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FULL-LENGTH REPORT

Decreased effective connection from the parahippocampal gyrus to the prefrontal cortex in Internet gaming disorder: A MVPA and spDCM study

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ABSTRACT

Objectives: Understanding the neural mechanisms underlying Internet gaming disorder (IGD) is essential for the condition's diagnosis and treatment. Nevertheless, the pathological mechanisms of IGD remain elusive at present. Hence, we employed multi-voxel pattern analysis (MVPA) and spectral dynamic causal modeling (spDCM) to explore this issue. *Methods:* Resting-state fMRI data were collected from 103 IGD subjects (male = 57) and 99 well-matched recreational game users (RGUs, male = 51). Regional homogeneity was calculated as the feature for MVPA based on the support vector machine (SVM) with leave-one- out cross-validation. Mean time series data extracted from the brain regions in accordance with the MVPA results were used for further spDCM analysis. *Results:* Results display a high accuracy of 82.67% (sensitivity of 83.50% and specificity of 81.82%) in the classification of the two groups. The most discriminative brain regions that contributed to the classification were the bilateral parahippocampal gyrus (PG), right anterior cingulate cortex (ACC), and middle frontal gyrus (MFG). Significant correlations were found between addiction severity (IAT and DSM scores) and the ReHo values of the brain regions that contributed to the classification. Moreover, the results of spDCM showed that compared with RGU, IGD showed decreased effective connectivity from the left PG to the right MFG and from the right PG to the ACC and decreased self-connection in the right PG. *Conclusions:* These results show that the weakening of the PG and its connection with the prefrontal cortex, including the ACC and MFG, may be an underlying mechanism of IGD.

KEYWORDS

Internet gaming disorder, parahippocampal gyrus, multi-voxel pattern analysis, spectral dynamic causal modeling

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INTRODUCTION

Internet gaming disorder (IGD) has been defined as a typical behavioral addiction characterized by compulsive game seeking, uncontrolled game playing, and the decision to play despite negative consequences (Dong, Li, Wang, & Potenza, 2017; Petry & O" Brien, 2013; Petry

et al., 2014). In spite of numerous neuroimage studies associated with this condition (Dong, Lin, Hu, Xie, & Du, 2015; Kim et al., 2015; Wang, Dong, Wang, Zheng, & Potenza, 2018; Zheng et al., 2019), the pathological mechanisms of IGD remain elusive. The investigation of the neurobiological substrates of IGD is a fundamental point that will shed light on the underlying mechanisms of the condition. Consequently, such mechanisms may be of great value in gaining insights into improving the specificity of diagnosis and efficacy of IGD treatments. For instance, IGD subjects demonstrated higher functional connectivity between frontal cortical regions and ventral striatum (Lorenz et al., 2013), and craving behavioral intervention for IGD could remediate the functional connectivity (Zhang et al., 2016).

Recently, studies have investigated the neural activities in the human brain during resting state (no stimuli, no tasks, and not falling asleep). These data are classified as resting-state fMRI (Zang, Jiang, Lu, He, & Tian, 2004). The data of resting-state fMRI are commonly analyzed via two methods: (1) Regional homogeneity (ReHo) measures the temporal synchronization of the time series of nearest neighbors and can be used to map local spontaneous neural activity, making it a useful tool for identifying changes in cerebral activities (Peng, Chen, Cui, Zhao, & Teng, 2016; Wu et al., 2015; Zang et al., 2004). (2) Functional connectivity (FC) can be used to map short or long-distance connectivity and provides multiple information that ReHo cannot reveal (Peng et al., 2016).

Previous studies on resting-state fMRI using conventional mass univariate analytical techniques to investigate the alterations of ReHo in IGD have suggested that localized connectivity in executive control, decision making, memory, and reward/loss processing system may involve anomalies (Dong, 2012; Kim et al., 2015; Liu, Gao, Osunde, Li, & Li, 2010; Park et al., 2010). One important limitation of these studies is the small sample size, which reduces sensitivity and presumably results in the lack of reliability of findings. In addition, all these published mass univariate studies investigating ReHo alterations between IGD participants and a control group aim to test whether some brain regions have any difference, rather than to test whether the differences are large enough for clinical utility (Hu et al., 2019).

Recently, researchers have developed a growing interest on the application of multi-voxel pattern analysis (MVPA) to develop brain signatures for the clinical diagnoses of relevant mental disorders (Woo, Chang, Lindquist, & Wager, 2017). Compared with the traditional univariate analysis, the MVPA has two strengths. First, MVPA takes the intercorrelation between voxels into consideration and thus may be sensitive in detecting subtle and spatially distributed alterations. Second, MVPA allows statistical inferences at the single-subject level and thus can be used to make diagnostic decisions of individual patients (Vieira, Pinaya, & Mechelli, 2017). MVPA methods have been successfully used to differentiate participants with substance addiction from control subjects based on ReHo (Zhang et al., 2011). However, no MVPA studies have investigated the utility of ReHo maps in distinguishing IGD subjects from a control group.

