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ADDICTIVE DISORDERS IN DSM-5 (JE GRANT, SECTION EDITOR)

# Internet Gaming Disorder

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**Abstract** Internet gaming is one of the most popular online leisure activities. These activities, particularly massively multiplayer online role-playing games, deliver pleasure, a sense of achievement, social interaction, and an immersive experience to online gamers. However, excessive online gaming may have negative consequences by limiting real-life experiences. Because of its prominent negative consequences and similarity to other addictive disorders, the loss of control over online gaming was termed 'internet gaming disorder' (IGD) and included in section III of the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5). In this review, we focus on the literature supporting IGD as an addictive disorder. We review epidemiologic, neurocognitive, and brain imaging studies to provide suggestions for future studies. We also discuss the intensity and frequency criteria used to distinguish subjects with IGD from casual online gamers. Finally, we recommend future studies to confirm the reliability and validity of the DSM-5 IGD criteria.

**Keywords** Internet gaming disorder · Substance use disorder · Criteria · Brain imaging · Validity

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## Introduction

Video games were first marketed in 1972 with the release of the first household gaming console, the Magnavox Odyssey [1•]. A study by the Entertainment Software Association reported that in the United States, 58 % of the population played video games, video games yielded US$20 billion in annual sales, and over 50 % of the population owned a gaming console. As the Internet has developed, these games have allowed individuals to engage both socially and competitively with players across the globe [1•]. Video games are now one of the most popular media for connecting people throughout the world. However, loss of control over video games played online has revealed a series of negative consequences. Because of its major mental health impact, the loss of control over online gaming was termed 'internet gaming disorder' (IGD) and included in section III of the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) [2]. Extensive studies have provided new perspectives of IGD [3]. This review focuses on the reasons IGD should be considered an addictive disorder and proposes diagnostic criteria for distinguishing IGD from casual online gaming.

## What Is Online Game Delivery?

Among Internet-based games, massively multiplayer online role-playing games (MMORPGs) are the most complex and require the most intensive social interaction [4]. Currently, MMORPGs are a very popular and enjoyable leisure activity. However, MMORPG players reveal a high (27.5 %) rate of IGD [5•], and playing MMORPGs is the most frequently cited activity in studies of Internet addiction. A MMORPG provides an immersive virtual environment in which users can interact with one another or with nonplayer characters [6]. Zanetta et al. [7] reported five distinct motivations for playing

MMORPGs: achievement, socializing, immersion, relaxation, and escape. Fuster et al. [8•] suggested that MMORPG players are interested mostly in social interaction and exploration. Lesser motivations include achievement, followed by identification with an avatar and escape from reality (dissociation). These reports suggest that people who play online games such as MMORPGs are attracted to online environments because they provide various psychological pleasures.

Previous studies indicate that optimal experiences motivate people to continue playing online games. Examples of optimal experiences include effective interaction with the system and pleasant social interactions with other gamers [9]. New Internet technologies that enable real-time interaction and a smooth visual field have resulted in gaming experiences comparable to those in the real world and have led to the development of effective delivery systems that provide high user satisfaction. Further, because most popular MMORPGs have extensive and well designed virtual worlds, players can express themselves in ways that would cause them discomfort in real life because of their appearance, gender, sexuality, and/or age. An MMORPG environment also enables users to experience teamwork in a fun and encouraging environment [10]. Although users may be attracted to the pleasure, sense of achievement, social interaction, and immersive experience provided by playing MMORPGs, excessive online gaming may have negative consequences by limiting real-life experiences.

## Is Loss of Control over Online Gaming an Addictive Behavior?

### Negative Consequences of Excessive Online Gaming

Of all online activities, online gaming has the strongest association with compulsive Internet use [11]. Excessive computer game playing without monetary rewards is considered problematic [12]. People who play MMORPGs experience more gaming-related problems compared with people who engage in other online activities [13•]. Further, addiction to online games, particularly MMORPGs, might be associated with sleep-related problems, such as insomnia and poor sleep quality [14]. Moreover, a stronger belief in the realism of the games and more time spent playing MMORPGs increase online support but decrease offline social support [15]. A prospective study of subjects assigned to play an MMORPG for 1 month reported that as the number of hours spent playing the MMORPG increased, health and sleep quality decreased, and interference with real-life social activity and academic performance increased [16]. In contrast, players with high in-game social support had fewer negative psychological symptoms. Additionally, heavy players had significantly less offline social support and a greater severity of negative symptoms. Other authors acknowledge that MMORPGs provide social support but raise concerns about the potential harm of excessive use [17]. Despite the reportedly positive effects of online gaming, excessive use of online games, particularly MMORPGs [18], can negatively affect psychological well-being, social interaction, and health.

