (2008) pointed that, just like competition, playing VVGs is the result of attacking intention, not the cause of it. In this case, VVGs are not significantly relevant to aggressive behaviors. At the same time, the catharsis theory of playing contends that playing VVG, especially action game, provide a way to drain the aggressive emotion and energy off, rather than increasing the aggressive belief. After enjoying themselves immersing in the games, the nervous feelings and extra energy were consumed, players are used to feeling entirely free from worry. Compared to researches based on self-report measures, neuropsychological researches are definitely more valid to testify the long-term effect.

This research was based on the comprehensive view of VVG effect without certain bias and based on what was shown in this study, it could be suggested that our research is more objective and convincing. However, our study also has some limitations and there are areas that need further exploration. The present study did not measure sensitivity to pain, so we cannot rule out the possibility that some of our findings were influenced by individual differences among the participants. On the other hand, although there were no gender-related differences on empathy shown in the present study, it still may be caused by the gender distribution. It should be noted that only males were examined in our research and the research is suitable when the participants are confined to males. Further studies should pay attention to gender distribution. Furthermore, unknown variations or inconsistencies in the functions of some brain regions and neural

circuits might explain the observed activations in some brain regions. Exploring the influence of VVGs on cognitive empathy and emotional empathy separately may provide the topic with more precise findings.

CONCLUSION

The observation that there were no significant differences between VG and NG suggests that individuals with VVG exposure may not have a deficit in their capacity for empathy. The differences in empathy for pain between individuals with VVG experience and non-VVG experience indicated that the desensitization effect of VVGs is not significant.

COMPLIANCE WITH ETHICAL STANDARDS

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained after detailed explanation of the study protocol, which was approved by the Ethics Committee of Southwest University. The Institutional Review Board at Southwest University (SWU) in Chongqing, China approved this consent procedure. Written informed consent was obtained from all participants. The Institutional Review Board at SWU approved all procedures. Informed consent was obtained from all individual participants included in the study.

AUTHOR CONTRIBUTIONS

Conceived and designed the experiments: XG and LW. Performed the experiments: XG, CL, and WP. Analyzed the data: CL, XG, WP, and MY. Wrote the paper: WP, XG, LW, and CL. Editing and Revisions: XG, AC, CL, and WP.

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Lack of Evidence That Neural Empathic Responses Are Blunted in Excessive Users of Violent Video Games: An fMRI Study

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The use of violent video games has been often linked to increase of aggressive behavior. According to the General Aggression Model, one of the central mechanisms for this aggressiveness inducing impact is an emotional desensitization process resulting from long lasting repeated violent game playing. This desensitization should evidence itself in a lack of empathy. Recent research has focused primarily on acute, short term impact of violent media use but only little is known about long term effects. In this study 15 excessive users of violent games and control subjects matched for age and education viewed pictures depicting emotional and neutral situations with and without social interaction while fMRI activations were obtained. While the typical pattern of activations for empathy and theory of mind networks was seen, both groups showed no differences in brain responses. We interpret our results as evidence against the desensitization hypothesis and suggest that the impact of violent media on emotional processing may be rather acute and short-lived.

Keywords: video games, violence, desensitization, General Aggression Model, Catalyst Model

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INTRODUCTION

The possible influence of violent video games (VVG) on human aggressive behaviour is hotly debated. According to research done in the context of the General Aggression Model (GAM) a direct and causal relationship between the use of VVG and aggressiveness (Anderson and Bushman, 2002) is postulated: aggressive or impulsive behavior is a short term result of both personal and situational variables like exposure to VVG. Therefore, an increase of aggression after exposure to VVG is hypothesized to appear as a result of cognitive cuing effects (Anderson and Dill, 2000). Long-term exposure to VVG on aggressive behavior according to the GAM leads to an increase in aggressive personality traits by learning, rehearsal and reinforcement of aggression-related knowledge structures. Also, a desensitization against violent content and a decrease of empathy and prosocial behavior has been postulated (Sparks and Sparks, 2002; Anderson et al., 2003; Huesmann et al., 2003).

The alternative Catalyst Model postulates only little or no effects of VVG use on human aggressive behavior (Ferguson et al., 2008). Following this model, aggressive behavior results primarily from biological factors and VVG only shape the style of aggressive expression. This view criticizes the GAM because of the discrepancy between its predictions and the recent violence

statistics (Ferguson, 2010), small effect sizes or poor quality meta-analyses (Kutner and Olson, 2008; Ferguson, 2015a), and the publication bias or selective reporting of only significant data (Elson and Ferguson, 2014; Ferguson, 2015b).

The literature regarding short term desensitization effects of VVG has been inconsistent. Some short term desensitization effects could be shown regarding physiological reactivity, i.e., reduction in heart rate or galvanic skin reactions to violent stimuli (Carnagey et al., 2007a,b; Staude-Muller et al., 2008). The P300 component of the event-related potential has also been found to be reduced after VVG use (Bartholow et al., 2006; Engelhardt et al., 2011). Other studies using violent and non-violent versions of the same game could not find differences in physiological markers like heart rate or skin conductance (Ballard et al., 2012; Chittaro and Sioni, 2012). A recent meta-analysis suggests a relationship between VVG use and decrease in empathy (and more desensitization) but only for short term effects (Anderson et al., 2010). Long term effects were not analyzed in this meta-analysis because of a lack of pertinent studies. To our knowledge only two studies focussed on long term desensitization effects of VVG use by the means of fMRI. In the first study small effects were shown but the results were not adequately corrected for multiple comparisons (Montag et al., 2012) which raise the possibility that the reported differences would not have survived adequate correction. Our group studied 28 male excessive VVG users and a matched control group with two experiments using emotional picture stimuli from the IAPS data base (Szycik et al., 2016). The user group had at least 3 h of VVG abstinence prior to experiment making the design more suitable for analyzing long term effects. VVG users showed similar brain responses as control subjects for emotional material indicating no specific desensitization effect of excessive long lasting VVG use.

As Montag et al. (2012) and Szycik et al. (2016) the current study focused on the long-term desensitization effects of VVG use but this time with an emphasis on empathy. For this reason we used a picture set, patterned after the materials of the Adult Attachment Projective Picture System (AAP; George and West, 2001), designed to elicit empathic / emotional reactions in situations with and without social interaction (Krämer et al., 2010; Beyer et al., 2014a,b). According to the Perception-Action-Model (PAM) of empathy (Preston and de Waal, 2002) and in keeping with previous results using the same stimulus set we hypothesized that pictures depicting another person's emotional state should elicit empathic reactions and concomitant neural activations. Furthermore, according to the desensitization hypothesis derived from the GAM that excessive VVG users should show decreased brain activity in the empathy network (Bzdok et al., 2012).

MATERIALS AND METHODS

All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the ethic committee of the Medical School Hannover. All participants were also provided with short briefing prior to the experiment. First possible contradictions for MRI measurements were cleared by standard questionnaire and then all necessary information regarding the study was given (e.g., experimental task). The subjects had also the possibility to ask questions before the experiment. After the experiment all subjects were provided with standard debriefing containing additional information regarding the study.

Participants

As use of VVG and aggressive behavior is more prevalent in men, only male participants were recruited. Inclusion criterion for the VVG user group was consumption of violent games of the first-person shooter category (e.g., Counterstrike, Call of Duty or Battlefield) for at least 4 years and for at least 2 h daily. First-person shooter games are centered on combat situations seen from the first-person perspective, involving virtual weapons (mostly automatic rifles). Control subjects did not have any experience with VVG (self-report). We also excluded all control subjects that reported a daily use of any video games. All participants were free of psychiatric and neurological disorders as assessed clinically by the senior author, a board-certified psychiatrist. One participant of the VVG group was excluded from the analysis due to taking antidepressant medication. All of the subjects had normal or corrected to normal vision. Experimental and control groups were matched for school education and age.

For the experiment 15 VVG users (mean age 22.8 $\pm$ 4.3 years) and 15 control subjects (mean age 22.1 $\pm$ 3.0 years) were recruited (difference n.s.). The VVG users had played violent games since 13.1 $\pm$ 4.4 years for about 4.0 $\pm$ 1.3 h daily.

To avoid possible immediate effects of violent games all participants refrained from playing for at least 3 h prior to the experiment during which time they were informed about the experiment and were prepared for data acquisition. The actual time without playing VVG before the experiment was considerably longer in most subjects.

Stimuli and Design

The experimental stimulation in this study is based on a previous publication and uses black- line drawings on a gray background (Krämer et al., 2010; Beyer et al., 2014a,b). The drawings were assigned to four conditions: emotionally negative social situations involving two interaction partners (EMOT-TWO), emotionally neutral social situations also involving two interaction partners (NEUT-TWO), emotionally negative situations involving one person (EMOT-ONE), and emotionally neutral situations involving one person (NEUT-ONE). Negative emotional stimuli depicted emotions like anger, sadness, pain or anxiety (**Figure 1**). The stimuli had been previously rated for their emotional content with consistent results across the individual subjects and significant differences for the specific categories (Krämer et al., 2010).

The stimuli were presented for 4 s in pseudorandom order each with varying interstimulus interval (ISI). For each of the four experimental categories 24 different stimuli were used. Between the stimuli a black central fixation cross was presented on gray background. ISI varied pseudo-randomly within each category

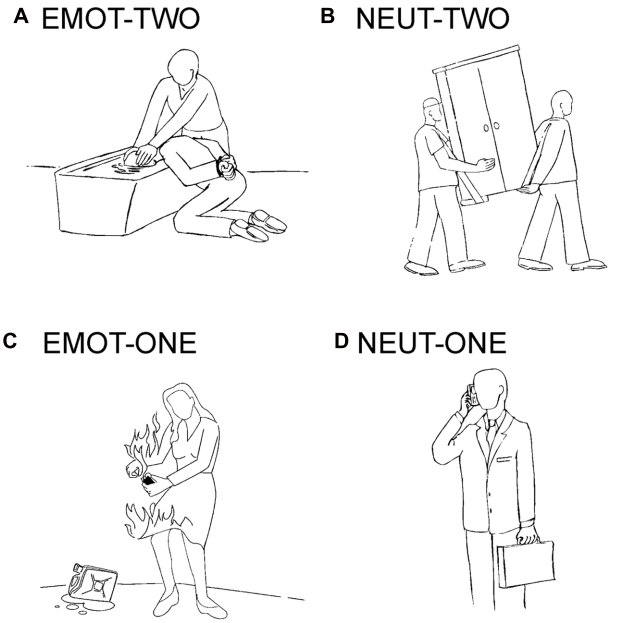

FIGURE 1 | Example stimuli. Depicted are examples of the drawings used in this study: **(A)** emotionally negative social situations involving two interaction partners (EMOT-TWO), **(B)** emotionally neutral social situations also involving two interaction partners (NEUT-TWO), **(C)** emotionally negative situations involving one person (EMOT-ONE), and **(D)** emotionally neutral situations involving one person (NEUT-ONE).

with 15 intervals of 6 s duration, 5 intervals of 8 s duration and 2 intervals each of 10 s and 12 s duration. During fMRI scanning participants were instructed to watch the pictures carefully and imagine how they would feel in the depicted situation. Presentation software (Neurobehavioral Systems, Inc.) was used to deliver stimuli. Stimuli were presented via an MRI-compatible video display mounted into prepared glasses (CinemaVision, Resonance Technology Inc., USA). Prior to fMRI scanning a test picture was presented to ensure good visibility of stimuli for each participant.

Image Acquisition

Magnetic-resonance images were acquired on a 3-T Siemens Magnetom Scanner (Erlangen, Germany) equipped with a standard head coil. A total of 545 T_2*-weighted volumes of the whole brain (EPI-sequence; TR 2000 ms, TE 30 ms, flip angle 80o, FOV 192 mm, matrix 64^2, 34 slices, slice thickness 3 mm, interslice gap 0.75 mm) near to standard bicommisural (AC-PC) orientation were collected. After the functional measurement a 3D high resolution T_1-weighted volume for anatomical information (MPRAGE-sequence; matrix 192 × 256^2, 1 mm isovoxel) was recorded. The subject's head was fixed during the entire measurement to avoid head movements.