One limitation of previous MVPA studies on addiction is the unknown brain region connectivity (Zhang et al., 2011). Nevertheless, the psychological process of addiction depends on interactions among certain brain regions. Studies on participants with IGD showed increased FC between regions that are also associated with cognitive control, reward processing, and memory processes (Hong et al., 2015; Ko et al., 2015). However, traditional FC evaluates the Pearson correlations among regions of interest (ROIs) through time series. This analytical approach cannot answer inquiries about the causal or direct connectivity among ROIs. Therefore, the interactions among the brain regions involved in IGD remain unclear.

Accordingly, spectral dynamic causal modeling (spDCM) can address this limitation because it has the capacity to reveal the effective connectivity (directional connectivity) among brain regions, compared with resting-state functional connectivity (Marreiros, Kiebel, & Friston, 2010). At present, spDCM is widely used in substance addiction studies, including cocaine, tobacco, and alcohol, and provides insights into the brain mechanisms underlying substance addiction (Ma, Steinberg, Cunningham, Lane, Bjork, et al., 2015; Ray, Xin, & Biswal, 2016; Tang, Razi, Friston, & Tang, 2016). To date, only one DCM study has evaluated IGD during resting state (Wang, Zheng, Du, & Dong, 2018). This study selected four ROIs in the default mode network with reference on previous studies for DCM analysis. Wang et al. (2018a,b) observed the decreased connectivity from the medial prefrontal cortex to the posterior cingulate cortex in an IGD group, and they believed that such connectivity may be a crucial biomarker for IGD. As the selection of ROIs in the resting state depends on prior knowledge, the process may neglect other meaningful areas that MVPA can provide.

Therefore, we aim to apply MVPA and spDCM analysis methods to evaluate (1) if MVPA approaches can classify IGD subjects from the control group and show brain regions that contributed most for the classification and (2) if the provided information on the effective connectivity among the brain regions will potentially help elucidate the mechanisms that cause IGD. This is the first exploratory study that combined MVPA and spDCM in IGD during resting state and is based on substance addiction studies. Thus, we hypothesized that (1) ReHo will potentially discriminate IGD individuals from healthy controls (Zhang et al., 2011); (2) brain regions that are involved in executive control, decision making, memory, and reward/loss processing contribute most to the classification (Elton et al., 2014; Zhang et al., 2011); and (3) IGD shows an abnormal effective connectivity pattern among the brain regions (Ray et al., 2016; Tang et al., 2016).

MATERIALS AND METHODS

Participants

We recruited 103 subjects with IGD (57 males) and 99 recreational game users (RGUs) (51 males) through posters and Internet advertisements (Table 1). Part of the data in

this study comes from our previous study (Wang et al., 2018a, 2018b) with 64 IGD subjects and 63 RGUs. Although there is overlap in subjects, however, all statistical methods are different and the results have no overlap with previous findings. All participants underwent structured psychiatric interviews (MINI-International Neuropsychiatric Interview) conducted by an experienced psychiatrist (Lecrubier et al., 1997), and individuals with psychiatric or neurological disorders were excluded in the study. No participants reported previous gambling or illicit drug (e.g., marijuana, heroin) experiences. Smoking and alcohol scores were measured using Fagerstrom Test for Nicotine Dependence and alcohol dependence syndrome scales (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991; Icd, 2011). None of participants addicted to smoking or alcohol. All participants were instructed not to use any addictive substances, including tobacco and caffeinated drinks, on the day of scanning.

The criteria for the selection of IGD and RGU have been reported in previous studies (Dong et al., 2019; Wang et al., 2019) and are briefly described 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 the proposed DSM-5 IGD criteria (Petry et al., 2014) (Table 1). The RGU participants were required to meet fewer than 5 (of 9) of the proposed DSM-5 criteria for IGD and to score less than 50 on Young's IAT. In addition, they must have played online games for a minimum of 2 years (enough time to develop IGD) and for at least 5 of 7 days in a week (frequency) and more than 14h (amount) per week. No significant group differences in age ($t = -1.168$, $P = 0.244$), gender ($\chi^2 = 0.297$, $P = 0.586$), gaming time per week ($t = 1.19$, $P = 0.235$), gaming history ($t = 0.89$, $P = 0.375$), and educational level ($t = -1.614$, $P = 0.108$) were observed in Table 1.

MRI data acquisition

The fMRI resting data were acquired using 3T MRI system (Siemens Trio). During the resting-state fMRI examination, the participants were instructed to keep their eyes closed and not fall asleep. Moreover, the subjects need to reduce head movements as much as possible. Specific parameters are as follows: repetition time (TR) = 2000 ms, interleaved 33 slices, echo time (TE) = 30 ms, thickness = 3.0 mm, flip angle = 90°, field of view = 220 × 220 mm, and matrix = 64 × 64. Each fMRI scan lasted for 420 s and included 210 imaging volumes. None of the participants had structural abnormalities upon visual inspection of the scans.

