

## Alterations in functional networks during cue-reactivity in Internet gaming disorder

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*Background:* Cue-induced brain reactivity has been suggested to be a fundamental and important mechanism explaining the development, maintenance, and relapse of addiction, including Internet gaming disorder (IGD). Altered activity in addiction-related brain regions has been found during cue-reactivity in IGD using functional magnetic resonance imaging (fMRI), but less is known regarding the alterations of coordinated whole brain activity patterns in IGD. *Methods:* To investigate the activity of temporally coherent, large-scale functional brain networks (FNs) during cue-reactivity in IGD, independent component analysis was applied to fMRI data from 29 male subjects with IGD and 23 matched healthy controls (HC) performing a cue-reactivity task involving Internet gaming stimuli (i.e., game cues) and general Internet surfing-related stimuli (i.e., control cues). *Results:* Four FNs were identified that were related to the response to game cues relative to control cues and that showed altered engagement/disengagement in IGD compared with HC. These FNs included temporo-occipital and temporo-insula networks associated with sensory processing, a frontoparietal network involved in memory and executive functioning, and a dorsal-limbic network implicated in reward and motivation processing. Within IGD, game versus control engagement of the temporo-occipital and frontoparietal networks were positively correlated with IGD severity. Similarly, disengagement of temporo-insula network was negatively correlated with higher game-craving. *Discussion:* These findings are consistent with altered cue-reactivity brain regions reported in substance-related addictions, providing evidence that IGD may represent a type of addiction. The identification of the networks might shed light on the mechanisms of the cue-induced craving and addictive Internet gaming behaviors.

**Keywords:** behavioral addiction, cue-reactivity, fMRI, functional brain networks, ICA, Internet gaming disorder

### INTRODUCTION

Internet gaming disorder (IGD), proposed to represent a putative behavioral addiction (Holden, 2001), has been included in the Section III of the fifth edition of the *Diagnostic and Statistical Manual for Mental Disorders* as a condition deserving further study (American Psychiatric Association, 2013). A common neurobehavioral basis of addictions may be classical and operant conditioning mechanisms that promote the acquisition and persistence of maladaptive behaviors (Heinz, Beck, Grusser, Grace, & Wrase, 2009; Heinz, Beck, Wrase, et al., 2009). That is, addiction-related cue conditioning is implicated in the development and relapse of addictive behaviors (Dickinson, Smith, & Mirenowicz, 2000; Robinson & Berridge, 1993). Thus, the examination of brain responses to Internet gaming cues among IGD may provide insight into one of the most important mechanisms of motivational and compulsive Internet gaming behavior (Tiffany & Conklin, 2000).

Cue-reactivity paradigms have been suggested to be a reliable and ecologically valid way to evaluate craving in substance use disorder and behavioral addiction (Ko et al., 2013; Pelchat, Johnson, Chan, Valdez, & Ragland, 2004; Potenza et al., 2003; Wilson, Sayette, & Fiez, 2004), such as IGD (Ko et al., 2013). These paradigms represent a model of cue-induced responses that provoke memory, positive anticipation, an imbalanced motivational state, withdrawal

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syndrome, rewarding drive, and lasting craving response (Ko et al., 2013; Sinha & Li, 2007; Skinner & Aubin, 2010).

Multiple studies have examined cue-induced brain reactivity in IGD using functional magnetic resonance imaging (fMRI) and found that IGD showed altered activity in several regions that were implicated in addictive disorders. Specifically, these regions include the orbitofrontal cortex (OFC), related to evaluation and expectancy of reward of stimuli; the nucleus accumbens and caudate, involved in reward processing; the anterior cingulate cortex (ACC), associated with attention and motivation processes; the parahippocampus, implicated in connecting environmental cues to the internal states; the dorsolateral prefrontal cortex (DLPFC), related to processing goal-directed behaviors; the amygdala, associated with initiating conditioned and unconditioned behavior; and the cuneus and precuneus, involved in processing visual memories associated with conditioned stimuli (Ko et al., 2009, 2013; Liu et al., 2017; Sun et al., 2012; Weinstein & Lejoyeux, 2015).

Increasing evidence in cognitive neuroscience suggests that an individual's behaviors are governed by the interactions of multiple brain regions (Park & Friston, 2013), which make up coherent functional networks (FNs; Smith et al., 2009). A certain brain region may participate in multiple cognitive processes interacting with other structures (Xu et al., 2013), particularly when it involves in multiple FNs. In this case, this brain region may not manifest as significant in general linear model (GLM) analyses, given that it may serve simultaneous but different or even opposite cognitive roles (Xu, Calhoun, & Potenza, 2015). As such, it is critical to identify FNs that integrate several brain regions for a given behavior. Group independent component analysis (ICA) of fMRI has been used to identify large-scale FNs by seeking sources of spatiotemporally coherent components that comprise the BOLD time course (Calhoun, Adali, Pearlson, & Pekar, 2001), and is able to identify alterations in task-related, concurrent, but opposite changes in time courses in the same brain regions that may not be detected by GLM-based analyses (Xu et al., 2015). Previous research using ICA in IGD has identified alterations in frontoparietal executive control networks during cognitive control and risky decision-making (Wang et al., 2016, 2017). However, less is known regarding potential FN alterations associated with cue-induced activity in IGD.

