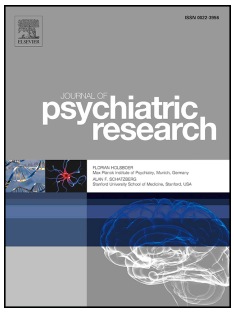
Journal Pre-proof



Neural classification of internet gaming disorder and prediction of treatment response using a cue-reactivity fMRI task in young men

Zi-Liang Wang, Marc N. Potenza, Kun-Ru Song, Xiao-Yi Fang, Lu Liu, Shan-Shan Ma, Cui-Cui Xia, Jing Lan, Yuan-Wei Yao, Jin-Tao Zhang

PII: S0022-3956(20)31073-6

DOI: https://doi.org/10.1016/j.jpsychires.2020.11.014

Reference: PIAT 4138

To appear in: *Journal of Psychiatric Research*

Received Date: 30 June 2020

Revised Date: 1 November 2020

Accepted Date: 5 November 2020

Please cite this article as: Wang Z-L, Potenza MN, Song K-R, Fang X-Y, Liu L, Ma S-S, Xia C-C, Lan J, Yao Y-W, Zhang J-T, Neural classification of internet gaming disorder and prediction of treatment response using a cue-reactivity fMRI task in young men, *Journal of Psychiatric Research*, https://doi.org/10.1016/j.jpsychires.2020.11.014.

Acknowledgements

Zi-Liang Wang analyzed the data and wrote the first draft of the manuscript. Kun-Ru Song, Lu Liu, Shan-Shan Ma, Cui-Cui Xia, Jing Lan and Yuan-Wei Yao contributed to fMRI data collection. Jin-Tao Zhang, Xiao-Yi Fang and Marc Potenza contributed in interpreting findings, editing, and revisions. All authors have approved the final manuscript.

Neural classification of internet gaming disorder and prediction of treatment response using a cue-reactivity fMRI task in young men

Zi-Liang Wang [1,10], Marc N. Potenza[2, 3, 4], Kun-Ru Song [1,10], Xiao-Yi Fang [5*], Lu Liu [5, 6], Shan-Shan Ma[1, 5], Cui-Cui Xia[7], Jing Lan[5, 8], Yuan-Wei Yao[1, 9], Jin-Tao Zhang[1,10, 11]*

1 State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing, China

2 Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA

3 Child Study Center, Yale University School of Medicine, New Haven, CT, USA

4 Department of Neuroscience, Yale University School of Medicine, Connecticut Mental Health Center, New Haven, Connecticut Council on Problem Gambling, Wethersfield, CT, USA

5 Institute of Developmental Psychology, Beijing Normal University, Beijing 100875, China

6 German Institute of Human Nutrition Potsdam-Rehbruecke, 14558 Nuthetal, Germany

7 Psychological Counseling Center, Beijing Normal University, Beijing 100875, China

8 The Family Institute at Northwestern University, Northwestern University, 60201, IL, USA

9 Department of Education and Psychology, Freie Universität Berlin, Berlin 14195, Germany

10 IDG/McGovern Institute for Brain Research, Beijing Normal University, Beijing, China

11 Beijing Key Lab of Applied Experimental Psychology, School of Psychology, Beijing Normal University，Beijing, China

Registry name: The behavioral and brain mechanism of IGD;

URL: https://www.clinicaltrials.gov/ct2/show/NCT02550405;

Registration number: NCT02550405.

Corresponding authors:
Xiao-Yi Fang, Ph.D., Professor
Institute of Developmental Psychology, Beijing Normal University, Beijing 100875, China
Beijing Normal University, No. 19, Xinjiekouwai street, Haidian District, Beijing 100875, China; Phone/Fax: +86 10 58808232,
E-mail: fangxy@bnu.edu.cn

Jin-Tao Zhang, Ph.D., Professor
State Key Laboratory of Cognitive Neuroscience and Learning and IDG/McGovern Institute for Brain Research, Beijing Normal University, No. 19, Xinjiekouwai street, Haidian District, Beijing 100875, China; Phone/Fax: +86 10 58800728,
E-mail: zhangjintao@bnu.edu.cn

Abstract

Background

Neural mechanisms underlying internet gaming disorder (IGD) are important for diagnostic considerations and treatment development. However, neurobiological underpinnings of IGD remain relatively poorly understood.

Methods

We employed multi-voxel pattern analysis (MVPA), a machine-learning approach, to examine the potential of neural features to statistically predict IGD status and treatment outcome (percentage change in weekly gaming time) for IGD.

Cue-reactivity fMRI-task data were collected from 40 male IGD subjects and 19 male healthy control (HC) subjects. 23 IGD subjects received 6 weeks of craving behavioral intervention (CBI) treatment. MVPA was applied to classify IGD subjects from HCs and statistically predict clinical outcomes.

Results

MVPA displayed a high (92.37%) accuracy (sensitivity of 90.00% and specificity of 94.74%) in the classification of IGD and HC subjects. The most discriminative brain regions that contribute to classification were the bilateral middle frontal gyrus, precuneus, and posterior lobe of the right cerebellum. MVPA statistically predicted clinical outcomes in the craving behavioral intervention (CBI) group (r = 0.48, p = 0.0032). The most strongly implicated brain regions in the prediction model were the right middle frontal gyrus, superior frontal gyrus, supramarginal gyrus, anterior/posterior lobes of the cerebellum and left postcentral gyrus.

Conclusions

The findings about cue-reactivity neural correlates could help identify IGD subjects and predict CBI-related treatment outcomes provide mechanistic insight into IGD and its treatment and may help promote treatment development efforts.