Image preprocessing

Preprocessing was conducted with DPABI v3.0 (Data Processing & Analysis for Brain Imaging: http://rfmri.org/dpabi), a toolbox based on MATLAB (Yan, Wang, Zuo, & Zang, 2016). The first 10 volumes of each participant were discarded to minimize the instability of the initial signal and adapt participants to the scanning environment, leaving 200 volumes. The rest of the process included slice timing, head-motion correction, and normalization. Data used in the present study met the criteria of head motion <2.5 mm or 2.5°. Nuisance signals, including six motion vectors, were regressed out. Then, temporal filtering (0.01–0.08 Hz) was performed to reduce the effect of low-frequency drift and high-frequency noise.

MVPA

ReHo calculation. The ReHo map of each subject was developed by calculating Kendall's coefficient concordance in accordance with the time series between a single voxel and 26 adjacent voxels of its neighbors in a voxel-wise manner (Zang et al., 2004).

Support vector machine analysis. Support vector machine (SVM) with linear kernel function was utilized as the classification algorithm in this study. SVM was applied by using the Pattern Recognition for Neuroimaging Toolbox (PRoNTo) (Schrouff, Rosa, Rondina, Marquand, & Chu, 2013) (http://www.mlnl.cs.ucl.ac.uk/pronto) to estimate the potential brain regions that contribute most in the calcification of IGD from RGU. Briefly, the main steps of the SVM method include (a) extracting the features and selecting discriminative regions, (b) training the SVM classifier model by training data and evaluating the performance of the SVM model using the evaluation data (Amarreh, Meyerand, Stafstrom, Hermann, & Birn, 2014; Dyrba, Grothe, Kirste, & Teipel, 2015).

Table 1. Demographic information and group differences

	IGD $N = 103$	RGU $N = 99$	t	P
Age (Mean ± SD)	21.06 ± 2.35	21.45 ± 2.31	−1.168	0.244
Educations (years) (Mean ± SD)	14.46 ± 1.85	14.89 ± 2.06	−1.614	0.108
IAT score (Mean ± SD)	64.07 ± 9.93	37.69 ± 6.77		
DSMscore (Mean ± SD)	5.89 ± 1.12	2.65 ± 1.38		
Gaming history (year) (Mean ± SD)	3.52 ± 1.05	3.34 ± 0.99	0.89	0.375
Game playing per week (hours) (Mean ± SD)	19.33 ± 9.40	20.70 ± 9.57	1.19	0.235

IGD: Internet gaming disorder; RGU: recreational game use; IAT: Internet addiction test; DSM-5: Diagnostic and Statistical Manual of Mental Disorders-5.

(a) extracting and selecting the features

In fMRI studies, the number of features is much more than the number of subjects, which leads to the "curse of dimensionality" in machine learning studies (Fort & Lambert, 2005; Martino et al., 2007). Feature extraction allows neuroimaging data (ReHo map) to transform into analyzable input data of SVM. In the present study, each 3D image was transformed into a column vector of features and each value corresponded to a single corresponding voxel intensity. Thus, this feature vector encoded the pattern of ReHo values.

By comparison, feature selection involves the selection of a subset of features, which facilitates learning (Noble William, 2006; Orrù, Pettersson, Marquand, Sartori, & Mechelli, 2012). In this study, feature selection includes identifying brain regions that are expected to differ between groups. The above procedures were automatically processed in PRoNTo's "Prepare feature set" programs.

(b) training the SVM classifier model by training data and evaluating the performance of the SVM model using the evaluation data

A leave-one-out cross-validation method was carried out to perform SVM classifier validation, where the feature selection was performed each time on the training partition of the data to avoid circularity effects. In this study, the method involved the exclusion of a single subject from each group and training the classifier using the remaining subjects. Consequently, the excluded subject pair was used to test the ability of the classifier to reliably classify new cases. The above procedures were repeated for each subject pair so that it could obtain a relatively unbiased estimate of generalizability (Orrù et al., 2012). The procedures were also automatically processed in PRoNTo's "Specify model" programs. The whole process has been described in detail in previous studies (Schnyer, Clasen, Gonzalez, & Beevers, 2017). To ensure the stability of the results (Varoquaux & Gaël, 2017), we conducted a fivefold cross-validation approach.

Once the SVM algorithm has been established, the performance evaluation is used to predict a new and previously unseen subject and decide which group it belongs (Orrù et al., 2012). A 1,000-times nonparametric permutation test (Cui, Xia, Su, Shu, & Gong, 2016; Ecker et al., 2010; Schnyer et al., 2017) was used to obtain a correct *P*-value to determine the statistical significance of the accuracy, sensitivity, and specificity. In detail, accuracy refers to the proportion of subjects correctly classified into the patient or control group. Sensitivity and specificity represent the proportion of subjects correctly classified. Moreover, receiver operating characteristic (ROC) analysis and the area under the ROC curve (AUC) were used to evaluate the performance of the classifiers. AUC represents the classification power of a classifier. The values of AUC range from 0 to 1 and a large AUC indicates a good classification ability (Cui et al., 2016; Fawcett, 2005).

