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Brain response features during forced break could predict subsequent recovery in internet gaming disorder: A longitudinal study

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ABSTRACT

Although internet gaming disorder (IGD) is associated with negative health measures, individuals may recover without professional intervention. Exploring neural features associated with natural recovery may provide insights into how best to promote health among people with IGD. Seventy-nine IGD subjects were scanned when they were performing cue-craving tasks before and after gaming was interrupted with a forced break. After one year, 20 individuals no longer met IGD criteria and were considered recovered. We compared brain responses in cue-craving tasks between these 20 recovered IGD subjects and 20 matched IGD subjects still meeting criteria at one year (persistent IGD). Recovered IGD subjects showed lower dorsolateral prefrontal cortex (DLPFC) activation than persistent IGD subjects to gaming cues at both pre- and post-gaming times. Significant group-by-time interactions were found in the bilateral DLPFC and insula, and these involved relatively decreased DLPFC and increased insula activation in the persistent IGD group during the forced break. Relatively decreased DLPFC activity and increased insula activity in response to gaming cues following recent gaming may underlie persistence of gaming. These findings suggest that executive control and interoceptive processing warrant additional study in understanding recovery from IGD.

1. Introduction

Internet gaming disorder (IGD) involves poorly controlled and repetitive gaming that is typically associated with impairment (school, work, relationships) and psychological distress (AmericanPsychiatricAssociation, 2013; Dong et al., 2013a; Meng et al., 2014; Petry et al., 2014a; Wang et al., 2016b). In 2013, IGD was included in Section 3 of the DSM-5 as a condition warranting further study (AmericanPsychiatricAssociation, 2013; Petry et al., 2014a; Wang et al., 2016b). The diagnostic entity proposed in the DSM-5 contains 9 inclusionary criteria sharing similarities to gambling disorder (Dong et al., 2013a; Petry et al., 2014a).

The prevalence of IGD varies across studies with estimates in European (5.0–15.2%) and Asian countries (2.5–23.4%) showing considerable variability (Cheng and Li, 2014; Kuss et al., 2014). A cross-culture online survey suggested 0.3%–1.0% qualified for a diagnosis of IGD based on the proposed DSM-5 criteria (Przybylski et al., 2017). This variability in prevalence estimates may relate in part to differences in assessment instruments and their thresholding (Lau et al., 2017).

Although IGD has been associated with multiple negative consequences including physical and psychological disorders, social deficits, and/or poor academic performance (AmericanPsychiatricAssociation, 2013; Dong et al., 2013a; Meng et al., 2014; Petry et al., 2014a; Wang et al., 2016), individuals may recover without professional intervention (Lau et al., 2017). Estimates of such remission ranges from 36.7 to 51.4% in individuals with internet addiction (Chang et al., 2014; Ko et al., 2014b), similar to findings in gambling disorder (Slutske, 2006; Slutske et al., 2010). While potential factors (e.g., decreases in depression) for remission in IGD have been proposed (Chang et al., 2014; Ko et al., 2014b, 2015), little is known regarding brain mechanisms underlying recovery processes in IGD. An improved understanding of neural factors relating prospectively to recovery in IGD may provide insight into individual differences relating to resiliency and vulnerability and could potentially help with the development of more targeted and effective

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interventions.

IGD has been included as an addictive disorder in the forthcoming eleventh edition of the International Classification of Diseases (ICD-11) (https://icd.who.int/browse11/l-m/en#/http%3a%2f%2fid.who.int%2ficd%2fentity%2f1448597234). Responses to cues in addictions may elicit cravings through specific neural pathways, and such responses have been linked to treatment outcomes (Chase et al., 2011; Jasinska et al., 2014b). Craving may promote engagement in addictive behaviors (Dong et al., 2017b, 2018b; Potenza et al., 2003; Sayette, 2016; Sinha and Li, 2007), is included as an inclusionary criterion for substance-use disorders (AmericanPsychiatricAssociation, 2013; Petry et al., 2014a) and may represent an important therapeutic target (Konova et al., 2013; Potenza et al., 2011, 2013). Thus, cue-elicited craving IGD could be a sensitive index in revealing the neural underpinnings of recovery.

Cue-elicited-craving tasks assess the degrees to which cues may capture attention and evoke responses in individuals with addictions (Jasinska et al., 2014a; Moeller and Paulus, 2018). Stronger subjective and physiological reactions to addiction-related cues have been observed in drug addictions (Carter and Tiffany, 1999), gambling disorder (Kober et al., 2016; Limbrick-Oldfield et al., 2017), and IGD (Dong et al., 2017c, 2018a; Zhang et al., 2016), and neural regions activated in response to disorder-related cues were found to overlap across drug, gambling, food and sexual cues (Noori et al., 2016). In addition, subjects' physiological and neural reactions during craving have been associated with relapse in addictions (Courtney et al., 2016).

Deprivation may occur when people are forced to stop hedonic behaviors. Such deprivation may lead to craving and mood instability (Detar, 2011; Field et al., 2004; Havermans et al., 2017; Taylor et al., 2005). Studies of tobacco-smoking subjects have found increased salience of smoking-related cues after nicotine deprivation (Robinson and Berridge, 2008), suggesting that attention and relevant brain responses may be biased towards smoking cues (Hester and Luijten, 2014; Jasinska et al., 2014b; Potenza et al., 2012; Volkow et al., 2013). Thus, the neural basis of cue-elicited craving during deprivation periods could be informative in studies of IGD, including with respect to understanding recovery from versus persistence of IGD.