Moreover, most studies on cue-reactivity in IGD examined neural responses to Internet gaming cues relative to non-gaming, non-Internet-related, or neutral object cues (e.g., mosaic pictures; Ko et al., 2009, 2013). However, reported alterations in neural responses to gaming-related cues in IGD might be, at least in part, ascribed to the experience of gaming-related cues as (a) having a positive valence or (b) being associated with Internet use in general. In fact, prior studies found a large overlap in the brain circuitry (e.g., OFC, striatum, and amygdala) that underlay reactivity to cocaine stimuli relative to other evocative, non-drug stimuli (e.g., sex), suggesting the need to distinguish the responses to positive valence from responses to addiction-related cues (Garavan et al., 2000).

In this study, we used a cue-reactivity paradigm that included Internet-gaming stimuli (i.e., game stimuli) and general Internet surfing stimuli (i.e., control stimuli) and

sought to identify FNs associated with game-control reactivity (i.e., the direct comparison of responses to Internet gaming vs. general Internet surfing cues) among IGD and age-matched control participants. Internet-related cues instead of neutral cues were used to partition out the potential effects of positive valence and more importantly those of Internet use. Focusing on ICA-identified, game-control-related networks, we aimed to (a) investigate group differences in FN engagement during game-control reactivity and (b) explore the correlations between FN engagement and clinical assessments within IGD (i.e., the severity of IGD and the craving for Internet gaming).

## MATERIALS AND METHODS

### *Participants and clinical assessments*

Given the higher occurrence of IGD among men (Ko et al., 2009), the final sample included 29 male IGD subjects and 23 matched healthy controls (HCs). This final sample of 52 subjects represents a subset of the individuals included in our previous report (Liu et al., 2017), as we used a stricter screen criteria on IGD. Participants represented a total of 432 males (319 potential IGD subjects playing Internet gaming frequently and 113 potential HCs playing Internet gaming occasionally), who were recruited through advertisements posted at local universities and completed initial web-based screening. Similar to our previous study (Zhang et al., 2016), IGD was diagnosed using the following criteria: (a) scores of the Chinese Internet Addiction Scale (CIAS; Chen, Weng, Su, Wu, & Yang, 2003)  $\geq 67$  (Ko et al., 2009), (b) spent more than half of the time online on games, and (c) spent  $\geq 14$  hr on Internet gaming per week (i.e., with averagely at least 2 hr spent on Internet gaming every day). The criteria of HC included (a) scores of CIAS  $\leq 60$  and (b) never spent  $\geq 2$  hr per week on Internet gaming. Additional criteria for all the participants included: (a) 18–30 years of age, (b) right-handed, (c) no history of other psychiatric or neurological illness, (d) no current or previous use of illegal substances or gambling, (e) not currently taking any psychotropic medications, and (f) suitable for magnetic resonance imaging (MRI) scanning. All the participants also completed the Beck Anxiety Inventory (BAI; Beck, Brown, Epstein, & Steer, 1988) and Beck Depression Inventory (BDI; Beck, Erbaugh, Ward, Mock, & Mendelsohn, 1961) to assess anxiety and depressive symptoms.

### *Cue-reactivity task*

The cue-reactivity task was the same as that used in our previous study (Liu et al., 2017). Briefly, 24 blocks were presented. Each block contained five stimuli, with each presented in a pseudorandom order for 3.7 s following a 0.3-s fixation cross. These blocks were divided into two separate runs, each of which included three game blocks (i.e., Internet gaming pictures) and three control blocks (i.e., general Internet surfing pictures) alternating with six mosaic baseline blocks (i.e., degraded mosaic stimuli of game and control cues following the corresponding game or control blocks). Following each game or control block, a

one-item 6-point Visual Analogue Scale (ranging from 1 = “not craving at all” to 6 = “severe craving”) lasting 4 s was used to assess the craving for Internet gaming or general online surfing, respectively.

### Image acquisition

MRI was conducted using a Siemens Trio 3-Tesla scanner (Siemens, Erlangen, Germany). Forty-one 3.0-mm axial fMRI data were acquired using an echo-planar imaging sequence with the parameters as follows: TR = 2,000 ms; TE = 25 ms; flip angle = 90°; matrix size = 64 × 64; resolution = 3 × 3 mm<sup>2</sup>. The slices were tilted 30° clockwise from the anterior commissure–posterior commissure (AC-PC) plane to obtain better signals in the OFC. One hundred forty-four high-resolution slices were obtained using T1-weighted sagittal 3-D magnetization prepared rapid gradient-echo sequence: TR = 2,530 ms; TE = 3.39 ms; TI = 1,100 ms; FA = 7°; and FOV = 256 × 256 mm; thickness = 1.33 mm in-plane resolution = 1 × 1 mm<sup>2</sup>.