For each model, the PRoNTo allows the calculation of images representing the weights per voxel and also images summarizing the weights per ROIs as defined by an atlas (Schrouff et al., 2013). The region contributions to the classification model can be ranked in a descending order, yielding a sorted list of regions. To investigate the classification power of specific locations in the brain, we computed vector weights and listed brain regions that are 5% of the absolute maximum and minimum weight vector values and have a cluster size >100 voxels across all regions.

Statistical analysis. The demographic characteristics of the subjects and the relationship between the ReHo value of the brain regions that contributed most to the classification and addiction severity (IAT and DSM scores) were statistically analyzed using R (www.R-project.org).

Spectral dynamic causal modeling

ROI selection and ROI-specific time series extraction. The selection of ROIs in the resting state depended on our MVPA results. For each ROI, a mask was created using the DPABI. After selecting seed regions, we performed a generalized linear model analysis to extract ROI-specific time series from the original preprocessed data for DCM analysis.

Fig. 1 illustrates the location of the five nodes with the corresponding time series.

Spectral dynamic causal modeling analysis. The spDCM analysis was performed by DCM 12 implemented in SPM 12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). After extracting the mean-corrected time series values of all nodes, we assumed that all participants used the same model and specified a "full" model for each subject. Here, "full" means that each node was assumed to be connected to all other nodes (Ma, Steinberg, Cunningham, Lane, Kramer, et al., 2015). The spDCM contained endogenous connectivity and was quantified by A matrix parameters because no experimental conditions are specified in the model (Friston, Kahan, Biswal, & Razi, 2014; Suchismita, Xin, & Biswal, 2016). Then, model estimation based on standard variational Bayes procedures (variational Laplace) under the frequency domain was performed. The convolution kernel of the model was converted into a spectrum and expressed in the frequency domain. This approximate Bayesian inference method can quickly estimate the connectivity parameters and logarithmic model evidence of first-level DCMs and effectively optimize the posterior probability of model parameters (Friston et al., 2014). After estimating all "full" models, we employed a DCM network discovery routine based on Bayesian model selection to conduct DCM structure inference at the group level. The routine implemented a greedy search for all possible model connectivity parameters ($2^8 = 256$ reduced model space), and the model with the highest posterior probability was selected as the optimal model. Then, Bayesian parameter averaging was adopted to separately obtain optimal sparse model parameters at the group level. For more fundamentals of the spDCM analysis, please refer to the related papers of Friston, Kahan, Biswal, and Razi (Friston et al., 2014).