Thus, the negative consequences are prominent in players who meet the criteria for IGD. Achab et al. [5•] reported that compared with a control group without IGD, subjects with IGD had higher rates of tolerance phenomena and significantly more social, financial, marital, family, and/or professional difficulties. The authors also reported that the IGD group had high rates of irritability, low mood, and sleep problems. Another prospective study further reported that adolescents with IGD had higher than normal depression, anxiety, and social phobias and lower than normal school performance [19]. Thus, Ng and Wiemer-Hastings [20] suggested that addiction to online gaming might have the same negative consequences as substance use disorder.

### Core Symptoms of IGD

A recent review suggests the following indicators of excessive online gaming activity: (1) excessive use, often associated with loss of a sense of time or neglect of basic drives; (2) withdrawal, including feelings of anger, tension, and/or depression, when the computer is inaccessible; (3) tolerance, including the need for better computer equipment, more software, or more hours of use; and (4) negative repercussions, including arguments, lying, poor achievement, social isolation, and fatigue [21]. King et al. [22] proposed three core presentations of IDG: (1) withdrawal, (2) loss of control, and (3) conflict. In 2003, the DSM-5 proposed diagnostic criteria for IGD.

The DSM-5, in section III, defines addiction to Internet gaming in conditions for further study and suggests that more evidence is needed before it is included as a standard disorder in the DSM system [2]. The DSM-5 criteria for IGD include several modifications of the diagnostic criteria used for substance use disorder, including tolerance, withdrawal, continued use despite negative consequences, failure to reduce Internet use, consistent Internet use that is greater than intended, and impaired psychosocial function. These criteria suggest that the clinical presentation of IGD resembles that of substance use disorder.

### Factors Associated with Internet Gaming Disorder (IGD)

As observed in substance use disorder [23], IGD is more common in males [24]. Older age, lower self-esteem, and

lower satisfaction with daily life are associated with a greater severity of addiction in males but not in females [24]. The personality characteristics associated with IGD include neuroticism, sensation seeking, trait anxiety, state anxiety, and aggression [25]. Comparisons with pathologic gamblers indicate that low conscientiousness and low extraversion are specific characteristics of IGD [26]. High levels of impulsivity also have been associated with IGD [27, 28]. Lastly, a prospective study found that high impulsivity is a risk factor for IGD [19]. Notably, several risk factors for IGD, including impulsivity, sensation seeking, and neuroticism, also are risk factors for substance use disorder [29–31].

Among adolescents, online games provide compensatory or extensive satisfaction of needs [32]. Pathologic gaming behavior is characterized by the use of games to escape dissatisfaction with daily life [13•, 33]. 'Negative escapism,' or negative reinforcement of game playing as a way to avoid everyday hassles and distress, was strongly associated with addiction to online gaming [34]. This association suggests that escape is a very important psychological mechanism contributing to IGD. Escape also is a core mechanism in negative reinforcement models of substance addiction [35].

These studies demonstrate that IGD shares several characteristics with substance use disorder, including personality traits and the reliance on Internet gaming as an escape mechanism. Therefore, the two disorders may share similar underlying mechanisms. Although several studies reported associations between Internet addiction and substance use disorder [36–38], the literature on comorbidity of IGD and substance use disorder is limited. Further empirical studies are needed to demonstrate a direct association.

## Neurocognitive Studies of IGD

A study of subjects with IGD showed impaired decision-making ability in a dice game task [39]. Compared with controls, the subjects with IGD also had a higher-than-normal positive implicit reaction to images associated with gambling, suggesting that implicit cognition also might be associated with dyscontrolled online gaming [40]. Further, Internet gaming addiction (IGA) presents cognitive biases toward information related to Internet gaming. These biases, as well as poor executive functioning skills (lower mental flexibility and response inhibition), might contribute to IGD [41]. Although these studies reported that cognitive characteristics associated with substance use disorder are similar to those in IGD, the number of reports is limited. Additional studies focusing on cognitive performance, cognitive control, implicit response, emotional control, and reward sensitivity are needed.