Acquisition of Psychometric Data

Prior to fMRI scanning data from different psychological questionnaires was collected. We used the German adaptation ("Der Saarbrücker Persönlichkeitsfragebogen zur Messung von Empathie") of the Interpersonal Reactivity Index (IRI) with its four subscales: PT- perspective-taking, FS- fantasy scale, EC- empathic concern, and PD- personal distress (Davis, 1980). To analyze potential group differences in aggressiveness we collected the data from the short version of the German questionnaire for aggressiveness factors K-FAF: "Kurzfragebogen zur Erfassung von Aggressivitätsfaktoren" (Heubrock and Petermann, 2008). To analyze the ability in emotional understanding, processing, or description the German adaptation of the Toronto Alexithymia Scale (Bagby et al., 1994) was used. To assess relevant personality traits we used the German adaptation of the Temperament and Character Inventory TCI (Cloninger, 1994) and The Inventory of Clinical Personality Accentuations ("Inventar Klinischer Persönlichkeitsakzentuierungen") to screen clinical personality aspects (Andresen, 2006).

fMRI Data Analysis

Analysis and visualization of the data were performed using Brain Voyager QX (Brain Innovation BV, Maastricht, The Netherlands) software (Goebel et al., 2006). First, a correction for the temporal offset between the slices acquired in one scan was applied. For this purpose the data was cubic spline interpolated. After this slice scan time correction a 3D motion correction was performed by realignment of the entire measured volume set to the first volume by means of trilinear interpolation. Thereafter, linear trends were removed and a high pass filter was applied resulting in filtering out signals occurring less than 2 cycles in the whole time course. Structural and functional data were spatially transformed into the Talairach standard space (Talairach et al., 1988) using a 12-parameter affine transformation. Functional EPI volumes were spatially smoothed with an 8 mm full-width half-maximum isotropic Gaussian kernel to accommodate residual anatomical differences across volunteers.

For the statistical model a design matrix including all conditions of interest was specified using a hemodynamic response function. This function was created by convolving the rectangle function with the model of Boynton et al. (1996) using $\Delta = 2.5$, $\tau = 1.25$ and $n = 3$. Thereafter, a multi-subject random effects (RFX) analysis of variance model (ANOVA) with two main within-subject factors and one between-subject factor was used for identification of significant differences in hemodynamic responses. The first within subject factor was emotional content (EMOT vs. NEUT), the second within subject factor was social relation (TWO vs. ONE). The between-subject factor was group (VVG users vs. control subjects). Additional as regressors of no interest we used overall six translation and rotation vectors derived for each dataset during the 3D motion correction.

Main effects of all factors and their interaction were considered. The false discovery rate threshold of q(FDR) < 0.01 (Genovese et al., 2002) was chosen for identification of the activated voxels. Voxels fulfilling these criteria are reported. The centers of mass of suprathreshold regions were localized using Talairach coordinates and the Talairach Daemon tool (Lancaster et al., 2000).

RESULTS

Questionnaire Data

Group differences were obtained only for the factor Novelty Seeking of the Temperament and Character Inventory [$t(28) = 2.126$, $p < 0.042$] and the scale Antisocial Personality of The Inventory of Clinical Personality Accentuations [$t(28) = 3.255$, $p < 0.003$]. VVG users showed higher scores for Novelty Seeking ($M = 25.27$, $SD = 4.59$ vs. $M = 20.47$, $SD = 7.44$) and for Antisocial Personality ($M = 22.13$, $SD = 5.89$ vs. $M = 16.13$, $SD = 4.03$) in comparison to controls. No further group differences were apparent in the questionnaires, in particular no differences were seen for empathy and aggression measures (for

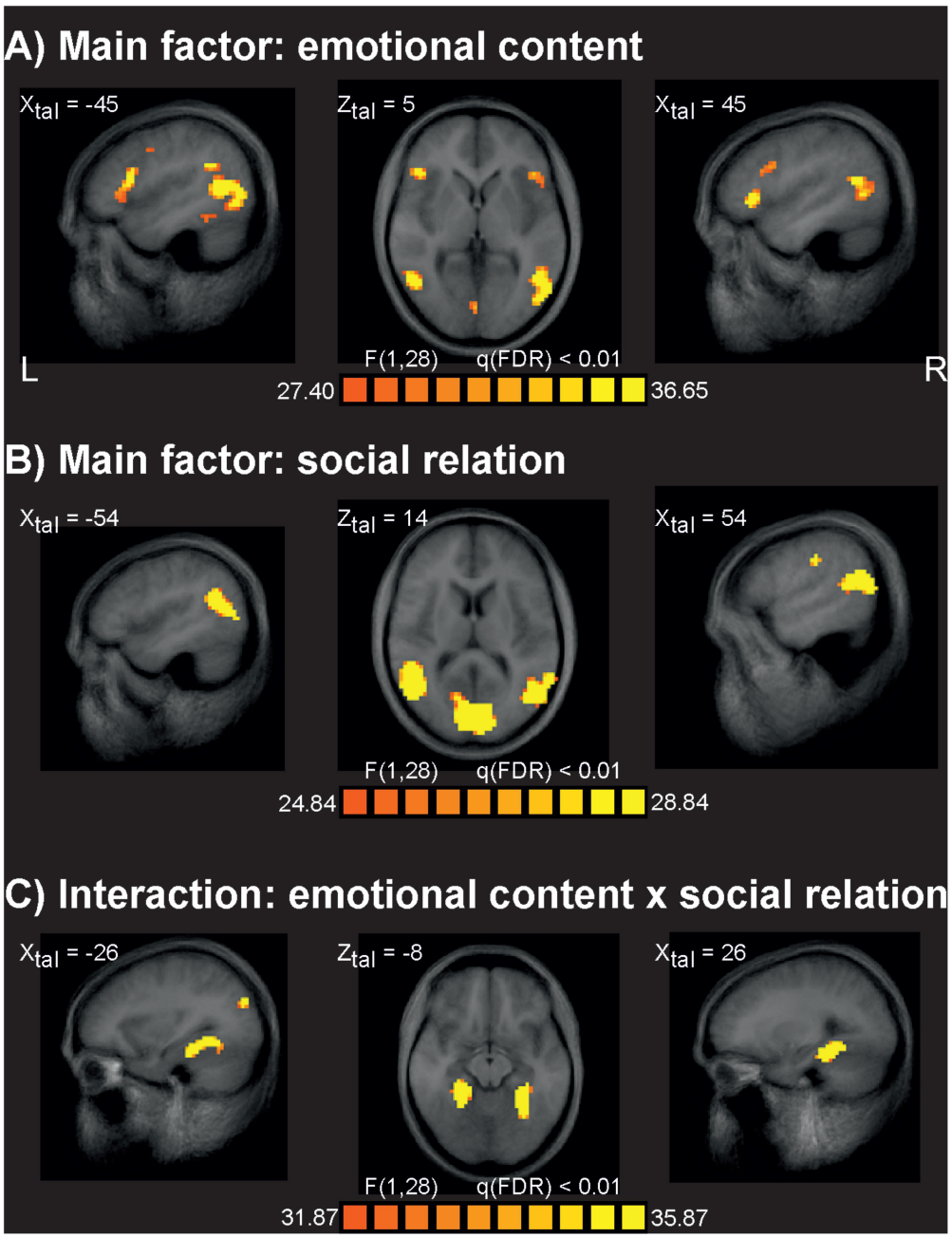

FIGURE 2 | Results of the fMRI data analysis. (A) Brain sites identified for the main factor emotional content responding for stimuli with emotional negative and neutral valence. **(B)** Brain sites identified for the main factor social relation, responding for stimuli depicting one person or two persons in social interaction. **(C)** Brain sites identified for the interaction of the main factor emotional content and social interaction. The factor group revealed no significant brain sites, also all other interactions resulted in no significant results. L, leftt; R, right; XZtal, Talairach coordinates.

the overview of all questionnaire data see Supplementary Material).

fMRI

The analysis of fMRI data revealed at q(FDR) < 0.01 strong effects for the main factor emotional content (**Figure 2A**). At a less strict level of q(FDR) < 0.05 additional typical activations often seen for the processing of emotionally relevant material were found, such as bilateral limbic structures including both amygdalae. The main effect of social interaction was significant for several brain areas at q(FDR) < 0.01 (**Figure 2B**) similar to earlier studies (Krämer et al., 2010; Beyer et al., 2014a,b). There were no significant differences between VVG users and controls at the level of q(FDR) < 0.01. To check for weak effects, this analysis was repeated at a very liberal threshold of $p = 0.01$, uncorrected, but again no reliable activation differences between groups were seen. We also analyzed all possible interaction effects at the q(FDR) < 0.01 significance level. Only the interaction of emotional content by social relation resulted in reliable brain activations related primarily to bilateral parahippocampal gyrus (**Figure 2C**). All other interactions including the factor group were not significant at this level. **Table 1** gives an overview about the identified brain sites for the main factors and interaction of the ANOVA analysis.

DISCUSSION

A central claim of the GAM regarding the effects of VVG is desensitization toward emotional stimuli. Although some evidence has been provided for short term effects of VVG in the sense of a decreased empathy and increased of aggressiveness (Carnagey et al., 2007a,b; Staude-Muller et al., 2008), long term effects have not been intensively investigated. Long term effects were the focus of the present study, which assessed neural responses to stimuli designed to elicit empathic reactions. To rule out short term effects of VVG, users had ben abstinent for at least 3 h prior to the measurements. Contrary to our initial hypothesis of a reduced activity in empathy related brain regions in VVG users, the fMRI data did not provide evidence for a neural desensitization in the processing emotionally salient stimuli. In fact, the responses of both groups were very similar and no group differences were observed even at relaxed statistical thresholds. This lack of a group main effect and of interaction effects involving the group factor is not due to a general lack of emotional reactivity in our participants. Indeed, we found robust activations for the factor emotional content in our dataset (**Figure 2A**) similar to those found previously in studies using the same materials (Krämer et al., 2010; Beyer et al., 2014a,b). These activations included areas already known as involved in processing of emotional content (limbic structures, ventromedial and ventrolateral prefrontal cortex) and areas involved in mentalizing or theory-of-mind process (e.g., regions around superior temporal sulcus) (Bzdok et al., 2012, 2013; Mutschler et al., 2013; Mitchell and Phillips, 2015; Morelli et al., 2015). Our paradigm clearly is sensitive to differences in emotional content. Also, aspects of social relation could be reliable observed in our data and were in line with the previous research (Adolphs, 2003; Krämer et al., 2010; Beyer et al., 2014a,b).

Thus, the lack of group differences in our fMRI data dues not suggests, that excessive VVG use leads to long term emotional desensitization and a blunting of neural responses related to empathy. This is corroborated by the questionnaire data which

TABLE 1 | Brain areas identified for the ANOVA.

Brain structure	Hemisphere	Talairach center of mass			Cluster size (mm^3)
		x	*y*	*z*	
Main Factor: emotional content					
Inferior Frontal Gyrus, BA13	R	44	26	3	1242
Inferior Frontal Gyrus, BA9	R	41	10	28	1458
Superior Temporal Gyrus, BA39	R	50	−52	14	4401
Lingual Gyrus, BA18	R	6	−75	3	648
Medial Frontal Gyrus, BA9	L	−1	47	30	918
Precentral Gyrus, BA44	L	−42	18	8	3645
Middle Frontal Gyrus, BA6	L	−39	−2	44	945
Middle Temporal Gyrus, BA39	L	−48	−57	9	9180
Main Factor: social relation					
Postcentral Gyrus, BA2	R	58	−19	33	837
Superior Temporal Gyrus, BA22	R	48	−53	16	6480
Cuneus, BA18	R/L	1	−72	18	34911
Superior Temporal Gyrus, BA39	L	−48	−59	17	6750
Interaction: emotional content x social relation					
Parahippocampal Gyrus, BA36	R	24	−38	−10	3294
Parahippocampal Gyrus, BA37	L	−28	−44	−10	3861
Middle Temporal Gyrus, BA19	L	−34	−78	26	540

did not reveal differences between VVG users and controls for empathy and aggression measures, even though some differences emerged for measures assessing novelty seeking and antisocial personality.