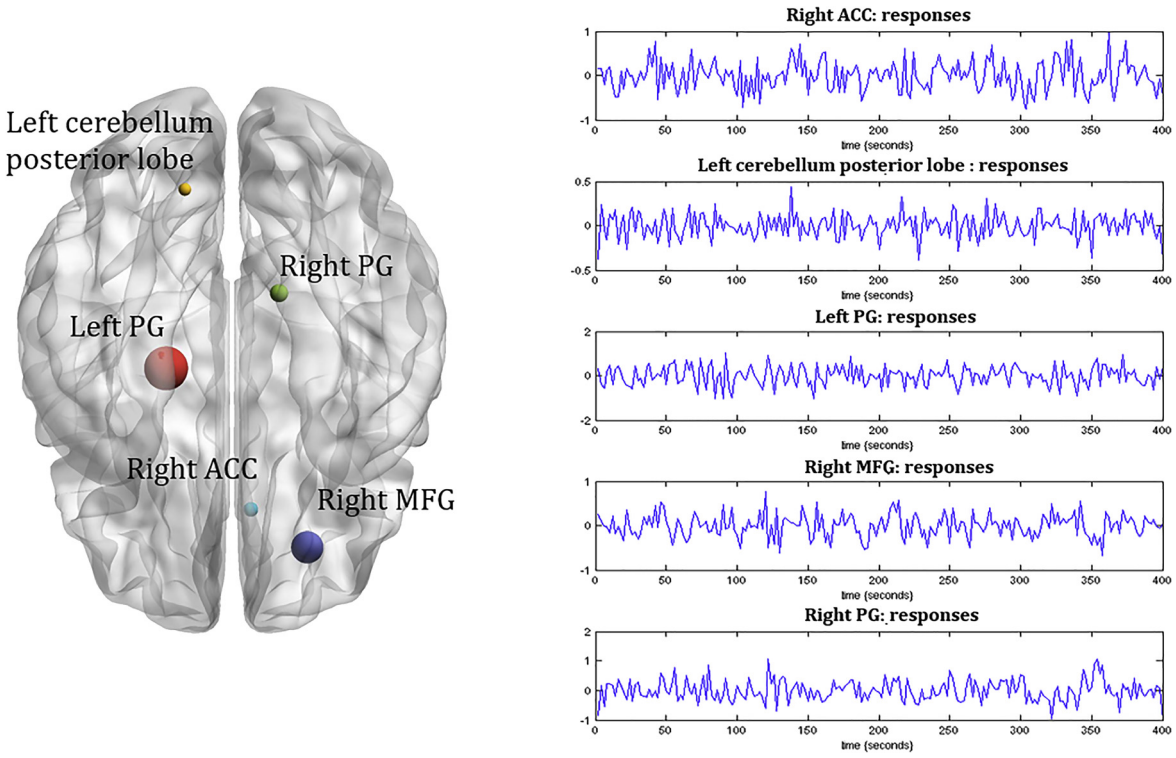

Figure 1. Time series used to invert the spectral dynamic causal modeling between the IGD subjects and RGUs. The figure was visualized with the BrainNet Viewer (http://www.nitrc.org/projects/bnv/). The nodes included the bilateral parahippocampal gyrus (left PG and right PG), left cerebellum posterior lobe, right ACC, and MFG. Corresponding time series are the principal eigenvariates of the regions

Correlation analyses were further conducted to investigate the relationship between mean effective strength and addiction severity (IAT and DSM scores).

Ethics

This study was approved by the Human Investigations Committee of Zhejiang Normal University and conformed to the Declaration of Helsinki. Written informed consent of each participant was obtained before the study.

RESULTS

MVPA results

Classifier evaluation and brain regions that contributed most to the classification. In the classification of the two groups, the AUC was 0.92 (Fig. 2a) and the accuracy was 82.67% (permutation $P = 0.001$) with a sensitivity of 83.50% and specificity of 81.82% (Fig. 2b and c). The AUC was 0.90 and the accuracy was 80.69% (permutation $P = 0.001$) with a sensitivity of 83.50% and specificity of 77.78% in fivefold cross-validation results. The most informative regions for the classification between IGD subjects and RGUs included bilateral parahippocampal gyrus (PG), right anterior cingulate cortex (ACC), middle frontal gyrus (MFG), and left cerebellum posterior lobe (Table 2; Fig. 2d).

Correlation between ReHo values and behavioral measures. We explored the relationships between the ReHo values of regions that contributed most to the classification and addiction severity (IAT and DSM scores) of all participants. Significant positive correlations (Bonferroni correction, $P = 0.005$) were found between addiction severity (IAT and DSM scores) and the ReHo values of the right ACC (IAT: $r = 0.282$, $P < 0.000$; DSM: $r = 0.266$, $P = 0.0001$) and MFG (IAT: $r = 0.331$, $P < 0.000$; DSM: $r = 0.315$, $P < 0.000$). The ReHo values of the bilateral PG (left: IAT: $r = -0.299$, $P < 0.000$, DSM: $r = -0.361$, $P < 0.000$; right: IAT: $r = -0.336$, $P < 0.000$, DSM: $r = -0.382$, $P < 0.000$) and left cerebellum posterior lobe (IAT: $r = -0.214$, $P < 0.000$; DSM: $r = -0.302$, $P < 0.000$) were negatively correlated with the addiction severity (IAT and DSM scores). Detailed information is shown in Table 3 and Supplement Figs 1–10. Although there is a positive or negative trend between ReHo values and IAT/DSM scores, however, these correlations did not reach statistical significance for each group (IGD and GRU) separately.

DCM results

Between-group differences. The differences between groups are shown in Table 4 and Fig. 3. The intrinsic self-connections of the right PG ($t = -2.23$, $P = 0.027$) was inhibitory