In the current investigation, we studied individuals with IGD and those with regular game use (RGU) using a cue-elicited-craving task prior to gaming and immediately following a forced break from gaming, with the latter intended to induce deprivation. This deprivation period was intended to be short-term and may or may not share features with withdrawal, a feature that has been debated with respect to its relevance to IGD (Starcevic and Aboujaoude, 2017). Prior craving studies of substance and gambling addictions have implicated corticostriato-thalamo-cortical and associated reward circuitry including ventral prefrontal, striatal, thalamic and insular regions during craving (Kilts et al., 2004; Kober et al., 2016; Limbrick-Oldfield et al., 2017; Potenza et al., 2012), and similar results have been found in studies of IGD (Dong et al., 2017c; Zhang et al., 2016). In the current study, we used a previously described cue-elicited-craving task involving a distracting executive function (naming whether there is a face in the image or not) to examine individuals with IGD and RGU, and among the IGD participants, those who subsequently recovered versus those with persistent IGD. We hypothesized that greater activation of reward regions would be observed in IGD relative to RGU subjects in response to gaming cues and lower activation of these regions would be identified in comparisons of IGD subjects demonstrating subsequent recovery as compared to those with persistent IGD.

When exposed to cues, subjects may vary in abilities or willingness to regulate their cravings. Thus, executive control regions like the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) may be involved in regulating craving (Engelmann et al., 2012; Kober et al., 2010b) and exerting inhibitory control (Hartwell et al., 2011; Lubman et al., 2004; Potenza et al., 2012). The more robust the brain responses in these areas to relevant cues may speculatively suggest an attempt to inhibit urges in response to cues. The decreased activation in the DLPFC in executive control tasks suggests potentially impaired function (Hartwell et al., 2011; Lubman et al., 2004; Potenza et al., 2012). In the current task involving a modest executive function task (identifying presence of absence of a face in an image), the DLPFC and ACC could theoretically be involved in processing conflicting information relating to gaming and non-gaming distracting information. We hypothesized that lower activation would be observed in IGD relative to RGU subjects in executive control regions in response to gaming cues and greater activation of these regions would be identified in comparisons of IGD subjects demonstrating recovery as compared to those with persistent IGD.

2. Methods

2.1. Ethics

The experiment conforms to the Code of Ethics of the World Medical Association (Declaration of Helsinki). The Human Investigations Committee of Zhejiang Normal University approved this research. All subjects were university students from Shanghai and were recruited through advertisements. All participants provided written informed consent before experimentation.

2.2. Subjects with IGD and regular game use (RGU)

Criteria for selection of IGD and RGU have been reported in our previous studies (Dong et al., 2017a, 2017c; Wang et al., 2017) and are described briefly below. IGD was determined based on scores of 50 or more on Young's online internet addiction test (IAT, www.netaddiction.com) (Young, 2009) and concurrently meeting proposed DSM-5 IGD criteria (Petry et al., 2014b) (Table 1). RGU participants were required to meet fewer than 4 (of 9) of the proposed DSM-5 criteria for IGD and score less than 50 on Young's IAT. In addition, they needed to have been playing online games for a minimum of 2 years (enough time to develop IGD) and on at least 5 of 7 days in a week (frequency) and more than 14 h (amount) per week.

In determining the IGD and RGU groups, academic achievements were also acquired to further verify their states and changes. We also obtained information on life events using a tracking survey. In the tracking survey (administered one year later), additional life events during this year were investigated including family support, free time, changes in romantic relationships, occupation, study habits, aspects of gaming, body health problems, and opinions regarding technologies.

2.3. Recovery from and persistence of IGD

We recruited and scanned 79 IGD subjects and 92 matched RGU subjects in June 2016. One year later, we surveyed the IGD participants again, and 59 agreed to participate. Among these 59 IGD subjects, 39 still met IGD criteria; however, 20 no longer met IGD criteria. Although they were still playing games, they met RGU criteria.

As the number of subjects with persistent IGD was greater than those who recovered (39 versus 20), we matched the recovered IGD subjects one-to-one with persistent IGD subjects by gender (all males), addiction severity (DSM-5, IAT) at study onset and age. In this way, we selected 20 recovered IGD subjects and 20 closely matched persistent IGD subjects. See detailed matching methods in the supplementary materials.

Additionally, we selected these 40 IGD subjects (20 recovered IGD, 20 persistent IGD) as the IGD group, and selected 40 RGU subjects for comparison. We contrasted these two groups which were formed to address specific questions relating to recovery from versus persistence of IGD and were derived from an independent sample from our previously published work using this task (Dong et al., 2017a).

Table 1
Demographic information.

IGD and RGU Subjects	IGD (n = 40)	RGU (n = 40)	*t*	*p*
Age, Years (mean ± SD)	20.93 ± 2.07	21.53 ± 2.17	−1.265	0.210
IAT score (mean ± SD)	62.03 ± 9.89	38.40 ± 9.27	11.021	< 0.001
DSM-5 score (mean ± SD)	5.50 ± 1.13	2.56 ± 1.36	10.553	< 0.001
Game playing per week (hours) (mean ± SD)	17.78 ± 8.75	18.85 ± 9.97	−0.513	0.610
Gaming history (months) (mean ± SD)	23.10 ± 3.20	22.95 ± 2.68	0.227	0.821
Education (years) (mean ± SD)	15.00 ± 1.93	15.17 ± 1.48	−0.454	0.651
Self-reported craving (mean ± SD)	46.20 ± 15.77	32.78 ± 14.05	2.025	0.030
Comparison between Recovered IGD and Persistent IGD Groups				
	Persistent IGD (n = 20)	Recovered IGD (n = 20)	*t*	*p*
Baseline Age, years (mean ± SD)	20.75 ± 2.17	21.10 ± 1.99	−0.530	0.599
Baseline IAT score (mean ± SD)	63.85 ± 11.24	60.20 ± 8.21	1.172	0.248
Baseline DSM-5 score (mean ± SD)	5.45 ± 1.10	5.55 ± 1.19	−0.276	0.784
Baseline Game playing per week (hours) (mean ± SD)	17.65 ± 7.13	17.90 ± 10.31	−0.089	0.929
Baseline Gaming history (months) (mean ± SD)	22.50 ± 4.30	23.70 ± 1.34	−1.192	0.246
Baseline Education (years) (mean ± SD)	14.65 ± 1.79	15.35 ± 2.06	−1.149	0.258
Self-reported craving (mean ± SD)	48.25 ± 13.86	44.15 ± 17.60	0.818	0.418
IAT score-RE (mean ± SD)	64.40 ± 9.25	41.60 ± 9.37	7.742	< 0.001
DSM-5 score- RE (mean ± SD)	5.45 ± 1.82	1.95 ± 1.10	7.361	< 0.001
Game playing per week (hours) -RE (mean ± SD)	22.00 ± 10.85	11.4 ± 8.30	3.471	0.001

IAT: Internet addiction test; DSM: Diagnostic and Statistical Manual of Mental Disorders; SD: Standard deviation; RE: re-measure after one year.