Further, any conclusions regarding cognitive function in IGD would be premature because of design limitations of the aforementioned studies, including a lack of direct comparisons between subjects with IGD and casual online game players. In fact, the effect of IGD on cognitive function is controversial. Because most controlled substances are known to have damaging effects on the brain, a reasonable assumption is that they impair cognitive function. However, most online games exercise several specific cognitive functions [4]. Moreover, because good performance in online gaming requires good cognitive function, the hypothesis that online gaming produces a deficit in cognitive function is questionable. Further studies comparing cognitive functions and behavioral characteristics between IGD and casual gaming are needed to clarify the role of cognitive function in the process of addiction to online gaming.

## Brain Imaging Studies

### Functional MRI

Functional MRI (fMRI) is one of the most important imaging tools for investigating the mechanisms of addiction, including response to a substance, vulnerability to addiction, characteristics or symptoms of addictive behavior, and consequences of addiction [42]. For imaging studies, fMRI is preferable to positron emission tomography (PET) and single-photon emission CT because it does not require radiation exposure. Other advantages are its wider availability, lower expense, and superior spatial and temporal resolution [43]. Thus, fMRI is the most widely used imaging tool for investigating subjects with IGD.

### The Cue-Induced Reactivity Paradigm

The cue-induced craving paradigm is the most common strategy for using fMRI to demonstrate brain correlates of the gaming urge in subjects with IGD. A 2009 fMRI study by Ko et al. [44] used a block design to study cue-induced reactivity in subjects with IGD. Compared with the control group, the IGD group had higher activations of gaming cue-induced reactivity in the right orbitofrontal cortex, bilateral anterior cingulate, right dorsolateral prefrontal cortex (DLPFC), right nucleus accumbens, and right caudate nucleus. The results also indicate that cue-induced brain reactivity in IGD resembles that in substance use disorder.

Another study with an event-related design showed that in response to gaming cues, subjects with IGD had higher-than-normal activations in the bilateral DLPFC, precuneus, left posterior cingulate, parahippocampus, and right anterior cingulate. The activation pattern was consistent with the model of substance use disorder developed earlier by Volkow et al. [45]. Further, compared with the remission group, the IGA group

had higher activations over the right DLPFC and left parahippocampus. Therefore, the authors suggested that the DLPFC and parahippocampus are potential markers of cue-induced brain activation in subjects currently in a state of addiction to online gaming [46]. Another block-design study demonstrated that subjects with IGD had higher brain activation over the DLPFC and parahippocampus in response to gaming cues. After 6 weeks of treatment with bupropion, the IGD subjects showed significant decreases in β values over the DLPFC. Therefore, the authors suggested that the effects of sustained-release bupropion on craving and brain activity may resemble those in IGD and substance use disorder [47].

Ko et al. [48] recruited subjects with comorbid IGD and nicotine dependence to investigate the brain correlates of gaming and the urge to smoke simultaneously. That is, the design of their study enabled comparisons of brain activation between a cue-induced gaming urge and cue-induced smoking craving in a single individual. In the comorbid group, brain patterns activated by gaming cues were similar to those activated by smoking cues. After subtracting the reaction of the control group, the comorbid group showed that the parahippocampus and anterior cingulate were activated by both the cue-induced gaming urge and the cue-induced smoking craving. A further conjunction analysis showed that both the gaming urge and smoking craving induced significant activations of the bilateral parahippocampal gyrus. Therefore, the authors concluded that the parahippocampus may be associated with mechanisms of cue-induced brain activities common to both IGA and nicotine dependence.

Despite the varying designs of the aforementioned studies of gaming cue-induced reactivity, they all reported cue-induced reactivity over the parahippocampus, anterior cingulate, precuneus, and DLPFC [44, 46–49]. Their consistent results indicate that these areas participate in the brain's reaction and account for cue-induced gaming urges.

