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Disrupted prefrontal regulation of striatum-related craving in Internet gaming disorder revealed by dynamic causal modeling: results from a cue-reactivity task

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Abstract

Background. Studies of Internet gaming disorder (IGD) suggest an imbalanced relationship between cognitive control and reward processing in people with IGD. However, it remains unclear how these two systems interact with each other, and whether they could serve as neurobiological markers for IGD.

Methods. Fifty IGD subjects and matched individuals with recreational game use (RGU) were selected and compared when they were performing a cue-craving task. Regions of interests [anterior cingulate cortex (ACC), lentiform nucleus] were selected based on the comparison between brain responses to gaming-related cues and neutral cues. Directional connectivities among these brain regions were determined using Bayesian estimation. We additionally examined the posterior cingulate cortex (PCC) in a separate analysis based on data implicating the PCC in craving in addiction.

Results. During fixed-connectivity analyses, IGD subjects showed blunted ACC-to-lentiform and lentiform-to-ACC connectivity relative to RGU subjects, especially in the left hemisphere. When facing gaming cues, IGD subjects trended toward lower left-hemispheric modulatory effects in ACC-to-lentiform connectivity than RGU subjects. Self-reported cue-related craving prior to scanning correlated inversely with left-hemispheric modulatory effects in ACC-to-lentiform connectivity.

Conclusions. The results suggesting that prefrontal-to-lentiform connectivity is impaired in IGD provides a possible neurobiological mechanism for difficulties in controlling gaming-cue-elicited cravings. Reduced connectivity ACC-lentiform connectivity may be a useful neurobiological marker for IGD.

Introduction

Although there is continuing debate regarding diagnostic criteria and thresholds for Internet gaming disorder (IGD) and whether IGD should be considered a psychiatric disorder, it has been included as a potential psychiatric disorder in DSM-5. Although debated (Aarseth et al., 2017; King & Gaming Industry Response, 2018; Rumpf et al., 2018; Saunders et al., 2017), the World Health Organization has recognized gaming disorder in the ICD-11 based on its clinical and public health impacts (http://www.who.int/features/qa/gaming-disorder/en/). IGD has been associated with multiple negative health measures and classified as an addictive behavior or behavioral addiction (Brand et al., 2019; Dong & Potenza, 2016; Dowling, 2014; Petry, Rehbein, Ko, & O'Brien, 2015; Wartberg, Kriston, Zieglmeier, Lincoln, & Kammerl, 2019). The negative consequences of IGD, including poor academic performance, excessive amounts of time spent gaming, and psychopathology like depression, have attracted widespread public concern, research, and clinical attention.

Impairments in executive control and reward processing have been suggested in recent IGD studies, implicating prefrontal and striatal regions. Neurocognitive research into IGD has identified differences in the function of the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), lentiform nucleus (as part of the basal ganglia), and other structures (Dong, Wang, Du, & Potenza, 2017a; Weinstein, Livny, & Weizman, 2017; Yao et al., 2017; Zheng et al., 2019). These regions are relevant to executive control, reward processing,

decision-making, and other processes. The DLPFC and ACC, core components of executive control networks (Dong, Liu, Zheng, Du, & Potenza, 2019a; Kober et al., 2010), show less activation in IGD relative to non-IGD (healthy control) subjects, suggesting that IGD subjects' executive control is impaired and they may not engage executive control effectively (Brand et al., 2019; Weinstein et al., 2017; Yao et al., 2017). These findings suggest biological mechanisms for clinical features of IGD and thus may provide insight into potential treatment targets. On the other hand, brain regions such as the lentiform, insula, or thalamus typically show greater activity in IGD relative to non-IGD subjects when these individuals are exposed to gaming-related cues, consistent with cue-elicited-craving responses in substance addictions (Bostan & Strick, 2018; Dong, Wang, Wang, Du, & Potenza, 2019b). Impaired executive control over strong motivational drives, especially in the setting of environmental gaming cues, may make it difficult for IGD subjects to cease gaming despite adverse consequences (Brand, Young, Laier, Wolfling, & Potenza, 2016; Dong et al., 2019a).

Several studies have examined executive control over reward processing in IGD. For example, one study reported inverse relationships between functioning of executive control and reward networks in IGD, suggesting that impairments in executive control may lead to inefficient inhibition of enhanced cravings related to excessive online gaming (Dong, Lin, Hu, Xie, & Du, 2015; Ma et al., 2019). Studies of problematic internet use showed an association between executive control and reward processing that suggested an imbalance of self-regulation as a result of diminished function of both systems (Qi et al., 2016; Weinstein, 2017). A study of individuals with recreational game use (RGU) as comparison subjects found that individuals with IGD showed lower prefrontal activation and higher cortico-striatal activation (Dong et al., 2020; Dong, Wang, Wu, & Potenza, 2017b). Another study related the striatum to cognitive-control deficits in IGD (Cai et al., 2016).

Several theoretical models describe reward and control systems and their interactions. The I-PACE (Interaction of Person-Affect-Cognition-Execution) model proposed that IGD may be the consequence of interactions between predisposing factors, including cognitive biases to gaming cues, affective and cognitive responses to situational triggers, and reduced executive functioning (Brand et al., 2016, 2019). Another prior model of IGD hypothesized that strong gaming motivations in conjunction with impaired executive control may lead to poor regulation of such desires, leading to addictive engagement (Dong & Potenza, 2014). Other models (e.g. Brand, Young, & Laier, 2014) have emphasized features of executive control and reward-seeking and their interaction in the etiology and maintenance of internet-use disorders like IGD.

Multiple studies have focused on regional brain activations that differ between IGD and control comparison subjects when performing specific tasks, placing findings of between-group regional activation differences into the context of the existing literature regarding purported functions of the brain areas. This type of approach, while valuable, does not reveal interactions among different brain regions or networks.

Analyses of functional connectivity (FC) permit exploration of interactions between different brain regions. FC may be assessed with respect to correlation, coherence, and spatial grouping based on temporal similarities (Fox & Raichle, 2007; Friston, Kahan, Razi, Stephan, & Sporns, 2014). FC analysis of resting-state data found weaker connectivity within executive-control regions in IGD *v.* control subjects that was associated with poorer cognitive control (Park et al., 2019). Additionally, resting-state data suggested imbalanced functional links between executive-control and reward networks in IGD (Bae, Han, Jung, Nam, & Renshaw, 2017; Dong et al., 2015). However, while these studies suggest possible neurobiological mechanisms underlying IGD, they also have limitations. First, they only provide temporal correlations between activations in specific brain regions and do not examine directionality of interactions. Second, most studies use resting-state data. Thus, they do not provide insight into brain function during specific cognitive functions such as responses to gaming cues, a behaviorally and clinically relevant aspect of IGD.