Keywords: internet; video games; craving; multi-voxel pattern analysis; addictive behaviors; behavior therapy

1 Introduction

Individuals with internet gaming disorder (IGD) often exhibit craving responses to gaming cues and poor executive control over gaming motivations (Dong et al., 2020; Petry et al., 2014). Despite multiple neuroimaging studies of IGD (Dong. et al., 2020; Ko et al., 2009; Liu et al., 2017; Wang et al., 2017; Zhang, Yao, Potenza, Xia, & Fang, 2016), neural mechanisms underlying craving to gaming cues in IGD remain poorly understood with respect to diagnostic and intervention outcome-related predictive applications. Investigations of neurobiological substrates of craving in IGD could provide insight into the ways to best classify and to treat individuals with IGD. Craving has been defined as an intense desire for experiencing a psychoactive substance or behavior (Blumenthal & Daniel, 2009). Cue reactivity and craving have been considered as central features of addictions generally and IGD specifically (Brand et al., 2019; Dong & Potenza, 2014; Liu et al., 2017). Craving may be elicited by addiction-related cues (Wang et al., 2017), and cue reactivity may contribute importantly to the development and maintenance of addictive behaviors (Carter & Tiffany, 1999; Goudriaan, Ruiter, Brink, Oosterlaan, & Veltman, 2010; Tong & Bovbjerg, 2007) and to relapse into addictive behaviors (Kosten, Scanley, Tucker, Oliveto, & Wexler, 2006; Marissen, Franken, Waters, Blanken, & Hendriks, 2006). Previous neuroimaging investigations of IGD have implicated involvement of the dorsolateral prefrontal cortex, middle frontal gyrus, anterior cingulate cortex, insula, and precuneus in response to gaming-related cues (Han et al., 2011; Ko et al., 2009;

Sun et al., 2012; Wang et al., 2017; Zhang et al., 2016).

Cue-reactivity tasks also provide an avenue for investigating neural mechanisms by which interventions may operate. Previous studies have examined how interventions exert effects on cue-induced brain activation in IGD. For instance, family therapy reduced gaming-cue-induced brain activation in frontal and occipital regions (Han, Kim, Lee, & Renshaw, 2012). Another study found that 6 weeks of treatment with bupropion for IGD decreased cue-induced craving and activation in the left superior frontal gyrus (Han, Hwang, & Renshaw, 2010). In the current study, the integrated CBI was developed with respect to behavioral intervention theories (Dong & Potenza, 2014), satisfaction of psychological needs for internet gaming (Mccarthy, Curtin, Piper, & Baker, 2010) and a craving integrated framework (Suler, 1999) for systematically investigating the effects of behavioral interventions for IGD. The CBI was conducted in group format and included modules on mindfulness and cognitive behavioral therapy (detailed in supplementary materials). Thus, the CBI aimed to help IGD subjects recognize and manage craving and gaming behaviors. Our previous study showed increased activation of the anterior insula from pre- to post-treatment after receiving the CBI (Zhang et al., 2016).

While these studies have provided useful insight into the neural correlates of cue-reactivity in IGD, they have typically used conventional mass univariate analytical techniques to investigate changes in blood-oxygen-level-dependent-signal-derived (BOLD-signal-derived) beta values related to exposure to gaming-related cues. As mass univariate studies investigating

beta values alterations between IGD participants and a control group aim to test whether some brain regions have differences in degrees of activation or deactivation, they are limited with respect to translating findings into clinical utility (Hu et al., 2019).

Recently, interest in data-driven, machine-learning approaches for investigating brain function has been growing, including those involving the application of multi-voxel pattern analysis (MVPA) to identify brain signatures for clinical diagnoses of mental disorders (Woo, Chang, Lindquist, & Wager, 2017). Compared with traditional univariate analyses, 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 classify participants with an addictive disorder and those without (Vieira, Pinaya, & Mechelli, 2017). MVPA methods have been successfully used to differentiate subjects with substance addiction from control subjects in task-based studies using functional magnetic resonance imaging (fMRI) (Elton, Chanon, & Boettiger, 2019; Sakoglu et al., 2019).

However, to the best of our knowledge, no studies have used MVPA to find brain signatures underlying cue reactivity that may predict classification of individuals with and without IGD. In the current study, an initial aim was to examine the potential of MVPA in classifying IGD subjects (versus HCs) using cue-reactivity data. A second aim was to examine the potential of MVPA in predicting treatment responses (percentage change in weekly gaming time) using baseline beta values in IGD

subjects receiving CBI treatment. Based on previous findings, we hypothesized that MVPA could be applied to cue-reactivity data to classify IGD subjects relative to HCs. We hypothesized that MVPA would implicate brain regions involved in executive control, reward/loss processing and craving (Han et al., 2011; Ko et al., 2009; Wang et al., 2017). We also hypothesized that neural correlates of cue-reactivity data at baseline could be used to predict CBI treatment outcomes, with the most informative regions including frontal regions (Han et al., 2012).

2 Materials and methods

This study was approved by the Human Investigations Committee of the State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University and conformed to the Declaration of Helsinki. Written informed consent of each participant was obtained before study participation.

2.1 Participants

We recruited 44 male subjects with IGD and 22 male HC subjects through posters and internet advertisements. Four IGD and three HC subjects were excluded due to excessive head motion. Therefore, data from 40 IGD and 19 HC subjects were included in final analyses. Twenty-three IGD subjects (CBI+ group) were willing to participate in a 6-week group CBI and were scanned before and after CBI. The remaining 17 IGD subjects (CBI− group) did not receive any intervention, but had similar intervals between scans as for the CBI+ group.

Inclusion criteria for IGD subjects were: 1) scores ≥67 on the Chen Internet Addiction Scale (CIAS) (Chen, Weng, Su, Wu, & Yang, 2003); 2) playing internet games for over 14 h per week for a minimum of one year. The inclusion criteria for HCs were: 1) scores of 60 or lower on the CIAS; and 2) never or occasional engagement (<2 h per week) in internet gaming. Data in this study come from our previous study (Zhang et al., 2016)(table1 and table 2); however, all statistical analytical methods are different and the results are unique relative to those described previously.

Insert Table 1 and Table 2 about here

2.2 Symptom assessment

Current severities of depression and anxiety were assessed using the Beck Depression Inventory (Beck, 1961) and the Beck Anxiety Inventory (Beck, Epstein, Brown, & Steer, 1988), respectively. Cigarette and alcohol use were recorded, and the Fagerstrom Test for Nicotine Dependence (Fagerstrom, 1978) and alcohol consumption questions from the Alcohol Use Disorders Identification Test (Bush, Kivlahan, McDonell, Fihn, & Bradley, 1998) were used to assess nicotine dependence and hazardous alcohol use, respectively. Weekly gaming time change (%) was calculated by post-treatment minus pre-treatment gaming hours/ pre-treatment gaming hours.