### Group independent component analysis

Spatial processing of functional data was performed in SPM8 (Wellcome Department of Cognitive Neurology, London, UK) and included reorientation to the AC-PC line, realignment, normalization to 3 × 3 × 3 mm<sup>3</sup> MNI space, and smoothing with a Gaussian kernel of 5 mm at full width half maximum.

The spatially processed images were then analyzed in a using the Group ICA of fMRI Toolbox (version 2.0e; <http://mialab.mrn.org/software/gift>). Briefly, data from all the participants were concatenated into a single data set and then were reduced in dimensionality using two stages of principal component analysis (Calhoun et al., 2001). To examine large-scale functional networks, 30 independent components were then extracted from the group aggregate with the Infomax algorithm (Abou-Elseoud et al., 2010; Bell & Sejnowski, 1995). Extraction was repeated 20 times using ICASSO to assess the stability of independent components (Himberg, Hyvärinen, & Esposito, 2004). The time course and spatial map for each component were back-reconstructed for each participant (Calhoun et al., 2001). One-sample *t*-tests were performed on Z-scaled spatial maps across all participants in SPM8 to determine regions positively significantly integrated into each component at a voxel-level family-wise error (FWE)-corrected  $p_{FWE} < 0.0001$  combined with a cluster extent threshold of 100 voxels.

Each of the 30 components had a cluster quality index greater than 0.8, indicating a highly stable ICA decomposition. We visually inspected the spatial maps, according to previous studies, visualization, and/or prior knowledge (Laird et al., 2011; Smith et al., 2009); 13 of the 30 extracted components were identified as representing artifacts and were excluded from all subsequent analyses.

### Model specification and task-relatedness

Modeling of the cue-reactivity task was performed in SPM8, including the onset of task events (i.e., game cues, control cues, and craving rating periods, while mosaic baseline

blocks were as reference), convolved with the canonical hemodynamic response function, and the motion parameters from realignment as regressors of no interest. In order to examine the task relevance of each component, a multiple regression was performed to compare component time courses with the modeled event time courses for the game, control, and craving-rating events. Resulting beta weights indicated the extent to which a given network was temporally associated with, or “engaged” during each task condition. Beta weights were averaged across both runs for game and control conditions for each subject.

### Statistical analyses of beta weights

To identify which of the 17 non-artifactual components represented cue-reactivity-related FNs, a “game-control” contrast, calculated as the beta weight difference between game cues relative to control cues, was examined with two within-group one-sample *t*-tests against zero using Bonferroni correction for multiple comparisons ( $\alpha$  as  $.05/34 = .0015$ ). Eight components displayed a significant difference from zero for “game-control” contrast, indicating differential engagement induced by the Internet gaming stimuli versus the general Internet surfing stimuli and were thus considered to represent FNs associated with game-control reactivity.

For the eight FNs associated with cue-reactivity in either IGD or HC, two-sample *t*-tests were performed between IGD and HC groups to examine the group differences in the “game-control” contrast. Because IGD reported higher anxiety, depression scores, and proportion of smoking than HC, we investigated the group differences in these eight FNs during cue-reactivity regressing BDI, BAI scores, and state of smoking (smoking = 1 and no smoking = 0). Four FNs showed altered activity in IGD (Bonferroni corrected  $\alpha$  as  $.05/8 = .0063$ ). FNs were labeled based on the primary regions of positive spatial integration in each network according to the known intrinsic connectivity networks (Allen et al., 2011; Laird et al., 2011; Smith et al., 2009).

Correlation analyses were used to explore relationships between FN engagement patterns and subjective craving ratings and addiction severity (score of CIAS and the time spent on Internet gaming per week) within the IGD. Moreover, exploratory correlational analyses were performed on the beta weights to examine potential interactions between FNs during cue-reactivity in IGD.

### Ethics

This study was approved by the institutional review board of the State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University (study number: ICBIR\_A\_0075\_001), with all participants providing written informed consent.

## RESULTS

### Demographic and behavioral characteristics

The demographic characteristics of the IGD and HC are shown in Table 1. Compared with HC, IGD reported higher