Most previous studies have focused on immediate effects of VVG use (Brockmyer, 2015). For example, Weber et al. (2006) looked at fMRI activations during the performance of violent computer games and reported a suppression of amygdala and anterior cingulate gyrus activity which was taken to suggest a blunted emotional reactivity. Other researchers reported a decreased interaction between amygdala and the lateral orbitofrontal cortex directly after exposure to violent media (Kelly et al., 2007). Gentile et al. (2014) reported suppression of fMRI responses to violent compared to non-violent video games in VVG users. Evidently, these studies used stimulation with violent media/games immediately before or even during the experiment and therefore the results may by influenced not only by desensitization but also by other factors such as increased attention toward motor actions or immediate activation of aggressive cognitions. In any case, these reflect only possible short term influence of VVG on emotional processing. Studies focussing on long term effects are rare and show results that are in line with the present study (Szycik et al., 2016).

The missing group effect in our fMRI data is not really surprising giving the fact that both groups showed also no differences in empathy and aggressiveness as assessed by psychological tests. Our data therefore is in line with the Catalyst Model of violent media influence on individual behavior which posits that these do not increase aggressive behavior but may influence the way how aggressive behavior is displayed. Therefore, aggressiveness itself results more from other aspects than violent media use. This idea is supported by our data. VVG users differ in personality trait Novelty Seeking. As Novelty Seeking is highly correlated with Sensation Seeking (Zuckerman et al., 1993) subjects with high values on this scale are vulnerable for risky activities and tend to excessive behavior resulting often both in substance related and behavioral addictions like e.g., excessive use of video games (Bardo et al., 1996; McCoul and Haslam, 2001; Roberti, 2004; Grucza et al., 2006; Wang et al., 2015). VVG users of our study also showed high values on the antisocial scale of the clinical personality inventory. This again may be the basis for specific problematic behavior often suggested for this population. In this sense VVG use might be a yet another symptom not the cause of problems in this group. One interesting question arises from the fact that the significant group difference in antisocial personality found in this study was not accompanied by significant differences in empathy scores. Empathy is only one part of many (e.g., disregard for social norms, rules, and obligations, incapacity to maintain enduring relationships, incapacity to experience guilt or to profit from experience) involved in the psychological construct of antisocial personality. Keeping that in mind or VVG group could score significant higher on antisocial personality without differing from the control group in empathy scores.

Before concluding our results we want to put some attention to the limitations of the study. Thus we did not found group differences in our fMRI data set. Null findings in imaging studies are notoriously problematic (Hupe, 2015) and may result also from to small effects in relation to the extent of the population included. One possibility to handle this problem is to decrease statistical threshold used with the risk of making "false positive" conclusions. We tried to maximize our ability to find group differences and to safeguard against "false negatives" and lowered the statistical threshold used to very liberal one of $p = 0.01$, uncorrected. But also after the adaptation of the threshold no group differences could be found. Second relevant limitation of this study relies on the fact, that our both populations were not controlled for consumption of other than VVG violent media, e.g., violent cinema movies or internet content. Thus we cannot rule out the possibility that our control subjects consumed in similar excessive extent other violent contents and have experienced desensitization at same level as our experimental group.

To summarize, our results provide additional evidence against the desensitization hypothesis of VVG use and human aggression. Research on media impact on aggressive behavior should focus on short term (influencing the subject's state) as well as long term impact (possibly influencing trait aggressiveness). Moreover, additional paradigms should be employed, e.g., facial expression tasks (van Zutphen et al., 2015), to examine these aspects within VVG users. Also the use of more ecological valid paradigms could be promising to put more light on this topic. Interesting approach could be to put individuals with VVG use and controls into situations requiring acting upon emotional stimuli like it is the case in the Taylor Aggression Paradigm. A number of recent imaging studies have used a version of this paradigm to assess impulsive aggression in response to provocation (Krämer et al., 2007; Beyer et al., 2014a,b, 2015; Dambacher et al., 2015; Gan et al., 2015).

AUTHOR CONTRIBUTIONS

GS designed the study, collected and analyzed the data, interpreted the results and wrote the manuscript. BM collected the data and supported the interpretation of the results. TM supported the interpretation of the data and wrote the manuscript. BtW designed the study, collected the data and supported the interpretation of the results.

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SUPPLEMENTARY MATERIAL

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Brain Structures Associated with Internet Addiction Tendency in Adolescent Online Game Players

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With the development of the Internet, an increasing number of adolescents play online game excessively, which leads to adverse effects on individuals and society. Previous studies have demonstrated altered gray-matter volume (GMV) in individuals with Internet gaming disorder (IGD), but the relationship between the tendency to IGD and the GMV across whole brain is still unclear in adolescents. In the present study, anatomical imaging with high resolution was performed on 67 male adolescents who played online game; and Young's Internet addiction test (IAT) was conducted to test the tendency to IGD. FMRIB Software Library (FSL) was used to calculate the voxel-based correlations between the GMV and the IAT score after controlling for the age and years of education. The GMVs of the bilateral postcentral gyri (postCG), the bilateral precentral gyri (preCG), the right precuneus, the left posterior midcingulate cortex (pMCC), the left inferior parietal lobe (IPL), and the right middle frontal gyrus (MFG) were negatively correlated with the IAT score. The correlation still existed between the IAT score and the GMVs of the bilateral postCG, the left preCG, the left pMCC, and the right MFG after controlling for the total time of playing online game. When the participants were divided into two groups according to the IAT score, the GMVs of these IAT-related brain regions were lower in high IAT score subgroup (IAT score >50) than in low IAT score subgroup (IAT score ≤50). Our results suggested that the GMVs of brain regions involved in sensorimotor process and cognitive control were associated with the IGD tendency. These findings may lead to new targets for preventing and treating the IGD.

Keywords: Internet gaming addiction, gray-matter volume, Internet addiction test, online game, adolescent

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INTRODUCTION

In the past decades, the Internet played an important role in our life. However, more and more adolescents surf the Internet and play online game excessively, which result in adverse effects on adolescents themselves and society. An epidemiological study demonstrated that Internet gaming disorder (IGD), a subtype of Internet addiction (IA) (1), was a very common mental health problem among Chinese adolescents (2). Therefore, more and more studies focused on the neuromechanism of IGD and aimed to contribute to the prevention and treatment of IGD.

Structural neuroimaging of brain could be used to investigate brain mechanisms about individual personality traits (3–5). Previous structural studies have found that individuals with IGD had

structural abnormalities in gray matter (GM), such as decreased gray-matter volume (GMV) or GM density in multiple cortical and subcortical areas (6–11), and increased GMV in frontal and temporal regions (8, 12). These studies suggested that multiple brain areas in the frontal, temporal, parietal, and subcortical regions such as ventral striatum were associated with IA, which contributed to the understanding of the neuromechanisms of IA. However, the majority of previous studies just focused on the IA or IGD diagnosed by clinical questionnaire such as Internet addiction test (IAT), and compared the differences in behavior and brain function and structure between the IGD individuals and healthy controls. As a matter of fact, not all the individuals who play online game suffer from the IGD (13). Therefore, investigation of the structural correlations in online game players with different levels of tendency to IGD, not only the individuals with IGD diagnosis, is necessary.

Recently, three studies directly focused on the neural associations of the tendency to the IA. Wen and Hsieh (14) explored the relationship between the whole brain functional connections and the level of IA in a group of young adults (19–29 years) and found two networks mainly consisted of frontal regions were correlated to the tendency of IA. Li et al. (15) reported that the structure and functional connectivity of the right dorsolateral prefrontal cortex were positively correlated with the IAT score in a group of healthy young adults (18–27 years). A study by Kühn (16) revealed that the GMV of the brain regions within fronto-striatal network correlated to excessive Internet use assessed by IAT score. Additionally, previous studies have also demonstrated that the GMV changes were related to the online game addiction severity in the IGD subjects. For example, a study by Weng et al. demonstrated that the GMVs of the right orbitofrontal cortex and bilateral insula were positively correlated with the online game addiction severity in the IGD subjects (7). Cai et al. reported increased GMV of nucleus accumbens was associated with the IAT score in the IGD individuals (17). A study by Zhou et al. showed that lower GMV in the right orbitofrontal cortex was related to higher online video gaming addiction severity within the Internet gamers (18). These studies demonstrated that brain structures and functions were associated with the level of IA. However, the relationship between the tendency to IGD and the GMV across whole brain was not yet clearly evaluated in adolescents (14–18 years). The adolescent between 14 and 18 years of age is in a critical period of psychological development and is prone to addiction and adverse effects (19, 20). Many studies regarding the substance addiction paid close attention to adolescents aged from 14 to 18 years (21, 22). A large-sample study demonstrated that the IGD is very common in Chinese elementary and middle school students with a incidence of 22.5% among those students who play online games (2). Therefore, it is more necessary to investigate the brain structural correlations with the tendency to IGD in adolescents (14–18 years).

Furthermore, previous studies demonstrated that long-term online game playing could lead to structural reorganization of the brain in online game players (12, 23, 24). The GMVs in the ventrolateral prefrontal cortex, the dorsolateral prefrontal cortex, the supplementary motor area, and the rostral anterior cingulate cortex were correlated with the duration of online game playing in the adolescents with IA disorder (6, 25). Therefore, whether the duration of online game playing affects the relation between the GMV and the tendency to IGD is worth studying.

In the present study, 67 male adolescents (14–18 years) who played online games were recruited. The voxel-based correlation analysis was conducted to detect the brain regions associated with IAT score before and after controlling for the total time of playing online game. Based on the previous studies, the prefrontal-striatal circuits are closely related to the addiction. Ventral striatum participated in the habit learning and rewarding process involved in addiction (26, 27), and the reduced control effect of prefrontal cortex on rewarding process is one of the mechanisms of addiction (28, 29). Therefore, we hypothesized that the IGD tendency may be associated with the brain regions related to the cognitive control (prefrontal cortex) and the rewarding process (ventral striatum). This study may lead to new targets for preventing and treating the IGD in adolescents.

MATERIALS AND METHODS

Subjects

Sixty seven right-handed adolescents (14–18 years old, average 15.54 ± 0.14) who played online game were recruited in this study. Twenty of 67 participants were the students of a Health School and 47 of 67 participants were the adolescents whose parents took them to a psychiatrist because of possible IGD. All participants received education for 6–12 years, ranging from primary school to senior high school. All of the participants spent more than 80% of the online time on playing online game. Only male adolescents were enrolled in this study because relatively small number of females play online games and suffer from IGD (2, 30). Exclusion criteria included the following: alcohol abuse or drug dependence; existence of any neurologic or psychiatric disease such as insomnia, migraines, tinnitus, and attention deficit hyperactive disorder; history of physical illness such as brain trauma, brain tumor, or epilepsy assessed according to clinical evaluations and medical records; MRI contradiction; and visible abnormalities on conventional MRI. The present study was approved by the Ethical Committee of Tianjin Medical University General Hospital, and all of the participants and their guardians provided written informed consent according to institutional guidelines.