Taken together, there exists a need for more sophisticated analytic approaches that allow for more concise mapping between brain activity and psychological states in IGD. Dynamic causal modeling (DCM) provides a principled means of characterizing roles of different brain regions by measuring their dynamic interactions/effective connectivity with other regions, inferring the strengths and directions of regional interactions (Daunizeau, David, & Stephan, 2011; Friston, Moran, & Seth, 2013). In addition, using Bayesian inferences during this process may provide a framework in which additional information (e.g. the directed influence one region may exert on another) may be extracted to provide insight into brain function (Harris, Rowe, Randeniya, & Garrido, 2018; Rigoux, Stephan, Friston, & Daunizeau, 2014).

An important feature of DCM is the capability of considering group-wise regions of interest (ROIs) in functional magnetic resonance imaging (fMRI) signals across a population of subjects and optimally determining change boundaries. DCM may thus delineate how dynamics in one brain region may influence dynamics in others, incorporating both a core set of interregional connections and modulations of those influences by experimental manipulations (Stephan et al., 2010). Effective connectivities between brain regions (the directed influence one region may have on others) may be either positive or negative, such that an increase in activity in one region may generate increases or decreases, respectively, in the rate of change in others (Davey, Breakspear, Pujol, & Harrison, 2017).

The aim of current study was to examine effective connectivities between executive-control-related brain regions and reward-related brain regions using DCM. As discussed above, interactions between these two systems may contribute importantly to the development and maintenance of IGD. Thus, we hypothesized that the modulatory regulation from executive-control-related brain regions [e.g. the prefrontal cortex (PFC)] to reward-seeking brain regions (e.g. the striatum) would be weaker in IGD relative to comparison subjects, which would provide additional evidence for how interactions between these two systems may operate in IGD.

Methods

Ethics

The experiment conforms to The Code of Ethics of the World Medical Association (Declaration of Helsinki). The study was approved by the Human Investigations Committee of Zhejiang Normal University. All participants were right-handed and provided written informed content before experiment.

Subjects

All participants were screened using Young's Internet addiction test (IAT) (Young, 2009), and the DSM-5 diagnostic criteria for

Table 1. Demographic information and group differences

Items	IGD ($n = 50$) (male = 35, female = 15)	RGU ($n = 50$) (male = 39, female = 11)	t	p
Age, years (mean ± S.D.)	23.16 ± 2.324	23.36 ± 1.987	0.462	0.645
IAT score (mean ± S.D.)	69.12 ± 10.939	31.9 ± 7.243	−15.210	<0.001
DSM-5 score (mean ± S.D.)	6.6 ± 1.191	2.3 ± 1.074	−14.727	<0.001
Gaming hours per week (mean ± S.D.)	18.52 ± 7.851	16.68 ± 7.498	−1.204	0.133
Education (years) (mean ± S.D.)	15.06 ± 1.834	15.42 ± 1.326	1.125	0.263
Self-reported craving before scan	51.22 ± 22.63	39.71 ± 20.21	6.142	<0.01
Self-reported craving during task (gaming cues minus typing cues)	2.42 ± 1.23	1.33 ± 0.86	5.251	<0.01

IGD, Internet gaming disorder; RGU, recreational game use; IAT, Internet addiction test; DSM-5, Diagnostic and Statistical Manual of Mental Disorders-5.
There was no significant difference in age, education, and the gaming time between the IGD and RGU group. The IAT scores and DSM-5 scores of the IGD group were significantly higher than those of the RGU group, per the inclusion criteria.

IGD (Petry et al., 2014). Subjects included in the IGD group needed to score more than 50 on Young's IAT and concurrently meet at least five DSM-5 inclusion criteria for IGD. We used relatively strict criteria for selecting IGD participants in order to focus on individuals experiencing more significant gaming problems given some current debates regarding severity of IGD (Aarseth et al., 2017; Billieux et al., 2017; King & Gaming Industry Response, 2018; Rumpf et al., 2018; Saunders et al., 2017).

Most people play video games; however, only a small percentage develops IGD. We selected individuals with RGU as a control group, which is to mitigate concerns regarding differences in gaming experience of control groups consisting of non-gaming individuals. The inclusion criteria for the RGU group were those used previously (Wang et al., 2017) and described briefly as follows: (1) scored less than 50 on Young's IAT; (2) met fewer than five DSM-5 criteria; (3) played online games more than 5 days per week (a frequency to define regular usage); and (4) played online games for more than 14 h per week (>2 h per day, an amount to define regular usage). To control subjects' familiarity to gaming cues, all subjects were familiar with the game of *League of Legends* and played the game for more than 1 year.

Exclusion criteria for all participants included current psychiatric disorders (e.g. depression, anxiety, schizophrenia, and substance-use disorders) assessed by structured psychiatric interviews (MINI) (Lecrubier et al., 1997) and previous or current gambling or use of illegal drugs (e.g. heroin and marijuana) or experiencing of any other types of addictions (e.g. to alcohol and tobacco). Participants were required not to take any medications or substances including tea and coffee on the day of scanning.

Table 1 shows the demographic information of the two groups.

Task and design

An event-related cue-reactivity task was used. The task includes two types of cue pictures: 30 gaming-related pictures and 30 typing-related pictures (neutral baseline). In each type, half of the 30 pictures contained a face and the other half contained a hand. As shown in Fig. 1*a*, gaming-related pictures showed a person playing the online game *League of Legends* on a computer, with half of the pictures showing faces and the other half showing hands. In typing-related pictures, the same person is typing an article on keyboard in front of a computer. During the task, participants were instructed to indicate via button press whether there was a face in the picture. Details of the task have been described previously (Dong, Wang, Du, & Potenza, 2018).