Table 1. Participants' characteristics and craving ratings

	IGD (n = 29) mean ± SD	HC (n = 23) mean ± SD	t/χ <sup>2</sup> /U/F	p
<b>Characteristics</b>				
Age	22.59 ± 2.24	23.09 ± 2.13	-0.82	.418
Years of education	15.52 ± 1.43	15.91 ± 1.47	-0.98	.333
CIAS scores	75.55 ± 7.64	45.65 ± 9.80	12.37***	<.001
Time Internet gaming (hours per week)	21.86 ± 9.82	0.92 ± 0.20 <sup>a</sup>	6.28***	<.001
Alcohol use (at least once per month)	25 <sup>b</sup> /0.86 <sup>c</sup>	17 <sup>b</sup> /0.74 <sup>c</sup>	1.25	.264
Cigarette use (at least once per month)	5 <sup>b</sup> /0.17 <sup>c</sup>	0 <sup>b</sup> /0.00 <sup>c</sup>	4.39*	.036
Depression severity (BDI scores)	7.86 ± 5.67	2.91 ± 3.04	4.03***	<.001
Anxiety severity (BAI scores)	5.48 ± 5.25	3.18 ± 3.16	1.96	.056
<b>Craving ratings</b>				
Background craving	29.83 ± 7.62	13.30 ± 6.93	41.35 <sup>d</sup> ***	<.001
Craving for Internet gaming	4.95 ± 1.16	1.52 ± 0.67	109.08 <sup>d</sup> (39.15) <sup>e</sup> ***	<.001
Craving for general Internet surfing	3.37 ± 1.21	2.94 ± 1.10	0.78 <sup>d</sup> (0.93) <sup>e</sup>	.383 <sup>d</sup> (.341) <sup>e</sup>
Craving (game-control)	1.58 ± 1.09	-1.42 ± 1.04	66.50 <sup>d</sup> (35.93) <sup>e</sup> ***	<.001

Note. SD: standard deviation; IGD: Internet gaming disorder; HC: healthy control; CIAS: Chinese Internet Addiction Scale; FTND: Fagerstrom test for nicotine dependence; BAI: Back Anxiety Inventory; BDI: Beck Depression Inventory; Background craving: assessed by an 8-item Likert scale adapted from the Questionnaire of Smoking Urges; Craving (game-control): scores of Craving for Internet gaming – scores of Craving for general Internet surfing stimuli.

<sup>a</sup>n = 6. <sup>b</sup>The number of participants. <sup>c</sup>The rate of alcohol and cigarette user. <sup>d</sup>F test regressing BAI, BDI, and state of smoke. <sup>e</sup>F test regressing BAI, BDI, state of smoke, and background craving.

\*p < .05. \*\*\*p < .001.

proportion of smoking, higher levels of depression, marginally significant higher anxiety, and higher craving for Internet gaming following game cues versus general Internet surfing cues.

*FNs during reactivity in IGD*

A total of four FNs were identified as related to game cues relative to general Internet surfing control cues (i.e, game-control) and differed in game-control engagement between

groups. The regional composition of each FN is provided in Table 2. In IGD, all the four FNs were more strongly engaged (or disengaged) during game cues relative to control cues. In comparison, among HCs, the four FNs were either more strongly engaged/disengaged during control cues or did not differ in engagement between cue conditions.

A temporo-occipital network (Figure 1), consistent with IC48 of Allen et al. (2011) and IC10 of Laird et al. (2011), consisted of coordinated signals in the bilateral middle occipital and temporal cortices. Activation in this network was

Table 2. Regional integration of altered game-control-related FNs

Network/region	Hemisphere	κ	x	y	z	Z
<b>Temporo-occipital network</b>						
Middle occipital gyrus/fusiform	R/L	4,922	33	-66	-12	30.15
<b>Temporo-insular network</b>						
Superior temporal gyrus/insula	R	2,344	42	-18	15	24.24
Superior temporal gyrus/insula	L	2,229	-36	-24	3	21.63
Supplementary motor area	R/L	364	6	-3	63	15.48
<b>Frontoparietal network</b>						
Middle frontal gyrus/inferior parietal lobe	L	4,347	-45	-42	45	23.08
Inferior frontal gyrus/middle frontal gyrus	R	774	45	9	33	18.06
Cerebellum posterior lobe	R	654	24	-75	-45	19.63
Middle temporal gyrus	L	506	-54	-54	-9	20.27
Inferior parietal lobule	R	403	33	-66	36	18.15
Inferior temporal gyrus	R	251	57	-48	-12	15.86
Middle frontal gyrus	R	205	30	6	54	14.24
Anterior cingulum	R/L	108	0	6	27	20.94
<b>Dorsal-limbic network</b>						
Midbrain/thalamus/putamen	R/L	2027	6	-21	-3	22.87
Cingulate gyrus/supplementary motor area	R/L	623	0	6	54	15.37

Note. Voxel-level family-wise error (FWE) corrected  $p_{FWE} < .0001$ , cluster extent threshold ( $\kappa$ ) > 100 voxels. Peak coordinates are reported in MNI space. FNs: functional networks.



