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Gender-related differences in cue-elicited cravings in Internet gaming disorder: The effects of deprivation

GUANGHENG DONG[1]*, HUI ZHENG[2], XIAOYUE LIU[2], YIFAN WANG[3], XIAOXIA DU[4] and MARC N. POTENZA[5,6,7,8]*

[1]School of Psychology, Fujian Normal University, Fuzhou, P. R. China
[2]Institute of Psychological and Brain Sciences, Zhejiang Normal University, Jinhua, P. R. China
[3]School of Psychology and Cognitive Science, East China Normal University, Shanghai, P. R. China
[4]Department of Physics, Shanghai Key Laboratory of Magnetic Resonance, East China Normal University, Shanghai, P. R. China
[5]Department of Psychiatry and Neurobiology, Child Study Center, Yale University School of Medicine, New Haven, CT, USA
[6]Connecticut Council on Problem Gambling, Wethersfield, CT, USA
[7]National Center on Addiction and Substance Abuse, Yale University School of Medicine, New Haven, CT, USA
[8]Connecticut Mental Health Center, New Haven, CT, USA

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Background: Online gaming has become a popular leisure activity, in which males more frequently develop Internet gaming disorder (IGD) compared to females. However, gender-related neurocognitive differences have largely not been systematically investigated in IGD. *Methods:* Cue-elicited-craving tasks were performed before game playing and immediately after deprivation operationalized as a forced break from gaming when the Internet was disconnected. Ninety-nine subjects with IGD (27 males and 22 females) or recreational game use (RGU; 27 males and 23 females) provided functional MRI and subjective data. Analyses investigating effects of group (IGD and RGU) × gender (male and female) at different times (pre-gaming, post-gaming, and post–pre) on cue-elicited craving and brain responses were performed. Correlations between brain responses and subjective measures were calculated. *Results:* In pre-, post-, and post–pre tests, significant gender-by-group interactions ($p < .001$, cluster size > 15 voxels) were observed in the left dorsolateral prefrontal cortex (DLPFC). Further analyses of the DLPFC cluster showed that in post–pre comparisons, results were related to less engagement of the DLPFC in IGD, especially in females. In addition, at post-test, significant interactions were observed in the caudate, as females with IGD showed greater activation as compared to those with RGU. *Discussion:* The results raise the possibility that women with RGU may show better executive control than men when facing gaming cues, which may provide resiliency against developing IGD; however, once they develop IGD, their gaming may impair their executive control and enhance their cravings for gaming, which may make it more difficult to quit gaming.

Keywords: Internet gaming disorder, gender, craving, executive control, dorsolateral prefrontal cortex, caudate

INTRODUCTION

Online gaming has become a popular leisure activity, and most individuals who play online games do so in a recreational, controlled manner, without showing symptoms of addiction, craving, or withdrawal (Kuss & Griffiths, 2012; Montag & Reuter, 2015; Viriyavejakul, 2008). However, a small proportion of people (0.3%–1.0%) exhibit poor control over their desires to play Internet games and qualify for a diagnosis of Internet gaming disorder (IGD; Kiraly et al., 2017; Przybylski, Weinstein, & Murayama, 2017). IGD has been associated with negative consequences including physical and psychological disorders, social deficits, and/or poor academic performance (King & Delfabbro, 2018; Lukavska, 2018; Petry et al., 2014; Rumpf et al., 2018; Starcevic & Billieux, 2018).

Multiple studies have shown that male online game players are more likely to develop IGD than females (Borgonovi, 2016). Studies have suggested that a minority of female and a majority of male adolescents play video games (Desai, Krishnan-Sarin, Cavallo, & Potenza, 2010), and the rates of IGD development appear particularly high in males. For example, studies have found that about 6.3% of boys and 2.4% of girls in China (Li, Yu, Zhang, & Jin, 2015) and 3.6% of boys and 1.9% of girls in Korea (Ha & Hwang, 2014) may experience IGD. Similar proportions have been observed in Taiwan (Ko et al., 2014) and

* Corresponding authors: Prof. Guangheng Dong, PhD; School of Psychology, Fujian Normal University, 1 Keji Road, Fujian Province, Fuzhou 321004, P. R. China; Phone: +86 158 6794 9909; Fax: +86 579 8228 2549; E-mail: dongguangheng@zjnu.edu.cn; Prof. Marc N. Potenza, PhD, MD; Department of Psychiatry and Neurobiology, Child Study Center, Yale University School of Medicine, 1 Church Street, New Haven, CT 06511, USA; Phone: +1 203 737 3553; Fax: +1 203 737 3591; E-mail: Marc.Potenza@yale.edu

elsewhere (Borgonovi, 2016). Video gaming problems in high-school students in the United States have been estimated at 4.9% of gamers, with boys were more likely to report gaming problems (5.8%) than girls (3.0%) (Desai et al., 2010). Data suggest that these differences are not related to differences in gaming skills as studies have observed that female gamers show comparable gaming skills to male gamers (Shen, Ratan, Cai, & Leavitt, 2016).

Gender-related differences have been observed in multiple addictive behaviors, including those relating to alcohol consumption (Bobzean, DeNobrega, & Perrotti, 2014), illicit drug use (Moran-Santa Maria, Flanagan, & Brady, 2014), and gambling (González-Ortega, Echeburúa, de Corral, & Polo-López, 2015; Potenza et al., 2001), including in rodent models (Hu, Crombag, Robinson, & Becker, 2004). Data suggest that females progress more rapidly from behavioral initiation to addiction (Becker, McClellan, & Reed, 2017; Bobzean et al., 2014; Moran-Santa Maria et al., 2014; Zakiniaeiz, Cosgrove, Mazure, & Potenza, 2017), and they exhibit greater vulnerability than males in terms of treatment outcome (Becker, 2016; Perry, Westenbroek, Jagannathan, & Becker, 2015; Sanchis-Segura & Becker, 2016). In addition, engaging in pleasurable activities activates reward systems, and females have shown greater dorsolateral striatal responses to drugs than males (Berridge & Kringelbach, 2015), which suggest potentially different neural mechanisms underlying responses in addictive processes.