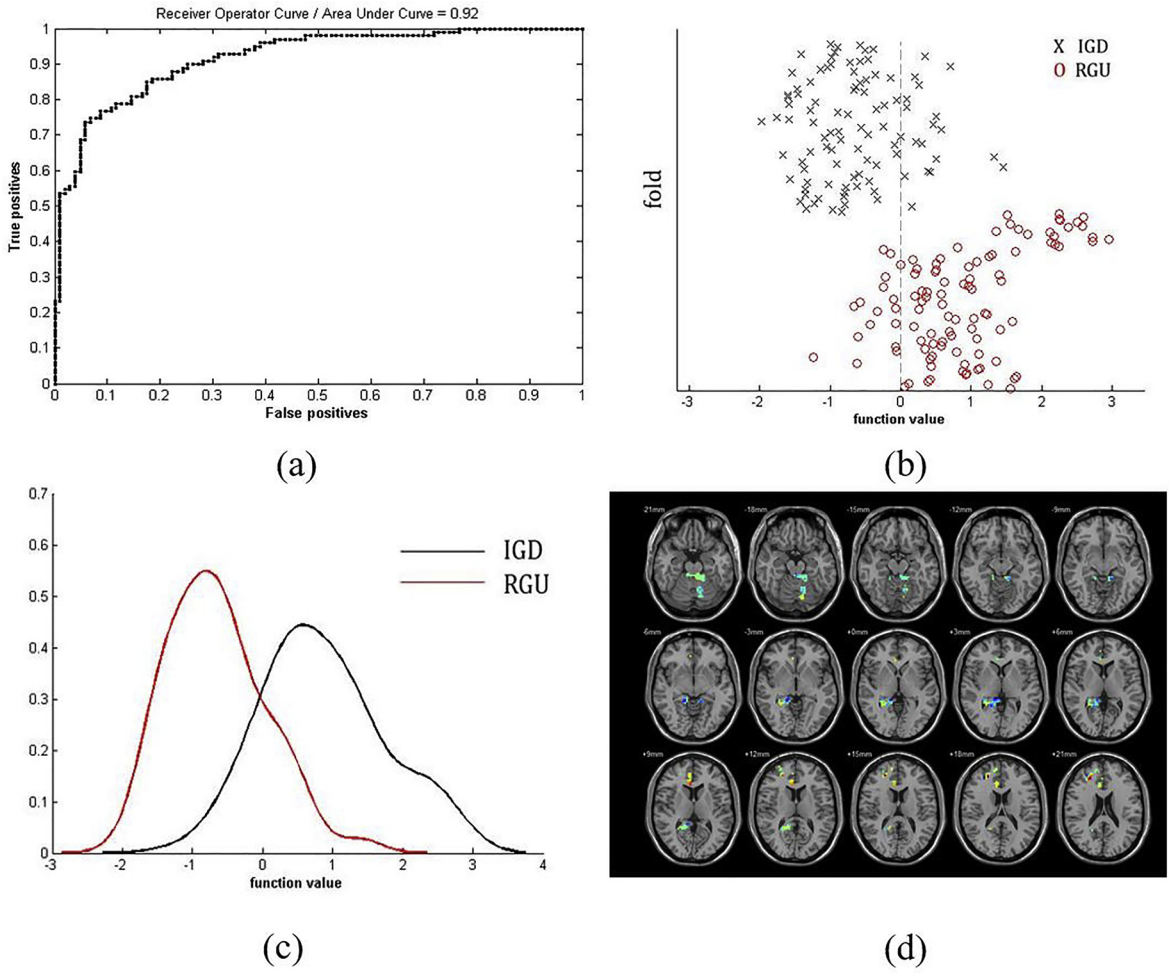

Figure 2. Discriminant results from the classification. (a) ROC curve shows the performance of the binary classifier. (b) Scatterplots show the discrimination between the two groups. (c) Histogram shows the distribution of the two groups. (d) Weight maps for the classifier. The weight vector represents the relative relevance of each voxel to classify the groups

and reached significance after the *t*-test. As the self-connections of nodes always showed inhibitory effects, the responses of the PG in IGD was disinhibited compared with that of RGU. Furthermore, the two extrinsic connections involving the bilateral PG showed significant differences. One was from the left PG to the right MFG ($t = -3.03$, $P = 0.003$), and the other was from the right PG to the ACC ($t = -2.99$, $P = 0.003$).

Table 2. Brain regions contributed most for classification

Brain regions	Hemisphere L/R	Peak MNI(mm)			Cluster size
		X	*Y*	*Z*	
PG	L	−21	−15	−14	435
Cerebellum posterior lobe	L	−15	−72	−36	109
PG	R	15	−39	−3	150
ACC	R	6	30	9	124
MFG	R	24	42	18	351

PG: parahippocampal gyrus; ACC: anterior cingulate cortex; MFG: middle frontal gyrus.

Correlation between the mean effective strength and behavioral measures. We observed negative correlations between addiction severity (IAT and DSM scores) and mean

Table 3. Correlation between ReHo value and behavioral measures

Brain Regions	Addiction Severity	*r*	*P*
Cerebellum posterior lobe (Left)	IAT	−0.214	<0.05[a]
	DSM	−0.302	<0.05[a]
PG (Left)	IAT	−0.299	<0.05[a]
	DSM	−0.361	<0.05[a]
ACC (Right)	IAT	0.282	<0.05[a]
	DSM	0.266	<0.05[a]
MFG (Right)	IAT	0.331	<0.05[a]
	DSM	0.315	<0.05[a]
PG (Right)	IAT	−0.336	<0.05[a]
	DSM	−0.382	<0.05[a]

IAT: Internet addiction test; DSM-5: Diagnostic and Statistical Manual of Mental Disorders-5; PG: parahippocampal gyrus; ACC: anterior cingulate cortex; MFG: middle frontal gyrus.
[a]Bonferroni correction.

Table 4. Effective connectivity parameters differences between groups

Model parameters	IGD	RGU	*t*	*P*
Left PG →Right MFG	−0.349 ± 0.57	−0.119 ± 0.49	−3.03	0.003
Right PG →Right ACC	−0.311 ± 0.59	−0.041 ± 0.68	−2.99	0.003
Right PG →Right PG	−0.768 ± 0.43	−0.631 ± 0.43	−2.23	0.027

IGD: Internet gaming disorder; RGU: recreational game use; PG: parahippocampal gyrus; ACC: anterior cingulate cortex; MFG: middle frontal gyrus.