2.4. Functional MRI procedures

The scanning procedure included three parts: cue-craving task before gaming (pre-gaming), game playing and a forced break to induce deprivation, and a cue-craving task after gaming (post-gaming) (Fig. 1A).

2.5. The cue-craving task

The cue-craving task used pre- and post-gaming has been described previously (Dong et al., 2017a, 2019) and is briefly described here. In each trial, a fixation was presented first for 500 ms, and then a stimulus was presented with a response needed; this stage lasted for up to 4000 ms. In this period, participants were asked to answer whether there was a face in the picture, and select 'yes' or 'no' via button press (1, yes; 2, no; with counter-balancing between subjects). The stimulus turned black after key-pressing and lasted for (4000 - the response time) ms. A jittered black screen was presented for a duration of 500–3500 ms. The evaluation stage followed: subjects were asked to evaluate the level of their cravings (on a scale from 1 (low) to 5 (high)) for the relevant stimuli. After another jitter ranging from 500 to 3500 ms, the next trial ensued. The current study focused on the 'response' stage in the task.

The task used 80 pictures divided into two categories: 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 Fig. 1B, in gaming-related stimuli, somebody is displayed playing a game on a computer, with some stimuli showing faces and others showing hands (Fig. 1C). In the typing-related pictures, the background imagery was similar except that somebody was typing into a document rather than gaming.

All stimuli pictures controlled for complexity and gender. In addition, we designed two copies of the task with different items (Copy A, B), and half of the participants received the 'A-B' sequence, the other half the 'B-A' sequence.

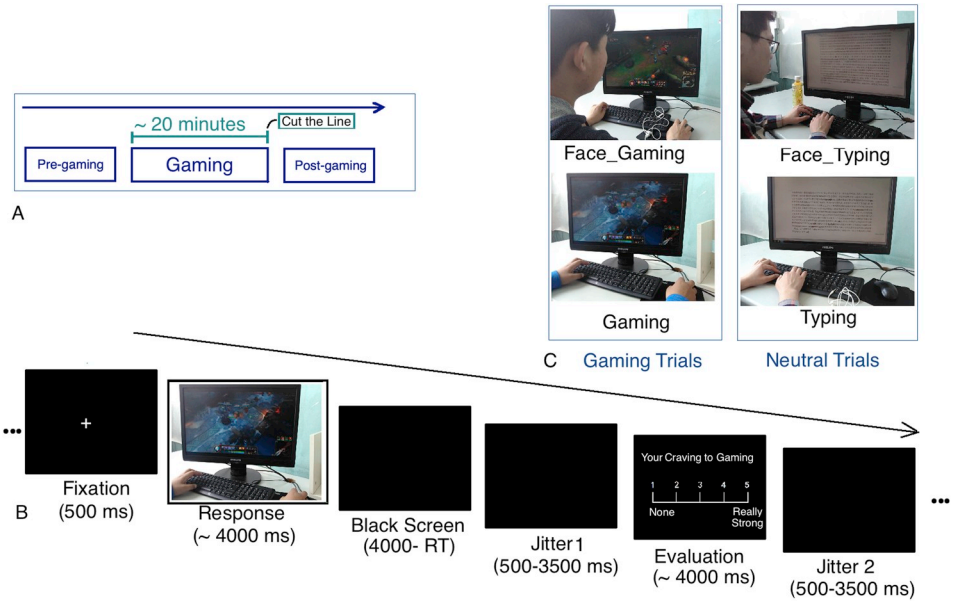

Fig. 1. Design of the cue-craving task in the current study
A: The study procedure consisted of three stages: pre-gaming cue elicitation, around 20 min of game-playing and post-gaming cue elicitation during deprivation operationalized as an unanticipated forced break.
B: The timeline of one trial in the current study
C: Examples of different types of stimuli pictures used in the current study.