2.3 Craving behavioral intervention (CBI)

The integrated CBI was developed on the basis of behavioral intervention theories. Since craving may impact significantly on the development and maintenance of IGD (Dong & Potenza, 2014), methods that focus on reducing craving may improve therapeutic outcomes and prevent relapse. CBI was conducted weekly and included six 2.5-hour sessions with 8 to 9 IGD subjects in each group. The details of the CBI are included in the supplemental materials.

2.4 fMRI paradigm

Participants completed the cue reactivity task, which has been previously described in detail (Zhang et al., 2016). Briefly, participants were asked to passively watch three kinds of videos [gaming video clips (G), matched control video clips (C) and fixation(F)] and to rate their craving immediately after each video clip using 7-point visual analog scales. Gaming video clips were screenshots selected from official websites or gaming forums by 10 additional Internet gaming players. Matched control video clips were selected from an unpopular online game which was not known to or played by any participants in the study. The order of the clips was fixed: G-F-C G-C-F C-F-G C-G-F F-C-G F-G-C. Each clip was 30 seconds followed by a 4-second rating screen. This task was presented by E-Prime 2.0 and lasted for 620 s.

2.5 Image acquisition

Data were acquired using a 3.0 T SIEMENS Trio scanner in the Imaging Center for Brain Research, Beijing Normal University. A gradient echo echo-planar imaging (EPI) sequence was obtained (TR =2000 ms; TE = 25 ms; flip angle = 90°; matrix = 64 × 64; resolution =3 × 3 mm2; slices = 41). The slices were tilted 30° clockwise from the AC-PC plane to obtain better signals in frontal regions. A T1-weighted sagittal scan was acquired for anatomical reference with EPI data (TR = 2530 ms, TE = 3.39 ms, TI = 1100 ms, FA = 7°, FOV =256 × 256 mm2, voxel size = 1 × 1 × 1.3 mm3, slice = 144).

2.6 Data pre-processing and calculation of activation maps

Imaging data were pre-processed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12). Functional data were realigned, coregistered with structural images, segmented for normalization to standard MNI space, and smoothed with a 5-mm Gaussian kernel at full width at half maximum (FWHM). Subjects with head motion >3 mm or 3° were excluded from further analysis.

A general linear model (GLM) was applied to identify blood oxygen level dependent (BOLD) activation. Three regressors were distinguished: gaming videos, control videos and craving ratings. Regressors were constructed by convolving the onsets of these stimuli with a canonical hemodynamic response function. Six realignment parameters were also included as regressors of no interest. A high-pass filter (128 Hz) was applied to remove low-frequency signal drift. A contrast image (beta value) between gaming and control videos (gaming minus control) was built to examine cue-induced brain activation. Beta maps of cue-induced brain activation were subsequently entered into MVPAs.

2.7 Multi-voxel Pattern Analysis (MVPA)

Beta values calculated in GLM analyses of baseline data were used for MVPA with two objectives: (1) classify IGD subjects and HCs; and, (2) predict treatment responses.

In the first step, machine-learning models were trained to classify IGD and HC

subjects using beta values. A support vector machine (SVM) classifier was used, and the implementation of the SVM was based on the Pattern Recognition for Neuroimaging Toolbox (PRoNTo) (Schrouff et al., 2013) (http://www.mlnl.cs.ucl.ac.uk/pronto). A leave-one-out cross-validation method was conducted to perform SVM classifier validation, where the feature selection was performed each time on the training partition of the data to avoid circularity effects. A 5,000-times non-parametric permutation test was used to obtain a correct p-value to determine the statistical significance of the accuracy, sensitivity, and specificity. More specifically, accuracy refers to the proportion of subjects correctly classified into the patient or control group. Sensitivity is the proportion of patients with IGD who test positive: P= True Positives / (True Positives + False Negative). Specificity is the proportion of patients without IGD who test negative: P = True Negatives / (True Negatives + False Positives) (Cui, Xia, Su, Shu, & Gong, 2016). 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 larger AUCs indicate better classification abilities (Tom, 2006). For each model, the PRoNTo allows the calculation of images representing the weights per voxel and also images summarizing the weights per regions of interest (ROIs) as defined by an atlas (Schrouff et al., 2013). The regional 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 were 5% of the absolute maximum and minimum weight vector values and had a cluster size >100 voxels across all regions.

In the second step, we aimed to predict treatment responses (percentage change in weekly gaming time) using baseline beta values in the CBI+ and CBI- groups respectively. Pattern regression analysis was implemented in PRoNTo (Schrouff et al., 2013) to investigate if it is possible to predict changes of weekly gaming time from patterns of brain activation during the cue-reactivity task. In the present study, we used the Gaussian Process Regression (GPR), which is a probabilistic regression approach (Seeger, 2005). To evaluate GPR performance, we used a leave-one-out cross-validation method. The performance of the pattern regression models was measured using two metrics of agreement between the predicted and the actual scores, Pearson's correlation coefficient (r) and normalized mean squared error (MSE). The correlation coefficient describes the strength of a linear relationship between two variables, with high correlations indicating better predictions. The normalized MSE is the mean of the squared differences between the predicted and actual scores divided by the range of predicted scores (i.e., maximum minus minimum values). It measures the error between the predicted and actual scores. A 5,000-times non-parametric permutation test was used to obtain a p-value to determine the statistical significance of *r* and MSE. To ensure greater balance in the number of people in the IGD and HC groups and to examine stability of the results (Varoquaux, 2018; Varoquaux et al., 2017), we conducted a subsample comparison that was more balanced in number (IGD = 23, HC=19) and used a 10-fold cross-validation approach. Finally, to

investigate the predictive power of specific locations in the brain, we computed vector weights and listed brain regions that were 5% or more of the absolute maximum and minimum weight vector values and had a cluster size >100 voxels across all regions. Further, the relationship between the beta value of the brain regions that contributed most to the prediction and weekly gaming time change were statistically analyzed using R (www.R-project.org).

3 Results

3.1 Classification evaluation and regional brain regions contributions

In the classification of the two groups, the AUC was 0.94 (Figure 1a) and the accuracy was 92.37% (p = 0.0002, permutation testing, 5000 times) with a sensitivity of 90.00% and specificity of 94.74% (Figure 1b and c). The most informative regions for classification of IGD versus HC subjects included the bilateral middle frontal gyrus (MFG), precuneus, and right posterior lobe of the cerebellum (Table 3; Figure 1d).