As a proposed behavioral addiction, IGD has shown similarities to these other addictions, including diminished executive control (Dong, Li, Wang, & Potenza, 2017; Wang et al., 2016; Yao et al., 2017), enhanced reward sensitivity (Brand, Young, Laier, Wolfling, & Potenza, 2016; Dong, Hu, & Lin, 2013; Dong, Huang, & Du, 2011; Dong & Potenza, 2014), disadvantageous decision-making (Dong & Potenza, 2016; Petry, Zajac, & Ginley, 2018; Wang et al., 2016), increased brain responses to gaming cues (Dong, Wang, Du, & Potenza, 2017), and poorer functional connectivity in executive-control networks (Dong, Lin, Hu, Xie, & Du, 2015). Most studies, to date, have involved entirely or predominantly in male samples. Given gender-related differences in other addictive behaviors and disorders, studies are needed to examine the extent to which findings in male populations with IGD may extend to or differ from those in female populations with IGD.

Responses in reward systems have been implicated in multiple addictions. Craving is a motivation that promotes engagement in addictive behaviors (Dong, Wang, Du, et al., 2017; Potenza et al., 2003; Sayette, 2016; Sinha & Li, 2007). Craving is a key feature of addictions and is included as an inclusionary criterion for substance-use disorders (American Psychiatric Association, 2013). It is a target for behavioral therapies like cognitive-behavioral therapy (Potenza et al., 2013). The neural correlates of craving in both substance and behavioral addictions include cortico-striatal-limbic circuitry (Kilts, Gross, Ely, & Drexler, 2004; Kober et al., 2016; Potenza et al., 2012). Multiple studies have identified gender-related differences in craving using cue-elicited craving tasks. For example, one study found that men with pathological gambling are sensitive to gambling-related cues, whereas women are more sensitive to negative mood states (Grant & Kim, 2002). Other data suggest that seeking behaviors of males are more related to positive reinforcement motivations, whereas females' behaviors are more related to negative reinforcement motivations (Zakiniaeiz, Cosgrove, Potenza, & Mazure, 2016). The extent to which such differences may extend to IGD warrants direct investigation.

Deprivation occurs when people are not allowed to do something that they desire. In addictions, deprivation may occur, for example, when somebody wishes to consume drugs, but is not allowed to do so. Deprivation may also occur when engagement in a behavior is forcibly stopped. In individuals with addictions, deficits in reward capacity may relate to feelings of deprivation, craving, and mood instability (Detar, 2011; Field, Mogg, & Bradley, 2004; Havermans, van Schayck, Vuurman, Riedel, & van den Hurk, 2017; Taylor, Langdon, & Campion, 2005). Studies have linked increased salience of smoking-related cues to nicotine deprivation (Robinson & Berridge, 2008), with visual processing of objects contributing to the phenomenon (Havermans et al., 2017). During periods of nicotine deprivation, heightened autonomic arousal has been observed in smokers (Abrams et al., 2017; Breland, Buchhalter, Evans, & Eissenberg, 2002). These and other findings suggest that smokers' attention is biased toward smoking cues, thus potentially influencing motivations and reward-related processes (Hester & Luijten, 2014; Jasinska, Stein, Kaiser, Naumer, & Yalachkov, 2014; Potenza et al., 2012; Volkow, Wang, Tomasi, & Baler, 2013). However, to date, little attention has been paid to the effect of deprivation in IGD, and a study of gender-related differences in these processes is needed.

Based on the above literature, we hypothesized that deprivation could elicit stronger cravings in IGD subjects as compared to those with recreational game use (RGU) during a cue-exposure task, and that there would be differences between male and female subjects, with males showing stronger cravings than females. Second, we hypothesized that gaming cues would activate cortical and striatal regions in males and females with differences relating to gaming status (IGD and RGU), and that these activations would relate to self-reported craving in males and females. Third, we hypothesized that both males and females with IGD would show greater craving and greater cortical and striatal brain activations following deprivation (operationalized as a forced break from gaming) as compared to prior to gaming.

MATERIALS AND METHODS

Subjects

Ninety-nine right-handed university students [IGD: 27 males and 22 females; recreational game use (RGU): 27 males and 23 females] were recruited for this study. Demographic information and group differences have been depicted in Table 1. All participants underwent structured psychiatric interviews (Mini International Neuropsychiatric Interview) proposed by an experienced psychiatrist (Lecrubier et al., 1997) and those with psychiatric/neurological disorders were excluded. In addition, no subjects reported previous experience with gambling or illicit drugs (e.g., marijuana and heroin). All subjects reported having played *League of Legends* (*LOL*, Riot Games) for more than 1 year.