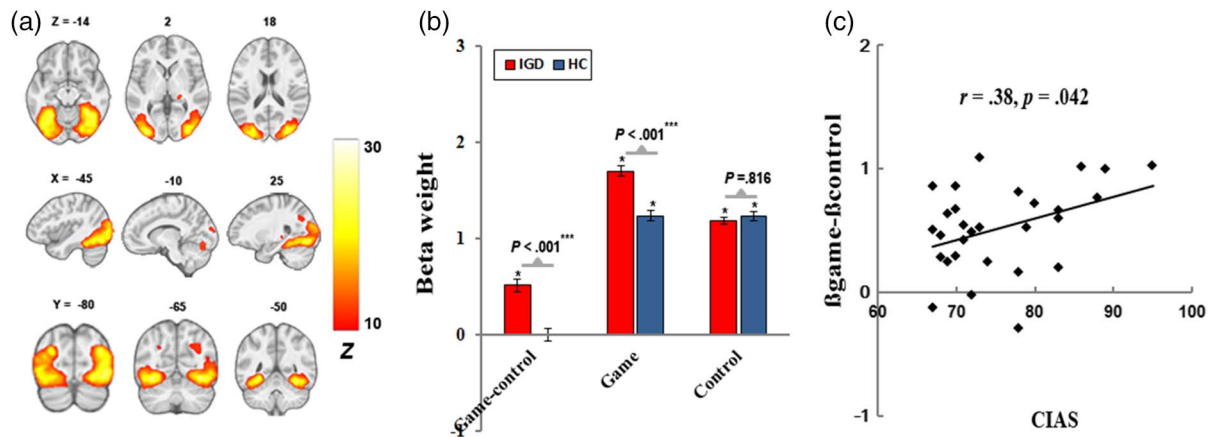


Figure 1. The temporo-occipital network. (a) Spatial map displayed at a threshold of  $p_{FWE} < .0001$  and cluster size ( $\kappa$ )  $> 100$ ; (b) greater engagement for “game-control” contrast in IGD; and (c) positive correlation of cue-induced FN engagement with CIAS scores

greater for the “game-control” contrast and positively correlated with the CIAS scores among IGD ( $r = .38, p = .042$ ).

A temporo-insular network (Figure 2), corresponding to IC17 of Allen et al. (2011) and IC16 of Laird et al. (2011), included coordinated signals in the bilateral primary auditory cortices, superior temporal gyrus (STG), and insular. IGD showed greater disengagement (negatively engaged) for the “game-control” contrast, and there was a negative association between activity of this network and craving for Internet gaming (following game cues vs. general Internet surfing cues) within IGD ( $r = -.39, p = .034$ ).

A frontoparietal network (Figure 3) incorporated regions involved in multiple frontal and attentional networks of Allen et al. (2011), including DLPFC, middle frontal cortex and inferior frontal cortex, middle temporal gyrus, and inferior parietal lobe (IPL). We found higher response to “game-control” contrast in this network and its positive correlation with hours spent on Internet gaming in IGD ( $r = .41, p = .027$ ).

A dorsal-limbic network (Figure 4), similar to IC21 in Allen et al. (2011) and IC3 of Laird et al. (2011), composed of coordinated signals in the putamen, thalamus, midbrain, and dorsal ACC. IGD showed greater engagement of this network in the “game-control” contrast than HC.

The exploratory between FN correlational analyses of “game-control” beta weights revealed that greater engagement of the frontoparietal network was positively associated with engagement of the temporo-occipital network ( $r = .60, p < .001$ ) and the dorsal-limbic network ( $r = .44, p = .016$ ), and negatively associated with disengagement of the temporo-insular network ( $r = -.37, p = .048$ ). In addition, engagement of the dorsal-limbic network was positively correlated with engagement of the temporo-occipital network ( $r = .37, p = .048$ ) (see Supplementary Figure S1).

## DISCUSSION

This study investigated functional brain networks associated with cue-reactivity in IGD. We identified four FNs that differed in engagement during Internet gaming stimuli as compared to general Internet surfing stimuli (game-control), and differed in engagement in IGD as compared to HC. Specifically in IGD, game-control engagement of the temporo-occipital and frontoparietal network was associated with severity of IGD (CIAS scores and hours spent on gaming, respectively). Game-control disengagement of a temporo-insular network was associated with craving.

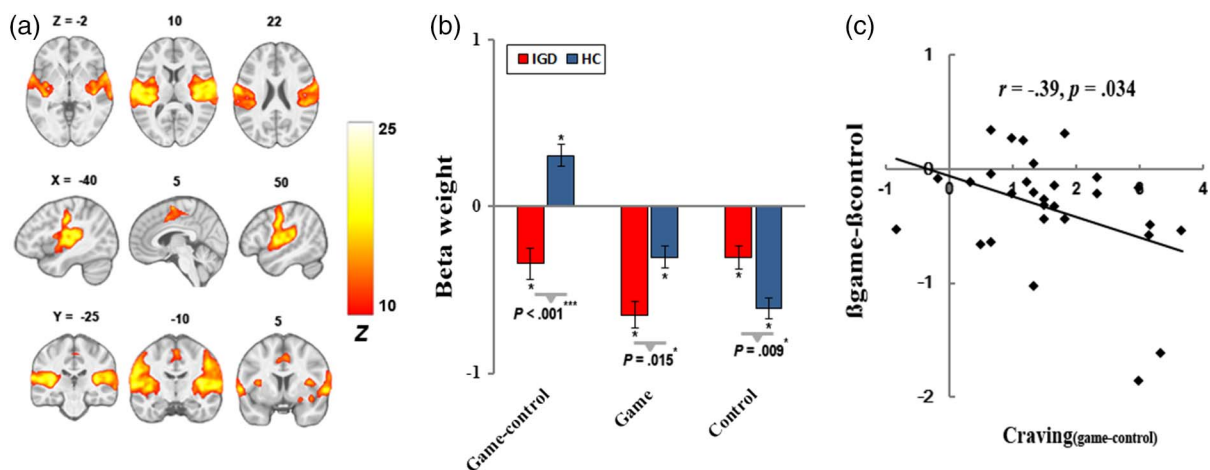


Figure 2. The temporo-insular network. (a) Spatial map displayed at a threshold of  $p_{FWE} < .0001$  and cluster size ( $\kappa$ )  $> 100$ ; (b) greater disengagement for “game-control” contrast in IGD; and (c) negative correlation of cue-induced FN activity with craving for Internet gaming