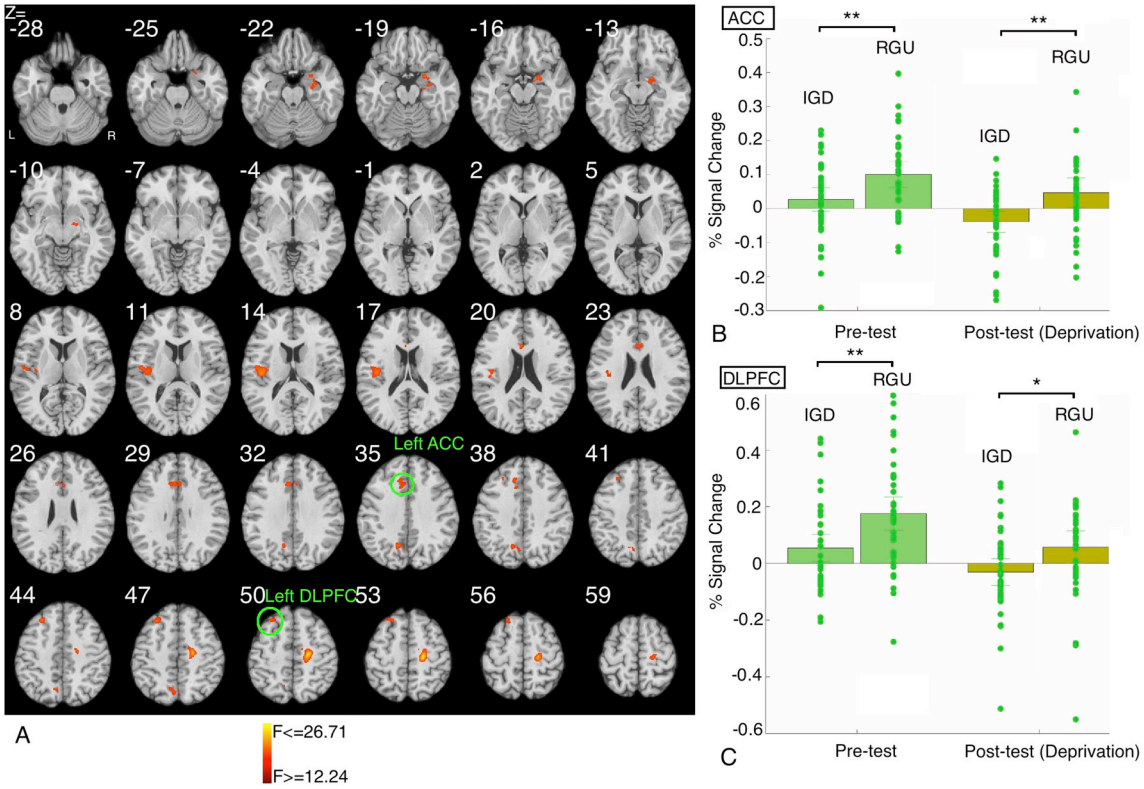

Fig. 2. Main effect of group (comparing IGD to RGU groups)
A: A main effect of group analysis implicated the left DLPFC, left ACC and other regions including the amygdala, hippocampus
B/C: Extracted beta weights show brain responses in the ACC and DLPFC.

2.6. Forced break

In the scanner, subjects were asked to play *League of Legends* (LOL) for one round. In general, one round of the LOL will take more than half an hour. However, at about 20 min after they started playing, we suddenly disconnected the Internet. This forced break was intended to create "deprivation." After 4 min, we instructed subjects there was something wrong with the internet and asked them to perform another cue-craving task.

2.7. Controlling for game genre

To control for types for gaming, we only recruited subjects (IGD and RGU) who regularly played LOL (Riot Games, Inc.) and had played the game for at least one year.

2.8. Data collection and pre-processing

Scanning was performed in the Shanghai Key Laboratory of Magnetic Resonance, East China Normal University. Structural images covering the whole brain were collected, using a T1-weighted three-dimensional spoiled gradient-recalled sequence (176 slices, TR = 1700 ms, echo time (TE) = 3.93 ms, slice thickness = 1.0 mm, skip = 0 mm, flip angle = 15°, inversion time = 1100 ms, field of view (FOV) = 240 × 240 mm, in-plane resolution = 256 × 256). Functional MRI was performed on a 3T scanner (Siemens Trio) with a gradient-echo EPI T2-sensitive pulse sequence in 33 slices (interleaved sequence, 3 mm thickness, TR = 2000 ms, TE = 30 ms, flip angle = 90°, field of view = 220 × 220 mm^2, matrix = 64 × 64). Stimuli were presented using an Invivo synchronous system (Invivo Company, www.invivocorp.com/) through a screen in the head coil, enabling participants to view the stimuli.

2.9. Data analysis

The data were analyzed using Neuroelf (http://neuroelf.net) as described previously (DeVito et al., 2012; Dong et al., 2013b). Neuroelf is a pipeline software based on SPM (http://www.fil.ion.ucl.ac.uk/spm/). Images were slice-timed, corrected, reoriented (manually), and realigned to the first volume. T1-co-registered volumes were normalized to a MNI template and spatially smoothed with a 6 mm FWHM Gaussian kernel. A general linear model (GLM) was applied to identify blood oxygen level dependence (BOLD) activation in relation to event types. The six head-movement parameters derived from the realignment stage were included as covariates of no interest. All types of trials (gaming-related, typing-related, missed or incorrect trials) were included as conditions in the model to account for potential influences on the results. A GLM was independently applied to identify voxels that were significantly activated for the different events of each condition. Second-level analysis treated inter-subject variability as a random effect. First, we determined voxels showing a main effect in different conditions. Presence or absence of life events during this period of time (a year) from all subjects was co-varied during this step (See 'Subjects with IGD and RGU' for the life events surveyed). Then we compared the recovered IGD subjects to persistent IGD subjects in gaming-related versus typing-related events. The results were corrected using $p < 0.001$, cluster > 30 voxels.

2.10. Correlation analyses

Correlations between brain response features and behavioral measures were performed to help better understand the main findings. We took the surviving clusters as ROIs for further analysis, and the beta values for each subject were extracted using group-level masks into individual space. For each ROI, a representative beta value was obtained by averaging the signal of all the voxels within the ROI.

Table 2
Brain regions showing significant differences when comparing IGD to RGU subjects.

Cluster Number	x,y,z[a]	Peak Intensity	Cluster Size[b]	Region[c]	Brodmann's Area
Main effect of group					
1	21,-21,54	26.71	66	R Precentral_Gyrus	4
2	−42,-18,15	17.67	62	L Insula	
3	−3,18,18	12.13	41	L Anterior Cingulate	33
4	24,0,-21	12.89	40	R Parahippocampal Gyrus	
5	−15,-60,36	13.23	32	L Precuneus	7
6	−27,30,45	14.12	31	L Middle Frontal Gyrus	8
Main effect of time					
1	−12,-45,-3	30.72	348	L Parahippocampal Gyrus	30
2	−21,6,24	25.63	336	L Lentiform Nucleus	
3	12,33,-12	29.34	282	R Anterior Cingulate	12
4	24,-24,30	29.61	214	R Caudate	
5	18,-24,-9	25.08	149	R Midbrain/Medial Geniculum Body	
6	6,36,3	19.45	125	R Anterior Cingulate	12
7	−30,-30,36	28.79	96	L Inferior Parietal Lobule	2
8	−39,-63,-15	19.13	58	L Fusiform Gyrus	
9	24,-87,3	18.70	55	R Middle Occipital Gyrus	18
Interaction between group and time					
1	−39,18,21	20.44	65	L Middle Frontal Gyrus	46
2	−36,54,-3	13.48	49	L Middle Frontal Gyrus L Inferior Parietal Lobule	47
3	−3,-27,-6	18.56	39	L Thalamus	
4	−45,-60,54	12.87	33		5

[a] Peak MNI Coordinates.
[b] Number of voxels. Alphasim correction, $p < 0.001$; Cluster size > 30 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.