Table 1. Demographic information and group differences

	Female, RGU (N = 23)	Male, RGU (N = 27)	Female, IGD (N = 22)	Male, IGD (N = 27)	F	p
Age (mean ± SD)	21.96 ± 1.92	23.07 ± 1.86	21.50 ± 1.87	22.19 ± 2.42	1.62	.150
IAT score (mean ± SD)	33.70 ± 6.66	34.00 ± 7.03	59.18 ± 9.55	64.59 ± 11.13	74.88	.000***
DSM-5 score (mean ± SD)	2.22 ± 1.17	2.00 ± 1.07	5.55 ± 1.06	5.85 ± 0.95	96.39	.000***
Game playing per week (hr) (mean ± SD)	14.74 ± 3.17	14.30 ± 10.62	15.05 ± 6.64	14.59 ± 8.34	0.85	.352
Gaming history (months)	26.35 ± 7.42	29.00 ± 7.77	29.55 ± 9.66	39.70 ± 12.44	9.69	.000***
Self-reported craving	30.52 ± 19.59	32.37 ± 12.33	47.41 ± 19.44	50.78 ± 16.33	9.26	.000***

Note. SD: standard deviation; IAT: Internet Addiction Test; RGU: recreational game use; IGD: Internet gaming disorder; DSM-5: fifth edition of *Diagnostic and Statistical Manual of Mental Disorders*.

IGD participants were selected based on scores on Young's Internet Addiction Test (IAT) and the nine fifth edition of *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) criteria of IGD (Petry et al., 2014; Young, 2009). Participants were diagnosed with IGD if they satisfied both of the following criteria: (a) scored 50 or higher on the IAT and (b) met at least five DSM-5 criteria.

RGU participants needed to score less than 50 on the IAT and meet less than five DSM-5 criteria for IGD. Second, they needed to play *LOL* for at least 1 year, more than 14 hr per week, and 5 or more days in a week, similar to IGD participants (Dong, Li, et al., 2017), but without showing any symptoms of physical or psychological dependence (see Table 1 for details).

Experimental protocol

The protocol consisted of three sections: performance of a cue-elicited-craving task, game-playing and the creation of deprivation, and performance of a cue-elicited-craving task during deprivation (Figure 1A).

The cue-craving task used at pre- and post-gaming times

The cue-elicited-craving task was performed at pre- and post-gaming times (Figure 1B), as detailed in our previous studies (Dong, Wang, Du, et al., 2017) and described briefly below. In one typical trial, after a 500 ms fixation, subjects were asked to respond (1 = yes, 2 = no, with counter-balancing between subjects) whether there is a face in the stimulus (up to 4,000 ms). After a jitter (1,500–3,500 ms), the evaluation stage followed, and subjects were asked to report the intensities of their craving [on a scale from 1 (low) to 5 (high)] for the relevant stimuli (4,000 ms, will be terminated by a button press). After another jitter (1,500–3,500 ms), the next trial ensued. We focused our analyses on the "response" stage in data analysis (Figure 1B).

Eighty pictures divided into two categories were used in this study: gaming-related and typing-related pictures (neutral baseline). Fifty percent of all pictures within each category contained a face, and the other half contained a hand. As shown in Figure 1C, in gaming-related stimuli, somebody is displayed playing a game on a computer, with

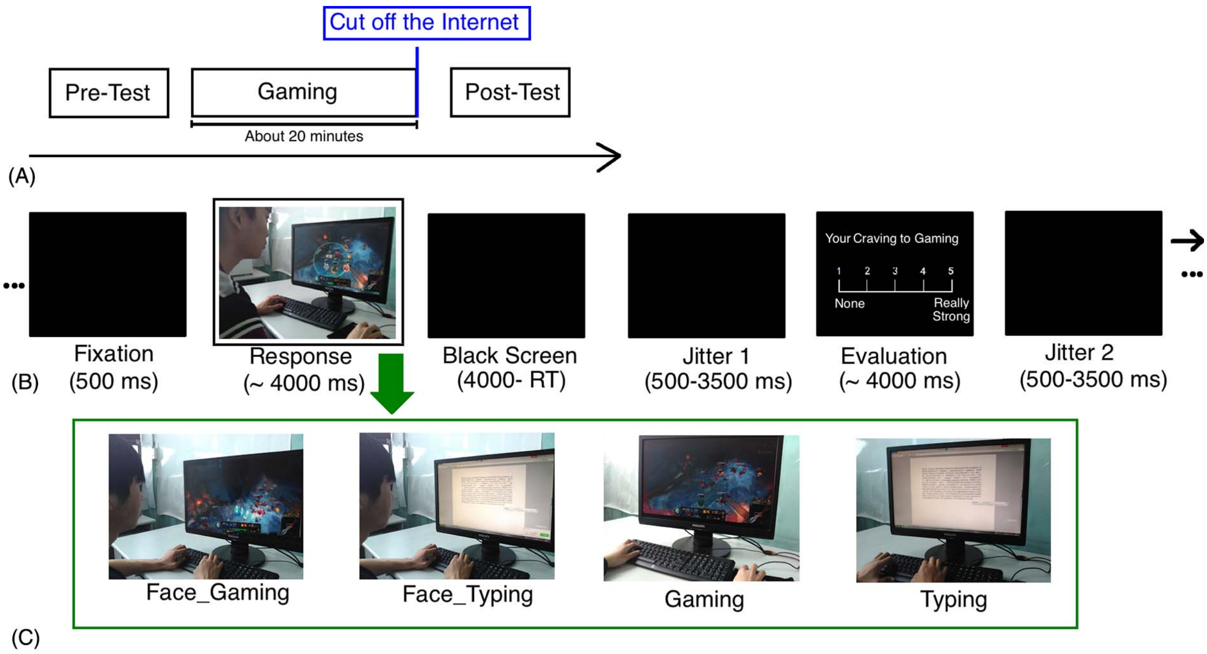

Figure 1. The structure of this study. (A) A schematic diagram of the study procedure. (B) The timeline of one trial in the cue-elicitation craving task. (C) Example stimuli used in this study

some stimuli showing faces and others showing hands. In the typing-related pictures, background imagery was similar except that somebody is typing rather than gaming.

