AKADÉMIAI KIADÓ

Journal of Behavioral Addictions

13 (2024) 2, 596–609

DOI:
10.1556/2006.2024.00011

FULL-LENGTH REPORT

Wanting-liking dissociation and altered dopaminergic functioning: Similarities between internet gaming disorder and tobacco use disorder

XUEFENG MA[1†], MIN WANG[1†], WEIRAN ZHOU[2], ZHAOJIE ZHANG[2], HAOSEN NI[1], ANHANG JIANG[2], YANBIN ZHENG[2], XIAOXIA DU[3], MARC N. POTENZA[4,5,6,7,8] and GUANG-HENG DONG[1*]

[1] Department of Psychology, Yunnan Normal University, Kunming, Yunnan Province, P.R. China

[2] Center for Cognition and Brain Disorders, School of Clinical Medicine and the Affiliated Hospital of Hangzhou Normal University, Hangzhou, P.R. China

[3] School of Psychology, Shanghai University of Sport, Shanghai, PR China

[4] Department of Psychiatry and Child Study Center, Yale University School of Medicine, New Haven, CT, USA

[5] Department of Neuroscience, Yale University, New Haven, CT, USA

[6] Connecticut Council on Problem Gambling, Wethersfield, CT, USA

[7] Connecticut Mental Health Center, New Haven, CT, USA

[8] Wu Tsai Institute, Yale University, New Haven, CT, USA

Received: November 2, 2023 • Revised manuscript received: January 10, 2024 • Accepted: March 9, 2024
Published online: April 17, 2024

ABSTRACT

Background: Although internet gaming disorder (IGD) has been included in the DSM-5 for approximately 10 years, debate remains regarding its existence and classification. *Methods:* The current research incorporated three approaches. First, implicit association tests were used to examine for potential dissociation between wanting and liking in IGD. Second, brain features in wanting and liking circuits were tested and compared with tobacco use disorder (TUD) when performing a cue-craving task to explore the neural features of wanting and liking. Third, dopaminergic systems were investigated in IGD and TUD using neuromelanin-sensitive MRI. *Results:* The implicit association test results supported a wanting-liking dissociation in IGD participants. Functional MRI data suggested neural correlates underlying wanting-liking dissociation in IGD and TUD participants, with positive correlations suggesting greater dissociation with increasing addiction severity. Neuromelanin results suggest dopaminergic differences in IGD and TUD relative to healthy control participants. *Conclusions:* A wanting-liking dissociation in IGD participants suggests gaming motivations in IGD relating to incentive sensitization rather than hedonic responses. The neuromelanin-sensitive MRI results suggest dopaminergic involvement in IGD and TUD. The findings suggest similar brain-behaviour mechanisms for IGD and TUD based on an incentive-sensitization model for addiction, having implications for potential therapeutic strategies and policy-based interventions.

KEYWORDS

addictive behaviours, compulsive behaviours, video games, internet gaming disorder, internet addiction, wanting-liking dissociation, dopamine

†Xuefeng Ma and Min Wang share the first authorship.

*Corresponding author.
E-mail: dongguangheng@ynnu.edu.cn

INTRODUCTION

Internet gaming disorder (IGD) is characterised by poorly controlled gaming behaviours leading to psychological distress and impairments in functioning (American_Psychiatric_Association,

2013; Ioannidis et al., 2019; Przybylski, Weinstein, & Murayama, 2017; H. Zheng et al., 2019). In 2013, IGD was included in the DSM-5 (Section III) as a possible condition warranting additional research (American_Psychiatric_Association, 2013). When the 11th revision of the International Classification of Diseases (ICD-11) was adopted at a World Health Assembly in 2019, gaming disorder was included as a "disorder due to addictive behaviours" (https://icd.who.int/en/).

Although the DSM-5/ICD-11 have defined criteria for diagnosing IGD/gaming disorder (Petry & O'Brien, 2013), debates regarding IGD remain (Brand et al., 2019; Kiraly & Demetrovics, 2017). For example, prevalence estimates of IGD have varied widely and ranged from less than 1% to approximately 50%, although more recent studies using formal criteria have found more consistent estimates clustering at the lower end of the range (Gao, Wang, & Dong, 2022; Mihara & Higuchi, 2017; Rehbein, Kliem, Baier, Mossle, & Petry, 2015). Potential risk factors for (G. Dong, Wang, et al., 2019; Strittmatter et al., 2016; Wartberg, Kriston, Zieglmeier, Lincoln, & Kammerl, 2019), negative effects of (G. Dong, Liu, Zheng, Du, & Potenza, 2019; van den Eijnden, Koning, Doornwaard, van Gurp, & Ter Bogt, 2018) and brain features of (Turel, He, Wei, & Bechara, 2020; M. Wang, Zheng, Zhou, et al., 2022; J. Zhang et al., 2021) IGD have varied across studies.

One debate has been whether IGD should be regarded as a mental disorder or moral panic (Aarseth et al., 2017; Potenza, 2018; Quandt, 2017; van Rooij et al., 2018). If IGD should be considered as a formal clinical disorder, its classification has been debated. For example, debates exist regarding whether defining IGD as an addictive disorder may over-pathologize everyday behaviours (King et al., 2019; Kuss & Gainsbury, 2021; Rumpf et al., 2018).

To obtain empirical data regarding whether IGD should be regarded as an addictive disorder, conducting research within the framework of prominent addiction theories and established addictive disorders is important.

Some studies have supported the classification of IGD as an addictive disorder. For example, investigations have found that IGD participants show impaired executive control (G. H. Dong, Wang, et al., 2021; L. Wang, Zheng, Wang, et al., 2022; M. Wang, Zheng, Zhou, et al., 2022; Z. Zhang, Zheng, Zhou, & Dong, 2023), enhanced reward sensitivity (G. Dong, Huang, & Du, 2011; G. Dong, Li, Wang, & Potenza, 2017; G. H. Dong, Dai, & Potenza, 2024; G. H. Dong, Dong, et al., 2021; Z. Zhang, Wang, et al., 2023), and craving when exposed to gaming cues (G. Dong, Wang, Du, & Potenza, 2017; J. Zhang et al., 2021). These features resonate with those of substance use disorders (SUDs). IGD and to tobacco use disorder (TUD) participants have shown overlapping involvement of regions within a fronto-limbic network, particularly the parahippocampus, when exposed to gaming/smoking cues (Ko et al., 2013). Other characteristics (e.g., personality features) appear similar across IGD and SUDs (Fisoun, Floros, Siomos, Geroukalis, & Navridis, 2012; Y. B. Zheng et al., 2021). Nonetheless, additional research may help with classifying IGD (van Rooij et al., 2018).