## Response Inhibition in IGD

Response inhibition is a common paradigm of the brain correlates of cognitive control, which is impaired in subjects with substance use disorder [50]. Several fMRI studies investigated cognitive control deficits in subjects with IGD. Dong et al. [51] performed an fMRI study with an event-related design to investigate brain correlates of the Stroop effect in adults with Internet addiction disorder (IAD). The IAD group showed greater activity over the anterior and posterior cingulate than the control group. The results of this study suggest that adults with IAD have impaired inhibitory control and diminished cognitive efficiency and cognitive control. This result supports a previous EEG study by Dong et al. [51], which indicated that compared with controls, the IAD group had less activation over the anterior and posterior cingulate in the conflict detection stage and required more cognitive effort to complete an inhibition task. To investigate brain correlates of response inhibition, Ko and coworkers [27] performed a block-design fMRI study of IGD subjects performing the go/nogo task. Compared with the IGD group, the control group showed greater brain activity over the right DLPFC and superior parietal lobe in response to gaming cue distraction. This finding suggests that the IGD group had impaired response inhibition under gaming distraction; that is, activations of the right DLPFC and superior parietal lobe were insufficient for maintaining the cognitive control and attention allocation required for response inhibition under gaming cue distraction. Ko et al. [28] further investigated brain activation of response inhibition in a study of the go/nogo task in an event-related study of subjects with IGD. Compared with controls without IGD, the IGD group exhibited higher brain activation when processing response inhibition over the left orbital frontal lobe and bilateral caudate nucleus. Additionally, activation over the right insula in response to error processing was lower in the IGD group than in the control group. Together, these results indicate that the altered response inhibition function observed in IGD resembles that in substance use disorder.

## Resting-State fMRI Study

Dong et al. [52] reported that IGD subjects had greater-than-normal regional homogeneity (ReHo) in the brainstem, inferior parietal lobe, left posterior cerebellum, and left middle frontal gyrus. However, the IGD subjects had lower-than-normal ReHo in the temporal, occipital, and parietal brain regions. Liu et al. [53] similarly demonstrated that IAD subjects had greater-than-normal ReHo over the cerebellum, brainstem, right cingulate gyrus, bilateral parahippocampus, right frontal lobe, left superior frontal gyrus, left precuneus, right inferior temporal gyrus, left superior temporal gyrus, and middle temporal gyrus. In Hong et al. [54], an IAD group showed lower functional connectivity (FC) spanning a distributed network. Most of the impaired connections involved the subcortical brain region. Ding et al. [55] reported that subjects with IGD exhibited increased FC in the bilateral cerebellum, posterior lobe, and middle temporal gyrus but decreased FC in the bilateral inferior parietal lobe and right inferior temporal gyrus. Three studies reported increased FC or ReHo over the cerebellum. However, Hong et al. [54] reported impaired connectivity in subjects with involvement of the subcortical brain regions. The inconsistent results of these four studies may have resulted from different definitions of Internet addiction, different indicators of FC, or different ages and numbers of subjects.

Other Imaging Studies

Both PET and arterial spin labeling perfusion MRI offer absolute quantification of cerebral blood flow (CBF). A PET study of subjects with IGD demonstrated significantly decreased glucose metabolism in the prefrontal, temporal, and limbic systems. Dysregulation of dopamine D2 receptors was observed in the striatum and was correlated with the number of years spent in excessive online gaming [56]. In Feng et al. [57], however, an IGD group had greater-than-normal CBF in the left inferior temporal lobe, left parahippocampal gyrus/amygdala, right medial frontal lobe/anterior cingulate, bilateral insula, right middle temporal gyrus, right precentral gyrus, left supplementary motor area, left cingulate, and right inferior parietal lobe. However, CBF was lower than normal in the left middle temporal gyrus, left middle occipital gyrus, and right cingulate gyrus. The inconsistent CBF observations reported in these two IGD studies may have resulted from the use of different imaging tools.

## Limitations and Controversial Issues in Previous Imaging Studies

Most of the aforementioned imaging studies reported similar brain activation, particularly for the craving response, in IGD and substance use disorder. However, conclusions regarding the brain mechanisms of IGD are premature because of several limitations of these studies. For example, the IGD subjects analyzed in these studies had extremely heterogeneous characteristics, such as widely varying online gaming activities. Further, most IGD subjects in these studies exhibited perfect online gaming performance, which would have been impossible with impairment in cognitive functions such as decision making, attention, concentration, and response inhibition, although their daily functioning in the real world was impaired.