Figure 1*b* shows the timeline of a sample trial in the task. First, a fixed 500 ms of a cross was presented, followed by a cue picture as stated above. All pictures were presented in a randomized order. Each picture was presented for up to 3000 ms, during which participants had to make a response. The screen turned to black after button pressing and lasted for 3000 − response time ms. Then, in the craving evaluation stage, participants were asked to evaluate the level of their craving for the corresponding stimuli on a 5-point scale ranging from 1 (no craving) to 5 (extremely high craving). This stage lasted for up to 3000 ms and was terminated by a button-press. Finally, a 1500–3500 ms blank screen was presented between each trial. The whole task contained 60 trials and lasted almost 9 min. The task was presented and behavioral data were collected using E-prime software (Psychology Software Tools, Inc.). Prior to fMRI, participants were asked to complete a 10-item gaming urge questionnaire based on a tobacco craving questionnaire using a 10-point response scale (Cox, Tiffany, & Christen, 2001).

Image acquisition

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]. fMRI 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, http://www.invivocorp.com/) through a screen in the head coil, enabling participants to view the stimuli.

Image preprocessing

The functional data were analyzed using SPM12 and Neuroelf (http://neuroelf.net) as described previously (DeVito et al., 2012; Dong, Hu, Lin, & Lu, 2013b; Krishnan-Sarin et al., 2013).

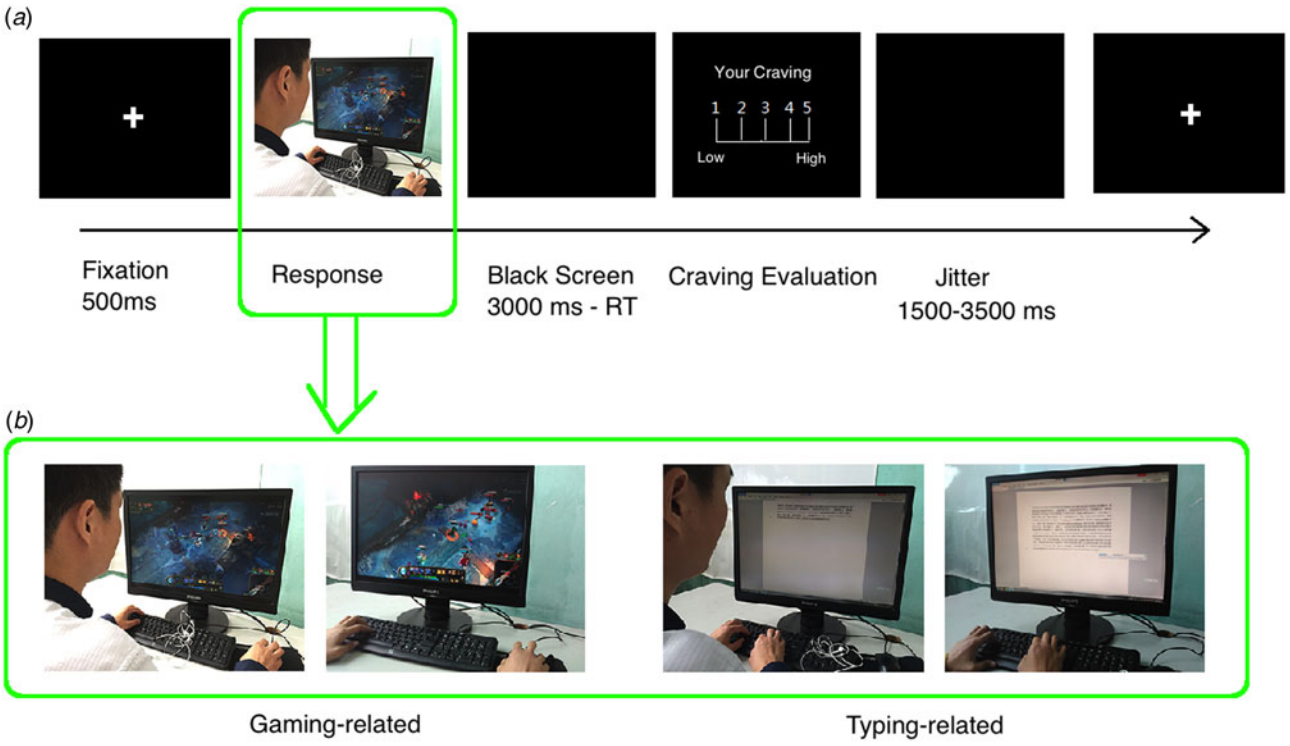


Fig. 1. The cue-craving task used in the current study. In this task, subjects were asked to react if there is a face in the stimuli. (*a*) The timeline of one trial in the current study. (*b*) The stimuli materials used in the current study.

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 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, and missed) were included as conditions in the model to account for potential influences on the results. A GLM was independently applied to each voxel to identify voxels that were significantly activated for the different events of each condition.

Defining the nodes

The nodes used in the current study were defined through the comparison between brain responses to gaming-related cues *v.* typing-related cues in all subjects (see Fig. 2*a* and Table 2). The results were family-wise correction-corrected at $p < 0.01$ and a voxel cluster threshold of 50. As the current study sought to examine interactions between executive-control and reward networks, identified regions within these networks were selected for use in DCM analyses. Specifically, a surviving cluster involving prefrontal brain regions [both the ACC and middle frontal gyrus (MFG) in one cluster] was selected given the ACC's and MFG's roles in executive control (Weinstein et al., 2017) and the lentiform nucleus was selected given its role in reward processing (Bamford, Wightman, & Sulzer, 2018; Bostan & Strick, 2018; Brand et al., 2016). Thus, we selected these brain regions as ROIs for further analysis in the current study (Fig. 2*b*).

In general, selecting ROIs in the current study met all of the following criteria: (1) showed significant activation in second-level analyses; (2) showed activation in previous addiction fMRI studies using cue-craving tasks, and; (3) were subordinate to executive-control or reward network. Consequently, surviving clusters involving prefrontal brain regions and the lentiform nucleus were selected as ROIs for the DCM analysis. Besides the prefrontal brain regions and lentiform, the bilateral posterior cingulate cortex (PCC) was identified in between-condition analyses. Given that the PCC has been implicated in addictions and cue responsivity (Jasinska, Stein, Kaiser, Naumer, & Yalachkov, 2014; Potenza et al., 2012), we also conducted additional analyses involving the PCC (Fig. 3*a*, *b*).