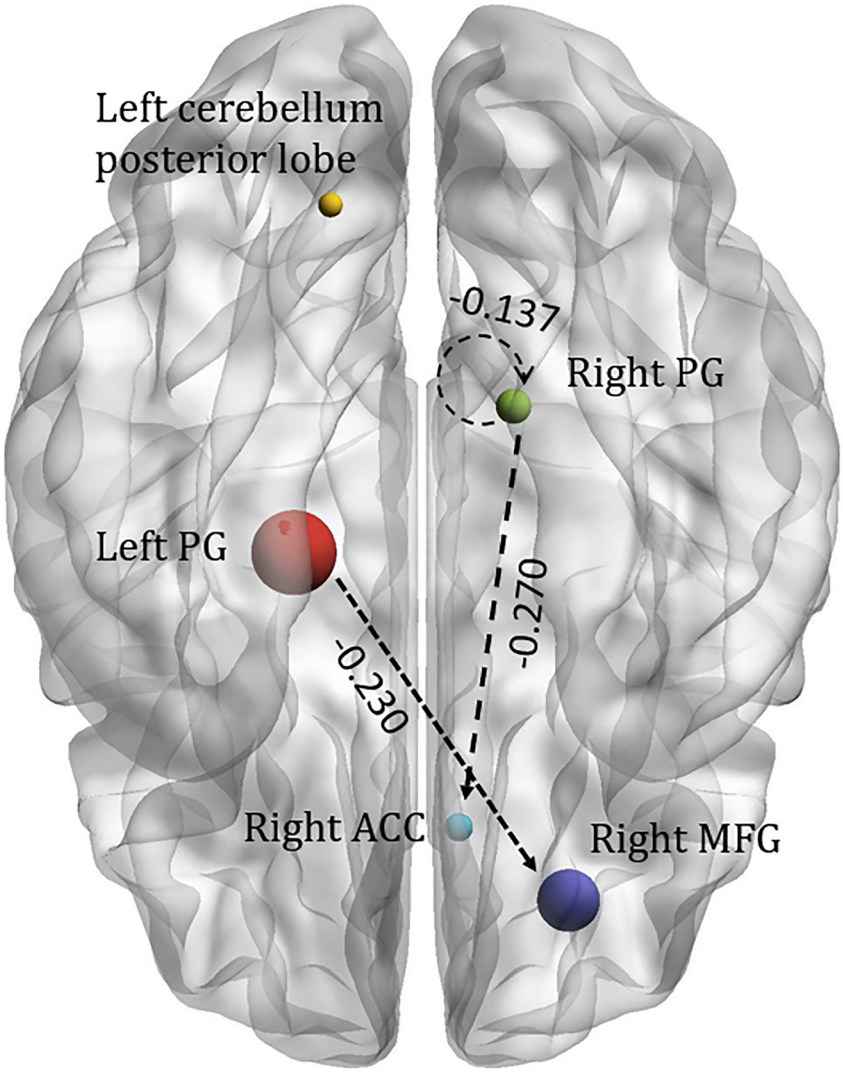

Figure 3. Effective connectivity difference between the IGD subjects and RGUs. This figure shows the significant decreased effective connectivity strength from the left parahippocampal gyrus to the right MFG and from the right PG to the ACC with weakened self-connection in the right PG. The dotted line indicates weakened connectivity in IGD

effective strength from the left PG to the right MFG (IAT: $r = -0.198$, $P = 0.005$; DSM: $r = -0.194$, $P = 0.006$) and from the right PG to the ACC (IAT: $r = -0.207$, $P = 0.003$; DSM: $r = -0.230$, $P = 0.001$) (Bonferroni correction, $P = 0.008$). Detailed information is shown in Table 5 and Supplement Figs 11–14. Although there is a positive or negative trend between the mean effective strength values and IAT/DSM scores, however, these correlations did not reach statistical significance for each group (IGD and GRU) separately.

DISCUSSION

The current study applied MVPA and DCM analysis methods to evaluate the neurobiological substrates of IGD during resting state. This study shows that image-based machine learning techniques can be used to distinguish IGD by using a ReHo map. The most informative brain regions for the classification are bilateral PG, right ACC, MFG and left cerebellum posterior lobe. These brain regions are

Table 5. Correlation between effective connectivity strength and behavioral measures

Model Parameters	Addiction Severity	*r*	*P*
Left PG → Right MFG	IAT	−0.198	0.005[a]
	DSM	−0.194	0.006[a]
Right PG →Right ACC	IAT	−0.207	0.003[a]
	DSM	−0.230	0.001[a]

IAT: Internet addiction test; DSM-5: Diagnostic and Statistical Manual of Mental Disorders-5; PG: parahippocampal gyrus; ACC: anterior cingulate cortex; MFG: middle frontal gyrus.
[a]Bonferroni correction.

related to the cognitive control system, memory/learning, and emotion regulation and might provide a new perspective for clinical diagnosis of IGD. In addition, the DCM results present the weakening of the PG and its connection with brain regions, such as ACC and MFG, in IGD. The significance of these findings is discussed below.