3. Results

3.1. Main effect of group in IGD and RGU subjects

A significant main effect of group implicated the left DLPFC, left ACC and insula (Fig. 2A, Table 2). Extracted beta weights from the DLPFC and ACC showed that the activation in the IGD group was lower than that in RGU group both at pre-gaming and post-gaming times (Fig. 2B and C).

A description of the results of main effect of time can be found in Table 2 and the supplementary materials.

3.2. Group-by-time interaction in IGD and RGU subjects

A group-by-time interaction implicated the left DLPFC and the thalamus (Fig. 3A; Table 2). Post-hoc analyses focusing on the DLPFC showed that the interaction was related to decreased activation in the IGD group at post-gaming relative to pre-gaming times and the opposite pattern in the RGU group (Fig. 3B). The interaction in the thalamus was related to an increased activation post-gaming as compared to pre-gaming in the IGD group that was greater than the increase in the RGU group (Fig. 3C). A significant positive correlation was observed between thalamic activation and self-reported cravings in IGD subjects (Fig. 3D).

3.3. Main effect of group in recovered IGD and persistent IGD subjects

Among recovered and persistent IGD subjects, a main effect of group analysis identified the bilateral DLPFC (Fig. 4A; Table 3). Recovered IGD subjects showed lower DLPFC activation than did persistent IGD subjects, in both left and right hemispheres (Fig. 4B and C).

The results of main effect of time can be found in Table 3 and the supplementary materials.

3.4. The group-by-time interaction

A group-by-time interaction implicated the bilateral insula and left DLPFC (Fig. 5A; Table 3). Further analysis showed that the interaction in the DLPFC was related to decreased activation in the persistent IGD group post-gaming relative to pre-gaming with the opposite pattern observed in recovered IGD subjects (Fig. 5B). The interactions in the insula were related to increased brain responses in the persistent IGD group at post-gaming relative to pre-gaming (Fig. 5C). A positive correlation was observed between brain response changes in the left insula (post-gaming versus pre-gaming) and the addiction severity changes (re-test minus original IAT score) in persistent IGD subjects (Fig. 5D).

4. Discussion

In this study, we examined IGD and RGU subjects to identify differences in neural responses to gaming cues at pre-gaming and post-gaming times, with the latter occurring immediately following an unanticipated forced break when participants were engaged in gaming. We then examined, within the IGD group, individuals who at one year had recovered from IGD as compared to those who showed persistent IGD. Our findings largely supported our *a priori* hypotheses in identifying reward-related and control-related regions in manners resonating with other findings in addictions. Specific findings and their implications are discussed below.

4.1. Group main and group-by-time interaction effects in IGD and RGU

A main effect of group indicated IGD as compared to RGU subjects showed less activation of executive control regions (DLPFC, ACC) in the setting of gaming cues at both pre-gaming post-gaming times. As such, the extent to which these findings relate to the development and/or maintenance of IGD warrants additional study.

A group-by-time interaction implicated the DLPFC and the thalamus. The interaction involving the DLPFC was related to decreased activation in the IGD group post-gaming (following a forced break)