Controlling for stimuli pictures

All pictures were taken in the same place (white wall background and a white desk with a black screen). Male and female faces were in proportion of 50:50 in both conditions. Subjects cannot distinguish emotions as only single sides of faces were included, which is to control for potentially confounding factors (e.g., emotions and accessories).

Controlling for task-performance motivation

Before scanning, participants were informed that a guaranteed 50 Yuan (≈8 US$) would be paid for their participation, and if they performed well, extra money would be presented, with an additional 0–50 Yuan based on their task performance (accuracy rates × 50). Accuracy rates (for identification of pictures with faces or no faces) were expected to approach/reach ceiling effects for the two groups.

Controlling for task repetition

The fMRI tasks in the pre- and post-tests were of the same type but differed in content, in order to avoid/minimize possible repetition effects. We generated two copies of the task with different items (Copies A and B). Half of each group of participants took part in an “A–B” sequence, and the other half received a “B–A” sequence in their pre- and post-gaming scans.

Forced break from gaming: The creation of deprivation

In the scanner, subjects were asked to play *LOL* for one round. In general, one round of *LOL* takes more than half an hour. However, at about 20 min later, participants started playing (after they engaged in fighting with their enemy for about 5 min), we suddenly shut off the Internet connection purposefully (participants were not instructed about the intentional nature of the disconnection). In this manner, deprivation was generated. About 4 min later, we informed participants there was something wrong with the Internet connection and asked them to perform another cue-elicited-craving task.

We selected the time point after participants started fighting with the enemy for about 5 min (at about 20 min after they started playing), because we believe that the fighting stage is climactic and thus the time at which it is best to create deprivation for inducing craving. Before this stage, all players are typically accumulating strength and moving to the enemy camp. In addition, to promote participants' familiarity with their gaming experiences, they were asked to log into the game with their own account.

Data collection

Structural images were collected using a T1-weighted three-dimensional spoiled gradient-recalled sequence covering the whole brain (176 slices, repetition time = 1,700 ms, echo time TE = 3.93 ms, slice thickness = 1.0 mm, skip = 0 mm, flip angle = 15, inversion time = 1,100 ms, field of view = 240 × 240 mm, in-plane resolution = 256 × 256). Functional MRI was performed on a 3T scanner (Siemens Trio, Malvern, PA, USA) with a gradient-echo EPI T2*-weighted-sensitive pulse sequence in 33 slices (interleaved sequence, 3 mm thickness, TR = 2,000 ms, TE = 30 ms, flip angle 90°, field of view 220 × 220 mm^2, matrix 64 × 64) (Dong, Hu, Lin, & Lu, 2013). Stimuli were presented using an in vivo synchronous system (www.invivocorp.com) through a screen in the head coil, enabling participants to view the stimuli. The whole experiment lasted for around an hour [pre-test and post-test (14 min each), T-1 structural (6 min), prepare for scanning and the time between different tasks (6 min), and gaming (~20 min)].

Data preprocessing

The functional data were analyzed using standard steps proposed by SPM12 (http://www.fil.ion.ucl.ac.uk/spm) and Neuroelf (http://neuroelf.net), as described previously (DeVito et al., 2012; Krishnan-Sarin et al., 2013). Images were slice-timed, reoriented, and realigned to the first volume, with T1-co-registered volumes used to correct for head movements. Images were then normalized to Montreal Neurological Institute space and spatially smoothed using a 6-mm FWHM Gaussian kernel. No subjects were removed from analysis because of head motion (the exclusion criteria were 2 mm in directional movement or 2° in rotational movement). A general linear model (GLM) was applied to identify blood oxygen-level-dependent (BOLD) activation in relation to brain activities. Different types of trials (gaming-related, typing-related, incorrect, or missed) were separately convolved with a canonical hemodynamic response function to form task regressors. The duration of each trial was 4,000 ms. The GLMs also included the six head-movement parameters derived from the realignment stage; the time they played the game in the scanner; and the time they played online games, age, and self-reported cravings. We focused analyses on voxels that were significantly activated for each event during the “response” stage.

Comparisons

We performed three analyses investigating group-by-gender interactions on: (a) cue-elicited craving before gaming [Gender (male and female) × Group (IGD and RGU) at pre-test]; (b) cue-elicited craving during deprivation [Gender (male and female) × Group (IGD and RGU) at post-test]; and (c) cue-elicited craving in post–pre test [Gender (male and female) × Group (IGD and RGU) at post-test using subjects' brain features at pre-test as a focus in the GLM model]. Voxel-wise 2 × 2 (Factor 1: IGD and RGU; Factor 2: male and female) repeated-measure analyses were conducted. In these analyses, we first investigated the interactions and main effects and then tested each factor to find factors underlying the interactions. The imaging results were corrected using family-wise error correction at voxel-level $p < .001$, with an extent of at least 15 voxels.

Correlation analyses

We first compared brain activations in the aforementioned comparisons and took surviving clusters as regions of interest (ROIs) to correlate with behavioral measures. For each ROI, a representative BOLD beta value was obtained by averaging the signal of all the voxels within it.

Ethics

This experiment was approved by the Human Investigations Committee of Zhejiang Normal University and conformed to The Code of Ethics of the World Medical Association (Declaration of Helsinki). All participants provided written informed consent before scanning.

RESULTS

Behavioral performance

As the task is easy and we did not ask participants to respond as soon as possible, the accuracy rates and response times in the current study may provide limited information (see Supplementary Material 1.1 and 1.2). At pre-test and at post-test, individuals with IGD reported stronger craving than did those with RGU, with males and females showing similar levels of craving. Comparable levels of craving were reported prior to gaming and following gaming deprivation during the forced break (Supplementary Material 1.3).