Insert Table 3 and Figure 1 about here

Two subsample comparisons more balanced in numbers of subjects [(IGD = 23(CBI+ group), HC = 19 or IGD = 17 (CBI- group), HC = 19)] were conducted. In the classification of the subgroups between the CBI+ and HC groups, the AUC was 0.94 and the accuracy was 90.48% (p = 0.0002, permutation testing, 5000 times) with a sensitivity of 86.96% and specificity of 94.74%. A subsample comparison more balanced in numbers (IGD = 23, HC=19) showed that the AUC was 0.92 and that the accuracy was 90.48% (p = 0.0002, permutation testing, 5000 times), with a sensitivity of 86.96% and specificity of 94.74%. The AUC was 0.91 and the accuracy was 88.1% (p = 0.0002, permutation testing, 5000 times) with a sensitivity of 82.61% and specificity of 94.74% in a 10-fold cross-validation analysis. In the classification of the subgroups between the CBI- and HC groups, the AUC was 0.94 and the accuracy was 91.67% (p = 0.0002, permutation testing, 5000 times) with a sensitivity of 88.24% and specificity of 94.74%. Thus, the subsample results are basically consistent with

the original ones.

3.2 Treatment-outcome evaluation and regional brain contributions

The correlation between actual and predicted changes in weekly gaming time was 0.48 in the CBI + group (p = 0.0032, permutation testing, 5000 times). The MSE for predicting treatment responses was 0.08 (p = 0.0026, permutation testing, 5000 times). The most informative regions for the prediction in the CBI + group included the right middle frontal gyrus, superior frontal gyrus, supramarginal gyrus, anterior/posterior lobe of the cerebellum and left postcentral gyrus (Table 4; Figure 2). The correlation between actual and predicted changes in weekly gaming time in the CBI- group was not statistically significant (r = -0.66, permutation testing, 5000 times, p = 0.872). The MSE for predicting treatment responses was 649.43 (p = 0.6429, permutation testing, 5000 times).

Insert Table 4 and Figure 2 about here

3.3 Correlations between brain regions that contributed most to classification and outcome predictions

We observed negative correlations between weekly gaming time change and beta values in the right middle frontal gyrus (r = -0.676, p < 0.001), middle/superior frontal gyrus (r = -0.821, p < 0.001), superior frontal gyrus (r = -0.689, p < 0.001), supramarginal gyrus (r = -0.670, p < 0.001), anterior lobe of the cerebellum (r = -0.566, p = 0.005) and left postcentral gyrus (r = -0.630, p < 0.001) in the CBI+ group

(Figure 3).

Insert Figure 3 about here

4 Discussion

To our knowledge, the present study is the first to investigate the usefulness of MVPA in analyzing cue-reactivity data to classify individuals with IGD and statistically predict treatment outcomes. The successful application of MVPA in predicting both classification and treatment outcomes has multiple implications. First, ROC curves and the observed accuracies indicated a high discriminating value for classification of IGD versus HC individuals based on neural correlates of cue reactivity. Second, in that baseline neural correlates of cue-reactivity could statistically predict CBI-related outcomes, the findings suggest potential clinical applications of fMRI measures. Taken together, the approach employed here may help clinicians identify individuals with IGD and possibly predict future outcomes prior to treatment initiation.

4.1 Classification of IGD and HC subjects

The different patterns of activation patterns in the IGD group compared to the HC group suggest that differences in neural correlates of cue reactivity may implicate clinical statuses. Multiple brain regions contributed to the classification, including the bilateral middle frontal gyrus and precuneus and right posterior lobe of the cerebellum. The results suggest important roles for these regions in cue-reactivity and are similar to our previous results based on GLM analyses. (Zhang et al., 2016) They are also in accordance with other prior findings (Dong et al., 2020; Ko et al., 2009; Sun et al., 2012). The middle frontal gyrus has been implicated in self-regulation, craving, impulse control and reward-related processes in addictions (Goldstein & Volkow,

2011), including IGD (Zheng et al., 2019) and as proposed in theoretical models of IGD (Dong & Potenza, 2014). The middle frontal gyrus has specifically been linked to cue reactivity in craving in IGD (Dong et al., 2020; Dong, Zheng, et al., 2018). Similarly, the precuneus has been linked to cue reactivity in substance addictions (Engelmann et al., 2012), particularly with respect to attentional tracking of stimuli and the preparation of motor behaviors (Cavanna & Trimble, 2006). As the precuneus has also been implicated in episodic memory retrieval (Cavanna & Trimble, 2006), precuneus involvement during cue-reactivity may be linked to memories of prior experiences that may promote craving. More recently, the precuneus has been implicated in cue-reactivity in IGD, with cue-related activation of the precuneus and functional connectivity between the precuneus and middle frontal gyrus related to IGD severity (Dong et al., 2020).

The most informative regions for classification also included the right posterior lobe of the cerebellum. The functions of the posterior lobe contribute importantly not only to movement and balance, but also to emotional and cognitive processes (Strata, Scelfo, & Sacchetti, 2011; Tirapu-Ustarroz, Luna-Lario, Iglesias-Fernandez, & Hernaez-Goni, 2011). Regional cerebral blood flow increases in the cerebellum during cue-induced craving have been related to cocaine use disorder (Bolla et al., 2003). However, precise roles for the middle frontal gyrus, precuneus and cerebellum in cue-reactivity in IGD warrant further investigation.

Interestingly, in our classification analysis, some reward-related brain regions (e.g., ventral and dorsal striatum) were not implicated. In a previous meta-analysis, these reward-related brain regions also did not show activation differences in cue-reactivity tasks (Zheng et al., 2019). One possible reason for these results may be that individuals with IGD in our study were in later stages of the addiction process, where game-related stimuli evoke less of a response than might actual gaming (Piazza & Deroche-Gamonet, 2013). However, this speculative notion warrants further examination.

4.2 CBI outcomes

MVPA identified that cue-related activations in the right middle frontal gyrus, superior frontal gyrus, supramarginal gyrus, anterior/posterior lobe of the cerebellum and left postcentral gyrus showed a pattern of high prediction ability relating to the treatment outcome of changes in weekly gaming time. Further, there were significant negative correlations between changes in weekly gaming time and beta values from including the right middle frontal gyrus, superior frontal gyrus, supramarginal gyrus, anterior lobe of the cerebellum and left postcentral gyrus in CBI+ group (Dong, Wang, Wang, Du, & Potenza, 2019; Dong, Zheng, et al., 2018). Previous univariate studies have been mixed in terms of relationships with treatments outcomes, with the activities in prefrontal cortex decreasing after family therapy intervention and increasing after bupropion treatment; these findings complement results of prior studies identifying regional changes related to pharmacological and psychological treatment of IGD (Han et al., 2010; Han et al., 2012).