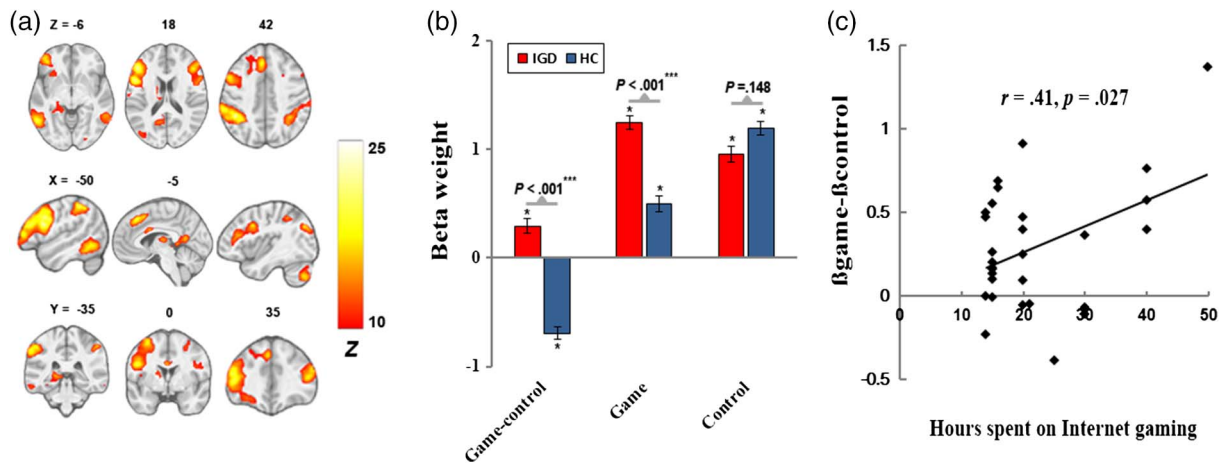


Figure 3. The frontoparietal network. (a) Spatial map displayed at a threshold of  $p_{FWE} < .0001$  and cluster size ( $\kappa$ )  $> 100$ ; (b) greater engagement for “game-control” contrast in IGD; and (c) positive correlation of cue-induced FN engagement with hours spent on Internet gaming

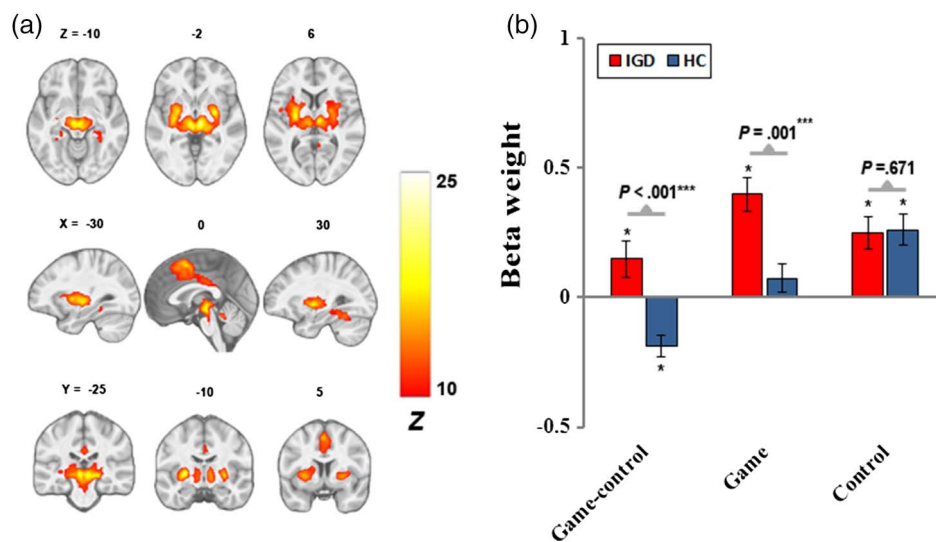


Figure 4. The dorsal-limbic network. (a) Spatial map displayed at a threshold of  $p_{FWE} < .0001$  and cluster size ( $\kappa$ )  $> 100$ ; (b) greater engagement for “game-control” contrast in IGD

However, engagement of a dorsal-limbic was not associated with any clinical measures. These results provide insights into cue-induced FN activity and possible mechanisms of craving and addictive behaviors in IGD. The identified four FNs were discussed in details as follows.