Imaging results

The main effects of gender and group in the different comparisons are presented in Table 1, with relevant figures presented in the Supplementary Material.

Gender-by-group effect prior to gaming

Prior to gaming, significant interactions were found in the left dorsolateral prefrontal cortex (DLPFC) (Figure 2A; Table 1). Post-hoc analysis of the DLPFC finding indicated that while females with IGD and RGU showed similar activations of this region, males with IGD showed less activation than males with RGU (Figure 2B). A significant negative correlation was observed between the brain responses in the DLPFC and self-reported craving in the entire sample, and this relationship was significant in males but not females (Figure 2C and D).

Gender-by-group effect post-gaming during deprivation

Following the forced break, significant gender-by-group interactions were observed in the left DLPFC and the caudate (Figure 3A; Table 2). Post-hoc analysis of the left DLPFC finding showed that the DLPFC activity was similar

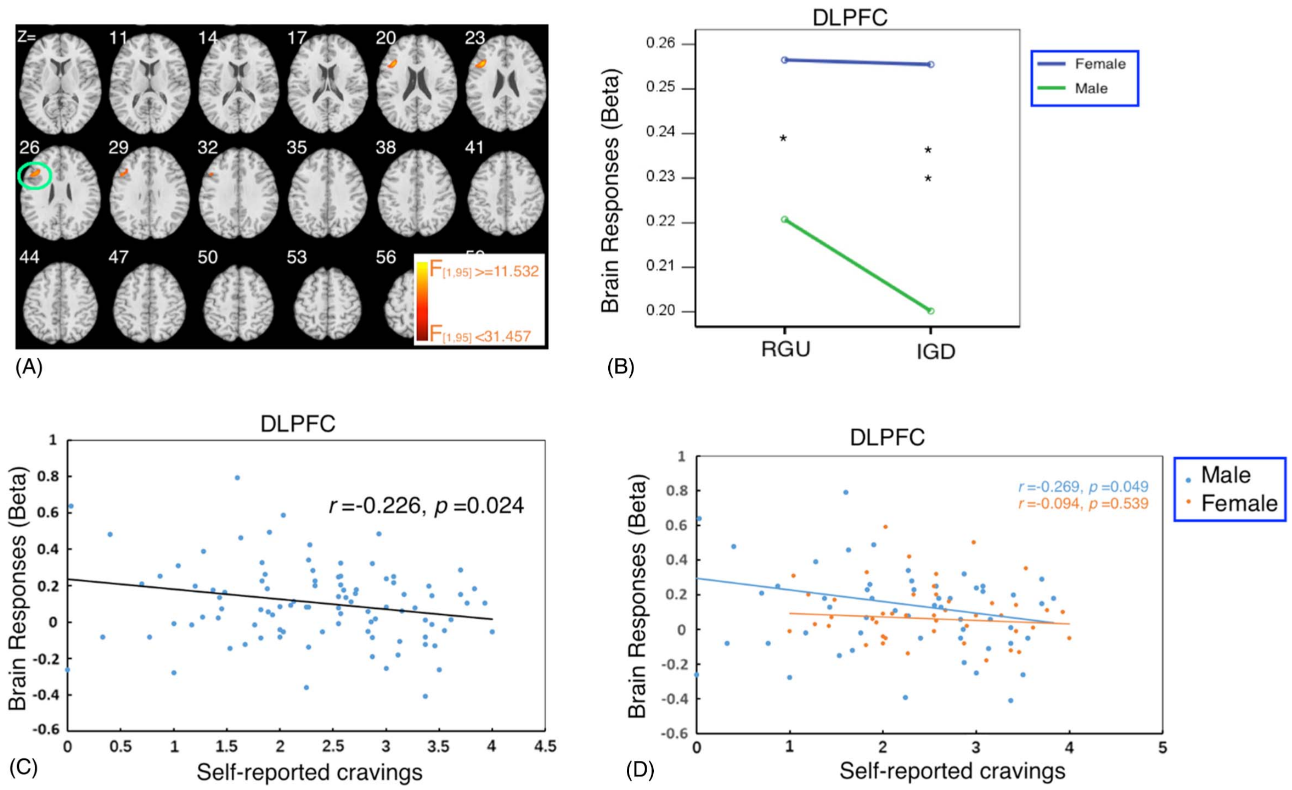

Figure 2. Gender-by-group interactions prior to gaming (pre-gaming). (A) The DLPFC showed a significant gender-by-group interaction prior to gaming. (B) Post-hoc analysis showed that the DLPFC difference was related to the IGD group relative to the RGU group showing relatively blunted DLPFC activation in males but not females. DLPFC activation was correlated with self-reported craving in all subjects (C) and in males but not females (D)