The prefrontal cortex, including the middle frontal gyrus and superior frontal gyrus, have been implicated in multiple processes including craving responses in IGD (Dong, Wang, et al., 2019; Dong, Zheng, et al., 2018), and prefrontal activations have been linked to natural recovery (without formal intervention) in IGD (Dong, Liu, Zheng, Du, & Potenza, 2019). The cerebellum has been implicated in multiple functions relating to IGD, including visual, emotional and cognitive processes (Strata et al., 2011; Tirapu-Ustarroz et al., 2011). The supramarginal and postcentral gyri are main sensory receptive regions for touch. Compared with our previous results based only on GLM analyses (Zhang et al., 2016), the results raise the possibility that neural mechanisms involved in integrating sensory information may relate to CBI's efficacy in important ways, as previously proposed in a cognitive-behavioral model (Dong & Potenza, 2014). Taken together, the existing findings suggest that craving responses, emotion and cognitive processes in individuals with IGD relate importantly to IGD treatment outcomes, although the extent to which the findings reflect factors or neural functions that arise during phases of IGD development is not yet understood.

4.3 Limitations and implications

A number of limitations of the present study may warrant mentioning. First, the sample size was limited. A small sample size is likely to lead to overly optimistic results during cross-validation (especially using a leave-one-out approach), possibly inflating the performance of the prediction model (Varoquaux, 2017; Varoquaux et al.,

2017). To ensure the stability of the results, we conducted a 10-fold cross-validation approach. The results are basically consistent with the original results. Future studies should use larger samples to replicate and extend findings of the current study. Second, only males were included in the current study. As gender-related differences have been observed in neural correlates of cue reactivity in IGD (Dong, Wang, Du, & Potenza, 2018; Dong, Wang, et al., 2019; Dong, Zheng, et al., 2018), future studies should examine the extent to which these findings apply to females. Third, this study did not combine different imaging modalities for classification and prediction. Given multimodality studies have implicated brain structure and function in cue reactivity in IGD (Dong et al., 2020), multimodal data may improve classification and outcome predictions and should be investigated in future studies. Fourth, experienced gamers without IGD were not included. It is possible that the MVPA is identifying individual differences in familiarity with the task stimuli rather than IGD *per se*. However, the results of our study are similar to other prior findings that involved experienced gamers and were based on GLM analysis (Dong et al., 2020; Sun et al., 2012). The results would potentially be strengthened had a group of gamers without IGD been included, and this approach should be used in future studies. Fifth, a psychiatric comparison group, such as individuals experiencing substance or gambling addictions, was not included; the inclusion of such a group could have helped determine more precisely the diagnostic specificity afforded by MVPA. Sixth, we used the reduction of weekly gaming time as an outcome measure as we did previously (Zhang et al., 2016). In IGD, there is no uniformly accepted treatment outcome measure, as is the

case with respect to other disorders [e.g., cocaine use disorder (Carroll et al., 2014; Roos et al., 2019)). As such, future studies should examine a wider range of treatment outcomes.

The present study was a proof-of-concept study designed to examine whether MVPA could be applied to cue-reactivity neuroimaging data to predict individual-level classification and to predict outcomes. The findings suggest possible clinical utility of cue-reactivity fMRI data with respect to diagnostic classification and treatment-outcome prediction. Additional research is needed to determine the extent to which the findings relate to CBI versus other treatments or improvement generally. Future studies are needed to examine those possibilities and the utility of MVPA in testing them. Compared with univariate analyses, MVPA has multiple advantages; it considers interregional correlations and provides numerical indicators for group membership without multiple comparison biases. Furthermore, with the acquisition of larger databases, MVPA represents a powerful tool in the search for psychiatric biomarkers. However, other machine-learning approaches (e.g., connectome-based-modeling approaches that have been used to identify regions and networks statistically predicting treatment outcomes in substance addictions (Lichenstein, Scheinost, Potenza, Carroll, & Yip, in press; Yip, Scheinost, Potenza, & Carroll., 2019)) also warrant consideration.

Conclusions

To our knowledge, this study is the first attempt to apply MVPA to cue-reactivity data in IGD. The findings suggest a possible method of using objective measures to diagnose IGD. More importantly, baseline data could predict clinical changes for a longitudinal treatment with an error of 8% and a prediction-outcome correlation of 0.48. Thus, the present approach offers a potentially useful tool for clinicians when determining the effectiveness of psychological behavioral treatment before executing treatment procedures, although this possibility needs further direct examination.

Acknowledgements

Zi-Liang Wang analyzed the data and wrote the first draft of the manuscript. Kun-Ru Song, Lu Liu, Shan-Shan Ma, Cui-Cui Xia, Jing Lan and Yuan-Wei Yao contributed to fMRI data collection. Jin-Tao Zhang, Xiao-Yi Fang and Marc Potenza contributed in interpreting findings, editing, and revisions. All authors have approved the final manuscript.

Competing interests

The authors declared that there were no competing interests exist. Dr. Potenza has consulted for and advised Opiant Pharmaceuticals, Idorsia, AXA, Game Day Data and the Addiction Policy Forum; has received research support from the Mohegan Sun Casino, Connecticut Council on Problem Gambling and the National Center for Responsible Gaming; has participated in surveys, mailings or telephone consultations related to drug addiction, impulse control disorders or other health topics; and has consulted for law offices and gambling entities on issues related to impulse control or addictive disorders.

Role of the funding source

This research was supported by National Natural Science Foundation of China (31871122 and 31170990). Dr. Potenza's involvement was supported by the Connecticut Council on Problem Gambling. The funders had no further role in study design; in the data collection, analyses and interpretation; the decision to publish, or preparation of the manuscript.

Data accessibility

Data are available upon reasonable request from the corresponding author at zhangjintao@bnu.edu.cn.

Reference

Beck. (1961). An Inventory for Measuring Depression. *Archives of General Psychiatry*(6), 561-571.