#### The temporo-occipital network

The temporo-occipital network has been linked to motivation and visual processing, and associated with viewing complex, often emotional, stimuli (Laird et al., 2011). In IGD, greater engagement of this network in response to the “game-control” contrast was consistent with the greater visual processing in the middle occipital cortex and fusiform gyrus induced by addiction-related cues as compared to evocative control stimuli in IGD (Liu et al., 2017; Lorenz et al., 2013), and during the “cannabis-food” contrast in cannabis addicts (Charboneau et al., 2013). In addition, the bilateral temporo-occipital coupling was also found to be

higher in obese as compared to control subjects (Olde Dubbelink et al., 2008).

We found that engagement of the temporo-occipital FN was positively correlated with the CIAS scores among IGD, which is consistent with positive correlations between occipital responses to addictive cues and the severity of alcohol/nicotine dependence (Claus, Ewing, Filbey, Sabbineni, & Hutchison, 2011; Smolka et al., 2006). Overall, these results suggest that IGD showed enhanced visual processing of Internet gaming cues (e.g., greater visual scanning or processing of the image details), and this visual processing became more salient with the severity of IGD increased.

#### The temporo-insular network

Negative engagement, or disengagement, of the temporo-insular network has been linked to the processing of salient visual or affective stimuli (Laird et al., 2011). For example,

insula has been implicated in avoidance learning and fear conditioning following exposure to aversive stimuli (Samanez-Larkin, Hollon, Carstensen, & Knutson, 2008). Thus, the insula and STG were deactivated by addiction-related cues in cannabis abusers (Charboneau et al., 2013), obesity (Garcia-Garcia et al., 2014), and IGD (Liu, Hospadaruk, Zhu, & Gardner, 2011). Moreover, we found that greater disengagement of the temporo-insula FN was correlated with increased game-craving rating within IGD. This association is in conflict with the positive correlation between activity of insula and craving reported in previous research (Abdollahi et al., 2015; Bonson et al., 2002; Naqvi, Rudrauf, Damasio, & Bechara, 2007). This discrepancy may be due to the core methodological differences between the GLM and ICA approaches and further research is needed to confirm this finding.

These results regarding the temporo-insula network suggest that response to gaming-cues in IGD may be similar to the substance users' response to drug cue (Franken, 2003). According to the conditioned model, the Internet gaming cues, as consequence of conditioning process, would become condition stimuli for IGD, inducing a conditioned craving response to gaming-related stimuli. Thus, IGD would engage more inhibition of auditory functioning to facilitate the detection and processing of visual addiction-relevant cues, perhaps resulting in higher craving (Ryan, 2002).

#### *The frontoparietal network*

The frontoparietal network has been implicated in multiple cognitive and executive processes, including attention, goal-direction, working memory, and cognitive control (Laird et al., 2011). Correspondingly, the greater activation of DLPFC and the IPL during addiction-related cues compared with other evocative stimuli has been previously identified in IGD (Sun et al., 2012; Weinstein & Lejoyeux, 2015) as well as in cocaine abusers (Garavan et al., 2000; Wilcox, Teshiba, Merideth, Ling, & Mayer, 2011).

The importance of this network in cue-reactivity can be reflected by the cognitive model that suggests addiction-related cues can trigger positive expectations and thus may encourage addictive behaviors (Skinner & Aubin, 2010). The positive correlation between cue-induced frontoparietal network engagement and hours spent on Internet gaming in IGD may indicate that IGD who spent more time on gaming may exhibit more memories of prior gaming experiences when seeing Internet gaming cues.

An alternative explanation for greater activation of the frontoparietal network might be greater identification with the virtual world. Studies found that massively multiplayer online role-playing games addiction has been associated with self-concept impairments and increased identification with ones' own avatar. Internet gamers display greater activity in parietal regions (especially in the left angular gyrus) during avatar reflection, and this response is associated with symptom severity (Lemenager et al., 2014, 2016). Correspondingly, multiple areas in the frontoparietal network, such as IPL (including the angular gyrus) and pre-frontal cortex, were found to be involved in theory of mind and self-other distinction (Frith & Frith, 2006; Schurz,

Radua, Aichhorn, Richlan, & Perner, 2014; Schurz, Tholen, Perner, Mars, & Sallet, 2017; van Veluw & Chance, 2014). Thus, individuals with IGD may be more inclined to form an identification with the virtual world that could be triggered by the gaming-related cues. In addition, the alternative explanation for the association between higher engagement of the frontoparietal network and dorsal limbic network may be that the identification with the virtual world was related to a motivation to escape into the virtual world in individuals with IGD. Future research is needed to verify and confirm these group difference and correlation findings.

#### *The dorsal-limbic network*

The limbic network has been associated with reward, motivation, and emotional processing (Laird et al., 2011). In this study, IGD displayed greater cue-induced engagement of an FN comprising mostly dorsal structures of the limbic system. For example, the dorsal striatum is considered to be closely associated with incentive salience for conditioned rewarding stimuli (Berridge & Robinson, 2003), and is implicated in the habituation and automatization of compulsive drug-seeking (Everitt & Robbins, 2013).