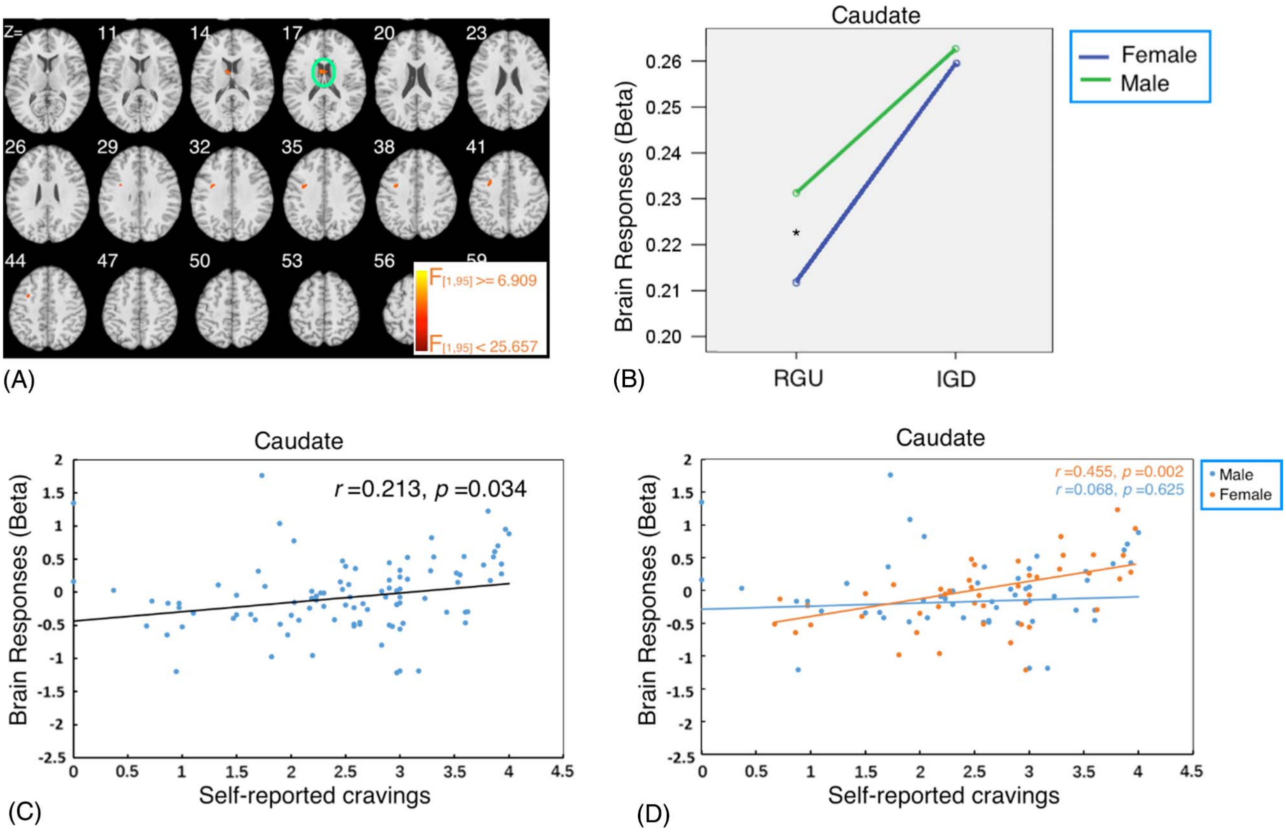

Figure 3. Gender-by-group interaction following gaming and during a forced break (post-gaming). (A) The caudate showed a significant gender-by-group interaction following gaming. (B) Post-hoc analysis showed that among RGU subjects, males showed greater caudate activation, whereas among IGD subjects, no gender-related difference was observed. However, caudate activation was greater in IGD relative to RGU subjects in both male and female subjects. Caudate activation positively correlated with self-reported craving in all subjects (C) and in females but not males (D)

in females with IGD and females with RGU, and males with IGD showed less activation than males with RGU in a manner similar to that observed at pre-test (data not shown). Post-hoc analysis of the caudate finding showed that IGD status was associated with greater activation of the caudate in both males and females, with similar activations observed across males and females with IGD and males with RGU showing greater caudate activation than females with RGU (Figure 3B). A significant positive correlation was found between activation of the caudate and self-reported cravings in the entire sample, and this relationship was significant in females but not males (Figure 3C and D).

Gender-by-group effect at post-pre gaming

In post–pre analyses, significant gender-by-group interactions were observed in the left DLPFC and the middle/superior temporal gyrus (Figure 4A; Table 1). Post-hoc analysis of the left DLPFC showed that DLPFC activation was relatively decreased at post–pre gaming among females with IGD, whereas activation was relatively increased at post–pre gaming in females with RGU. In males, DLPFC activation was relatively decreased at post–pre gaming in both the IGD and RGU groups. These findings were significantly different across gender groups within both the RGU to IGD groups (Figure 4B). A negative correlation was found between the brain response changes in the DLPFC at post–pre gaming and self-reported cravings in the entire sample, with the relationship significant among females but not males (Figure 4C and D). The interactions of right middle temporal gyrus and right superior temporal gyrus are presented in the Supplementary Material.

DISCUSSION

In this study, we examined gender-related differences in subjective and neural responses to gaming cues in before and after an episode of gaming during which a forced break during gaming was introduced. Men and women showed differences in gaming-cue-elicited responses in cortical and striatal regions in manners that were sensitive to group (IGD and RGU) and time (pre-gaming and post-gaming). Our hypotheses were partially supported, and implications are discussed below.

IGD, gender, and blunted DLPFC activation

In both pre- and post-tests, IGD subjects showed decreased DLPFC activation relative to RGU subjects when facing gaming cues, in both male and female subjects. Multiple studies have indicated that the DLPFC contributes importantly to executive control. In addicted subjects, DLPFC activation may enable individuals to inhibit desires and control the

Table 2. Gender, diagnosis, and brain activation findings at pre-gaming and post-gaming