Questionnaire

Internet addiction test was used to assess the severity of the tendency to IGD in this study. The IAT consists of 20 items and the answers of these questions were described as 1–5 score (1 = "rarely" to 5 = "always") (31). The total score of 20 items measures the severity of Internet dependency. The experience of online game playing was assessed *via* a self-report questionnaire that questioned about the length and amount of playing. The total time of playing online game was calculated as hours per day multiplied by the days of playing online games. Intelligence Quotient (IQ) of all participants was tested using Standard Raven's Progressive Matrices. The anxiety and depression were

texted by using the self-rating anxiety scale (SAS) and the self-rating depression scale (SDS).

Structural MRI

Structural images were obtained using a Siemens 3.0 T scanner (Magnetom Verio, Siemens, Erlangen, Germany). A series of 192 contiguous sagittal high-resolution anatomical images were obtained using a three-dimensional T1-weighted volumetric magnetization-prepared rapid gradient-echo sequence with the following parameters: TR = 2000 ms, TE = 2.34 ms, TI = 900 ms, flip angle = 9°, FOV = 256 mm × 256 mm, slice thickness = 1 mm, matrix size = 256 × 256.

Voxel-Based Morphometry (VBM) Analysis

All structural images were preprocessed with the VBM8 toolbox[1] of the SPM8 (Wellcome Department of Imaging Neuroscience, London, UK)[2] running on MATLAB R2010a (Math Works Inc., Sherborn, MA, USA). Three-dimensional geometric correction was performed during reconstructing the images. After that, the individual native images of all participants were segmented into GM, white matter (WM), and cerebral spinal fluid (CSF), and the GM segments were normalized to the Montreal Neurological Institute template by diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) (32). The registered GM images were then modulated by dividing the Jacobian of the warp field to correct for local expansion or contraction. The isotropic Gaussian kernel of 8-mm full width at half maximum was adopted to smooth the modulated GM images. The mean image of normalized GM from all participants was used to create a GM mask whose threshold was set at a value of 0.3 (pixels with computed GM fraction values >30% were selected). Then the GM mask was used as an explicit mask for the statistical analysis to exclude the pixels with low GM probability values.

Statistical Analysis

Voxel-wise multiple regression analysis was carried out to explore the correlation between the GMV and the IAT score across all participants after controlling for the age and years of education. The non-parametric permutation approach (33) was accomplished by the randomize tool commanded in FMRIB Software Library (FSL)[3]. The threshold-free cluster enhancement (TFCE) analysis was performed as it combines cluster extent and height into one statistic and does not require an arbitrary choice of a cluster forming threshold (34). The correlation between the GMV and the IAT score was assessed using permutation-based non-parametric testing with 5,000 random permutations. The statistical threshold for significance was defined at $P < 0.01$. For clarifying whether the duration of online game playing affected the correlation between the GMV and the IAT, Voxel-wise multiple regression analysis was conducted again when adding the total time of playing online game as a nuisance covariate.

[1]http://dbm.neuro.uni-jena.de/vbm/.

[2]http://www.fil.ion.ucl.ac.uk/spm/software/spm8.

[3]http://www.fmrib.ox.ac.uk/fsl/index.html.

Clusters with correlation between the GMV and the IAT score were defined as regions of interest (ROIs), and the average GMV within each ROI was extracted. ROI-based correlation analysis was conducted between the average GMV and the IAT score after controlling for the age and years of education. Then, all of the participants were divided into two subgroups, the high IAT score group (IAT score >50, $N = 30$) and the low IAT score group (IAT score ≤50, $N = 37$). The difference in the GMV between the two subgroups was tested by General Linear Model analysis, controlling for the age and years of education. The significance levels were both set at $P < 0.05$.

RESULTS

Participants had a median score of 46 on the IAT which was used to assess the IGD tendency. Subjects spent average 5.5 h/day on playing online games and lasted for average 56 months. The clinical and demographic characteristics are listed in **Table 1**.

Voxel-wise correlation analysis revealed that the GMVs of the bilateral postcentral gyri (postCG), the bilateral precentral gyri (preCG), the right precuneus, the left posterior midcingulate cortex (pMCC), the left inferior parietal lobe (IPL), and the right middle frontal gyrus (MFG) were significantly correlated to the IAT score (**Figure 1**; **Table 2**). **Figure 2** shows the ROI-based correlations between the GMV and the IAT score. After the total time of playing online game was added as a nuisance covariate, the correlation still existed between the IAT and the GMV of the bilateral postCG, the left preCG, the left pMCC, and the right MFG (**Figure 3**; **Table 3**).

As seen in **Table 4**, when the participants were divided into the two subgroups according to the IAT score, the subgroup with high IAT score (IAT score >50) had lower GMV in the seven of eight regions compared with the subgroup with low IAT score group (IAT score ≤50) ($P < 0.05$).

DISCUSSION

In the present study, the association between the GMV and IGD tendency was evaluated within the whole brain in adolescent online game players. After controlling for the effect of the total time of playing online game, the GMVs of the bilateral postCG, the left preCG, the left pMCC, and the right MFG were still

TABLE 1 | Participant's characteristics.

Item	Mean ± SD/median (range)
Age (years)	15.54 ± 0.14
Education (years)	9.40 ± 0.18
IQ	47.89 ± 0.76
Time of playing online game per day (hours)	5.47 ± 4.72
Duration of playing online game (month)	55.97 ± 31.71
Total time of playing online game (hours)	5760 (240–37,260)[a]
IAT score	46 (22–92)[a]
SAS	39.64 ± 7.61
SDS	44.81 ± 10.28

IAT, Internet addiction test; IQ, intelligence quotient; SAS, self-rating anxiety scale; SDS, self-rating depression scale.

[a]The variables present with non-normal distribution.

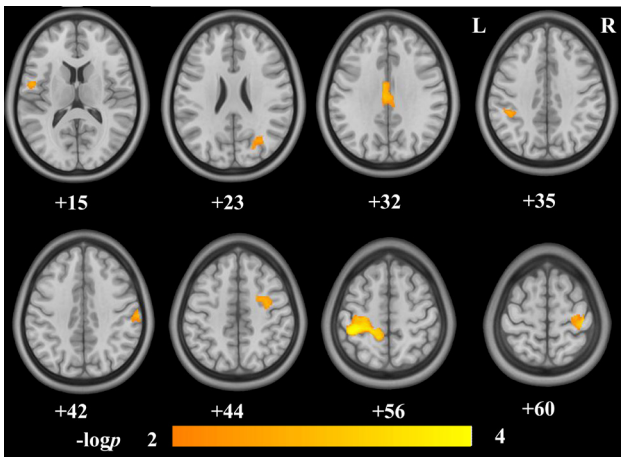

FIGURE 1 | Brain regions showing negative structural correlates to Internet addiction test (IAT) score in adolescent online game players. The IAT score was negatively correlated to the gray-matter volumes (GMVs) of the bilateral postcentral gyri, the bilateral precentral gyri, the right precuneus, the left posterior mid cingulate cortex, the left inferior parietal lobule, and the right middle frontal gyrus. The numbers below the images are the Montreal Neurological Institute coordinates at *z*-axis. The colorbar represents the –log *p*.

TABLE 2 | Brain regions showed structural correlates to Internet addiction test (IAT) score.

Region	Peak MNI coordinates			*P*-value	Cluster size (voxels)
	X	*Y*	*Z*		
L_PreCG	–51	–3	15	0.0055	302
R_PreCG/PostCG	42	–25.5	60	0.0026	619
L_PreCG/PostCG	–40.5	–37.5	55.5	0.0002	4898
R_PostCG	63	–21	42	0.0044	262
R_Precuneus	30	–67.5	22.5	0.0053	502
L_pMCC	–4.5	–18	31.5	0.0040	555
L_IPL	–39	–39	34.5	0.0047	192
R_MFG	28.5	–3	43.5	0.0053	475

IPL, inferior parietal lobule; MFG, mid frontal gyrus; MNI, Montreal Neurological Institute; PreCG, precentral gyrus; PostCG, postcentral gyrus; pMCC, posterior mid-cingulate cortex; L, left; R, right.

negatively correlated to the IGD tendency. The adolescents with lower GMV in the brain regions related to sensorimotor process and cognitive control had higher IGD tendency.

It was consistent with the hypothesis that the GMV in MFG, as a part of prefrontal cortex involved in cognitive controls (35, 36), was negatively correlated with the IGD tendency. Structural and functional abnormalities were widely reported in individuals with IGD (37–40). For example, less activation in the prefrontal cortex was found in the IA (40). Previous studies demonstrated the lower GM density and GMV in the prefrontal cortex in the IGD individuals (37, 39). Smaller amplitude of low-frequency fluctuation within the right MFG was also revealed in the IGD individuals (41). Abnormal activation in the prefrontal cortex was also found in drug-addicted individuals such as the marijuana users and the abstinent cocaine abusers (42–44). Similar changes in functional connectivity of the prefrontal cortex were revealed in the individuals with alcohol dependence and the individuals with IGD (45, 46). These studies demonstrated that the structural or functional condition of prefrontal cortex was associated with the addiction. In this study, the GMV of the right MFG was negatively correlated to the IAT score, and was lower in the high IAT score subgroup than that in the low IAT score subgroup. Structural abnormality in the right MFG might lead to the impairment of cognitive control in online game players. As a result, the online game players could not control their problematic online game playing and exhibited a higher tendency to the IGD.

Incongruent with the hypothesis, we did not find the GMV of the ventral striatum correlating with the IAT score. The ventral striatum is a critical region related to the addiction, and usually presents abnormal activation in individuals with addiction (26, 27). In our study, we focused on adolescent online game players but not only the IGD individuals, which might be a possible explanation to the negative result of ventral striatum. However, this negative result should be verified in the future study with large sample size.

Unexpectedly, the preCG, postCG, and the pMCC involved in the sensorimotor process showed negative correlations with the IAT score. The preCG played a major role in the motor planning and conducting (47). Adolescence is a critical period of neural development, and is prone to be affected by the environmental factors. Previous studies demonstrated that the alcohol and drug use might change the GMV in the developing brain of adolescents (48). A study showed longer use of the methamphetamine was associated with the GMV reduction in the preCG (49). In our study, the GMV of preCG was lower in the high IAT score subgroup than that in the low IAT score subgroup. Considering prevention and suppression of the action is conceptually associated with the primary motor cortex (50), the decreased GMV of preCG might be related to the IGD tendency. The postCG consists of the primary sensory cortex and is involved in integrating sensory information (24). The negative correlation between the GMV of the postCG and the IAT score means the lower GMV of this region in individuals with higher IAT score. Abnormal function connectivity of the postCG was found in adolescents with IGD (51). The decreased GMV and cortical thickness of the postCG were also revealed, respectively, in heroin users (52) and adolescents with online gaming addiction (53). The impaired postCG may lead to abnormality in receiving, processing, and integrating body-relevant signals and may fail to guide ongoing behavior related to arousal, attention, stress, reward, and conditioning, and finally associated with the addiction (54). In this study, negative structural correlations to the IAT score were also found in the left pMCC. The pMCC exhibits extensive functional connectivity with brain regions involved in the sensorimotor network (55, 56) and has important role in processing sensorimotor integration and motor control (57). The sensorimotor areas not only control the basic aspects of movement but can also shape human behavior (58). The functional properties of sensorimotor network may be relevant for automatized/compulsive behaviors in addiction (59). Sensorimotor cortex impairments were also reported in individuals with cocaine addiction (60, 61) and alcohol ingestion (62). Taken together, the reduction of the GMVs within the preCG, postCG, and the pMCC might have association with the