Beck, Epstein, N., Brown, G., & Steer, R. A. (1988). An inventory for measuring clinical anxiety: psychometric properties. *Journal of Consulting and Clinical Psychology, 56*, 893-897. doi:10.1037//0022-006x.56.6.893

Blumenthal, & Daniel. (2009). The American Psychiatric Publishing Textbook of Substance Abuse Treatment. *JAMA The Journal of the American Medical Association, 301*, 776.

Bolla, K. I., Eldreth, D. A., London, E. D., Kiehl, K. A., Mouratidis, M., Contoreggi, C., . . . Neuroimage, A. S. K. J. (2003). Orbitofrontal cortex dysfunction in abstinent cocaine abusers performing a decision-making task. *Neuroimage, 19*, 1085-1094.

Brand, M., Wegmann, E., Stark, R., Muller, A., Wolfling, K., Robbins, T. W., & Potenza, M. N. (2019). The Interaction of Person-Affect-Cognition-Execution (I-PACE) model for addictive behaviors: Update, generalization to addictive behaviors beyond internet-use disorders, and specification of the process character of addictive behaviors. *Neuroscience and Biobehavioral Reviews, 104*, 1-10. doi:10.1016/j.neubiorev.2019.06.032

Bush, K., Kivlahan, D. R., McDonell, M. B., Fihn, S. D., & Bradley, K. A. (1998). The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. *Archives of Internal Medicine, 158*, 1789-1795. doi:10.1001/archinte.158.16.1789

Carroll, K. M., Kiluk, B. D., Nich, C., Devito, E. E., Decker, S., Lapaglia, D., . . . Dependence, A.

(2014). Toward empirical identification of a clinically meaningful indicator of treatment outcome: Features of candidate indicators and evaluation of sensitivity to treatment effects and relationship to one year follow up cocaine use outcomes. *137*, 3-19.

Carter, B. L., & Tiffany, S. T. J. A. (1999). Cue-reactivity and the future of addiction research. *Addiction, 94*, 349-351.

Cavanna, A. E., & Trimble, M. R. (2006). The precuneus: a review of its functional anatomy and behavioural correlates. *Brain, 129*, 564-583. doi:10.1093/brain/awl004

Chen, S. H., Weng, L. J., Su, Y. J., Wu, H. M., & Yang, P. F. (2003). Development of Chinese Internet Addiction Scale and its psychometric study. *Chinese journal of psychology, 45*, 279-294.

Cui, Z., Xia, Z., Su, M., Shu, H., & Gong, G. (2016). Disrupted white matter connectivity underlying developmental dyslexia: A machine learning approach. *Human Brain Mapping, 37*, 1443-1458. doi:10.1002/hbm.23112

Dong, Liu, Zheng, Du, X., & Potenza, M. N. (2019). Brain response features during forced break could predict subsequent recovery in internet gaming disorder: A longitudinal study. *Journal of Psychiatric Research, 113*, 17-26.

Dong, & Potenza. (2014). A cognitive-behavioral model of Internet gaming disorder: Theoretical underpinnings and clinical implications. *Journal of Psychiatric Research, 58*, 7-11.

Dong, Wang, Du, & Potenza. (2018). Gender-related differences in neural responses to gaming cues before and after gaming: implications for gender-specific vulnerabilities to Internet gaming disorder. *Social Cognitive and Affective Neuroscience, 13*,

1203-1214.

Dong, Wang, M., Wang, Z., Zheng, H., Du, X., & Potenza, M. N. (2020). Addiction severity modulates the precuneus involvement in internet gaming disorder: Functionality, morphology and effective connectivity. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 98*, 109829. doi:10.1016/j.pnpbp.2019.109829

Dong, Wang, Z., Wang, Y., Du, X., & Potenza, M. N. (2019). Gender-related functional connectivity and craving during gaming and immediate abstinence during a mandatory break: Implications for development and progression of internet gaming disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 88*, 1-10.

Dong, Zheng, H., Liu, X., Wang, Y., Du, X., & Potenza, M. N. (2018). Gender-related differences in cue-elicited cravings in Internet gaming disorder: The effects of deprivation. 1-12.

Dong., Wang, M., Liu, X., Liang, Q., Du, X., & Potenza, M. N. (2020). Cue-elicited craving-related lentiform activation during gaming deprivation is associated with the emergence of Internet gaming disorder. *Addiction Biology, 25*, e12713. doi:10.1111/adb.12713

Elton, A., Chanon, V. W., & Boettiger, C. A. (2019). Multivariate pattern analysis of the neural correlates of smoking cue attentional bias. *Pharmacology, Biochemistry and Behavior, 180*, 1-10. doi:10.1016/j.pbb.2019.03.001

Engelmann, J. M., Versace, F., Robinson, J. D., Minnix, J. A., Lam, C. Y., Cui, Y., . . . Cinciripini, P. M. (2012). Neural substrates of smoking cue reactivity: a meta-analysis of fMRI studies. *Neuroimage, 60*, 252-262. doi:10.1016/j.neuroimage.2011.12.024

Fagerstrom, K. O. (1978). Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment. *Addictive Behaviors, 3*, 235-241. doi:10.1016/0306-4603(78)90024-2

Goldstein, R. Z., & Volkow, N. D. (2011). Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nature Reviews: Neuroscience, 12*, 652-669. doi:10.1038/nrn3119

Goudriaan, A. E., Ruiter, M. B. D., Brink, W. V. D., Oosterlaan, J., & Veltman, D. J. (2010). Brain activation patterns associated with cue reactivity and craving in abstinent problem gamblers, heavy smokers and healthy controls: an fMRI study. *Addiction Biology, 15*, 491-503.