The incentive-sensitization theory of addiction proposed by Berridge and Robinson (Berridge & Kringelbach, 2015; Berridge & Robinson, 2016) provides a rationale for differentiating addictions from other behaviours. In this theory, they proposed that how much a reward is wanted is dissociable from how much a reward is liked. Wanting may be understood as a motivation to approach, obtain, and consume something desired, whereas liking may be understood as a hedonic response that something may elicit. Generally, wanting and liking go together, so that incentive salience links to feelings of pleasure. However, wanting and liking may be dissociable, and incentive salience may occur either in opposition to liking or in its absence (Berridge & Robinson, 2016; Winkielman, Berridge, & Wilbarger, 2005). According to this theory, hypersensitivity to incentive motivational (wanting) effects of drugs (and drug-related stimuli) is hypothesized to lead to increasingly compulsive patterns of drug-seeking and drug-taking behaviors. This suggests that although individuals with SUDs may show craving to relevant stimuli, they may not like the effects of the substances, even if they want to use them.

In this theory, incentive motivational aspects of drugs are hypothesized to be dissociable from their hedonic effects: wanting drugs increases to problematic levels without such increases in drug liking (T. E. Robinson & Berridge, 1993, 2000). Studies of addictions have reported dissociation in adults with cocaine use (Parvaz, Moeller, & Goldstein, 2016), heavy alcohol consumption (Tibboel, De Houwer, Spruyt, et al., 2015), opioid use disorder (Lubman, Peters, Mogg, Bradley, & Deakin, 2000), and other SUDs (Vanderschuren & Pierce, 2010). Attraction to specific reward cues may make some individuals more susceptible to developing addictions when they initiate engagement in addictive behaviours (M. J. Robinson, Fischer, Ahuja, Lesser, & Maniates, 2016).

Questions exist regarding how best to measure dissociation of wanting and liking. In animals, wanting and liking may be operationalized based on facial expressions (liking) and consumption (wanting). However, in humans, facial expressions and drug consumption are suboptimal indicators as humans can hide facial expressions and inhibit impulses (Tibboel, De Houwer, & Van Bockstaele, 2015). Implicit association tests (IATs) may assess wanting-liking dissociations, as nonconscious wants can be triggered in some circumstances by subliminal stimuli, even though individuals may not report changes in subjective feelings, while increased motivations are revealed behaviourally, including in people with addictions (Tibboel, De Houwer, & Van Bockstaele, 2015).

Individuals may develop neural incentive-sensitization if they consume drugs for sufficient durations and at sufficient dosages (Berridge & Robinson, 2016). Different brain circuitry may underlie wanting and liking. Wanting may involve preferentially dopaminergic projections, whereas liking may involve a more restricted set of hedonic hotspots (described in (Berridge & Kringelbach, 2015)). The incentive-sensitization theory of addiction suggests that wanting may escalate independently of liking as addictions become more severe, perhaps via sensitization of brain mesolimbic

systems (T. E. Robinson & Berridge, 1993). As studies have observed neural dissociation in people with addictions, neuroimaging may provide relevant data regarding IGD.

The dopamine system has been linked to rewarding effects of addictive drugs, particularly habitual intake (Runegaard et al., 2019; Volkow, Michaelides, & Baler, 2019). Although dopamine has been implicated in multiple types of addictions (Wise & Jordan, 2021), debate exists regarding the centrality of dopamine across addictions (Nutt, Lingford-Hughes, Erritzoe, & Stokes, 2015). In vivo dopaminergic measures may provide insight into how IGD may share features with SUDs.

Neuromelanin (NM) is a product of dopamine metabolism that may accumulate over time in dopamine neurons of the substantia nigra. NM-sensitive MRI (NM-MRI) may assess inter-individual variability in regional NM (Cassidy et al., 2019). Specifically, the NM-MRI signal in the substantia nigra may constitute a proxy for function of dopamine neurons in the nigrostriatal pathway. Thus, the non-invasive NM-MRI is a promising tool for investigating in vivo roles for dopamine in neuropsychiatric disorders (Cassidy et al., 2019), including addictions (Cassidy et al., 2020).

Using behavioral, brain, and dopaminergic measures, the current study aimed to explore features of IGD and provide evidence regarding whether IGD shared features with SUDs. First, an IAT was used to assess wanting-liking dissociation in IGD with the hypothesis that IAT-related biases would exist in IGD. Second, based on an observed dissociation, we further tested neural circuitry to explore whether IGD show similar features TUD. We hypothesized that IGD and TUD participants would show neural features linked to wanting-liking dissociations based on previously implicated neurocircuitry. Third, we assessed dopaminergic measures in IGD and TUD participants using NM-MRI. Based on the existing literature (Vaccaro & Potenza, 2019), we hypothesized dopaminergic involvement in IGD and TUD.

STUDY 1. IAT TEST FOR CRAVING AND LIKING

METHODS

Participants

Thirty-five IGD and 39 healthy control (HC) participants with regular game use (RGU) were recruited. Demographic information is listed in supplementary Table 1. Additionally, 25 fishing enthusiasts were recruited as another group of HC participants (detailed descriptions of and results from this group are in supplementary files).

Task and procedure

The tasks in the current study were modified based on the published study on heavy coffee drinkers (Koranyi, Brückner, Jäckel, Grigutsch, & Rothermund, 2020). The Liking-Implicit Association Test (L-IAT) and the Wanting-Implicit Association Test (W-IAT) are described and available on the TC LAB website (https://www.testcloudlab.com/testcloud-study/index). Before starting the tasks, we obtained written informed consent from all participants. Participants next completed demographic and IGD assessments (see supplementary Table 1). Subsequently, participants finished the W-IAT and L-IAT (Fig. 1A illustrates the two IATs). The order of the IATs was counterbalanced across participants.