Volumes of interest (VOIs) were obtained by significant activation clusters, which were determined by a second-level random effects univariate analysis. Within these regions, we took the coordinates of the peaks of the clusters (local maxima in the statistical map) as the VOI centers with 6 mm radii to extract the representative time series for the region and the search radii of local maxima were restricted to 15 mm concurrently using the F-contrast adjust time series, following the approach described previously (Hillebrandt et al., 2014; https://en.wikibooks.org/wiki/SPM/Timeseries_extraction). The same VOIs were used across subjects.

Dynamic causal modeling

Interactions between prefrontal brain regions and the lentiform nucleus

We focused our analyses on interactions between executive control and reward regions. Thus, we focused on two pathways: prefrontal cortex [using the ACC/MFG cluster peak (in the ACC) as an ROI] to the lentiform nucleus; and, the lentiform nucleus to the ACC in each hemisphere, separately.

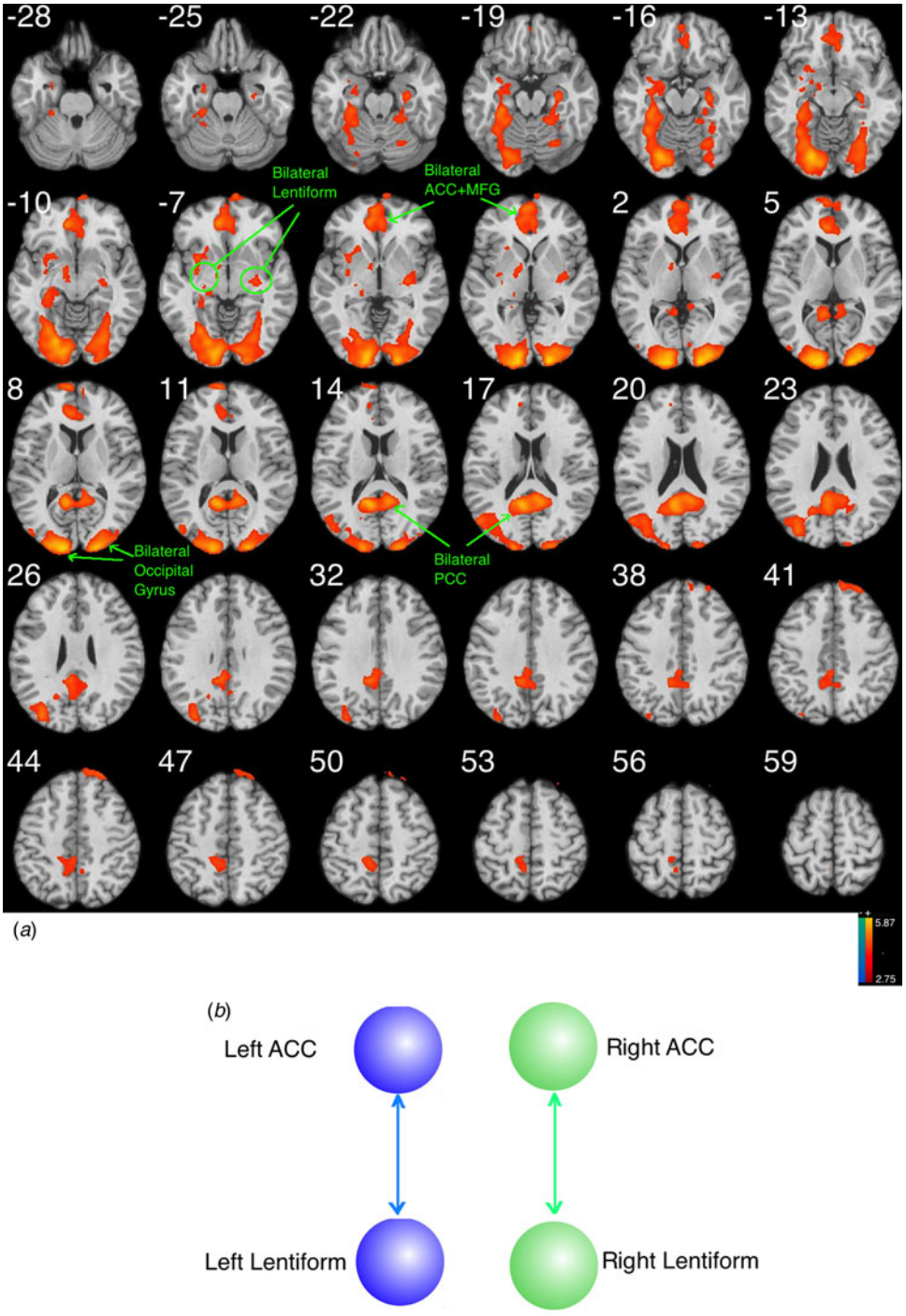


Fig. 2. The node selection in the current study. (*a*) Brain responses when comparing gaming-related cues to typing-related cues in all subjects. We can observe bilateral prefrontal brain regions (ACC + MFG), bilateral lentiform nucleus, bilateral PCC, bilateral occipital gyrus were activated during this process. (*b*) According to the main goal of the current study, we set to explore the interactions between executive control network and reward network, we selected ACC and lentiform as ROIs for further analysis.

Including the PCC in the model

A three-region (six for bilateral hemispheres) stochastic dynamic causal model was specified for each subject. With bi-directional effective connections between the ACC, lentiform, and PCC, we specified a 'full' model where gaming-related cues could elicit coordinated activations in IGD and RGU subjects (Fig. 3*a*,*b*) and then inverted it for all subjects.

Stochastic DCM

The fMRI data were analyzed by the means of stochastic DCM in the current study. After extracting the principal eigenvariate of all ROIs, we assumed that all subjects used the same model and specified a 'full' model for each subject. Here, 'full' means that: (1) each ROI was assumed to be connected to all other ROIs (nine endogenous connections, including three self-connections);

Table 2. Regions demonstrating differences in gaming *v.* typing cues

Cluster number	*x*, *y*, *z*[a]	Cluster size[b]	Region[c]	Brodmann's area
1	21, −99, 3	384	R Cuneus	
2	−15, −99, 6	434	L Cuneus	
3	−9, −54, 15	237	L Posterior cingulate	30
4	9, −51, 18	257	R Posterior cingulate	30
5	−9, 42, −9	268	L Medial frontal gyrus	11
			L Anterior cingulate	
6	9, 42, −3	117	R Medial frontal gyrus	11
			R Anterior cingulate	
7	30, −18, −21	91	R Lentiform nucleus	
			R Parahippocampal gyrus	
8	−30, −12, −15	54	L Lentiform nucleus	

[a]Peak MNI coordinates.
[b]Number of voxels. Alphasim correction, $p < 0.01$, cluster size >50.
[c]The brain regions were referenced to software Xjview (http://www.alivelearn.net/xjview8) and verified through comparisons with a brain atlas.