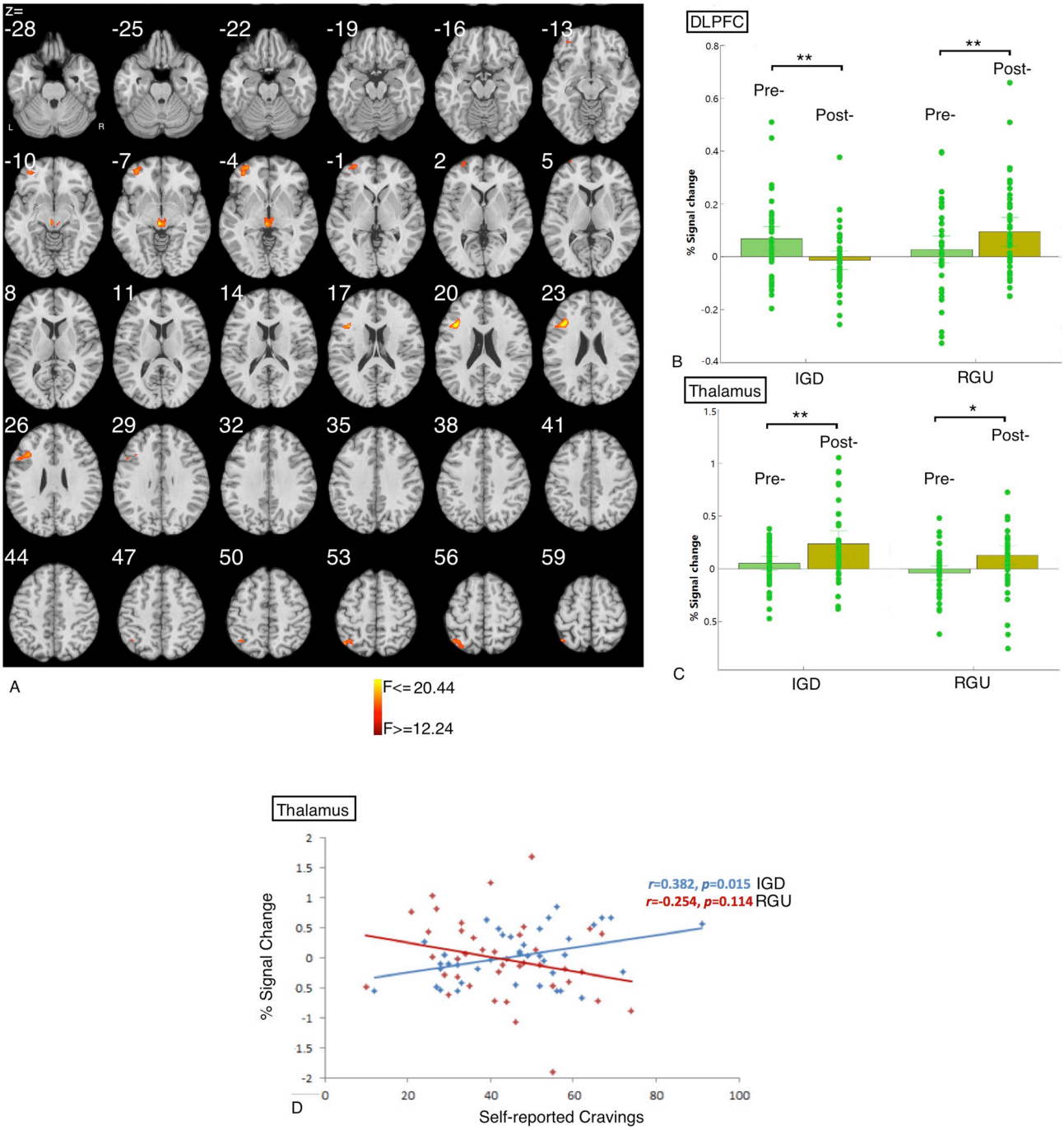

Fig. 3. Group-by-time interactions in IGD and RGU subjects
A: A group-by-time interaction implicated the left DLPFC and thalamus.
B/C: Extracted beta weights show brain responses in the DLPFC and thalamus
D: Correlations between thalamic activation and self-reported cravings in IGD and RGU groups.

relative to pre-gaming and the opposite pattern in the RGU group. These findings suggest that, as compared to pre-gaming responses, following gaming and when encountering an unanticipated forced break from gaming (at a time when typically highly engaged in gaming), the IGD group showed relatively less recruitment of the DLPFC. In contrast, the RGU group showed the opposite pattern. The DLPFC has been implicated in inhibitory control and such diminished recruitment in the IGD group following gaming in particular suggests an important context (immediately following gaming) that may be linked importantly to the development and/or maintenance of IGD (Dong et al., 2015; Dong and Potenza, 2014). Several meta-analyses suggest control regions like the DLPFC become more active during the presentation of substance-related cues as compared to non-substance-related cues (Boswell and Kober, 2016; Chase et al., 2011; Engelmann et al., 2012; Kuhn and Gallinat, 2011; Miller, 2000), possibly suggesting efforts to control behaviors in response to cues as the DLPFC has been implicated in regulating craving (Kober et al., 2010a). Furthermore, a case study has linked transcranial direct current stimulation of the DLPFC to improvement in gambling behaviors in an individual with gambling disorder (Martinotti et al., 2018), suggesting that altering DLPFC function may improve functioning in behavioral addictions. The current craving task includes a relatively simple cognitive component

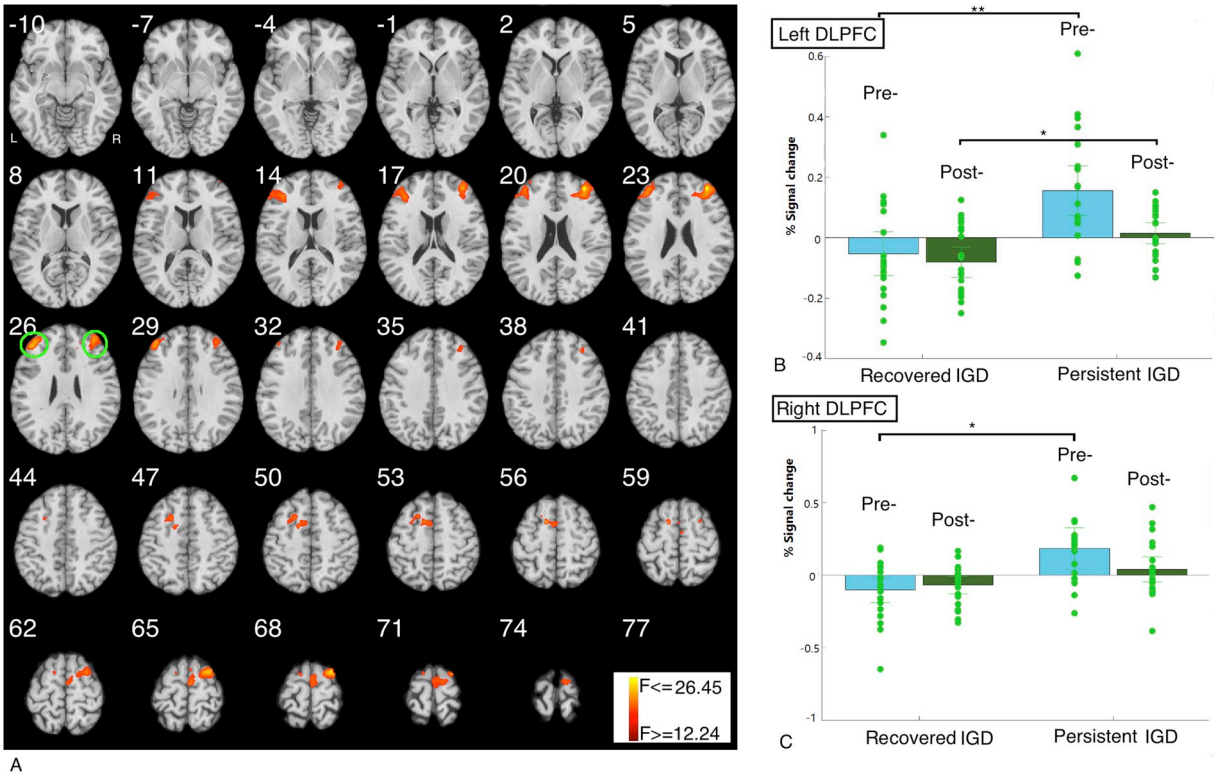

Fig. 4. Main effect of group (comparing recovered IGD to persistent IGD)
A: A main effect of group identified bilateral DLPFC
B/C: Extracted beta weights show brain responses in the bilateral DLPFC.