Cluster number	x, y, z[a]	Peak intensity	Cluster size[b]	Region[c]	Brodmann's area
Pre-gaming					
Main effect of gender					
1	24, 68, −3	23.849	42	Right superior frontal gyrus	10
2	31, −10, 43	17.239	22	Right middle frontal gyrus	5
3	12, −70, 1	13.529	129	Right lingual gyrus	
4	−52, 34, −14	13.015	37	Left inferior frontal gyrus	47
5	38, −30, −22	12.604	28	Right parahippocampal gyrus	36
6	66, −4, 9	12.213	45	Right superior temporal gyrus	11
Main effect of group					
1	−26, −10, 43	16.794	38	Left middle frontal gyrus	6
2	−6, −3, −30	11.756	26	Left cingulate gyrus	24
3	14, 32, −30	9.710	31	Right orbital gyrus	11
Gender-by-group interactions					
1	−21, −9, 45	16.25	25	Left DLPFC	46
Post-gaming					
Main effect of gender					
1	33, −57, 26	14.672	22	Right medial temporal gyrus	39
2	60, 35, 7	13.526	32	Right inferior frontal gyrus	46
Main effect of group					
1	−22, 13, −38	21.202	22	Left superior temporal gyrus	38
2	−51, 24, −13	11.720	25	Left inferior frontal gyrus	47
Gender-by-group interactions					
1	−3, 0, 18	11.14	16	Left caudate	
2	−33, 3, 42	10.34	25	Left DLPFC	46
Gender-by-group interactions in post-gaming versus pre-gaming					
1	−25, 6, 45	10.93	23	Left DLPFC	46
2	72, −36, 0	12.04	50	Right middle temporal gyrus	39
3	69, 6, 45	13.21	36	Right superior temporal gyrus	22

Note. DLPFC: dorsolateral prefrontal cortex.
[a]Peak MNI coordinates. [b]Number of voxels. Alphasim correction, $p < .001$; Cluster size >15 contiguous voxels. [c]The brain regions were referenced to the software Xjview (http://www.alivelearn.net/xjview8) and verified through comparisons with a brain atlas.

extent of participation in reward-seeking behaviors (Enokibara, Trevizol, Shiozawa, & Cordeiro, 2016; Everitt et al., 2007; Goldstein & Volkow, 2011; Lee, Park, Namkoong, Kim, & Jung, 2018; Sofuoglu, DeVito, Waters, & Carroll, 2013). Changes in activity in the left DLPFC using repetitive transcranial magnetic stimulation and transcranial direct current stimulation may reduce cue-induced craving in individuals with nicotine, cocaine, and methamphetamine dependence (Enokibara et al., 2016; Feil & Zangen, 2010; Li et al., 2013; Shen, Cao, et al., 2016). Preclinical studies have identified PFC hypoactivity in addiction, and activating the PFC could reduce drug-seeking behaviors in both animals (Chen et al., 2013) and humans (Terraneo et al., 2016). The negative correlation between self-reported craving and DLPFC activation in this study suggests not only that lower DLPFC activation may be accompanied with enhanced cravings for addiction-related cues, but also that enhanced DLPFC activation may be a target for treatment development in IGD as it is in other addictions (Dong, Li, et al., 2017; Wang et al., 2016; Yao et al., 2017).

When considering gender groups, we found that blunted DLPFC activation was observed only in male subjects. According to the role of DLPFC discussed above, the finding may in part explain why male players show higher rates of IGD than female players do. Namely, males in response to gaming cues may show less DLFPC activation and this may relate to poorer executive control over cravings when facing gaming cues, and this possibility warrants direct examination, given the implications relating to prevention and treatment of IGD. Importantly, other brain regions and mechanisms may be important to consider in intervention development for females with IGD.

IGD, gender, and increased caudate activation

At post-gaming, a significant interaction between gender and group was found in the caudate. Further post-hoc analysis of activity in this brain region showed that male as compared to female RGU subjects showed higher caudate activation post-gaming, with males and females with IGD showing similar patterns of activation. Of note, relatively increased caudate activation was observed in male and female subjects with IGD relative to those with RGU, suggesting that this difference in the RGU may relate to resiliency from developing IGD in females relative to males.

The caudate has been described as a component of reward circuitry and may promote motivations to pursue rewards (Dong, Wang, & Potenza, 2016; Grahn, Parkinson, & Owen, 2008). Multiple studies and theoretical models have suggested that reward systems contribute to IGD (Brand et al., 2016; Dong, Hu, & Lin, 2013; Dong et al., 2011; Dong & Potenza, 2014). Higher activation of the caudate may relate to increased striatal dopamine synthesis