(2) it was assumed that the gaming cues acted as a driving input entering directly on all ROIs; and (3) it was assumed that the gaming cues modulated all endogenous connections. The full models were then inverted for all subjects (i.e. model estimation).

After that, we performed a DCM network discovery routine that automatically searches over all possible reduced models of a full model and uses post-hoc model selection to select the optimal one for each subject. The optimal sparse model was found at the group level, using Bayesian parameter averaging. Finally, we took the estimated connectivity parameters from the subject's optimization model and ran classical statistics such as independent sample *t* tests.

Correlations between clinically relevant measures and effective-connectivity values

We analyzed the correlations between the connectivity parameters and the clinical/behavioral measures of IGD subjects (IGD/IAT severity, self-reported craving to cues) to relate the neural results to clinically relevant measures.

Results

Behavioral performance

IGD subjects showed higher self-reported craving scores than RGU subjects before scanning (IGD, 51.22 ± 22.63; RGU, 39.71 ± 20.21; $t = 6.142$, $p < 0.01$) and during scanning (IGD, 2.42 ± 1.23; RGU, 1.33 ± 0.86; $t = 5.251$, $p < 0.01$). The findings suggest that manipulations in the current task were successful.

Fixed connectivity

In the entire sample, DCM estimates demonstrated significant positive endogenous influences between the ACC and the lentiform (Table 3). Group comparisons revealed significant interactions between these brain regions in the left and right hemispheres, separately.

In the left hemisphere, group comparisons showed that RGU subjects showed higher positive effects than IGD subjects in both ACC-to-lentiform and lentiform-to-ACC pathways. In the right hemisphere, no group differences were observed in the lentiform-to-ACC pathway or the ACC-to-lentiform pathway (Table 3; Fig. 4*a*).

Effects of gaming cues

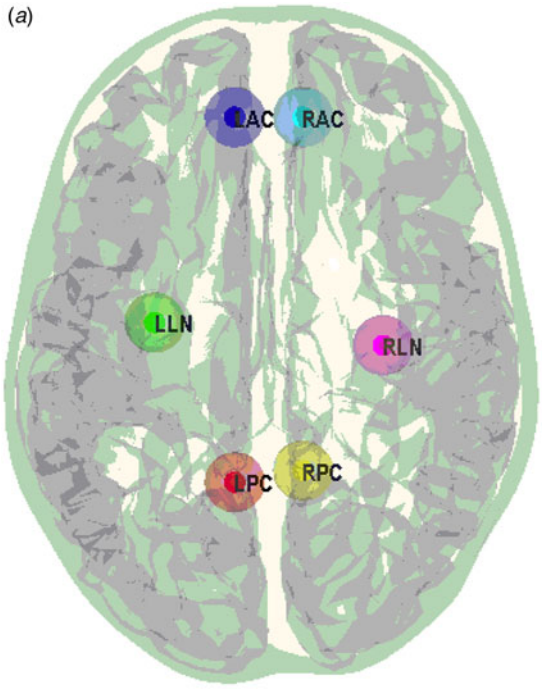
The modulatory effects of gaming (gaming *v.* typing cues) showed that there was a positive effect on the left lentiform-to-ACC pathway in RGU but not in IGD subjects. Group comparisons showed that IGD subjects showed a trend toward lower scores compared with RGU subjects in the effect of the left ACC-to-lentiform pathway ($p = 0.056$), although modulatory effects were not significant in either subject group. In the right hemisphere, no group differences were found in these parameters (Table 3; Fig. 4*b*).

Correlation with clinically relevant factors

A negative correlation was found between the DSM-5 score and the modulatory effect from the ACC to the lentiform in the left hemisphere in IGD subjects (Fig. 4*c*). A significant correlation was observed in IGD subjects between self-reported cravings before scan and modulatory effect from ACC to lentiform in the left hemisphere ($r = -0.287$, $p = 0.043$) (Fig. 4*d*). A similar trend was observed in IGD subjects between self-reported cravings before scanning and modulatory effects from the ACC to lentiform in the left hemisphere ($r = -0.233$, $p = 0.083$).

Including the PCC in the model

Parameter estimates were calculated using the Bayesian model averaging over a model space partitioned according to whether gaming cues directly influenced activity in the PCC. Findings demonstrated significant fixed effects between the left PCC to lentiform, left PCC to left ACC, left lentiform to PCC, and left ACC to left PCC. Similar relationships were observed in the right hemisphere. In both hemispheres, IGD and RGU were not distinguished on these fixed effects.



Name	Voxels	Location (mm)
LAC	33	-9 42 -9
LLN	33	-30 -12 -15
LPC	33	-9 -54 15
RAC	33	9 42 -3
RLN	33	30 -18 -21
RPC	33	9 -51 18

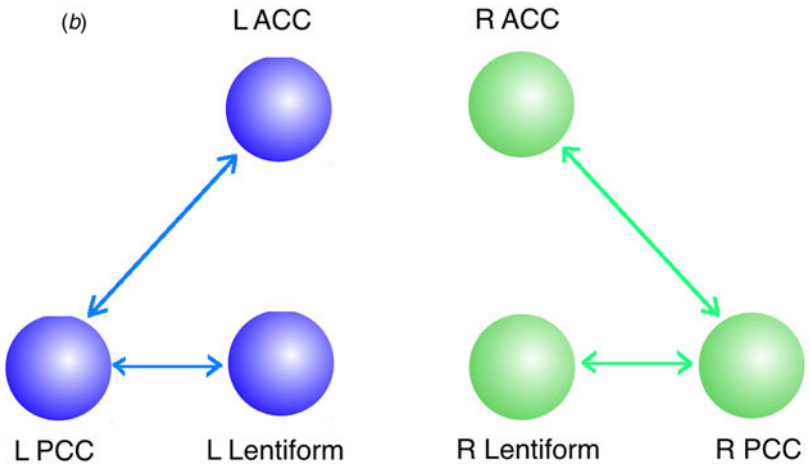


Fig. 3. When including the PCC in the model. (*a*) The location of the nodes we selected in the current study. (*b*) The model we set to explore in the current study. LAC: left anterior cingulate; LLN: left lentiform nucleus; LPC: left posterior cingulate; RAC, right anterior cingulate; RLN: right lentiform nucleus; RPC, right posterior cingulate. (The software only accepts name within three letters.)