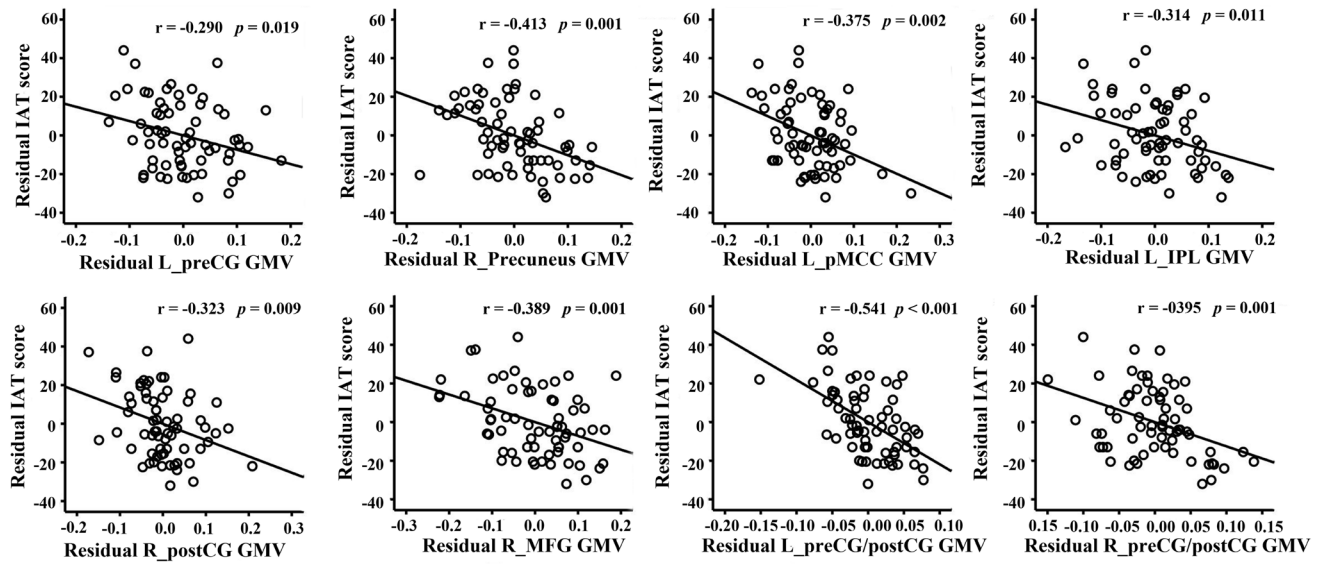

FIGURE 2 | Regions-of-interest (ROI)-based correlation analysis between the gray-matter volume (GMV) and the Internet addiction test (IAT) score. The residual was used because the age and years of education were controlled during correlation analysis.

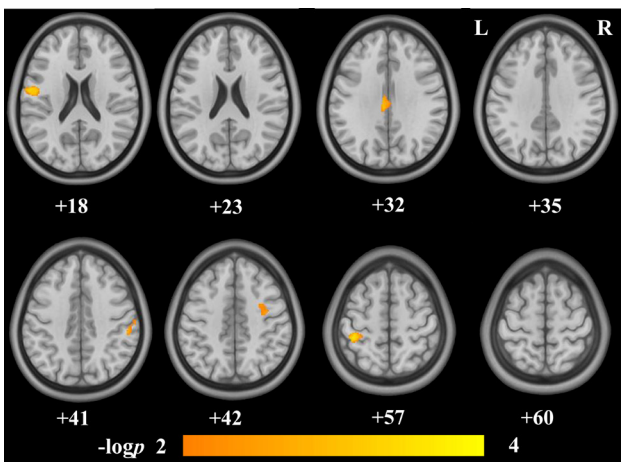

FIGURE 3 | Brain regions showing negative structural correlates to Internet addiction test (IAT) score in adolescent online game players after controlling for the total time of playing online game. The IAT score was negatively correlated to the gray-matter volumes (GMVs) of the bilateral postcentral gyri, the left precentral gyrus, the left posterior mid cingulate cortex, and the right middle frontal gyrus. The numbers below the images are the Montreal Neurological Institute coordinates at *z*-axis. The colorbar represents the −log *p*.

TABLE 3 | Regions showed structural correlates to Internet addiction test (IAT) score after controlling for the total time of playing online game.

Region	Peak MNI coordinates			*P*-value	Cluster size (voxels)
	X	*Y*	*Z*		
L_PreCG	−49.5	−7.5	18	0.0032	1,116
L_ PreCG/PostCG	−40.5	−37.5	57	0.0020	284
R_PostCG	54	−30	40.5	0.0055	159
L_pMCC	−6	−24	31.5	0.0049	222
R_MFG	34.5	−7.5	42	0.0063	173

MFG, mid frontal gyrus; MNI, Montreal Neurological Institute; PreCG, precentral gyrus; PostCG, postcentral gyrus; pMCC, posterior midcingulate cortex; L, left; R, right.

TABLE 4 | Regions-of-interest (ROI)-based comparisons of the gray-matter volume (GMV) between the two subgroups.

ROIs	High IAT score subgroup (*N* = 30)	Low IAT score subgroup (*N* = 37)	*T*	*P*
L_PreCG	0.465 ± 0.071	0.487 ± 0.067	−1.285	0.203
R_PreCG/PostCG	0.433 ± 0.046	0.462 ± 0.059	−2.229	0.029
L_ PreCG/PostCG	0.464 ± 0.044	0.507 ± 0.033	−4.604	<0.001
R_PostCG	0.524 ± 0.058	0.566 ± 0.071	−2.62	0.011
R_Precuneus	0.457 ± 0.071	0.506 ± 0.067	−2.882	0.005
L_pMCC	0.614 ± 0.062	0.649 ± 0.067	−2.148	0.035
L_IPL	0.496 ± 0.069	0.546 ± 0.066	−3.015	0.004
R_MFG	0.544 ± 0.103	0.620 ± 0.074	−3.50	0.001

IPL, inferior parietal lobule; MFG, mid frontal gyrus; PreCG, precentral gyrus; PostCG, postcentral gyrus; pMCC, posterior mid cingulate cortex; L, left; R, right.

abnormalities of the sensorimotor network, and further associated with the IGD tendency.

In the present study, the negative correlations between the IAT score and the GMVs of the right preCG/postCG, the left IPL, and the right precuneus disappeared after controlling for the effect of the total time of playing online game. The preCG/postCG was involved in sensorimotor process (63); the IPL and the right precuneus were closely related to the visual and intentional processing (64–66). Gaming process requires players to pay full attention to the tiny change in the screen for a long time then injures their visual ability (65), which might have a relationship with the GMV reduction in the visual attention-related regions. Previous studies demonstrated decreased GMV of precuneus (8) and decreased cortical thickness of the IPL (53) in the individuals with online game addiction. Our results indicated that the GMV reduction in some brain regions related to the visual attention and

sensorimotor process was influenced by the total time of playing online game, namely had a cumulative effect of playing online game.

Several limitations should be noted in our study. First, although some correlations were revealed between the brain GMV and IAT score, the causality cannot be clarified in this correlation analysis. The observed lower GMV in the adolescents with higher IAT score may be a result of excessive online game playing or a preexisting condition which is sensitive to IGD. Second, the IAT is a subjective questionnaire and more objective methods for evaluating the tendency to IGD are needed. Third, the total time of playing online games was just a probable measure and might be not accurate enough. Fourth, we could not rule out the effect of game genre on the results, which should be considered in the future study. Finally, only male adolescents were recruited in our study. Therefore, the present findings are restricted to male adolescent online game players.

CONCLUSION

In this study, the structural correlation to the IGD tendency was investigated in a group of adolescent online game players. The GMV of brain regions related to the sensorimotor process and cognitive control were found to be associated with the IAT score. The lower GMV of the regions related to sensorimotor process and cognitive control might attribute to the high IGD tendency, which might lead to new targets for preventing and treating the IGD in adolescents.

ETHICS STATEMENT

The present study was approved by the Ethical Committee of Tianjin Medical University General Hospital, and all of the participants and their guardians provided written informed consent according to institutional guidelines.

AUTHOR CONTRIBUTIONS

NP, YY, XL, and QZ designed research. XQ, XD, GD, YZ, and QZ performed research. YY was involved in the clinical assessment. NP, YZ, GD, and QZ analyzed data. NP, YZ, XL, YY, and QZ wrote the paper.

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The 2D:4D Marker and Different Forms of Internet Use Disorder

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Internet use disorder (IUD) presents a growing problem worldwide. Among others, it manifests in loss of control over Internet usage and social problems due to problematic Internet use. Although IUD currently is not an official diagnosis in DSM-5 or ICD-10, mounting evidence suggests that IUD indeed could be categorized as a behavioral addiction. On a systemic neuroscientific level, IUD is well characterized and dysfunctions in the fronto-striatal-limbic loop have been observed in persons being afflicted with IUD. On a molecular level underlying these neural dysfunctions less is known. Therefore, the present research investigates the influence of prenatal testosterone as measured *via* the 2D:4D marker of the hand on IUD. Testosterone represents an interesting hormonal marker, because sex differences in IUD have been observed, e.g., males show higher tendencies toward Internet gaming disorder (IGD) or females toward overusage of online social networks (both compared to the contrary sex). In $N = 217$ participants associations between the 2D:4D marker of the hand and both unspecified IUD and specific forms of IUD were investigated. It appeared that more female hands (right side; characterized by higher digit ratio of the index to the ring finger, i.e., >1, meaning lower prenatal testosterone) were associated with lower IGD ($rho = -0.17$, $p = 0.01$, $N = 211$). This effect was driven by the facet of loss of control of Internet Gaming in the whole sample ($rho = -0.20$, $p < 0.01$, $N = 211$) and the female subsample ($rho = -0.20$, $p = 0.02$, $N(f) = 137$). Aside from this, a negative association appeared between the facet of loss of control of generalized IUD and the right digit ratio in males underlining earlier work. In sum, the present work demonstrates that the 2D:4D marker is an interesting marker for Internet addiction and can be easily included as a biomarker to understand the biological underpinnings of Internet (over-)usage.

Keywords: 2D:4D marker, digit ratio, androgen, prenatal testosterone, Internet addiction, problematic Internet use, Internet gaming disorder, Internet use disorder

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INTRODUCTION

Currently, about 3.75 billion users of the world population are online.[1] Being online provides users with manifold opportunities to stay in touch with people over long-distance, communicate easily and find information quickly as long as a smartphone/Internet signal is available. Despite these positive effects of growing digital worlds, more and more researcher worldwide discuss if excessive use of

[1] http://www.internetlivestats.com (accessed on 14th of October 2017).

digital channels might reflect addictive behavior [see review by Ko et al. (1); see compendium by Montag and Reuter (2)].

Different terms have been suggested to describe excessive online usage including *compulsive Internet use*, *problematic Internet use*, *Internet addiction*, and due to recent advances in DSM-5 also *Internet use disorder* (IUD). IUD was coined in line with the inclusion of the term Internet gaming disorder (IGD) in DSM-5 in its appendix (3, 4). IUD can be described by symptoms such as loss of control over one's own Internet usage, problems in private and business life due to excessive use, withdrawal symptoms when not being online and development of tolerance, to name a few. Although researchers need to be careful not to overpathologize everyday life (5), mounting evidence suggests that digital overusage in its extreme forms indeed could pose dramatic problems as also underlined by some drastic news reports from Asia [including death cases; e.g., see Ref. (6)]. Prevalence rates of IUD vary across the world with Asian countries (7) being more afflicted than Western countries. In Germany, about 1% of the population is addicted to the Internet according to representative numbers from the PINTA study (8).

The last years have seen a vivid scientific discussion on the nature of IUD (2), in particular also if there exists a generalized IUD, which needs to be contrasted with specific forms of IUD (9). Generalized IUD[2] refers to general overusage of many online channels and spending too much time in digital worlds, whereas specific forms of IUD rather exclusively describe persons who overuse one online-channel such as shopping, gaming, pornography, gambling, and social networks (hence online communication). With the diversity of available online channels also the prevalence of IUD in males and females changed. Whereas in the early years of the Internet, Internet usage, and related addictive behavior was more associated with being male, things have dramatically changed in the last years. Whereas online shopping (10) and online social networking channels (11) are more associated with being female, overusage of platforms being related to pornography (12), Internet gaming (13), or online gambling (14) are more a domain of males.