Han, D. H., Bolo, N., Daniels, M. A., Arenella, L., Lyoo, I. K., & Renshaw, P. F. (2011). Brain activity and desire for Internet video game play. *Comprehensive Psychiatry, 52*, 88-95. doi:10.1016/j.comppsych.2010.04.004

Han, D. H., Hwang, J. W., & Renshaw, P. F. (2010). Bupropion sustained release treatment decreases craving for video games and cue-induced brain activity in patients with Internet video game addiction. *Experimental and Clinical Psychopharmacology, 18*, 297-304. doi:10.1037/a0020023

Han, D. H., Kim, S. M., Lee, Y. S., & Renshaw, P. F. (2012). The effect of family therapy on the changes in the severity of on-line game play and brain activity in adolescents with on-line game addiction. *Psychiatry Research, 202*, 126-131. doi:10.1016/j.pscychresns.2012.02.011

Hu, X., Zhang, L., Bu, X., Li, H., Li, B., Tang, W., . . . Huang, X. (2019). Localized Connectivity

in Obsessive-Compulsive Disorder: An Investigation Combining Univariate and Multivariate Pattern Analyses. *Frontiers in Behavioral Neuroscience, 13*, 122. doi:10.3389/fnbeh.2019.00122

Ko, C. H., Liu, G. C., Hsiao, S., Yen, J. Y., Yang, M. J., Lin, W. C., . . . Chen, C. S. (2009). Brain activities associated with gaming urge of online gaming addiction. *Journal of Psychiatric Research, 43*, 739-747. doi:10.1016/j.jpsychires.2008.09.012

Kosten, T. R., Scanley, B. E., Tucker, K. A., Oliveto, A., & Wexler, B. (2006). Cue-Induced Brain Activity Changes and Relapse in Cocaine-Dependent Patients. *Neuropsychopharmacology, 31*, 644-650.

Lichenstein, Scheinost, Potenza, Carroll, & Yip. (in press). Dissociable neural substrates of opioid and cocaine use identified via connectome-based predictive modeling. *Molecular Psychiatry*.

Liu, L., Yip, S. W., Zhang, J. T., Wang, L. J., Shen, Z. J., Liu, B., . . . Fang, X. Y. (2017). Activation of the ventral and dorsal striatum during cue reactivity in Internet gaming disorder. *Addiction Biology, 22*, 791-801. doi:10.1111/adb.12338

Marissen, M. A. E., Franken, I. H. A., Waters, A. J., Blanken, P., & Hendriks, V. (2006). Attentional bias predicts heroin relapse following treatment. *Addiction, 101*, 1306-1312.

Mccarthy, Curtin, Piper, & Baker. (2010). Negative reinforcement: Possible clinical implications of an integrative model. *Substance Abuse and Emotion*.

Petry, N. M., Rehbein, F., Gentile, D. A., Lemmens, J. S., Rumpf, H. J., Mossle, T., . . . O'Brien, C. P. (2014). An international consensus for assessing internet gaming disorder using

the new DSM-5 approach. *Addiction, 109*, 1399-1406. doi:10.1111/add.12457

Piazza, & Deroche-Gamonet. (2013). A multistep general theory of transition to addiction. *Psychopharmacologia, 229*(3), 387-413.

Roos, C. R., Nich, C., Mun, C. J., Babuscio, T. A., Mendonca, J., Miguel, A. Q. C., . . . Kiluk, B. D. (2019). Clinical validation of reduction in cocaine frequency level as an endpoint in clinical trials for cocaine use disorder. *Drug and Alcohol Dependence, 205*, 107648. doi:10.1016/j.drugalcdep.2019.107648

Sakoglu, U., Mete, M., Esquivel, J., Rubia, K., Briggs, R., & Adinoff, B. (2019). Classification of cocaine-dependent participants with dynamic functional connectivity from functional magnetic resonance imaging data. *Journal of Neuroscience Research, 97*, 790-803. doi:10.1002/jnr.24421

Schrouff, J., Rosa, M. J., Rondina, J. M., Marquand, A. F., Chu, C., Ashburner, J., . . . Mourao-Miranda, J. (2013). PRoNTo: pattern recognition for neuroimaging toolbox. *Neuroinformatics, 11*, 319-337. doi:10.1007/s12021-013-9178-1

Seeger, M. (2005). Gaussian Processes for Machine Learning. *International Journal of Neural Systems, 14*, 69-106.

Strata, P., Scelfo, B., & Sacchetti, B. (2011). Involvement of cerebellum in emotional behavior. *Physiological Research, 60*, 39-48.

Suler. (1999). To get what you need: Healthy and pathological use. *Cyberpsychol Behav, 2*(5), 385-393.

Sun, Y., Ying, H., Seetohul, R. M., Xuemei, W., Ya, Z., Qian, L., . . . Ye, S. (2012). Brain fMRI study of crave induced by cue pictures in online game addicts (male adolescents).

Behavioural Brain Research, 233, 563-576. doi:10.1016/j.bbr.2012.05.005

Tirapu-Ustarroz, J., Luna-Lario, P., Iglesias-Fernandez, M. D., & Hernaez-Goni, P. J. R. D. N. (2011). Cerebellar contribution to cognitive process: Current advances. *53*, 301-315.

Tom, F. (2006). An introduction to ROC analysis. *Pattern Recognition Letters, 27*, 861-874.

Tong, C., & Bovbjerg, D. H. (2007). Smoking-related videos for use in cue-induced craving paradigms. *Addictive Behaviors, 32*, 0-3044.

Varoquaux. (2018). Cross-validation failure: small sample sizes lead to large error bars. *Neuroimage, 180*, 68-77.

Varoquaux, Pradeep, Reddy, Raamana, Denis, Engemann, & Andrés. (2017). Assessing and tuning brain decoders: Cross-validation, caveats, and guidelines. *Neuroimage, 145*, 166-179.

Vieira, S., Pinaya, W. H., & Mechelli, A. (2017). Using deep learning to investigate the neuroimaging correlates of psychiatric and neurological disorders: Methods and applications. *Neuroscience and Biobehavioral Reviews, 74*, 58-75. doi:10.1016/j.neubiorev.2017.01.002

Wang, L., Wu, L., Wang, Y., Li, H., Liu, X., Du, X., & Dong, G. (2017). Altered Brain Activities Associated with Craving and Cue Reactivity in People with Internet Gaming Disorder: Evidence from the Comparison with Recreational Internet Game Users. *Frontiers in Psychology, 8*, 1150. doi:10.3389/fpsyg.2017.01150

Woo, C. W., Chang, L. J., Lindquist, M. A., & Wager, T. D. (2017). Building better biomarkers: brain models in translational neuroimaging. *Nature Neuroscience, 20*, 365-377. doi:10.1038/nn.4478

Yip, Scheinost, Potenza, & Carroll. (2019). Connectome-Based Prediction of Cocaine Abstinence. *American Journal of Psychiatry, 176*, 156-164. doi:10.1176/appi.ajp.2018.17101147

Zhang, J. T., Yao, Y. W., Potenza, M. N., Xia, C. C., & Fang, X. Y. (2016). Effects of craving behavioral intervention on neural substrates of cue-induced craving in Internet gaming disorder. *NeuroImage: Clinical, 12*, 591-599.