Because most cognitive skills applied to online games are similar to those studied in cognitive task research, a diagnosis of impaired brain function based on performance of a cognitive task should be made cautiously until the deficit is evaluated further and confirmed by a behavioral assessment. Thus, a rational hypothesis based on clinical experience and on the literature is essential before performing a brain imaging study. Further, the power of statistical analyses performed in previous fMRI studies of IGD was limited by small sample sizes. Finally, previous studies did not apply consistent definitions of IGD. Because the DSM-5 proposes diagnostic criteria for IGD, future work should define IGD consistently according to these criteria.

## Distinguishing IGD from Casual Internet Gaming: DSM-5 Criteria for IGD

An epidemiologic study in adolescents demonstrated that 4.2 % fulfilled five criteria for pathologic playing [12]. In a study by Grusser et al. [58], 11.9 % of participants (840 gamers) fulfilled diagnostic criteria for addiction with regard to their gaming behavior. Gentile et al. [19] reported a 9 % prevalence of pathologic gaming. A study from the Netherlands reported a small group of addicted online gamers (3 %), representing about 1.5 % of all children aged 13–16 years [59]. Together, these studies indicate that although IGD is a global phenomenon, the prevalence varies widely. However, interpreting the data is difficult because these studies did not apply a consistent definition of IGD [60].

Thus, the DSM-5 provides the criteria for IGD in section III as a set of research criteria that might contribute to accuracy in diagnosing IGD globally. The nine criteria for IGD are preoccupation, withdrawal, tolerance, unsuccessful attempts at control, loss of interest, continued excessive use despite psychosocial problems, deceit, escape, and functional impairment [2]. Notably, deceit, escape, and preoccupation are the same criteria used to diagnose gambling disorder [2]. Loss of interest is another proposed criterion [61]. Other criteria are similar to those used in the fourth edition of the DSM to diagnose substance use disorder.

For a diagnosis of IGD, the DSM-5 requires at least five of the nine criteria for IGD [2]. In contrast, it requires only two criteria for a diagnosis of substance use disorder. Many addictive substances, such as cocaine and heroin, are illegal and are used by only a small population, and legal addictive substances such as alcohol and tobacco have well known negative health effects. Thus, the low minimum of two criteria is adequate to discriminate between individuals with and those without substance use disorder. However, Internet gaming is a popular recreational activity among the younger generation, and a higher cutoff point is needed to discriminate between addicted and nonaddicted online gamers. A recent empiric study of data obtained in interviews of online gamers supports the cutoff point for IGD applied in the DSM-5 [62].

Petry et al. [63] attempted to establish a uniform wording of diagnostic criteria for IGD based on an international consensus. Each diagnostic criterion for IGD was translated into several languages. In addition to providing a practical way to diagnose IGD, the criteria have greatly improved the reliability and consistency of IGD diagnoses made in different geographic regions.

In practice, IGD is very difficult to distinguish from casual gaming. For example, the major desires that lead to excessive Internet gaming in adolescents, including the achievement of success, creation of social relationships, and immersion in an environment that differs from reality [21], are the same desires that lead to IGD [7]. The games that are most effective in

delivering user satisfaction and pleasure, such as MMORPGs, are also the games most likely to be played by subjects with IGD. Thus, an IGD diagnosis cannot be based only on excessive online gaming activity. Without criteria for defining the intensity and frequency of online gaming behavior, behavior that is simply excessive might be misdiagnosed as IGD. We suggest the following intensity or frequency criteria for IGD based on our experience in interviewing participants for our IGD studies [62]:

### Preoccupation

Subjects with IGD exhibit preoccupation with online gaming, even during other activities, at least three times a week.

### Withdrawal

Petry et al. [63] suggested that an individual's immediate reaction to stopping a game should not be interpreted as a withdrawal symptom. Further, an intense desire to play an online game should be interpreted as a craving rather than a withdrawal symptom. Online gaming has no direct biologic effects, and psychological symptoms of withdrawal vary in presentation, onset, and duration. We suggest that withdrawal symptoms in IGD should be defined as symptoms that occur at least 3 hours after the most recent gaming activity and that can be relieved by further online gaming activity. Although 86.7 % of IGD subjects declared that they could not abstain from online gaming for 2 or 3 days [62], the presentation of symptoms was ill-defined. Thus, further studies are needed to establish a clear definition of withdrawal symptoms.