(identify whether or not the picture includes a face), and in this setting the gaming cues may present a conflicting distractor from performing this task. Studies have shown differences in brain responses in frontal brain regions in IGD subjects (as compared to those without) when performing inhibitory control tasks (Dong et al., 2010, 2012; Ko et al., 2014a), reflecting poor impulse control (Dong et al., 2011, 2014; Wang et al., 2016; Yuan et al., 2016), which is consistent with findings regarding prefrontal cortical dysfunction in substance addictions (Everitt et al., 2007; London et al., 2000; Schoenbaum and Shaham, 2008).

Among IGD and RGU subjects, a significant interaction also implicated the thalamus. Post-hoc analyses showed that the interaction was related to increased activation post-gaming versus pre-gaming in the IGD group that was greater than the corresponding increase in the RGU group. The thalamus is considered a key relay region including within reward systems (Haber and Knutson, 2010). The ventral striatum projects to the ventral tegmental area, which, in turn, projects back to the prefrontal cortex, via the medial dorsal nucleus of the thalamus (Haber et al., 1993; McFarland and Haber, 2002). Imaging findings suggest that primary and secondary rewards may increase thalamic activation (Haber and Knutson, 2010). In the current study, a

Table 3
Regions differing between recovered IGD and persistent IGD groups.

Cluster Number	x,y,z[a]	Peak Intensity	Cluster Size[b]	Region[c]	Brodmann's Area
Main effect of group					
1	36,48,21	12.89	40	R Middle Frontal Gyrus	9,46
2	−42,39,27	26.45	88	L Middle Frontal Gyrus	9,46
3	24,9,66	20.35	51	R Medial Frontal Gyrus	9
4	−12,9,57	16.06	48	L Medial Frontal Gyrus	9
Main effect of time					
1	−36,24,21	29.36	54	L Middle Frontal Gyrus	46
3	54,-27,54	24.54	39	R Postcentral Gyrus	5
4	−39,-63,-12	26.21	38	L Fusiform Gyrus	
5	0,-72,0	18.65	51	L Lingual Gyrus	
6	27,-15,39	21.65	47	R Precentral Gyrus	
7	27,-27,3	21.30	31	R Thalamus	
Interaction between group and time					
1	−33,27,15	18.10	77	L Insula	
2	39,12,9	22.43	36	R Insula	
3	−63,-30,39	16.28	43	L Inferior Parietal Lobule	1
4	9,42,6	21.07	38	R Anterior Cingulate	12
5	−24,45,6	18.93	33	L Middle Frontal Gyrus	46

[a] Peak MNI Coordinates.
[b] Number of voxels. Alphasim correction, $p < 0.001$; Cluster size > 30 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.