Liking-IAT (L-IAT)

In the L-IAT, participants were instructed to assign stimuli to one of four categories via key-press. The target stimuli included 8 game-related images (e.g., game graphics) and 8 cartoon images. The attributional stimuli were 8 positive images and 8 negative images selected from the International Affective Picture System (IAPS) (https://www.umass.edu/research/guidance/international-affective-picture-system-iaps). The task started with the attribute classification practice module where participants pressed the right button on the screen for positive pictures and the left for negative pictures. Subsequently, participants practiced target stimulus classification (16 trials) with the same two buttons as previously. After that, participants completed the first formal joint module in which goals and attributes appeared in random order in alternating trials (64 trials). After that, a reverse assignment of target category exercise blocks (16 trials) was performed, and participants completed another joint quiz, also with reverse assignment of target categories (64 trials). Whether game stimuli were first assigned to the left or right response keys was balanced between participants. All stimuli were presented in the center of the screen until a response was detected. The practice module feedback included correct/error messages for keystrokes.

Wanting-IAT (W-IAT)

Relative to the L-IAT, the greatest difference for the W-IAT is that it involves a motivational wanting response for one of the attribute categories. All participants were asked to avoid smoking or playing games one hour before the task and were also not allowed to smoking/gaming prior to assessment. Participants completed several questionnaires taking approximately 30 min before task performance. These steps were undertaken to enhance participants' motivational states (to elicit 'I want' states). There are two types of computer graphic pictures: gaming and cartoon. As attribute stimuli, we used eight juice-related and eight neutral pictures from the IAPS database that were to be classified as either "I want" or "I don't want." The W-IAT started with an attribute categorization practice block (16 trials), where participants needed to press the left key for "I want" and right for "I don't want" pictures using a two-button keypad. The subsequent steps in the W-IAT, including the target and corresponding stimuli and the general procedure, were consistent with the L-IAT (Fig. 1A).

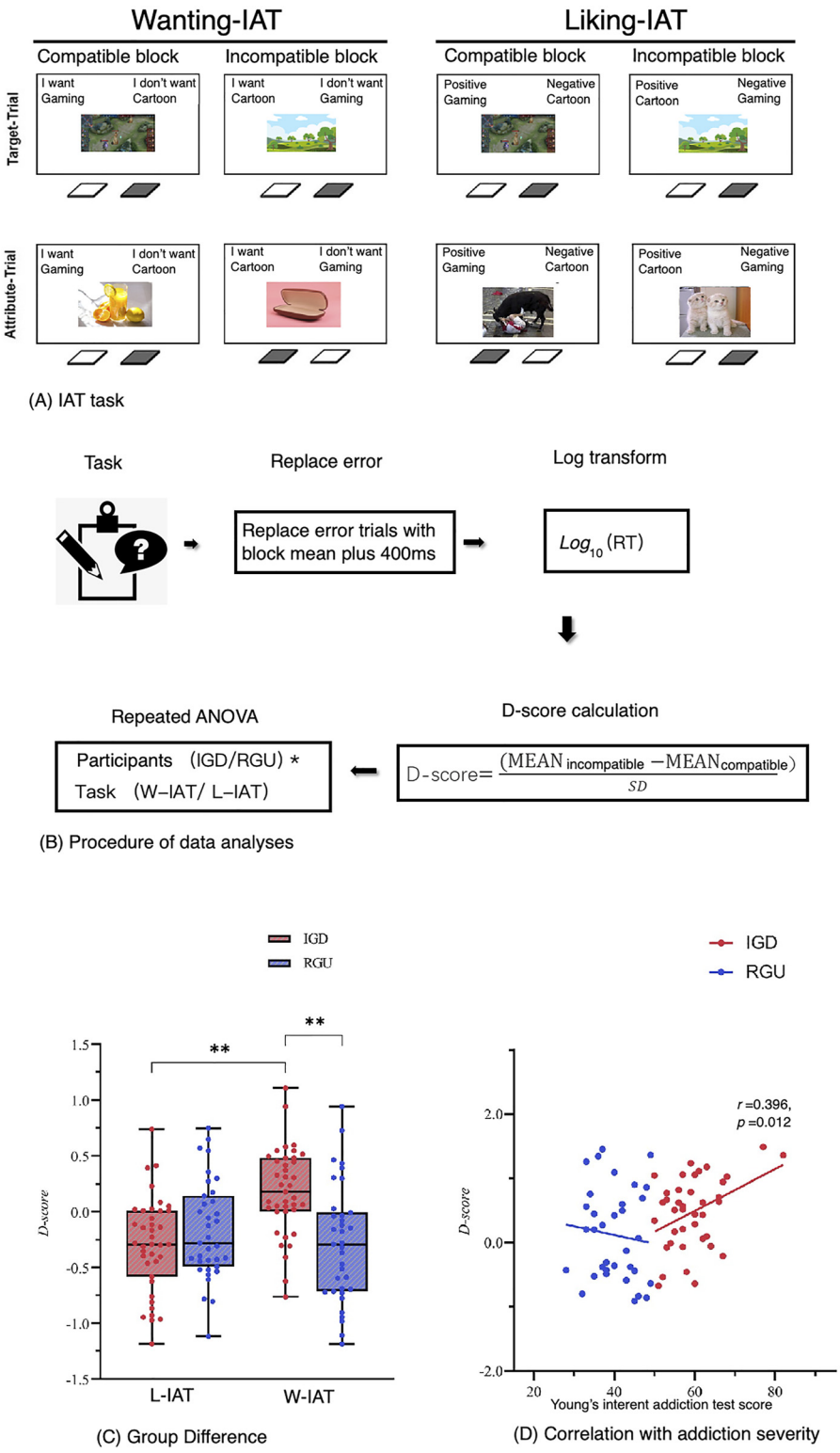

Fig. 1. Behavioral measures implicating wanting-liking dissociation in IGD during performance of an implicit association test (IAT). (A) Depiction of sample trials in the compatible blocks and the incompatible blocks of the Wanting-IAT and the Liking-IAT. (B) The data analytic procedure. (C) Group * task analyses. (D) Correlations between d-score differences (W-IAT minus L-IAT) and addiction severity measures

Data analysis

IAT effect scores were calculated based on d-score measures (Greenwald, Nosek, & Banaji, 2003). For the IAT, we use the following terms. A compatible module refers to a module with the same key as an attribute word that matches the target concept and implicit attitude, and an incompatible module refers to a module with different buttons. The d value is calculated by averaging the reaction of the compatible module and the noncompliant module, and the larger the d value, the greater the difference in the reaction of the compatible and noncompliant modules, and the more obvious the preference for the compatible attitude. The formula for calculating the d-score value is $d = \frac{RT_{noncompliant不} - RT_{compatible}}{SD_{all\ correrct\ responses}}$. We used data from two joint modules to compute d-scores. Trials with latencies >10,000 ms and participants for whom more than 10% of trials had latencies less than 300 ms were excluded. Error trials involve incorrect key classifications, and, as defined according to the IAT improvement algorithm proposed by Greenwald et al. (Greenwald et al., 2003), the error trials were also included in the calculation of response averages. Each error latency was replaced with the block mean plus 400 ms, and the resulting values were log-transformed and d-scores computed. IAT effects were submitted to a 2 (group: IGD vs. RGU) × 2 (IAT type: W-IAT vs. L-IAT) ANOVA with repeated measurement (Fig. 1B).