### Tolerance

Subjects with an extended history of IGD exhibited diminishing satisfaction from playing online games; however, online gaming time had reached a ceiling among most of these subjects. Most expressed tolerance symptoms as feeling unsatisfied even after excessive online gaming.

### Unsuccessful Attempts at Control

Even casual gamers occasionally may fail to control their game-playing time; however, they play mostly on weekends and the consequences are limited. Subjects with IGD usually have attempted to stop or control their online gaming time because of repeated negative consequences; however, they either have had no success or have failed after a short period of abstinence. We suggest that intensity be evaluated before determining whether an individual fulfills this criterion.

### Loss of Interest

Loss of interest represents the pathology of a reward system in addictive behavior, that is, decreased sensitivity of reward circuits and enhanced sensitivity of memory circuits to conditioned addiction expectations [45]. In actuality, most casual gamers replace some of their hobbies with online gaming to satisfy their need for achievement. Therefore, we suggest further assessment of whether real-world motivations, such as work-related achievement in adults and school-related achievement in adolescents, are reduced or even eliminated by excessive online gaming activity.

### Continued Online Gaming Activity Despite Negative Consequences

Because some minor negative consequences, such as a sleep deficit of 1 or 2 hours on weekends or arguing with parents about online gaming activity, also are experienced by casual gamers, we suggest assessing whether subjects believe that their online gaming activity is problematic. This acknowledgement is essential to fulfill the criterion. Notably, most individuals whose IGD is in remission continue their online gaming activity but limit its duration. Therefore, continued online gaming does not meet the criterion if it is limited or controlled.

### Deceptive Behavior Regarding Online Gaming Activity

This criterion has had the lowest diagnostic accuracy (68.0 %) and was noted in only 44.0 % of adult subjects with IGD [62]. Thus, its validity for diagnosing IGD is not empirically supported.

### Escape

Escape is an essential motivation to use online gaming [8•], not only among subjects with IGD but also for casual gamers. We consider this criterion fulfilled if the individual turns to online gaming as the first and most important option for relieving stress. Further, this escaping behavior should occur repeatedly and should have reduced the individual's ability to cope with stress.

### Jeopardy of Losing or Loss of a Significant Relationship/Job/Educational Opportunity

This criterion represents one of the most important negative consequences of IGD. We suggest that this criterion actually be a prerequisite for an IGD diagnosis.

With adequate intensity and frequency criteria and an understanding of the pathology of IGD symptoms, the diagnosis

of IGD might be well validated based on the DSM-5 criteria. However, further studies are needed to establish a consensus for defining the criteria and to demonstrate their validity and reliability.

## Future Studies

Because IGD is a newly emerging disorder, we recommend the following studies to improve our understanding of its mechanisms and treatment.

1. Expert consensus or empiric data supporting guidelines for diagnosing IGD based on the DSM-5 IGD criteria for intensity and frequency.
2. Studies of functional impairment in IGD as well as its course, remission rate, and relapse rate.
3. Prospective interview studies of the causal relationship between IGD and comorbid psychiatric disorders such as attention deficit hyperactivity disorder, depression, hostility, and social phobia.
4. Imaging studies of the essential mechanisms of addiction that apply the DSM-5 criteria for IGD, with an adequate number of subjects (a minimum of 20), a reasonable hypothesis, and an integrated design.
5. Studies of gender differences in mechanisms of IGD.
6. Cross-cultural studies to compare IGD in different countries.
7. Empiric studies to develop standard treatments, such as cognitive behavioral therapy and medications, for IGD.

## Conclusions

Because the definition of IGD was included in the DSM-5 only recently, conclusions based on previous studies using different criteria are premature. However, most studies support the existence of IGD and its negative effects on social interaction and psychological well-being. Cognitive and imaging studies have revealed similar brain characteristics in IGD and substance use disorder. Although these studies indicate that IGD may be considered an addictive disorder, the criteria used to recruit subjects with IGD were based on the literature. Therefore, future studies should consistently apply the aforementioned DSM-5 criteria to increase our understanding of the nature of IGD.

### Compliance with Ethics Guidelines

**Conflict of interest** Chih-Hung Ko declares he has no Conflict of Interest.

**Human and Animal Rights and Informed Consent** This article is not based on any study of human or animal subjects performed by any of the authors.

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