Internet use disorder has been characterized well on a systemic neuroscientific level with dysfunctions of the fronto-striatal-limbic loop as also seen in other forms of substance-dependent addictive-behavior (15, 16). On a molecular level, much less is known. Clearly, the molecule dopamine represents an important transmitter system in the brain to explain craving for online content, when a person afflicted is confronted with a relevant online cue. This mirrors in striatal (over-)activity in fMRI setup, e.g., when online gamers are confronted with stills from the favorite game in a brain scanner (17). It is well known that the striatal region occupies a high number of D_2 receptors [e.g., Ref. (18)]. Persons suffering from IUD have been associated with lower D_2 receptors (19, 20), something also observed in alcoholics (21, 22). Aside from dopamine, also the transmitter systems of serotonin (23) and acetylcholine (24) have been implicated in playing a role for IUD.

[2]In the following, we speak of *unspecified* instead of generalized IUD, because a person filling in a measure for generalized IUD might implicitly think about his/her most prevalent online channel(s).

One of the most recent models to understand specific forms of IUD represents the I-PACE model of Brand et al. (3) targeting the interaction of person, affect, cognition, and execution variables to understand IUD. This model explicitly states among the person variables *biology* to play an important role to understand the genesis and maintenance of specific types of IUD. This has been also underlined by heritability estimates derived from twin studies in the last years [e.g., Ref. (25, 26)]. A roadmap to study the molecular basis of IUD was missing until recently. To close this gap, Montag et al. (27) published an affective neuroscience framework. In this context, an easy and rather obvious candidate to understand IUD might be the steroid hormone testosterone (before testing the many candidates as proposed in Montag's model). Given the often-observed sex-dimorphism in the different forms of IUD as presented above, sex steroids might be crucial to understand individual differences in IUD from the perspective of a molecular psychologist.

An easy way to assess biological marker giving insights into prenatal testosterone represents the 2D:4D marker of the hand [see overview in Ref. (28)]. Prenatal sex steroids, such as its well-known representative testosterone, regulate brain structure and function (29) as well as finger growth during embryogenesis [again see, Ref. (28)]. The 2D:4D marker is assessed via measuring the length of the index (second digit—2D) to the length of the ring finger (fourth digit—4D; see also Section "Materials and Methods"). It has been demonstrated that female hands are usually characterized by higher digit ratios (hence longer index to ring finger) compared to male hands (characterized by lower digit ratios—hence longer ring compared to index finger). This effect is in particular pronounced for the right hand (30), although it is still not clear why this is the case. Moreover, and of importance to note, also males with more female hands, and females with more male hands can be observed in the population. The 2nd to 4th finger ratio is stable over life [Manning et al. (31); see also evidence from fetal development by Malas et al. (32)]. Different lines of arguments have been put forward to understand why the digit ratio of the hand indeed could represent an indirect marker for the prenatal (but not actual) testosterone level (33). Among these are direct links between the 2D:4D ratio to prenatal testosterone levels, but most pronounced in its link to prenatal testosterone to estradiol ratios (34). In addition, evidence comes from molecular genetic association studies linking a polymorphism of the androgen receptor gene to individual differences in the 2D:4D ratio (35). For more details, see Manning (28).

The 2D:4D marker has been investigated in the realm of many different research areas, in particular those where a sex-dimorphism can be observed (such as that more males than females are affiliated with a certain condition and vice versa). As examples, lower 2D:4D ratios have been associated with autism (36, 37), and higher 2D:4D ratios associate with schizophrenia (38); see also links with schizotypal personality traits as presented by Zhu et al. (39). The 2D:4D marker has been investigated in the context of stuttering (40) and further relationships between the 2D:4D marker and psychological/behavioral phenotypes were identified, such as lower 2D:4D finger ratios account for reproduction success and dominance (41), number of life-time sexual partners (42) and neuroticism

(43, 44) as well as cooperativeness whereas aggression appeals lead to more pro-social behavior for high 2D:4D ratios (45, 46). Smaller index-to-ring-finger ratios (hence more male hands) have also been linked to personal qualities and characteristics such as athletic performance (47, 48), spatial abilities (49–52), abstract reasoning (53), and numeric abilities (54–56).

Recently, the 2D:4D ratio of the hand was also investigated in the context of IUD. Lower 2D:4D values of the right hand (which means more typical male hands with longer ring finger compared to index finger) in males were associated with unspecified IUD (57), an effect potentially driven by a specific form of IUD—namely IGD—which was not assessed in this work [only the 20 item Internet Addiction Test (IAT) was administered]. In line with this idea, Kornhuber et al. (58) demonstrated lower 2D:4D ratio values in young males diagnosed with video game addiction, compared to healthy controls. Deriving from these first results, higher prenatal testosterone could represent a vulnerability factor to develop IUD, in particular in males.

As these first works did not address potential associations between 2D:4D and the manifold specific forms of IUD, we aimed with the present research to answer several questions. First of all, we aimed at the replication of the finding that lower digit ratios would predict higher tendencies toward IGD, in particular in males (but perhaps also females). Finally, with this study, it is the first time that data on possible associations between other specific forms of IUD and the digit ratio are presented. For IUD in the realm of online activities being more visible in females (shopping, social networking), we expected more female hands (hence higher digit ratios), for the remaining online channels (pornography, gambling), we expected higher tendencies toward IUD being more associated with more male hands (lower 2D:4D ratio). As Montag et al. (59) demonstrated that Internet communication disorder (ICD) highly overlaps with generalized/unspecified IUD, we aimed with the present sample to revisit the question how different forms of IUD are linked to each other. Given that this earlier work could not address the question if such associations are independent of gender, we present this kind of data in the supplement for further studies.

MATERIALS AND METHODS

Participants and Sociodemographic Characteristics

For this study, we used data collected from November 2016 till May 2017 of $N = 217$ participants from the Ulm Gene Brain Behavior Project (UGBBP). The mean age of our sample was M = 23.41 years (SD = 7.77) and consisted of 77 men and 140 women. Most of them (83.9%) were students (182). A total of 204 participants had German (94.0%) as a mother tongue including bilingually grown up participants; however, the remainder of the participants could understand and use the German language. Overall, 76.5% (166) of the participants were qualified for university (German "Abitur"), seven had a baccalaureate ("Fachabitur"), 15 participants finished the 10th grade on a German secondary school ("mittlere Reife") and one finished the German "Hauptschule," i.e., completed high school. A 1st university degree including one polytechnic degree was held by 27 participants and one holds an advanced technical college certificate. Regarding handedness, 91.7% were right-, 6.9% left-handed and 1.4% stated to use both hands equally. All participants filled in the questionnaires described in the next section and provided a scan of the left and right hand. The study was approved by the local ethic committee of Ulm University, Germany.

Questionnaires

Short Version of Internet Addiction Test (s-IAT)

We collected data on unspecified IA tendencies with the German s-IAT based on the original test by Young (60). The s-IAT consists of two factors, namely loss of control/time management (LoCTM) and craving/social problems (CSP) with six items for each factor (61). All items can be answered on a 5-point-likert scale (1 = "never," 2 = "rarely," 3 = "sometimes," 4 = "often," and 5 = "very often") with a possible range from 12 to 60. Scores above 30 until 37 ($30 < \text{s-IAT} \leq 37$) indicating a slightly increased (problematic) Internet use. Scores over 37 are considered as pathological Internet use. Cronbach's alpha for the complete questionnaire was $\alpha = 0.85$ (LoCTM: $\alpha_{LoCTM} = 0.79$, CSP: $\alpha_{CSP} = 0.74$).

s-IAT Scales

The s-IAT represents five specific problematic Internet use categories—online computer gaming (A1), online gambling (A2), compulsive online buying (A3), online pornography (A4), online social networking (A5). Each category consists out of four items whereas two items each are used to collect data for the factors LoCTM and CSP, respectively. Items to gather information on LoCTM where phrased as follows: "How often do you find that you spend more time with (e.g., online gaming) than you intended?" and "How often do you neglect household chores to spend more time with (e.g., online gaming)?" The following items were used to retrieve information on CSP: "How often do you feel preoccupied with the (e.g., online gaming) when offline, or fantasize about (e.g., online gaming)?" and "How often do you choose to spend more time with (e.g., online gaming) over going out with others?" A 5-point-likert scale (same as in the s-IAT) was used. Cronbach's alpha for these five scales each consisiting of four anchor items showed the following reliabilities: $\alpha_{A1} = 0.87$, $\alpha_{A2} = 0.64$, $\alpha_{A3} = 0.77$, $\alpha_{A4} = 0.83$, $\alpha_{A5} = 0.79$.

2D:4D Ratios

To determine 2D:4D ratios, we used scans of both hands. The length of the fingers was measured in pixels (scan resolution 300–400 dpi) starting at the middle of the closest crease to the palm to the fingertip. The measurement was conducted with the graphical software GIMP version 2.8.14.[3] The 2D:4D ratio was obtained by dividing the length of the index finger by the length of the ring finger. All 2D:4D measurements were executed by two independent raters and then averaged. The reliability of the two raters was high: The interclass correlation coefficients (ICC) with absolute agreement definition of 2D:4D quotients was $ICC(\text{left}) = 0.97$ and $ICC(\text{right}) = 0.96$. Correlations between the 2D:4D values

[3] http://www.gimp.org.

of the two raters were r(left) = 0.93 and r(right) = 0.93 (both at $p < 0.01$).

Statistical Analysis

Statistical analyses were executed with the SPSS version 24.0.0.1 for MAC. Non-parametric testing was applied due to the not normally distributed variables age, s-IAT, and the s-IAT scales. The data of both left and right 2D:4D hand ratios were normally distributed. To identify potential differences between these groups, an independent sample t-test was used. We conducted a Mann–Whitney U test to check for differences in Internet related variables depending on gender. Spearman correlations were applied to analyze associations between age, Internet variables, and finger ratios.

Data Cleaning

Since a broken or injured finger can lead to length variations with tremendous influences on the 2D:4D ratio, the following participants were excluded from the sample.

Six participants reported a broken index finger (4 left, 2 right) and seven a broken ring finger (4 left, 3 right). Furthermore, a total of 24 participants reported no information concerning broken fingers that is why we inspected the scans of their hands visually. Since no abnormalities were found, these participants remained in the sample. Moreover, the left index finger of one participants was extremely short (2D:4D ratio = 0.81; 4.9 SD away from mean). Since we did not have any further information rendering a reasonable explanation for this fact, we decided to exclude this participant (only the left hand) from the sample. Consequently, data of $N_L = 208$ left 2D:4D ratios and $N_R = 212$ right 2D:4D ratios could be used for the analyses. Additionally, one participant did not give information on the s-IAT scale online gaming, which leads to a sample size reduced by 1 for analyses including the specific IA factor online gaming. Moreover, another participant gave no information for the 3rd item of online shopping that is why N is reduced by 1 in some tables.

RESULTS

Descriptive Statistics and Inferential Statistics for Age, Gender, and Questionnaire Data/Ratios

The means (M) and SD for all questionnaire measures and 2D:4D ratios are presented in **Table 1**. As depicted in **Table 2**, we observed higher digit ratios in the right hand in females compared to males [$t(212) = -2.34$, $p = 0.02$]. Gender also influenced several IUD scores (see again **Table 1**). Among these are higher scores for males compared to females in online gaming ($U = 2{,}790$, $p < 0.01$), online gambling addiction ($U = 4{,}693$, $p < 0.01$) and in online pornography addiction ($U = 2{,}010$, $p < 0.01$). For online communication addiction, females showed higher scores than males ($U = 4{,}397$, $p = 0.02$). No significant differences were found for s-IAT scores and online shopping addiction.