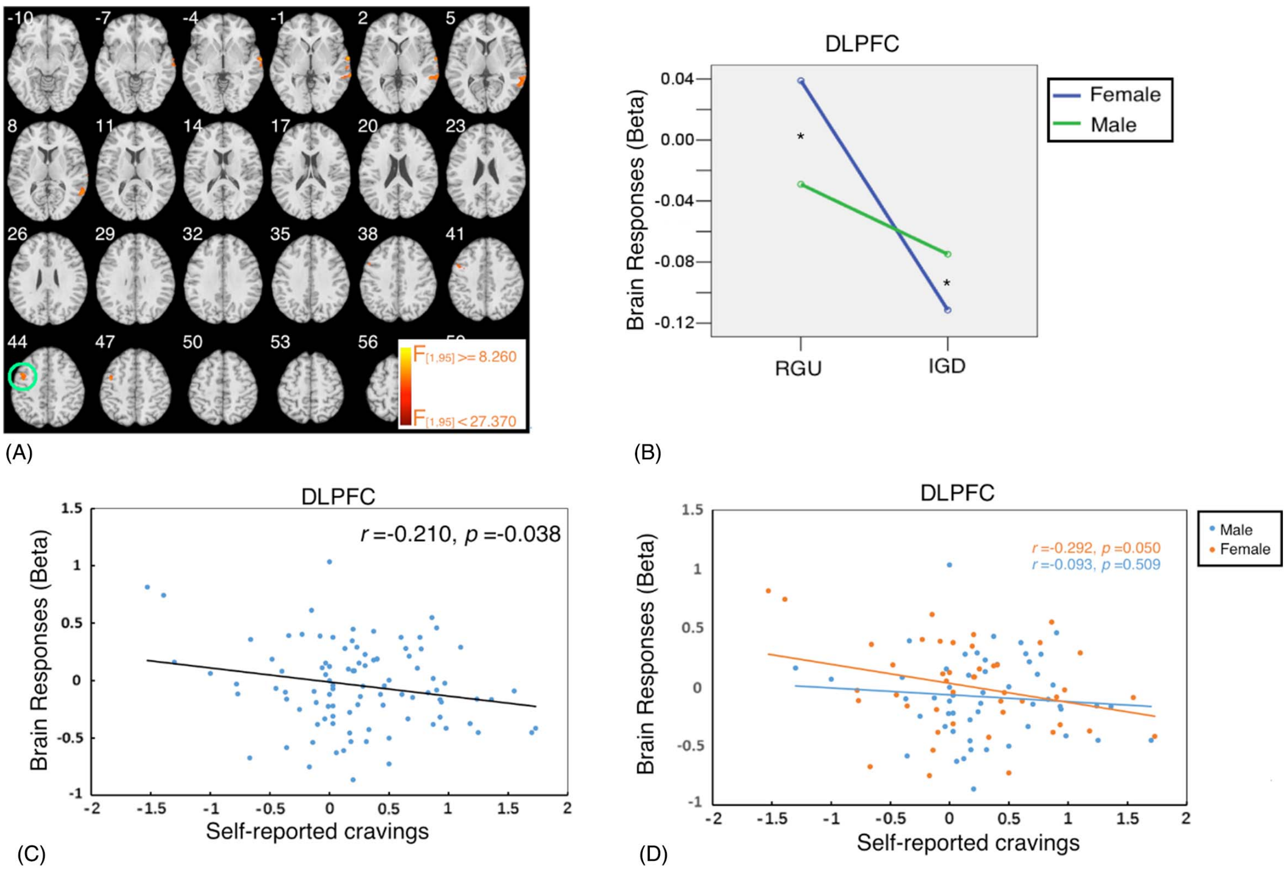

Figure 4. Gender-by-group interaction in post-gaming versus pre-gaming comparison. (A) The DLPFC showed a significant gender-by-group interaction in the post-gaming versus pre-gaming comparison. (B) Post-hoc analysis showed that the DLPFC activation in IGD relative to RGU subjects was blunted to a greater degree in females as compared to male subjects. Changes in DLPFC activation correlated inversely with self-reported craving in all subjects (C) and in females but not males (D)

(Harle, Zhang, Ma, Yu, & Paulus, 2016; Perry et al., 2015; van Holst et al., 2017). The positive correlation between caudate activation and self-reported craving suggests that the higher the caudate activates when experiencing gaming cues, the greater the motivation to game.

The current findings suggest specific neural mechanisms underlying craving responses in IGD, consistent with prior findings (Dong et al., 2011; Dong & Potenza, 2014; Dong, Wang, Wu, & Potenza, 2017) and extending the understanding to females. Craving may shift people's attention toward addiction-related cues (Sayette, 2016; Tiffany, 1990) and influence the evaluation of addiction-related information (Sayette, Schooler, & Reichle, 2010), motivating individuals to pursue immediate satisfaction rather than long-term rewards (Balodis & Potenza, 2015; Berridge & Kringelbach, 2015; Dong & Potenza, 2016; Piper, 2015; Wilson et al., 2014). In this study, the positive correlation between caudate activation and self-reported cravings suggests neural mechanisms that may relate to IGD vulnerability and persistence, although these need to be examined directly in future longitudinal studies.

Gender and post-gaming activations during a forced break

In this study, a forced break was introduced to elicit a deprivation condition. A significant group-by-gender interaction was noted in the left DLPFC for post-gaming versus pre-gaming cue elicitation. Post-hoc analysis showed that within female subjects there was a greater difference in DLPFC activation in the IGD versus RGU groups as compared to that within the male subjects.

Given the role of the DLPFC in executive control as discussed above, the finding raises the possibility that females with IGD may have particular difficulties in controlling their gaming behaviors in the setting of cravings in response to gaming cues following gaming during a forced break (Dong, Wang, Du, et al., 2017). This finding suggests that females with IGD may find it particularly difficult to remit once they have developed IGD. However, these notions are currently speculative and warrant direct examination in future studies. Nonetheless, this interpretation would resonate with gender-related differences in substance addictions, which have observed that females exhibit more rapid escalation from casual drug taking to addiction, exhibit greater withdrawal responses during abstinence, and demonstrate greater poorer treatment outcome relative to males (Becker et al., 2017; Bobzean et al., 2014; Moran-Santa Maria et al., 2014).

Strengths and clinical implications

This study has multiple strengths. This is the first study to examine gender-related difference in cue elicitation responses in IGD responses. The study includes a sizable number of females and a comparison group with comparable levels of gaming.

The current findings have several clinical implications. First, gender-related differences in responses to gaming cues in IGD and RGU subjects suggest differences in mechanisms by which IGD may operate in females and males. These findings may provide a foundation for identifying possible neural markers in developing interventions and evaluating mechanisms linked to treatment outcome. Second, the current findings raise the possibility that gender may need to be considered in the selection of therapies in the treatment of IGD, and the possibility that interventions targeting cravings may operate in a gender-sensitive fashion.

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Authors' contribution: GD designed the task and wrote the first draft of the manuscript. HL, XL, and YW collected and analyzed the data and prepared the figures and tables. XD contributed in collection and preparation of the data. MNP contributed in editing, interpretation, and revision processes. All authors contributed to and have approved the final version of the manuscript.

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