According to the incentive salience theory, the salience of gaming and gaming-related stimuli would increase through Pavlovian conditioning (Robinson & Berridge, 1993). Consequently, the presence of gaming-related cues alone can act as a conditioned reinforcer (Dickinson et al., 2000) and then induces higher activation of reward system and reward processing (Volkow, Wang, & Baler, 2011). Consistently, greater activation in mesolimbic dopamine reward circuits was also found in drug addicts and IGD (Claus et al., 2011; Due, Huettel, Hall, & Rubin, 2002; Garavan et al., 2000; Liu et al., 2011).

The lack of associations between the engagement of this network and the severity of IGD or the craving for Internet gaming might be explained by the neural mechanisms of transition from goal-directed drug use to habitual, compulsive drug use, and possible mediation of dorsal striatum for the habitual compulsive behavior (Everitt & Robbins, 2013).

#### *General discussion*

Neurobiological models of addiction posit that addiction-related cues provoke enhanced activation of the visual, memory, reward, and motivation processing that may commandeer executive control systems (Volkow et al., 2010). Consistent with these theories of substance-related addiction, current findings of viewing Internet gaming cues relative to general Internet surfing cues indicated greater engagement of visual, attentional, motivational, reward, and executive systems and greater disengagement of the auditory processing system in IGD. This pattern of FN engagement indicates IGD's attentional and emotional bias toward gaming cues, which may elicit increased craving and ultimately can lead to addictive gaming behaviors. The consistent findings, with previous GLM-based research on cue-reactivity in IGD (Ko et al., 2013; Weinstein & Lejoyeux, 2015), obesity (Wiemerslage et al., 2016), and

substance addictions (Volkow et al., 2010), provide further evidence for that the mechanisms of behavioral addiction resemble those in substance addiction (Potenza, 2008).

Furthermore, the interactions between these FNs may provide further insights for the understanding of the cue-induced craving and Internet gaming behaviors in IGD, and perhaps addictive behaviors more broadly. Exploratory correlational analyses revealed that the frontoparietal network was positively correlated with the temporo-occipital and dorsal-limbic networks, and negatively associated with the temporo-insular network. These correlations may indicate a coordination among these networks in experiencing the Internet gaming cues toward final planning for, and partaking in, Internet gaming behaviors. Specifically, the frontoparietal network may draw attention to addiction-related cues through integration of sensory input from the temporo-occipital and temporo-insular networks, linking the stimuli to gaming memories (Goldman-rakic & Leung, 2002), and planning gaming behaviors through interactions with the reward and motivational processing in the dorsal-limbic network (Mitchell, 2011; Skinner & Aubin, 2010).

Several theoretical models have stressed the important role of reward sensitivity and craving underlying the development and maintenance of IGD. These models suggest enhanced craving responses are associated with reduced executive functioning and inhibitory control, and the reductions in executive control in turn lead to diminished inhibition of motivation-seeking and craving. Such imbalances would promote maladaptive decision-making, resulting in excessive Internet gaming and eventually IGD. Furthermore, the excessive Internet gaming and the gratification perceived would lead to an increase in cue-reactivity and craving, through conditioning and reinforcement processes. A vicious cycle is formed to heavy the severity of IGD (Brand, Young, Laier, Wolfing, & Potenza, 2016; Dong & Potenza, 2014).

Note that our findings using the ICA approach revealed some inconsistencies in brain activity associated with cue-reactivity relative to prior GLM-based studies of cue-reactivity in IGD. This discrepancy is likely due to the core methodological differences between the GLM and ICA approaches. That is, ICA identifies components of regional signals that contribute to large-scale distributed networks, whereas GLM examines the aggregate, emergent BOLD signal in a particular region. This outlines the complexity of regional activations and the necessity to consider interactions with other structures to provide nuanced understanding of the function of a certain region, particularly as it may integrate into multiple functional networks.

#### Limitations

Features of this study may limit the generalizability of the current findings to other IGD populations. First, given that we only recruited male participants, future studies involving both male and female participants are needed to identify the potential unique cue-reactivity processes among female IGD subjects. Second, IGD participants in this study represented a sample of students enrolled in Chinese universities and thus the findings may not be generalized to a broader clinical population. Finally, as this was a cross-sectional study,

it cannot be determined if the observed alterations in FN engagement represent a consequence of IGD or a vulnerability factor that may have predisposed participants to developing IGD.

## CONCLUSIONS

To our knowledge, this is the first report identifying alterations in the functional brain networks involved in the cue-reactivity in IGD. Compared with HC, individuals with IGD displayed altered engagement of four distinct FNs, involved in sensory processing, attention, memory, motivation, and executive functioning, in processing Internet gaming cues relative to general Internet surfing cues. These findings are consistent with cue-reactivity alterations reported in individuals with substance-related addictions and provide further evidence that IGD may represent a behavioral addiction.

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