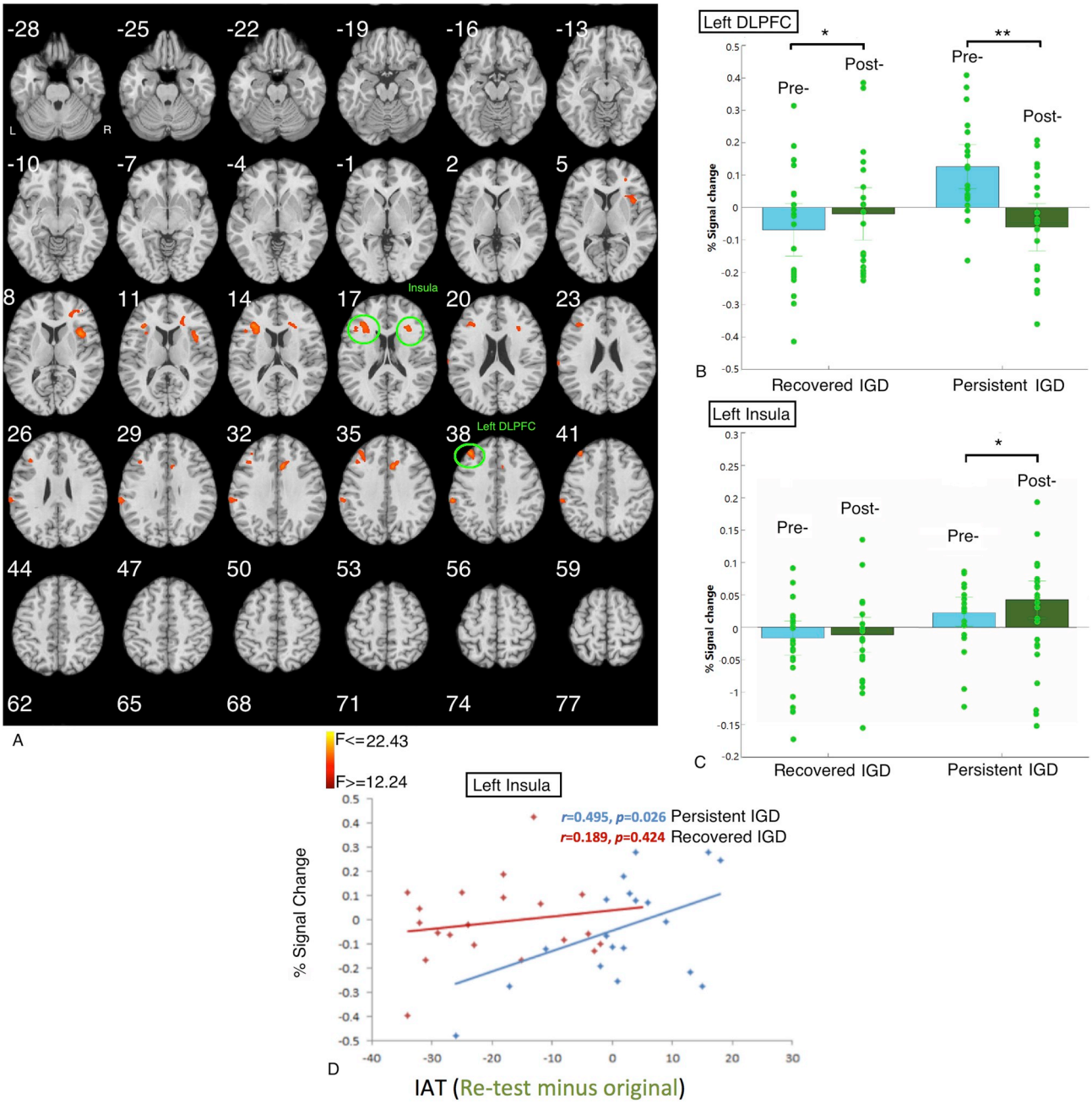

Fig. 5. Group-by-time interactions in recovered IGD and persistent IGD groups
A: A group-by-time interaction implicated the left DLPFC, right ACC and bilateral insula.
B/C: Extracted beta weights show brain responses in the left DLPFC and left insula.
D: Correlations between left insula activation (post-gaming minus pre-gaming and IAT changes (re-test minus original) in recovered IGD and persistent IGD groups.

positive correlation between self-reported craving and thalamic activation suggests that greater thalamic activation may promote craving in IGD subjects. Thus, the current results suggest that the forced-break post-gaming context enhanced IGD subjects' thalamic-related craving more so than in RGU subjects, resonating with our previously reported findings in IGD (Dong et al., 2017c) and those in substance addictions (Potenza et al., 2012).

4.2. Group main and group-by-time interaction effects in recovered and persistent IGD

Among recovered and persistent IGD subjects, a main effect of group effect implicated the DLPFC. However, the post-hoc analyses indicated that the recovered as compared to the persistent group showed less activation, contrary to our *a priori* hypotheses. The extent to which this finding may relate to aspects of conflict monitoring in the setting of performing a mild executive functioning task in the setting of gaming cues warrants further examination. Further examination of the role for the DLPFC (e.g., in other tasks and during interventions for IGD) is also needed in order to clarify the current findings relating to main effect of group.

The interaction findings may also provide insight into a role for the DLPFC in recovery. The observed group-by-time interaction in the DLPFC was related to decreased activation in the persistent IGD group post-gaming relative to pre-gaming with the opposite pattern observed in recovered IGD subjects. The findings taken together suggest a

complex involvement of the DLPFC in cue-elicited craving in IGD, perhaps relating to the heterogeneity of the DLPFC and the contexts in which cues are presented.

A group-by-time interaction also implicated the insula. Post-hoc analysis found the interaction in the insula was related to increased brain responses in the persistent IGD group at post-gaming relative to pre-gaming times. Data suggest that the insula is a key neural structure in interoceptive processes including those related to the perceived effects of drugs (Naqvi and Bechara, 2009), experiencing of conscious drug urges and translation of interoceptive signals into conscious feelings and behavioral biases during decision-making that involves uncertain risk and reward (Chikama et al., 1997; Naqvi and Bechara, 2009, 2010). When the amygdala receives information about the presence of drug cues (via environmental stimuli or thoughts of drug use), it may operate through internal representations of drug-related bodily states in the insula (Baxter and Murray, 2002; Naqvi and Bechara, 2009). Significant positive correlations were found between left insula activation and changes in measures of internet addiction in the group with persistent IGD, with greater insular activation related to worsening internet addiction. In sum, the increased insular activation in the group with persistent IGD post-gaming in conjunction with the correlations with changes in severity of internet addiction suggests that the insula may contribute to cue-elicitation processes in IGD in manners similar to other addictions, including behavioral addictions like gambling disorder (Kober et al., 2016; Limbrick-Oldfield et al., 2017). Further, the data suggest a role for the insula in natural recovery and possibly in treatments for IGD.

4.3. Limitations, summary and conclusions

The current study has several noteworthy limitations. First, all subjects were male, which limits the generalizability of findings. Investigation of these processes is needed in females. Second, the sample consisted of young adults from China who played predominantly LOL. The extent to which the findings generalize across age groups, jurisdictions and different types of games also requires additional investigation. The forced break in this study was intended to induce a short-term deprivation. The extent to which this deprivation may constitute withdrawal was not examined directly and could be a focus of future studies given controversies surrounding withdrawal symptoms in IGD (Starcevic and Aboujaoude, 2017). The measure of life events was not validated and was relatively blunt. Given the impact that IGD may have in multiple domains, more detailed assessment of life events using validated instruments is needed in order to place neuroimaging findings into more detailed contexts.

The current study investigates for the first time neural substrates related to natural recovery from IGD with a specific focus on cue-elicited brain responses pre- and post-gaming, with the latter occurring immediately following a forced break from gaming. The study has multiple strengths including a comparison group with RGU. Specific neural substrates previously implicated in addictions and their treatment were identified, with specific roles for the DLPFC, dorsal ACC, thalamus and insula suggested by the results.

Contributors

Guangheng Dong designed the study and wrote the first draft of the manuscript, Xiaoyue Liu collected and analyzed the data and prepared the tables, figures. Hui Zheng and Xiaoxia Du collected the data. Marc Potenza contributed in editing, interpretation and revision processes. All authors contributed to and have approved the final manuscript.

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Conflicts of interest

The authors report that they have no financial conflicts of interest with respect to the content of this manuscript. Dr. Potenza has received financial support or compensation for the following: Dr. Potenza has consulted for and advised INSYS, Shire, RiverMend Health, Opiant/Lightlake Therapeutics and Jazz Pharmaceuticals; has received research support from the NIH, Veteran's Administration, Mohegan Sun Casino, the National Center for Responsible Gaming, and Pfizer pharmaceuticals; 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 legal, gambling and other entities on issues related to addictive and impulse-control disorders; provides clinical care in the Connecticut Department of Mental Health and Addiction Services Problem Gambling Services Program; has performed grant reviews for the NIH and other agencies; has edited journals; 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 reported no biomedical financial interests or other potential conflicts of interest.

Appendix A. Supplementary data

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