Ethics

The experiment conforms to The Code of Ethics of the World Medical Association (Declaration of Helsinki). The Human Investigations Committee of Hangzhou Normal University approved this research. Participants were recruited through advertisements.

All participants provided written informed consent before the experiment/scan.

The procedure for recruiting participants across study arms was the same, as were participant inclusion/exclusion criteria. The procedure and demographic information are detailed in the supplementary materials (Participant selection and supplementary Tables 1–3). Subjects in different studies were totally different.

RESULTS

The IGD (n = 39, male n = 14, age = 18.360 ± 7.478 years) and RGU (n = 35, male n = 8, age = 20.090 ± 6.926 years) groups were age-/gender-matched. The main effect of group, F (1, 72) = 5.719, p = 0.019, indicated that the IGD group (M = −0.058, SD = 0.050) showed a greater IAT effect relative to the RGU group (M = −0.231, SD = 0.052). The main effect of IAT type was also significant, F (1, 72) = 15.955, p < 0.001, reflecting the W-IAT having a stronger effect (M = 0.004, SD = 0.048) compared to the L-IAT (M = −0.293, SD = 0.055) (Fig. 1C). A significant interaction effect, F (1,72) = 5.928, p = 0.017, showed that IGD differed from RGU participants in terms of W-IAT scores, with the IGD group having higher levels of craving for game cues compared to the RGU group (M = −0.106; SD = 0.108), and there was no such difference (the group difference between IGD and RGU in D-scores) in L-IAT scores (M = −0.479; SD = 0.102). The D-score difference (W-IAT minus L-IAT) was positively correlated with IGD severity (r = 0.396, p = 0.012) (Fig. 1D).

DISCUSSION FOR STUDY 1

A wanting-liking dissociation in IGD participants was observed using an IAT. Specifically, IGD participants showed higher wanting-liking dissociation than individuals with RGU. The correlation results showed that as IGD severity increased, the wanting-liking dissociation increased, similar to what has been reported in addictive behaviours and disorders related to cocaine and opioids (Parvaz et al., 2016; M. J. Robinson et al., 2016). The results suggest common features across IGD and SUDs, supporting the notion that IGD may be regarded as an addictive disorder.

STUDY 2. NEURAL CIRCUITRY UNDERLYING WANTING AND LIKING IN IGD AND TUD

METHODS

Participants

Sixty-Five IGD, 31 TUD, and 71 individuals with neither disorder were recruited (all HC participants had gaming experience and no smoking experience). Inclusion/exclusion criteria and demographic information are provided in supplementary Table 2.

Task

Participants performed a cue-craving task during fMRI as described previously (Zhou et al., 2021). Figure 1A depicts the task procedures and the timeline for one trial of the task.

First, participants were asked to fixate their sight on a cross in the centre of the screen for 500 ms. Then, cues were presented for approximately 3,000 ms, and participants were instructed to respond whether there was a face in each picture by pressing button '1' ('yes') or '2' ('no'). The duration of the cue was terminated by a button press or lasted up to a maximum of 3,000 ms if participants did not respond (missed trials). A black screen was presented that lasted approximately 3,000 ms after participants pressed the button. During the subsequent craving evaluation stage, participants were asked to evaluate the level of craving for each stimulus on a 5-point Likert-like scale (ranging from '1' (no craving) to '5' (extremely strong craving)). This stage lasted 3,000 ms and was terminated by button press. Finally, a black screen appeared for 1,500–3,500 ms before the next

trial was presented. The task included 90 trials and lasted approximately 15 min.

The 60 pictures in the task were divided into two categories: for IGD, 30 gaming-related and 30 typing-related (neutral baseline); for TUD, 30 smoking-related and 30 typing-related. In each category, half contained a face, and the other half contained a hand. In gaming/smoking-related pictures, a person was displayed playing the online game or smoking in front of a computer (Fig. 1A). Typing-related pictures were considered neutral stimuli. The trials were presented randomly.

Data pre-processing

Functional volumes were slice time-corrected and realigned using the Statistical Parametric Mapping (SPM) 12 package (http://www.fil.ion.ucl.ac.uk/spm), co-registered and normalized to the Montreal Neurological Institute (MNI) template brain, and spatially smoothed using a 4 mm full-width-at-half-maximum Gaussian kernel. Six participants were removed from analyses because of head motion (exclusion criteria were 3 mm in directional movement or 2° in rotational movement; the excluded participants were not counted as participants in supplementary Table 2).

Task-related functional connectivity was assessed using the CONN toolbox (https://www.nitrc.org/projects/conn) in MATLAB. For each participant, CONN implemented CompCor, a method for identifying principal components associated with segmented white matter (WM) and cerebrospinal fluid (CSF). In a first-level analysis, CompCor components and first-order derivatives of motion were entered as confounds and regressed from the BOLD signal. Additional pre-processing steps including high-pass filtering (0.008 – 0.09 Hz), linear detrending, and regression of outlying functional volumes (>97th percentile in normative sample; global-signal z-value threshold = 5, subject-motion mm threshold = 0.09) and were conducted using the artifact removal toolbox (ART) (https://www.nitrc.org/projects/artifact_detect/). Because CompCor can account for subject movement effects and other sources of noise in the BOLD signal, the global signal was not regressed.