Our results show that age is partially correlated with both right hand ratios and online gaming behavior in females, but not in males. Noteworthy, evidence from literature shows, that 2D:4D markers are stable over life (please see introduction). Nevertheless, we assume that age could be a nuisance variable that might affect some of the following analysis (all correlations are depicted in the Table S2 in Supplementary Material).

Relationship between Specific Forms of IUD and Unspecified IUD Including Gender Effects

A correlation matrix of all IUD scales shows several significant correlations (Table S4 in Supplementary Material). Of note and in line with an earlier study by Montag et al. (59), the highest and most robust association could be observed between ICD (A5) and general s-IAT score ($rho = 0.40$; $p < 0.01$). The second highest associations could be observed between both Internet Pornography Disorder (IPD, A4) ($rho = 0.31$; $p < 0.01$) and IGD (A1) correlated with unspecified IUD ($rho = 0.30$; $p < 0.01$). Going beyond these findings, it is noticeable that general s-IAT values correlated highest with IGD (A1) in males ($rho_{m,A1} = 0.52$, $p < 0.01$) and with ICD (A5) in females ($rho_{f,A5} = 0.48$, $p < 0.01$). Therefore, we consider gender as an important variable to get more detailed information about these associations. Please note, that the trend-results remained unchanged when using partialized correlations controlling for age. Only in males, Internet Shopping Disorder (ISD, A3) ($r = 0.39$, $p < 0.01$) correlated significantly and higher than in usual bivariate correlations with general s-IAT (Table S5 in Supplementary Material).

2D:4D Ratios in Reference to Unspecified IUD (s-IAT) Online Gaming (A1), Online Gambling (A2), and Online Pornography (A4) in Left/Right Hands

We found an inverse association between the finger ratios in right male hands and the sub-facet LoCTM of the s-IAT ($rho_R = -0.24$, $p = 0.04$, $N_{R,m} = 74$) and a negative correlation independent of gender between the 2D:4D ratio of the right hand and IGD (A1) ($rho_R = -0.17$, $p = 0.01$, $N = 211$). The effect is driven by the facet of loss of control of Internet Gaming in the whole sample ($rho = -0.20$, $p < 0.01$, $N = 211$) and the sub-facet LoCTM in the female sample [rho_R(LoCTM) = −0.20, $p = 0.02$, $N = 137$]. For online gambling, we discovered a negative association ($rho_R = -0.17$, $p = 0.01$, $N = 212$) driven by the sub-facet CSP in the female sample ($rho_R = -0.17$, $p = 0.05$, $N = 138$).

IPD in the entire sample also negatively associates to right hand finger ratios ($rho_R = -0.16$, $p = 0.02$, $N = 212$, A4) triggered by both sub-facets (rho_R(LoCTM) = −0.15, $p = 0.03$, $N_{R,m} = 212$, rho_R(CSR) = −0.15, $p = 0.03$, $N_{R,m} = 212$) but could not be found in male or female subsamples. No significant associations for the left hand could be observed (further results are depicted in **Table 3**). Please note that we do not control for age in the presented analysis, because IGD was not associated with age in the complete sample.

The right 2D:4D ratio of females was inversely correlated with IGD symptoms in the aforementioned sub-facet [rho_R(LoCTM) = −0.20, $p = 0.02$, $N = 137$]. LoCTM was not associated with age on the right-hand side. For online gambling, the sub-facet CSP is

TABLE 1 | Descriptive statistics of age and Internet variable data for the entire sample and split by gender.

	Entire sample *N* = 217						Females *N(f)* = 140		Males *N(m)* = 77	
Variables	**M (all)**	**SD (all)**	**SEM**	**Min**	**Max**	**Skew**	**M (f)**	**SD (f)**	**M (m)**	**SD (m)**
Age	23.41	7.77	0.53	16	63	3.54	22.59	6.73	24.91	9.23
s-IAT	24.88	6.73	0.46	12	57	0.97	24.39	6.31	25.77	7.41
s-IAT$_{LoCTM}$	15.20	4.44	0.30	6	30	0.36	15.11	4.41	15.36	4.51
s-IAT$_{CSP}$	9.67	3.02	0.21	6	27	1.77	9.27	2.50	10.40	3.70
Cut-off score for problematic Internet use according to Pawlikowski et al. (61): s-IAT > 30 with *N* = 38, *N(f)* = 24, *N(m)* = 14										
s-IAT (>30)	35.26	5.54	0.90	31	57	2.35	34.13	3.83	37.21	7.42
s-IAT$_{LoCTM}$ (>30)	21.55	2.85	0.46	16	30	0.59	21.88	1.94	21.00	4.00
s-IAT$_{CSP}$ (>30)	13.71	3.83	0.62	8	27	1.35	12.25	2.71	16.21	4.26
Cut-off score for unproblematic Internet use according to Pawlikowski et al. (61): s-IAT ≤ 30 with *N* = 179, *N(f)* = 116, *N(m)* = 63										
s-IAT (≤30)	22.67	4.55	0.34	12	30	−0.15	22.37	4.61	23.22	4.42
s-IAT$_{LoCTM}$ (≤30)	13.85	3.43	0.26	6	21	−0.05	13.72	3.36	14.11	3.58
s-IAT$_{CSP}$ (≤30)	8.82	1.95	0.15	6	14	0.42	8.66	1.96	9.11	1.92
Scales A1–A5 assessing different forms of Internet use disorder: *N* = 217, *N(f)* = 140, *N(m)* = 77										
A1 s-IAT[a]	5.44	2.60	0.18	4	17	2.28	4.75	1.58	6.97	3.38
A1 s-IAT$_{LoCTM}$[a]	2.85	1.52	0.10	2	10	2.23	2.40	0.88	3.66	2.03
A1 s-IAT$_{CSP}$[a]	2.69	1.25	0.09	2	9	2.35	2.35	0.83	3.31	1.59
A2 s-IAT	4.09	0.40	0.03	4	8	6.18	4.01	0.12	4.22	0.64
A2 s-IAT$_{LoCTM}$	2.03	0.20	0.01	2	4	6.93	2	0	2.09	0.33
A2 s-IAT$_{CSP}$	2.06	0.25	0.02	2	4	4.80	2.01	0.12	2.13	0.38
A3 s-IAT[b]	5.91	2.34	0.16	4	16	1.68	6.06	2.39	5.62	2.23
A3 s-IAT$_{LoCTM}$[b]	3.15	1.49	0.10	2	9	1.49	3.29	1.59	2.91	1.28
A3 s-IAT$_{CSP}$	2.75	1.06	0.07	2	8	1.79	2.77	1.03	2.71	1.12
A4 s-IAT	5.33	2.22	0.15	4	20	2.47	4.42	1.01	6.97	2.81
A4 s-IAT$_{LoCTM}$	2.66	1.28	0.09	2	10	2.32	2.14	0.50	3.62	1.66
A4 s-IAT$_{CSP}$	2.66	1.07	0.07	2	10	2.48	2.29	0.63	3.35	1.35
A5 s-IAT	8.45	3.00	0.20	4	16	0.37	8.76	3.04	7.88	2.85
A5 s-IAT$_{LoCTM}$	4.73	1.90	0.13	2	10	0.39	4.90	1.91	4.43	1.85
A5 s-IAT$_{CSP}$	3.71	1.40	0.10	2	8	0.58	3.86	1.43	3.45	1.32

M, mean; SD; SEM; s-IAT, short version of the IAT; s-IAT > 30, problematic Internet use starts with values greater than 30 (61), sub-facets of s-IAT: LoCTM, loss of control/ time management; CSP, craving/social problems; s-IAT A1: online gaming; s-IAT A2: online gambling; s-IAT A3: online shopping; s-IAT A4: online pornography; s-IAT A5: online communication.

[a]N is reduced by 1 (one female participant missed to enter their 4 values for A1 online gaming), N = 216, N(f) = 139.

[b]N is reduced by 1 (one female participant missed to enter the 3rd item of the s-IAT A3 question set: online shopping, A3 s-IAT$_{CSP}$ remains unaffected), N = 216, N(f) = 139.

also associated with 2D:4D [$rho_R = rho_R(\mathrm{CSP}) = -0.17$, $p = 0.01$, $N = 138$]. Due to the significant association between age and craving for online gambling, we controlled for age (for further results, please refer to **Table 3** and Table S2 in Supplementary Material).

Given that none of the associations beyond unspecified IUD/ IGD were hypothesized (in terms of earlier existing works on 2D:4D and different forms of IUD), these results would not hold for multiple testing. Nevertheless, we present them for future research endeavors.

DISCUSSION

Before coming to the first hypothesis, we revisit the question if in particular female hands show higher digit ratios than male ones. We could find such a significant difference in the right hand of our participants, which is in line with what has been observed most robustly in the literature (30). To further check if our collected data set is valid in the context of the investigation of IUD data, we tested in the result section often observed gender differences on the unspecified IUD score and the specific IUD scores as summarized in the introduction. For IUD in the areas of gaming, gambling and pornography usage, we replicated the well-known findings that males show significant higher scores. In contrast, females showed significantly higher scores in ICD than males. For IUD in the area of online shopping, no significant differences could be observed, although descriptive statistics point toward the observed findings in the literature with higher scores in females toward males. In sum, the findings both with respect to the present 2D:4D ratios and IUD data are largely in line with what has been presented in the research field before and demonstrates the validity of our data.

2D:4D Ratios and Tendencies toward IGD

The main focus of our study was to revisit the association between lower 2D:4D markers and higher IGD tendencies as

TABLE 2 | Gender specific differences of hand ratios (*T*-test) and s-IAT scales (Mann–Whitney *U* Test).

2D:4D ratios	Females $N_L = 137$, $N_R = 138$		Males $N_L = 71$, $N_R = 74$		*T*-test	
	M	SD	M	SD	*T*-score	*p*
Left hands: $N_L = 208$, $df = 206$	0.98	0.03	0.97	0.03	−0.72	0.47
Right hands: $N_R = 212$, $df = 210$	**0.98**	0.03	**0.97**	0.03	**−2.34**	**0.02**
IUD-VAR: $N = 217$, $df = 215$	$N(f) = 140$ ($N(f) = 139$[a,b])		$N(m) = 77$		Mann–Whitney *U*	
	MR		MR		*U*	*p*
Generalized IUD: s-IAT	105.25		115.82		4,865	0.24
Online gaming: s-IAT A1[a]	**90.07**		**141.77**		**2,790**	**<0.01**
Online gambling: s-IAT A2	**104.02**		**118.05**		**4,693**	**<0.01**
Online shopping: s-IAT A3[b]	113.06		100.27		4,718	0.14
Online pornography: s-IAT A4	**84.86**		**152.90**		**2,010**	**<0.01**
Online communication: s-IAT A5	**116.10**		**96.10**		**4,397**	**0.02**

IUD-VAR, Internet use disorder variable; MR, mean rank; s-IAT A1 to s-IAT A5 scales.
[a]N is reduced by 1 (one female participant gave no information for online gaming).
[b]N is reduced by 1 (one female participant gave no information for the 3rd item of online shopping).
Significant findings are displayed in bold letters.

observed in the literature in males. The studies in the field by Kornhuber et al. (58) and Canan et al. (57) both observed lower 2D:4D ratios (hence higher prenatal testosterone levels) to be associated with higher tendencies toward IUD in males. To be more precise, Kornhuber et al. (58) linked lower 2D:4D ratios to higher video game addiction when contrasting $N = 27$ online gaming addicts with $N = 27$ healthy controls. They used the *CSAS II* measure for assessing and classifying video gaming addiction. The authors report that "CSAS II is based on the Internet Addiction Scale ISS-20, which has been extended and adapted to assess video game addiction" (p. 2). In Canan et al. (57), Young's 20 item IAT was administered to assess unspecified IUD. Furthermore, as the authors did not assess IUD tendencies in other specific online areas, nevertheless they asked for frequent online activities of the study's participants and split the IUD scores (testing generalized IUD) in subsamples according to the most frequented online channel of each user. For example, this resulted in N = 55 out of $N = 650/652$ persons who reported to frequently spent time online for gaming. The unspecified IUD scores for these 55 participants were then compared to the unspecified IUD scores of the subsample reporting social network use ($n = 315$) and streaming videos ($n = 206$) and others ($n = 74$). The resulting statistic in Canan et al. (57) underlined that the observed lower 2D:4D markers in males with higher unspecified IUD might be accountable for overusage in the online gaming niche.