One of the most consistent findings from the current study is that the most informative brain region for the classification is the prefrontal cortex network, including the right ACC and MFG (Zhang et al., 2011), and the ReHo values of ACC and MFG are negatively correlated with addiction severity (IAT and DSM scores). The prefrontal cortex network is involved in cognitive control (Royall et al., 2002), and this finding suggested a relationship between the impaired control and the longtime of playing an Internet game even when IGD subject expresses the desire to refrain from playing.

Previous studies have shown that the ACC and MFG play important roles in cognitive control, including error processing and decision making related to reward through the memory (Posner & Dehaene, 1994; Walton & Mars, 2007). The impact of various brain regions on IGD is not isolated; some studies have suggested that IGD subjects showed abnormal function connection among PG, ACC, and MFG (Kim et al., 2015; Liu et al., 2010). In our study, we further observed decreased effective connectivity from the left PG to the right MFG and from the right PG to the ACC and decreased self-connection in the right PG. This finding might provide a new perspective for treatment of IGD.

The most informative brain regions for the classification between IGD subjects and RGUs included the bilateral PG, whose ReHo value was negatively correlated with addiction severity (IAT and DSM scores). The PG is part of the default network and plays a critical role in the formation of the pathological memory of substance addiction (Slamberova et al., 2014). In the case of long-term withdrawal of patients with addiction, drug-related stimulus conditions can still strongly recall the experience of using drugs, which is known as "addiction memory" (Dunbar & Taylor, 2016). The pathological memory is closely related to acquiring drug addiction (Hyman, Malenka, & Nestler, 2006). In an experimental mouse model of addiction, Jasinska, Stein, Kaiser, Naumer, & Yalachkov (2014) found that stimulating the hippocampus can lead to a strong craving for drugs. The blockade of beta adrenergic receptors in the dorsal hippocampus of rats reduced drug seeking and induced the relapse of the cue (Otis, Fitzgerald, & Mueller, 2014). Several studies associated with cocaine-dependent participants noted that participants exposed to cocaine cues showed strong craving for drugs and an increased activity of the hippocampus (Castilla et al., 2016; Goldstein & Volkow, 2012). The abnormal bilateral PG may be related to the formation of the addiction memory, which is needed to further study in IGD group.

The PG contributes to memory recall, possibly through the representation and retrieval of contextual information (Eichenbaum, Yonelinas, & Ranganath, 2007). The prefrontal cortex, including the ACC and MFG, is also involved in this process (Weible, 2013). The ACC is also a key structure in the brain networks involved in mood regulation (Caetano et al., 2006), and MFG is related to the modulation of emotions (Drabant, McRae, Manuck, Hariri, & Gross, 2009). A study has showed that IGD subjects substantially exhibited blunted neural responses in the ACC and MFG in response to negative affective cues and during emotion regulation (Yip et al., 2018). The generation and modulation of negative emotions are not only affected by a certain brain area. Decreased effective connectivity from the bilateral PG to the prefrontal cortex, such as the right MFG and ACC may be the underlying mechanisms of emotion problem in IGD subjects and provide a new perspective for treatment of IGD. Further work is needed to determine the specificity mechanisms of negative emotion problem in the IGD group.

The most informative regions for the classification also included the left cerebellum posterior lobe, whose ReHo value was negatively correlated with addiction severity (IAT and DSM scores). The functions of the cerebellum posterior lobe are not limited to movement and balance as it also plays an important role in emotion and cognitive processes (Strata, Scelfo, & Sacchetti, 2011; Tirapu, Luna, Iglesias, & Hernaez, 2011). Regional cerebral blood flow apparently increases in the cerebellum when craving is induced by a cocaine cue (Bolla et al., 2003), which may be related to emotional processes and attention during cue induction (Paradiso, Anderson, Ponto, Tranel, & Robinson, 2011; Takeuchi et al., 2011). Previous studies also found alterations of ReHo in subjects with IGD, and the results suggest that online game playing enhances brain synchronization in sensory–motor coordination (Dong, Huang, & Du, 2012). However, this contention cannot be confirmed in this present study and needs to be investigated by a follow-up study.

Although the findings of this study provide new insights into IGD, it has several limitations of note. First, data from groups with no gaming experiences can be collected to identify the differences between the three groups (healthy control, IGD, and RGU). The results will be remarkable if a group of nongamers is included. Second, this study did not combine different imaging data for classification;

multimodal data may provide a better perspective to classify IGD from RGU in future studies. Moreover, we innovatively estimated the most discriminative brain regions to show preliminary results. Excluded brain regions may also contain valuable information, and these regions should receive full considerations in future research.

CONCLUSIONS

The current study clearly shows that distinguishing IGD subjects from RGUs at the individual level is possible using MVPA. The brain regions with high weight include the bilateral PG, right ACC, and MFG. Moreover, the results of DCM showed that compared with RGU, IGD showed decreased effective connectivity from the left PG to the right MFG and from the right PG to the ACC and decreased self-connection in the right PG. These results show that the weakening of the PG and its connection with the prefrontal cortex, including the ACC and MFG, may be an underlying mechanism of IGD.

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SUPPLEMENTARY MATERIAL

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