Functional network construction

Based on Berridge's and Robinson's incentive-sensitization theory and brain regions they proposed for wanting and liking circuits (Berridge & Robinson, 2016), we referenced an in vivo atlas (Pauli, Nili, & Tyszka, 2018) of brain subcortical nuclei and the AAL template. Specifically, we selected the following nodes within a wanting circuit (the substantia nigra, the amygdala, the caudate, the putamen, and dorsolateral prefrontal cortex) (functional connectivity (FC) displayed in red in Fig. 2B). We selected the ventral pallidum, the insula, and the orbitofrontal cortex within a liking circuit (FC displayed in green in Fig. 2B). Values were extracted for IGD and TUD groups when facing gaming/smoking and neutral cues. BOLD signal was extracted from each ROI during the cue-craving task (with the onset of extraction relating to the appearance time of the gaming/smoking cues), and bivariate correlations were computed between each pair of ROIs for each participant. ROI-ROI networks were computed for each participant. The detailed ROI selection process could be found in the supplementary materials.

Statistical analyses

In second-level analyses, variance analysis and paired sample t tests were performed using SPSS version 24.0 (IBM Corporation, Armonk, NY, USA). First, paired-sample t tests analyzed changes in the liking and wanting networks (average numbers of FCs in the networks) in the three groups, respectively. Subsequently, analysis of covariance (ANCOVA) evaluated differences across the three groups in each network. Finally, to explore relationships between network FC and addiction severity, the IAT, DSM or FTND (Fagerstrom test for nicotine dependence) scores were calculated to assess the correlations with the average FC in liking or wanting networks for all participants.

RESULTS

Liking (Liking_Craving -Liking_Neutral) and wanting (Wanting_Craving -Wanting_Neutral) circuits were calculated for each individual separately. Next, mean FC values were calculated.

Figure 2C depicts the liking circuit in the three groups, although the liking in IGD and TUD are lower than that in healthy control, however these difference did not reach statistical difference ($F = 1.271$, $p = 0.331$). Figure 2D depicts FC differences in wanting circuits between the three groups ($F = 3.425$, $p = 0.033$), with IGD ($t = 2.723$, $p = 0.032$) and TUD ($t = 3.537$, $p = 0.014$) participants showing greater FC strength compared to HC participants.

We next compared within-group differences in these two circuits and did not observe significant difference in healthy group ($t = 0.603$, $p = 0.548$; Cohen's $d = 0.301$). Significant group differences were observed in IGD ($t = -2.73$, $p < 0.05$) and TUD circuit ($t = -3.27$, $p < 0.05$) groups (Fig. 2E).

We next correlated the circuit values with addiction severity measures (for IGD and HC participants, measured by DSM-5 proposed criteria for IGD; for TUD, measured by the FTND). For HC participants, correlations for liking and wanting were in the same direction (Fig. 2F). In IGD and TUD participants (Figure 2G and H), with increasing disorder severity, correlations with wanting and liking went in different directions: as liking decreased, wanting increased.

DISCUSSION FOR STUDY 2

Relative to HC participants, IGD and TUD participants showed greater FC in wanting circuitry when facing gaming/smoking cues. Resonating with the current findings, stronger FC related to reward processing and in reward systems has been reported in participants with TUD (Le Foll et al., 2022;