Our study goes beyond the described published findings, because (a) we assessed IUD in five different specific domains

TABLE 3 | Correlations of left and right hand ratios with Internet addiction variables including gender effects (Spearman's *rho*).

	2D:4D LEFT hands			2D:4D RIGHT hands		
	Entire sample $N_L = 208$	Females $N(f)_L = 137$	Males $N(m)_L = 71$	Entire sample $N_R = 212$	Females $N(f)_R = 138$	Males $N(m)_R = 74$
s-IAT	−0.01	−0.02	0.01	−0.04	0.05	−0.19
s-IAT$_{LoCTM}$	−0.02	−0.03	−0.01	−0.05	0.05	**−0.24***
s-IAT$_{CSP}$	0.03	0.02	0.06	−0.01	0.02	−0.03
Online gaming: A1 s-IAT[a]	−0.10[a]	−0.11[a]	−0.06	**−0.17***,[a]	**−0.17***,[a]	−0.04
A1 s-IAT$_{LoCTM}$[a]	−0.10[a]	−0.15[a]	−0.01	**−0.20****,[a]	**−0.20***,[a]	−0.10
A1 s-IAT$_{CSP}$[a]	−0.07[a]	−0.05[a]	−0.06	−0.11[a]	−0.10[a]	0.02
Online gambling: A2 s-IAT	−0.11	−0.14	−0.07	**−0.17***	**−0.17***,[d]	−0.13
A2 s-IAT$_{LoCTM}$[c]	0.01	[c]n.a.	0.04	−0.09	[c]n.a.	−0.08
A2 s-IAT$_{CSP}$	−0.11	−0.14	−0.10	**−0.16***	**−0.17***,[d]	−0.13
Online shopping: A3 s-IAT[b]	0.07[b]	0.09[b]	−0.01	0.06[b]	0.12[b]	−0.16
A3 s-IAT$_{LoCTM}$[b]	0.11[b]	0.11[b]	0.07	0.09[b]	0.13[b]	−0.11
A3 s-IAT$_{CSP}$	0.00	0.03	−0.08	−0.01	0.04	−0.15
Online pornography: A4 s-IAT	−0.05	−0.08	0.08	**−0.16***	−0.11	−0.05
A4 s-IAT$_{LoCTM}$	−0.04	−0.11	0.05	**−0.15***	−0.15	−0.03
A4 s-IAT$_{CSP}$	−0.02	−0.05	0.13	**−0.15***	−0.11	−0.03
Online communication: A5 s-IAT	0.02	0.01	−0.01	−0.02	0.04	−0.20
A5 s-IAT$_{LoCTM}$	0.01	−0.02	0.04	−0.03	0.03	−0.20
A5 s-IAT$_{CSP}$	0.01	0.05	−0.08	−0.02	0.03	−0.18

Correlation (2-tailed) is significant at the 0.01 level (**), at the 0.05 level (*); sub-facets of s-IAT: LoCTM, loss of control/time management; CSP, craving/social problems; s-IAT A1 to s-IAT A5 scales.
[a]N is reduced by 1 (one female participant did not provide information for online gaming): for LEFT hands $N_L = 207$, $N(f)_L = 136$; for RIGHT hands $N_R = 211$, $N(f)_R = 137$.
[b]N is reduced by 1 (one female participant did not provide information for the 3rd item of online shopping, A3 s-IAT$_{CSP}$ remains unaffected): for LEFT hands $N_L = 207$, $N(f)_L = 136$; for RIGHT hands $N_R = 211$, $N(f)_R = 137$.
[c]All female participants chose the lowest value: M = 2, SD = 0.
[d]p = 0.05.
Significant findings are displayed in bold letters.

(gaming, gambling, shopping, pornography, communication) as well as unspecified IUD. Furthermore, and (b) the present work did not use a cut-off to search for subgroups of addicted or non-addicted persons. Instead we searched for continual associations between healthy and pathological usage of the Internet (and specific online channels) in the complete investigated sample of $N = 217$ participants. At first glance, our findings are in line with what has been observed in the works by Kornhuber et al. (58) and Canan et al. (57), namely that lower 2D:4D ratios of the right hand are associated with higher IGD. However, we also observed that this correlation was driven by female participants for the right hand and it could not be found in males. This is surprising, because earlier studies observed this effect exclusively in males.

In order to find an explanation for this occurrence, we compare our study's participants with those from the earlier published research. First of all, both of us, found the same associations with respect to the right digit hand ratios and IUD questionnaire. This speaks against the idea, that our sample would be somewhat different from what has been observed in the literature. The Kornhuber et al. study only investigated (video game addicted vs. healthy) males and naturally their sample is hard to compare with the participants from the present work. Canan et al. [(57), p. 32] report for their sample, that "Women were more likely to use the Internet for social networking and streaming videos than were men. Compared to women, a higher proportion of men reported Internet gaming as their most frequent Internet activity ($p < 0.001$)". In light of this, we believe that our samples do not strongly differ in these areas. Asides, we assessed addictive tendencies in the "Big Five of IUD" as mentioned above, whereas the Canan et al. (57) study only assessed in what areas the Internet usually is used (no addictive tendencies have been directly assessed here and the categories investigated only overlap in parts). Therefore, our studies are only comparable to a certain extent. Moreover, and of importance, the facet loss of control of generalized IUD was inversely associated with right 2D:4D ratios in the present male sample supporting the findings associating the digit ratio with generalized IUD as reported by Canan et al. (57) to some extent.

Our findings suggest that further reasons might be considered for not observing the association between digit ratios and IGD in males, but only females. First, the study by Canan et al. (57) has been conducted in Turkey. As our study stems from Germany, cultural differences could account for the present results. These factors might include differences in personality, where differences between Turkish and German samples have been observed (62). In this study, Western Europeans (including Germany) scored lower on agreeableness and conscientiousness compared to Middle Eastern countries (including Turkey). Such differences could influence associations as observed in the present work, because the 2D:4D marker has been also associated with personality (43, 44). In addition, our present study only included a relatively small group of males ($n = 77$ males vs. $n = 140$ females), because we recruited the present sample mainly in psychological classes. Therefore, our statistical power to detect the same effects for males as for females is smaller. In contrast to the power hypothesis, there is a low observed correlation between right hand digit ratio and IGD in the male group of participants in **Table 3**: $rho = -0.04$, $p = 0.72$, $N = 74$. In sum, the digit ratio of the right hand might not be exclusively linked to IGD in males (57, 58), but can be linked to IGD in females. Therefore, female participants being under stronger influence of prenatal testosterone (or prenatal testosterone to estradiol level) might also show more male online behavior in terms of IGD. Developing from the present results, future studies clearly should recruit females to investigate putative links between IGD and the digit ratio of the (right) hand. Again, we state that when assessing generalized IUD in our male participants, more similar findings can be observed to what has been reported by Canan et al. (57).

Beyond this, no further robust association could be observed with any other specific area of IUD. Note, that the associations between 2D:4D ratio and tendencies toward overusage of online gambling or pornography will not be further discussed, because they would not hold for multiple testing given the lack of set up á priori hypothesis (although we set up directed hypothesis, only empiricial evidence was existing on IGD/unspecified IUD and 2D:4D before our study). This underlines that prenatal testosterone might be exclusively linked to IGD/unspecified IUD but not to any other areas when assessing IUD in different contexts. Nevertheless, this statement might be revised, when other researchers also observe our associations between 2D:4D and gambling/pornography usage. It needs to be remembered that the present study investigated a largely healthy student sample population (and the scores on the IUD questionnaires where highly skewed toward the lower end of the distribution). In particular with the sex-dimorphisms observed in many areas of online usage, clinical samples might reveal different outcomes.

Revisiting the Question on the Link between Unspecified IUD and Specific Forms of IUD under Consideration of Gender

The last aim of our study was to revisit findings from an earlier study by Montag et al. (59) observing in six independent samples from diverse cultural background that ICD is most strongly linked with unspecified IUD. This earlier study could not consider gender as an independent variable (although assessed), because the samples differed strongly in gender ratios, e.g., one of the investigated samples only had 9 males and 66 females (Germany, paper-pencil sample) or other, more well distributed samples (23 males and 28 females; China, paper-pencil sample), were still too small to search for robust gender differences with respect to the IUD correlations. The only sample from this earlier study, in which such an association could have been examined stemming from China (online sample), but it was generally not in the realm of this earlier work given the many differences in the socio-demographics across all samples investigated. Therefore, we return to this question in the present work. For the complete sample, we could replicate the finding that tendencies toward ICD are most strongly associated with unspecified IUD ($r = 0.40^{**}$, see Table S5 in Supplementary Material). Splitting these results into a male and female subsample reveals that this association is

driven by the female subsample ($r = 0.50^{**}$), whereas in males it is weaker ($r = 0.29^{**}$). The second and third strongest association between specific forms and unspecified IUD was shopping ($r = 0.34^{**}$) and pornography ($r = 0.28^{**}$) in females. In males, significant associations occurred most prominently with gaming ($r = 0.57^{**}$), pornography ($r = 0.53^{**}$) and shopping ($r = 0.39^{**}$). Perhaps except for the pornography-unspecified IUD link, the associations are in line with the gender differences observed in the literature.

Our new data clearly show that association patterns between specific forms of IUD and unspecified IUD need to be investigated also in the context of males and females. This said, the general observed robust association between ICD and unspecified IUD by Montag et al. (59) is supported in the present finding. It needs to be mentioned that a large sample stemming from China including much more males than females (281 vs. 63) also observed strong associations between tendencies toward ICD and unspecified IUD [complete sample: $rho = 0.68$, $p < 0.01$; males: $rho = 0.67$, $p < 0.01$; females: $rho = 0.70$, $p < 0.01$, (59)]. Finally, the measures to assess the different forms of specific Internet addictions differed between the present and our earlier work. Clearly, the associations between specific forms of IUD and unspecified IUD are complicated and simple correlations analysis need to be enhanced by moderation/mediation analysis in the near future taking into account variables such as Internet Use Expectancies as well as Gratification and Compensation Processes for each domain [aside from the already mentioned gender and cultural dimensions; see also Ref. (3)].

CONCLUSION

The present study found further evidence for a role of the 2D:4D marker of the right hand in IGD. Our findings indicate that lower digit ratios (hence higher prenatal testosterone levels) are associated with higher tendencies toward IGD. Noteworthy, our findings could only be observed in females and not males, something, which could only be partly explained (probably a higher *n* of males is warranted and/or more afflicted male persons compared to the subclinical sample investigated in the present work). In males, a negative association appeared between the digit ratio of the right hand and generalized IUD (facet loss of control) supporting the findings of Canan et al. (57). Future studies need to include even larger, more gender-balanced samples to investigate the rather small (but also robust) associations between the 2D:4D marker and IGD.

ETHICS STATEMENT

The study was approved by the local ethic committee of Ulm University, Germany. Under https://www.uni-ulm.de/einrichtungen/ethikkommission-der-universitaet-ulm/ the official website of the ethic committee can be found.

AUTHOR CONTRIBUTIONS

CM, MM, and MB designed the study. MM carried out the statistical analysis. MM drafted the method and result section (and supplement). All statistical analyses were checked by BL. MM and JM carried out the measurement of the hands. CM wrote the first draft of the introduction. CM and MM wrote the first draft of the discussion. MB, RS, and BL critically revised the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://www.frontiersin.org/article/10.3389/fpsyt.2017.00213/full#supplementary-material.

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