Table 3. Fixed and modulatory effects when exposed to gaming cues between the ACC and lentiform nucleus in the left and right hemispheres

	RGU ($n = 50$)			IGD ($n = 50$)			RGU *v.* IGD	
Parameters	*r*	t^a	*p*	*r*	t^a	*p*	*t*	*p*
Fixed effects								
LACC→LLN	0.035	9.343	<0.001	0.023	7.630	<0.001	2.535	0.013
LLN→LACC	0.040	9.968	<0.001	0.027	7.102	<0.001	2.409	0.018
RACC→RLN	0.029	10.226	<0.001	0.029	9.255	<0.001	−0.101	0.919
RLN→RACC	0.038	14.596	<0.001	0.033	11.058	<0.001	1.194	0.236
Modulatory effects								
LACC→LLN	0.006	1.520	0.135	−0.003	−0.978	0.333	1.933	0.056
LLN→LACC	0.004	2.440	0.018	0.000	−0.001	0.999	1.478	0.143
RLN→RACC	0.000	0.165	0.870	−0.003	−0.873	0.387	0.775	0.440
RACC→RLN	0.003	1.532	0.132	0.002	0.858	0.395	0.380	0.705

LACC, left ACC; LLN, left lentiform nucleus; RACC, right ACC; RLN, right lentiform nucleus.
[a]Compared with random distribution.

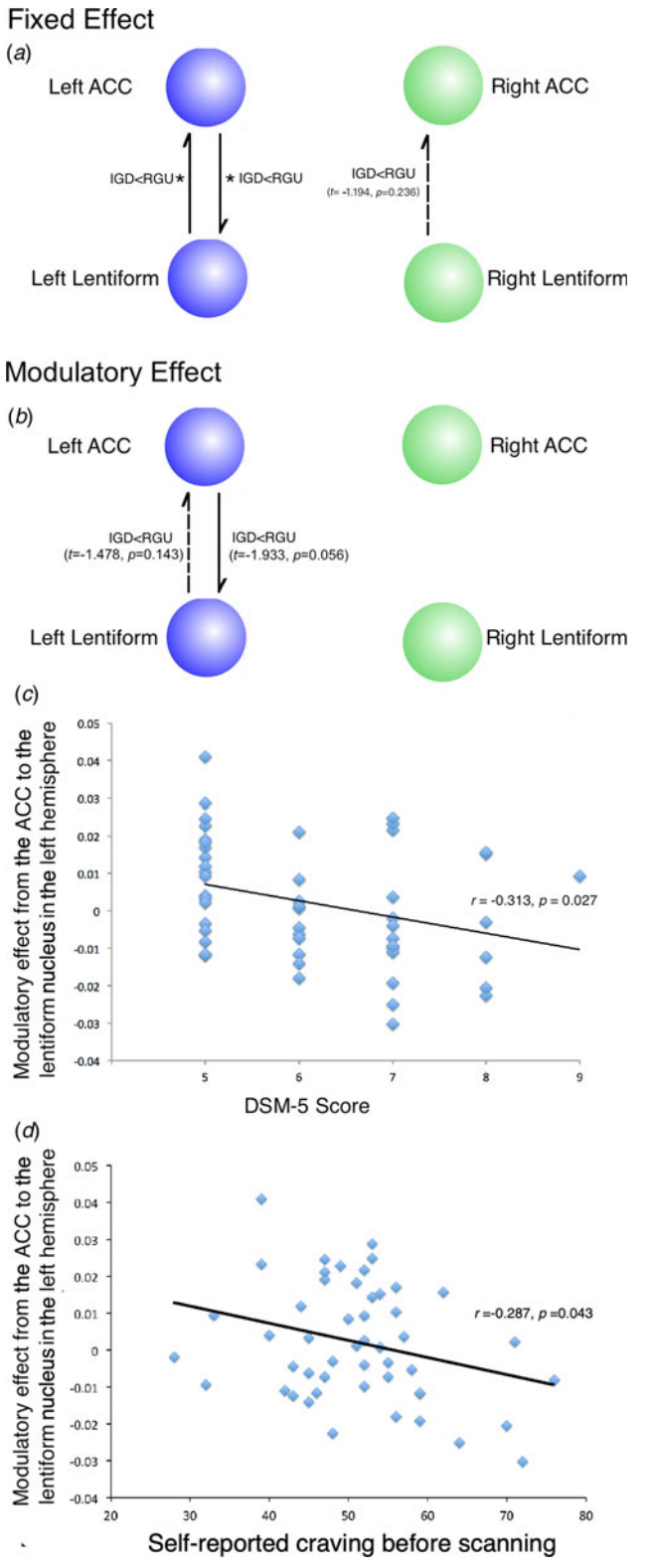


Fig. 4. Fixed effect and modulatory effect between IGD and RGU. (*a*) In fixed effect, IGD subjects show lower ACC to lentiform and lentiform to ACC connectivity then RGU in the left hemisphere. A positive effect was observed in lentiform to ACC in the right hemisphere, although it does not reach statistical significance. (*b*) In modulatory effect, IGD subjects show lower ACC to lentiform connectivity in the left hemisphere. No interactions were found in the right hemisphere. (*c*) Negative correlation was found between DSM-5 score and the modulatory effect from ACC to lentiform in the left hemisphere. (*d*) Negative correlation was observed between self-reported cravings and modulatory effect from ACC to lentiform in the left hemisphere in IGD subjects.

With respect to modulatory effects of gaming cues, IGD subjects showed marginal effects ($p = 0.051$) with respect to left ACC to left PCC connectivity and significant ($p = 0.023$) effects on right ACC to right PCC connectivity (Table 4). Findings within the RGU group and between-group differences were not significant.

In the left hemisphere, data suggested that gaming cues drove PCC activity in the RGU but not IGD group (direct effects, Table 4). A group difference ($p = 0.031$) was found in the left PCC, in which the RGU group showed significantly lower scores than the IGD group. In addition, IGD subjects showed marginally higher ($p = 0.052$) PCC-to-lentiform connectivity than RGU subjects in modulatory effects (Table 4; Fig. 5). In the right hemisphere, no significant results were observed among these brain regions.