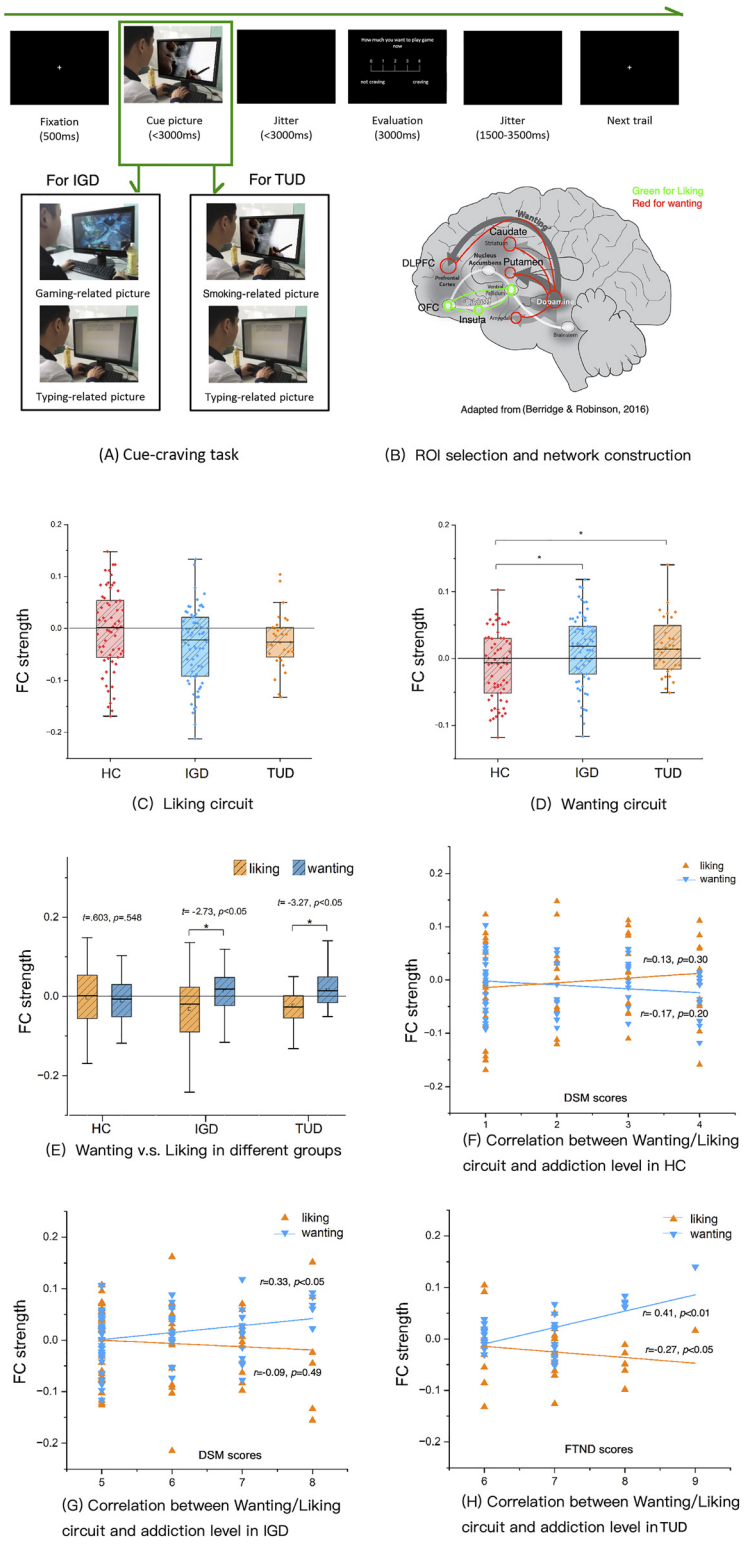

Fig. 2. The dissociation of wanting and liking neural circuitry in IGD and TUD.
(A) A sample trial in the task. (B) The ROIs (red circle) and functional connectivity assessments selected in wanting circuitry (red dots) and in liking circuitry (red circle, red dots); (C) Functional connectivity in liking circuitry in different groups. (D) Functional connectivity in wanting circuitry in different groups. (E) Within-group analyses of liking and wanting circuitry in different groups. (F) Correlations between functional connectivity in wanting and liking circuitry and addiction severity in HC participants. (G) Correlations between functional connectivity in wanting and liking circuitry and addiction severity in IGD participants. (H) Correlations between functional connectivity in wanting and liking circuitry and addiction severity in TUD participants

Pistillo, Clementi, Zoli, & Gotti, 2015) and IGD (G. H. Dong, Wang, et al., 2021; Han et al., 2018; M. Wang et al., 2020).

The FC in the wanting circuit was significantly stronger than in liking circuitry in IGD and TUD groups. Besides, the correlation results suggested that with increasing disorder severity, wanting scores increased in both IGD and TUD participants, whereas liking scores did not. According to the incentive-sensitization theory of addiction (Berridge & Robinson, 2016), wanting and liking dissociate for addictive disorders, and this dissociation may be a useful marker in determining whether behaviours are addictive. For TUD, a wanting-liking dissociation has been observed previously (Selby, Harrison, Fozard, & Kolokotroni, 2020), and was supported in correlations with addiction severity. For IGD, similar results were observed. The findings suggest as these disorders become more severe, neurobiological foundations of wanting may supersede those for liking for individuals with either IGD or TUD. Although numerically a patten suggesting dissociation was observed between the three groups (in HC liking > wanting, IGD wanting > liking and TUD wanting > liking), these findings did not reach statistical significance. As such, the findings suggest possible similarities and differences relating to wanting and liking relationships among the 3 groups.

In the current study, the functional connectivity among regions in wanting circuitry is correlated with addiction severity, but not in liking circuitry, which suggests potential neural mechanisms of wanting sensitization. This possibility warrants further direct examination. Additionally, regions involved in liking and wanting may overlap, and further research is needed to understand better how circuits, especially those related to liking, operate and change over time in addictions.

As such and given findings from other studies, wanting-liking dissociation may underlie engagement in addictive behaviours across gaming and SUDs.

STUDY 3. DOPAMINERGIC FEATURES IN IGD AND TUD

Wanting-liking dissociation studies revealed altered behavioral and neural features in IGD. To examine potential involvement of dopaminergic systems, NM-MRI was used to examine individuals with and without IGD.

NM is a byproduct of dopamine and catecholamine synthesis, primarily found in the dopaminergic neurons of the substantia nigra (SN) and the noradrenergic neurons of the locus ceruleus (LC) (Graham, 1979). Initially, NM-MRI was developed as a candidate biomarker for Parkinson's disease, which is marked by the depletion of dopaminergic neurons in the SN and noradrenergic neurons in the LC, showing a reduction in NM-MRI (Sasaki et al., 2006). When investigating the relation to dopaminergic alterations, NM-MRI contrast-to-noise ratios (CNRs) were positively related to dopamine release in the dorsal striatum and resting blood flow in the SN in patients with schizophrenia. According to these results, NM-MRI in the SN could serve as a proxy of individual differences in presynaptic dopaminergic function (Wieland, Fromm, Hetzer, Schlagenhauf, & Kaminski, 2021). Thus, we suggest that the enhancement of NM-MRI signal may be related to the stacking effects of dopamine neurons in the SN, although the precise etiology is not known with certainty.

METHODS

Participants

Sixteen IGD, 14 TUD, and 30 HC participants were recruited. Inclusion/exclusion criteria were the same as in the first two studies and are detailed, along with demographic information, in supplementary materials (see supplementary Table 3).

Imaging protocols

NM-MRI images were obtained with the following parameters: 10 slices with slice thickness = 3 mm; TR = 260 ms; TE = 2.68 ms; flip angle = 40°; FoV = 178 × 220; matrix = 337 × 512; magnetization transfer frequency offset = 1,200 Hz; NEX = 8 and total acquisition time = 8.04 min. High-resolution T1-weighted images were acquired with the following parameters: 192 sagittal slices with a slice thickness = 1 mm, TR = 2,530 ms, TE = 2.34 ms, FoV = 256 × 256 mm2, flip angle = 7°, matrix = 256 × 256.

Data processing

The preprocessing procedure in this study included the registration of NM-MRI images to T1-weighted images, and all analyses were done in native space. The approach followed the NM-MRI standard processing procedure described in Ohtsuka et al. (2013). As the NM is mainly deposited in the SN, we selected the lateral, central, and medial parts of the SN as ROIs and manually delineated them in native space. We delineated these ROIs on individual T1 images and extracted ROI signals on NM-MRI images by registration with T1. Subsequently, we used anatomical reference regions, which do not contain NM (such as the cerebral aqueduct) to calculate contrast-to-noise ratios (CNRs). In order to obtain these CNRs, the signal intensity in the SN is set in ratio to the added signal intensities of the SNcand a region without NM using the formula described in the manuscript. Finally, we conducted a between-group contrast.

Two of our authors performed the analysis following the two methods provided by Prasad et al. (2018) and Ohtsuka et al. (2013), separately. All extraction standards strictly follow their protocols. We present the results using Prasad's method in the main manuscript, and put the other into the supplementary materials. These results of these two methods show great consistency (the intraclass correlation coefficient is 0.82).

The ROI selections were: (1) one slice below the midpoint of the mammillary body as level 1; (2) the midpoint of the mammillary body as level 2, and (3) one slice above the midpoint of the mammillary body as level 3 (Figure 3A and B). For each level, circular ROIs with 2 mm radii were drawn on the lateral, central parts (Fig. 3C) of bilateral substantia nigra (SN), as well as anterior to the cerebral aqueduct to extract signal intensities (SIs). The definition of CNRs of the lateral and central SN were as follows:

$$CNR = \frac{SI_{SNc} - SI_N}{SI_N} \quad (1)$$

Here SI_{SN} was the mean SI of the central or lateral parts of the *SN*, while SI_N was the mean SI of the anterior to cerebral aqueduct.

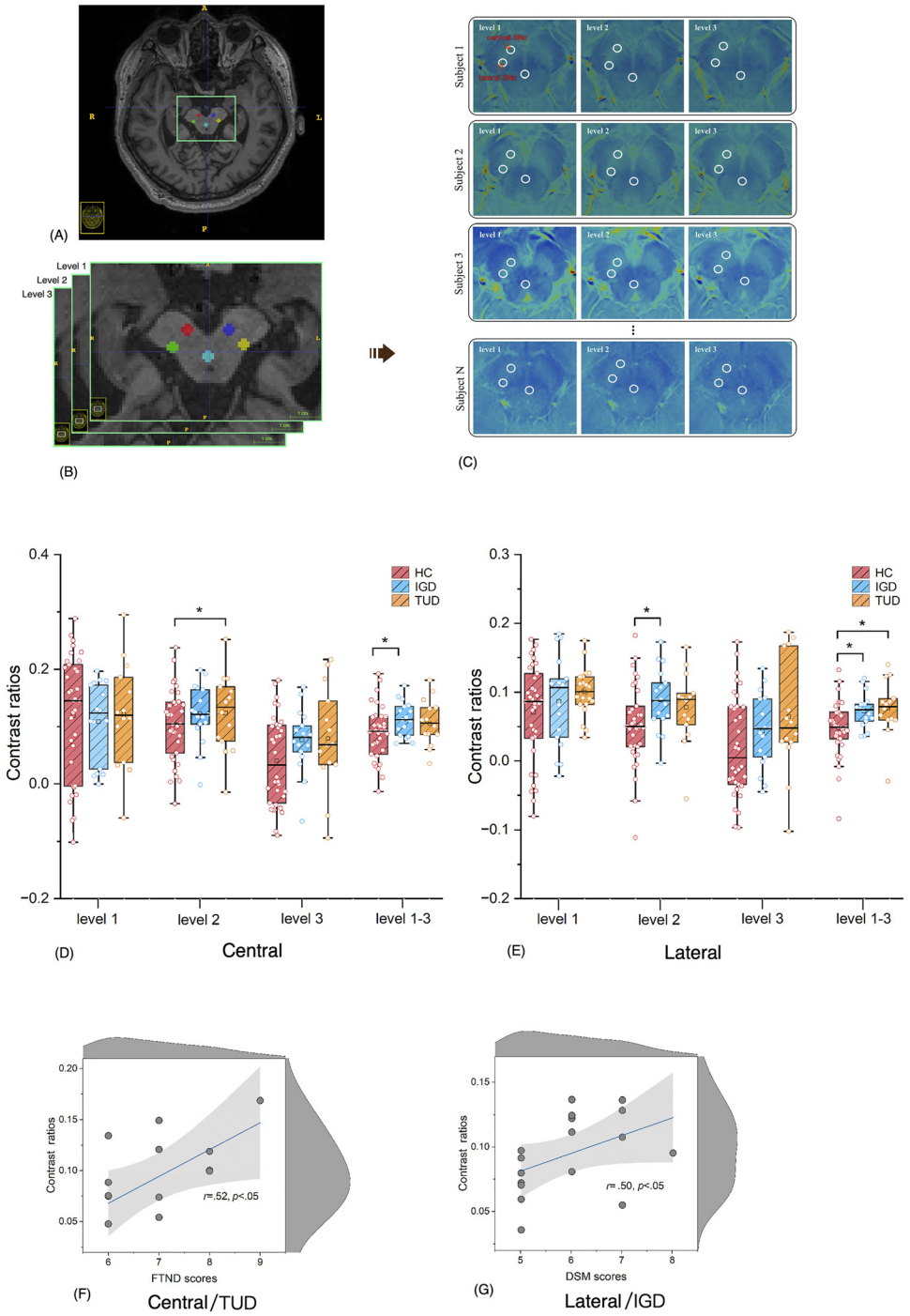

Fig. 3. NM-MRI measures in IGD and TUD as compared to HC participants.
(A) The ROIs selected; (B) Three levels of NM ROIs; (C) The lateral and central ROI selections in different participants; (D) The NM features in different groups at levels 1,2,3 and 1–3 in central ROIs; (E) The NM features in different groups at levels 1,2,3 and 1–3 in lateral ROIs; (F) Correlations between NM scores in central ROIs and addiction severity measures in TUD participants. (G) Correlations between NM scores in lateral ROIs and addiction severity measures IGD participants

Statistical analysis

The intraclass correlation coefficient was used to determine intra-rater and inter-rater reliabilities. One-way ANOVAs were performed to compute the differences in CNRs among the TUD, IGD and control groups. Significance was set at $p < 0.05$.

RESULTS

As shown in Fig. 3D and E, group differences were observed in NM scores (the contrast ratio). In central ROIs, a significant group difference was observed ($F = 3.324$, $p = 0.029$) between IGD and HC in level 1–3 and a significant group difference was observed between TUD and HC in level 2 ($F = 3.267$, $p = 0.030$).

In lateral ROIs, significant group differences were observed between IGD and HC ($F = 3.103$, $p = 0.037$), TUD and HC ($F = 3.422$, $p = 0.022$) in level 1–3 and a significant group difference was observed between IGD and HC in level 2 ($F = 2.921$, $p = 0.041$).

When correlating the NM values to their behavioral measures, the results showed that in central ROIs, the NM values were associated with addiction severity measures in TUD participants ($r = 0.52$, $p < 0.05$) (Fig. 3F), and in IGD participants ($r = 0.46$, $p = 0.065$) (although did not reach statistical significance) in central ROIs; In lateral ROIs, significant correlation was observed between the NM values and addiction severity in IGD ($r = 0.50$, $p < 0.05$) (Fig. 3G), and in TUD participants ($r = 0.42$, $p = 0.139$).