Discussion

Behaviorally, IGD relative to RGU subjects showed higher craving scores to gaming cues before and after gaming. The imaging results provide further support for prefrontal–striatal interactions distinguishing groups with IGD and those with RGU. Our hypotheses were partially supported, as described below.

Interactions between prefrontal brain regions and the lentiform nucleus

Significant group differences were observed on some fixed effects. In fixed connectivity, IGD subjects show significant lower lentiform-to-ACC and ACC-to-lentiform connectivity than RGU in the left hemisphere. In modulatory effects, IGD subjects trended toward showing lower ACC-to-lentiform connectivity than RGU subjects in the left hemisphere, although the relationship was not significant in either group. However, the inverse relationship between the modulatory effects relating to ACC-to-lentiform connectivity in IGD subjects in the left hemisphere was inversely related to IGD severity, suggesting the clinical relevance of this relationship.

The ACC and MFG have been implicated in executive control (Engelmann et al., 2012; Goudriaan, Ruiter, Brink, Oosterlaan, & Veltman, 2010; Ko et al., 2009; Liu et al., 2017; Sun et al., 2012), which refers to tendencies to successfully inhibit improper behaviors or thoughts in complex environments (Goldstein & Volkow, 2011). Neuroimaging and neuropsychological studies have suggested that executive functions contribute importantly to prevent the development and maintenance of internet-use disorders (Brand et al., 2016; Dong & Potenza, 2014), in a manner similar to substance addictions (Bechara, 2005; Volkow et al., 2010). Several models of IGD have proposed that impaired executive functioning and inhibitory control may be central to IGD (Brand et al., 2016; Dong & Potenza, 2014), consistent with data linking to impaired response inhibition in individuals with IGD or substance addictions (Dong et al., 2017b).

As part of the basal ganglia, the lentiform is an important component of multiple processes including how people respond to rewards. As such, it has been implicated in the development and maintenance of addictions (Koopmann et al., 2019; Walker et al., 2018). Enhanced brain responses in the lentiform nucleus may suggest reward sensitivity or relate to cravings in response to specific cues (Kearney-Ramos et al., 2018), consistent with findings in IGD groups and models of IGD (Brand et al., 2016; Dong et al., 2017a, 2019a, 2019b).

In the current study, IGD subjects relative to RGU subjects showed lower ACC-to-lentiform and lentiform-to-ACC fixed

Table 4. Fixed and modulatory effects among PCC, ACC, and lentiform nucleus in the left and right hemispheres and direct PCC effects

	RGU ($n = 50$)			IGD ($n = 50$)			RGU *v.* IGD	
Parameters	*r*	t^a	*p*	*r*	t^a	*p*	*t*	*p*
Fixed effects								
LPCC→LLN	0.027	11.764	<0.001	0.025	13.638	<0.001	0.483	0.630
LPCC→LACC	0.067	16.095	<0.001	0.065	17.086	<0.001	0.423	0.673
LLN→LPCC	0.034	12.916	<0.001	0.034	15.617	<0.001	0.029	0.977
LACC→LPCC	0.068	16.407	<0.001	0.063	17.052	<0.001	0.859	0.392
RPCC→RACC	0.037	11.220	<0.001	0.037	9.813	<0.001	−0.041	0.968
RACC→RPCC	0.036	11.365	<0.001	0.036	8.288	<0.001	0.115	0.909
RLN→RPCC	0.042	13.619	<0.001	0.040	12.400	<0.001	0.483	0.630
RPCC→RLN	0.031	12.057	<0.001	0.029	9.738	<0.001	0.394	0.694
Modulatory effects								
LACC→LPCC	−0.004	−2.004	0.051	−0.001	−0.682	0.498	−1.124	0.264
LPCC→LACC	0.002	0.799	0.428	0.001	0.314	0.755	0.321	0.749
LLN→LPCC	−0.002	−0.571	0.571	−0.001	−0.465	0.644	−0.105	0.917
LPCC→LLN	−0.001	−0.406	0.686	0.006	2.143	0.037	−1.948	0.052
RPCC→RACC	−0.001	−0.645	0.522	−0.002	−0.659	0.513	0.081	0.936
RACC→RPCC	−0.006	−2.340	0.023	−0.003	−0.863	0.392	−0.798	0.427
RLN→RPCC	−0.003	−1.092	0.280	−0.003	−1.134	0.262	−0.011	0.991
RPCC→RLN	−0.002	−0.887	0.397	0.001	0.632	0.531	−1.058	0.293
Direct effects								
LPCC	−0.003	−2.640	0.011	0.001	0.481	0.633	−2.188	0.031
RPCC	−0.002	−1.457	0.151	0.001	1.219	0.229	−1.899	0.060

LACC, left ACC; LLN, left lentiform nucleus; RACC, right ACC; RLN, right lentiform nucleus; LPCC, left PCC; RPCC, right PCC.
[a]Compared with random distribution.
The *p* values in this table were not corrected for multiple comparisons.

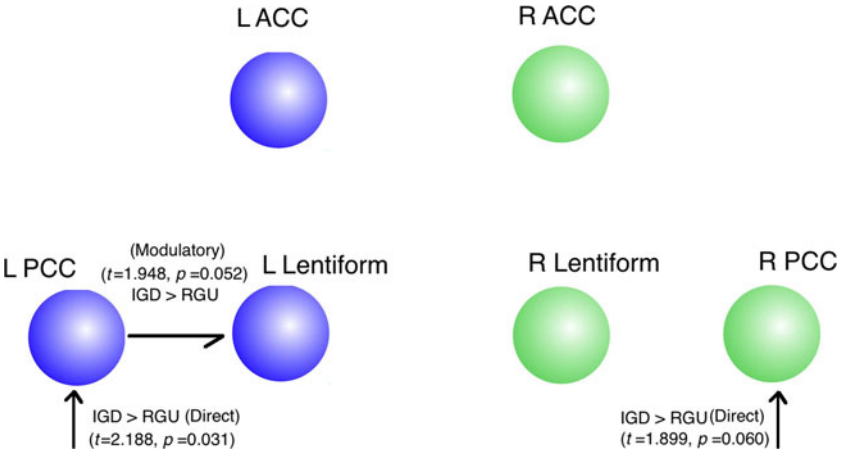


Fig. 5. The role of PCC in the DCM model. Group differences on direct effect from the gaming cues were found in left and right PCC. IGD subjects show significant higher score than RGU subjects. Group difference on modulatory effect showed IGD subjects show higher PCC to lentiform connectivity than RGU in the left hemisphere.