DISCUSSION FOR STUDY 3

In the current study, TUD and IGD participants showed higher NM values than did HC participants. NM-MRI values may reflect dopaminergic measures and provide insight into neuropsychiatric illnesses (Cassidy et al., 2019) such as Parkinson's disease which is characterized by degeneration of dopamine neurons in the SN Prasad et al. (2018). MN may constitute a biomarker for Parkinson's disease (Sulzer et al., 2018). As dopamine systems have been implicated in some addictive disorders (Runegaard et al., 2019; Volkow et al., 2019), NM could potentially be a biomarker for addictions. The current study found that TUD and IGD participants showed higher NM values relative to HC participants, suggesting that SN neurons may differ in dopamine function in TUD and IGD. The current study showed that TUD and IGD participants showed higher NM values relative to HC participants. These findings may suggest that SN neurons may have greater activity and release more dopamine in these disorders. Such a currently speculative interpretation would be consistent with some other behavioural and brain findings in other TUD studies (Le Foll et al., 2022; Pistillo et al., 2015), which have identified the mechanisms by which nicotine in tobacco affects the brain reward system and causes addiction.

Both IGD and TUD participants showed higher NM values than HC participants, although NM values did not positively correlate with addiction severities in a statistically significant fashion. However, the positive directionality and magnitudes of the r values in associations between NM values and addiction severity measures for both IGD and TUD suggest the need for further investigation in larger samples. The present results suggest that IGD participants' dopamine neurons may be functionally different, in a similar manner as in TUD participants. The extent to which these findings may relate to reward systems in IGD and TUD warrants additional study (Le Foll et al., 2022; Lin, Liang, & Luo, 2021; Pistillo et al., 2015; Volkow et al., 2019). Longitudinal studies may provide insight into whether such measures may reflect causes or consequences of gaming behaviours in IGD.

GENERAL DISCUSSION

IGD showed a wanting-liking dissociation as demonstrated in behavioural performance on the IAT. A subsequent neuroimaging study provided insight into brain correlates of wanting-liking dissociations in IGD and TUD. According to the incentive-sensitisation theory of addiction, wanting-liking dissociation may constitute an important marker in differentiating addiction from other hedonic behaviours. The third study suggested that dopaminergic systems in IGD and TUD were similarly different from those in people with neither disorder. These results provide further support for considering IGD as an addictive disorder.

The dissociations between liking and wanting, the altered brain functions along with this change, and the sensitized dopaminergic features all suggest that the gaming cravings could overwhem their irrational self-control and made IGD participants persist in gaming behaviours despite negative consequences. Different explanations may explain such behaviours. For example, IGD participants may exhibit impaired executive control over gaming-related cravings (G. Dong, Wang, et al., 2017; M. Wang, Zheng, Zhou, et al., 2022). Disadvantageous decision-making in IGD may involve myopia in choosing immediately satisfying behaviours and not those with longer-term positive effects (G. Dong & Potenza, 2014; G. H. Dong et al., 2024; Y. Wang et al., 2016). Imbalanced sensitivities to primary and secondary rewards in IGD may promote gaming over other behaviours (Zhou et al., 2021). These explanations are reasonable and have been empirically supported. Wanting-liking dissociation may also contribute. Wanting-liking dissociation may contribute to continued gaming despite negative consequences and relate to some of the other explanations listed above. Further, dopamine mechanisms may contribute to these processes, and the current NM findings suggest similar dopamine features involve in IGD and TUD. In sum, the dissociation of wanting-liking in IGD provides a reasonable mechanism to unify multiple explanations, may operate similarly in IGD and TUD and provide further

support for the conceptualization of IGD as an addictive disorder. Further, the current study suggests dopaminergic similarities between IGD and TUD.

LIMITATIONS

Several limitations should be noted. First, most participants were young adults. Some have noted that younger individuals, namely teenagers, may be at particular risk for IGD (Gao et al., 2022). Thus, individuals of wider age ranges should be included in future studies. Second, given influences of COVID-19, our data collection was terminated at an early stage. Thus, the NM study had fewer participants than initially anticipated. Third, in some analyses, we observed results that did not reach statistical significance, and future studies with larger samples are warranted. Fourth, the current study tried to qualify the dopaminergic activity and nigrostriatal pathway in IGD participants, however, the changes in the mesolimbic pathway from the VTA may be opposite in the dorsal vs ventral striatum, due to D1 vs D2 adaptations. Which might affect the final results.

CONCLUSIONS

Using behavioural, neural, and dopamine measures, and by comparing IGD with TUD, the current study showed that IGD participants showed wanting-liking dissociations and similar NM measures linked to IGD and TUD, suggesting similar dopaminergic involvement across disorders. The current study may help explain why IGD participants continue gaming despite adverse consequences and define more precisely similarities between IGD and SUDs within established theoretical frameworks for addictive disorders.

Funding sources: The current research was supported by the Innovation Team Program in Philosophy and Social Science of Yunnan Province (Research on psychological adaptation and development of China's ethnic minority students in border areas), and The Technology Talent and Platform Plan of Yunnan Province Science and Technology Department (202405AC350075). The funding agencies did not contribute to the experimental design or conclusions, and the views presented in the manuscript are those of the authors and may not reflect those of the funding agencies. Dr. Marc Potenza's involvement was supported by the Connecticut Council on Problem Gambling.

Authors' contribution: ZZ contributed to the task preparation, data collection, data analyses, and figure preparation in study 1. XA, WZ, and AJ contributed to the data analyses and figure preparation in study 2; XM, MW and HN contributed to the data analyses and figure preparation in study 3; YZ and XD contributed to data collection and preprocessing. GHD designed this research and organized the whole draft of the manuscript. MP revised and improved the manuscript.

Conflicts of interest: The authors report no conflicts of interest with respect to the content of this manuscript. Dr. Potenza has consulted for Opiant Therapeutics, Game Day Data, Baria-Tek, the Addiction Policy Forum, AXA and Idorsia Pharmaceuticals; has been involved in a patent application with Yale University and Novartis; has received research support from Mohegan Sun Casino, Children and Screens, and the Connecticut Council on Problem Gambling; has participated in surveys, mailings or telephone consultations related to drug addiction, impulse-control disorders or other health topics; has consulted for and/or advised gambling and legal entities on issues related to impulse-control, internet use and addictive disorders; has performed grant reviews for research-funding agencies; has edited journals and journal sections; has given academic lectures in grand rounds, CME events and other clinical or scientific venues; and has generated books or book chapters for publishers of mental health texts. The other authors do not report disclosures.

Data availability: The data stored at our lab-based network attachment system: http://QuickConnect.cn/others. ID:guests; PIN dong@123.COM.

SUPPLEMENTARY MATERIALS

Supplementary data to this article can be found online at https://doi.org/10.1556/2006.2024.00011.

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