effects with respect to connectivities in the left hemisphere. According to psychophysiological implications of the FC findings (Havlicek et al., 2015; Stephan et al., 2010), lower values in ACC-to-lentiform and lentiform-to-ACC in IGD subjects suggest the interactions among these two brain regions may be less efficient in IGD subjects than in RGU subjects. Blunted bi-directional interactions between these brain regions in IGD suggest that brain regions responsible for executive control may not be able to exert top-down control over cue-elicited brain responses and that bottom-up drive may be less linked to top-down control. The negative correlation between addiction severity, craving level (baseline out of the scanner and cue-elicited craving during scanning) and ACC-to-lentiform connectivity also provides support for this conclusion. The bi-directional effects

suggest a disconnection in IGD that may perpetuate persistent gaming despite adverse consequences. The current results extend those of prior studies that have found enhanced basal ganglia responses to gaming cues in IGD (Dong, Huang, & Du, 2011; Yao et al., 2017) and studies suggesting impaired executive control in IGD (Dong et al., 2015, 2019b).

When exposed to gaming cues, increased activation in the bilateral ACC (and MFG) and lentiform was observed in all subjects. With respect to modulatory effects, DCM analyses suggested in the left hemisphere the possibility of higher positive modulation of the effective connectivity from the ACC to lentiform nucleus in RGU subjects than in IGD subjects in between-group analyses (trend level of $p = 0.056$). In the right hemisphere, while the RGU group showed a modulatory effect in the effective connectivity from the lentiform nucleus to ACC that was significant and numerically larger than that in the IGD group, no between-group differences were observed. These findings suggest that if IGD subjects show reduced gaming-cue-related modulatory effects in interactions between the ACC and lentiform nucleus, they may not be particularly robust. Nonetheless, the findings suggest the possibility that when exposed to gaming cues, IGD subjects may show modestly blunted interactions between top-down and bottom-up processes, consistent with prior models and findings (Kuss & Griffiths, 2012; Kuss, Pontes, & Griffiths, 2018; Petry et al., 2014).

Taking the fixed connectivity and the modulatory effect findings together, data suggest prefrontal to lentiform connectivity impairments in IGD subjects that may be relatively independent of gaming cues. The results provide support for proposed IGD models (Brand et al., 2019, 2016; Dong & Potenza, 2014).

The role of the PCC in IGD

In addition to examining interactions between the ACC and lentiform nucleus, we investigated a possible role for the PCC in IGD in cue-elicited responses. The results suggest that the PCC is an important input source for gaming-related cues. Specifically, IGD subjects showed higher direct effects than RGU subjects in PCC activation in the left hemisphere with a similar trend on the right. No between-group differences were observed for fixed or modulatory effects, suggesting that direct effects may most strongly be implicated in IGD.

The PCC has been implicated in many addictions, especially in cue reactivity (Jasinska et al., 2014; Potenza et al., 2012). In drug- or alcohol-use disorders, the PCC has been found to be activated by drug cues, particularly in individuals with long or intensive histories of use (Cousijn et al., 2013; Filbey et al., 2008; Franklin et al., 2011; Tapert et al., 2003; Yalachkov, Kaiser, & Naumer, 2012). A relatively higher PCC response to cocaine-related cues also distinguished patients who relapsed to cocaine use from those who did not (Johnson, Chen, Schmitz, Bordnick, & Shafer, 1998; Kosten et al., 2006). With respect to nicotine addiction, self-reported craving for a cigarette was found to positively correlate with cue-induced responses in the PCC (Kang et al., 2012; Owens et al., 2017), and resisting craving was associated with increased activity in the PCC (Brody et al., 2007). The PCC was also implicated in responses to gaming cues in IGD subjects (Dong, DeVito, Huang, & Du, 2012; Dong, Hu, & Lin, 2013a; Dong et al., 2017a).

Although the PCC has been widely implicated in cue responsivity in addictions, few studies have examined connectivity of the PCC in addictions. The PCC links to many brain structures (Zuo et al., 2012). Greater PCC connectivity has been implicated in longer time to relapse in alcohol-use disorder (Zakiniaeiz, Scheinost, Seo, Sinha, & Constable, 2017). While PCC connectivity has been implicated in some studies of individuals with addictions or at elevated risk for addiction [e.g. in youth with prenatal cocaine exposure (Zakiniaeiz et al., 2017b)], it has rarely been directly examined in IGD, although decreased insula-to-PCC cue-elicited activity has been reported following treatment of IGD (Zhang et al., 2016). The current findings suggest that the PCC acts in a direct fashion with respect to gaming-cue responsivity in IGD, and that it may transmit information to relevant brain regions (e.g. the ACC or lentiform nucleus). These findings may differ from those in depression in which self-appraisal processes may drive PCC activity, with the PCC positively then influencing the medial prefrontal cortex, directly and indirectly (Davey et al., 2017). More studies are needed to define more precise roles for the PCC and how it may interact with other brain structures in IGD.

Strengths and clinical implications

The current study has multiple strengths. First, it used DCM to investigate directional connectivity between executive-control and reward regions. Second, the study includes a sizable number of subjects and a well-controlled comparison group. Limitations include the cross-sectional nature of the study, the predominance of males and the limited geographic recruitment, restricted age range and certain gaming-related aspects. For example, the study focused on individuals familiar with League of Legends. Further, the RGU group on average met some criteria for IGD and thus may be considered at elevated risk for IGD. This may have led to relative blunting of between-group differences. In other words, sub-diagnostic levels of IGD in the RGU may have led to less robust between-group differences having been observed. However, some of these limitations may also represent strengths (e.g. by limiting sample variability), and the findings provide further insight into the neurobiological underpinnings of IGD.

The current results have clinical implications. First, the findings provide a foundation for possibly identifying treatment targets (e.g. with interventions that may alter cortical activity like transcranial direct current stimulation or repetitive transcranial magnetic stimulation). Second, training IGD subjects to control their cravings through behavioral techniques may involve cognitive mechanisms (e.g. cognitive behavioral therapy) or approaches that might target subcortical processes more directly (e.g. mindfulness-based approaches), and these warrant additional investigation in IGD.

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