Zheng, H., Hu, Y., Wang, Z., Wang, M., Du, X., & Dong, G. (2019). Meta-analyses of the functional neural alterations in subjects with Internet gaming disorder: Similarities and differences across different paradigms. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 94*, 109656. doi:10.1016/j.pnpbp.2019.109656

Figure Legends:

Figure 1: MVPA findings related to IGD classification.

(a) The ROC curve shows the performance of the binary classifier. (b) Scatterplots show the discrimination between the two groups. (c) The histogram shows the distributions of the two groups. (d) Weight maps are shown for the classifier. The weight vector represents the relative relevance of each voxel in classifying the groups.

Figure 2: MVPA findings related to treatment outcome

(a) A scatterplot showing relationships between actual and predicted changes in weekly gaming time change (%) for the model based on baseline data. Weekly gaming time change (%) is (post-treatment minus pre-treatment gaming hours) divided by pre-treatment gaming hours. (b) Weight maps are shown for the classifier. The weight vector represents the relative relevance of each voxel to classify the groups.

Figure 3: Correlation between regional brain activation at treatment onset and subsequent changes in weekly gaming time (%) in the CBI+ group.

Weekly gaming time change (%) is (post-treatment minus pre-treatment gaming hours) divided by pre-treatment gaming hours. (a) Negative correlations between changes in weekly gaming time change (%) and beta values in the right middle frontal gyrus (r = -0.676, $p < 0.001$). (b) Negative correlations between changes in weekly gaming time change (%) and beta values in the middle/superior frontal gyrus (r = -0.821, $p <$ 0.001). (c) Negative correlations between changes in weekly gaming time change (%) and beta values in the superior frontal gyrus (r = -0.689, $p < 0.001$). (d) Negative

correlations between changes in weekly gaming time change (%) and beta values in the anterior lobe of the cerebellum (r = -0.566, p = 0.005). (e) Negative correlations between changes in weekly gaming time change (%) and beta values in the supramarginal gyrus (r = -0.670, p < 0.001). (f) Negative correlations between changes in weekly gaming time change (%) and beta values in the left postcentral gyrus (r = -0.630, p < 0.001).

Table 1. Demographics and internet gaming characteristics of IGD and HC subjects at baseline.

	IGD (n=40) Mean±SD	HC (n=19) Mean±SD	*t/χ2*	*p*
Age (years)	22.05±1.78	22.89±2.23	-1.566	0.123
Education（years）	15.85±1.86	16.57±1.98	-1.377	0.174
CIAS score	79.87±8.67	42.11±8.27	15.856	<0.001
Durations of weekly gaming(hours)	26.81±10.04	1.66±0.57[a]	4.285	<0.001
Craving differences (gaming – control)	1.75 ± 1.21	0.31 ± 0.59	6.14	<0.001
BAI score	5.33±5.91	2.01±3.27	2.23	0.03
BDI score	9.23±5.43	2.77±4.33	4.42	<0.001
Alcohol use	30/40	13/19	0.28	0.6
AUDIT-C score	3.20±1.90[b]	2.23±1.17[c]	1.7	0.1
Tobacco use	4/40	0/19	-	-
FTND score	3.25±0.5	-	-	-

IGD = internet gaming disorder; HC = healthy control; S.D. = standard deviation; CIAS = Chen Internet Addition Scale; AUDIT-C = alcohol consumption questions from the Alcohol Use Disorders Identification Test; FTND = Fagerstrom Test for Nicotine Dependence; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory.

[a]n = 3.

[b]n = 30.

[c]n = 13.

[d]n = 4.

Table 2. Demographics and internet gaming characteristics of CBI+ and CBI− groups.

	CBI+(n=23) Mean±SD	CBI-(n=17) Mean±SD	*t*	*p*
Age (years)	21.91±1.83	22.01±1.89	-0.15	0.89
Education（years）	16.01±1.81	15.29±1.91	1.31	0.2
BAI score	3.78±3.61	7.63±7.71	-1.85	0.08
BDI score	8.83±5.73	9.56±5.08	-0.41	0.46
CIAS score: baseline	82.09 ± 8.75	76.88 ± 7.85	1.94	0.06
CIAS score: second test	60.26 ± 9.83	70.35 ± 7.80	-0.05	0.96
Craving for gaming clips: baseline	5.30 ± 1.21	5.43 ± 1.17	-0.33	0.74
Craving for gaming clips: second test	3.42 ± 1.50	4.75 ± 1.44	-2.82	0.008
Durations of weekly gaming, hours: baseline	27.20±10.42	27.35±11.13	-0.33	0.74
Durations of weekly gaming, hours: second test	11.36 ± 8.07	23.24±17.51	-2.82	0.008

CBI+ = subjects with internet gaming disorder who received craving behavioral intervention; CBI− = subjects with internet gaming disorder who did not receive craving behavioral intervention; S.D. = standard deviation; CIAS = Chen Internet Addition Scale; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory

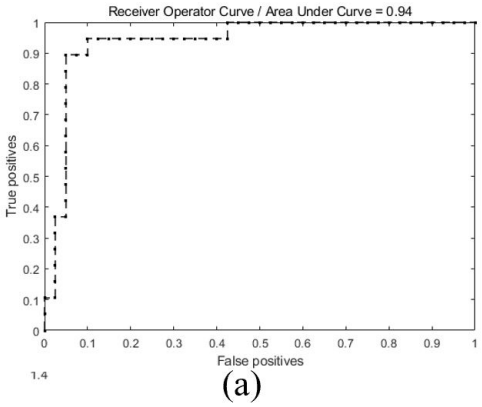
Table 3. Brain regions contributing most to IGD classification

Brain regions	Hemisphere L/R	Peak MNI(mm)			Cluster size
		X	Y	Z	
middle frontal gyrus	L	-27	3	66	239
middle frontal gyrus	R	27	9	66	146
precuneus	L	-6	-75	39	160
precuneus	R	3	-60	60	1025
cerebellum posterior lobe	R	0	-30	-54	500

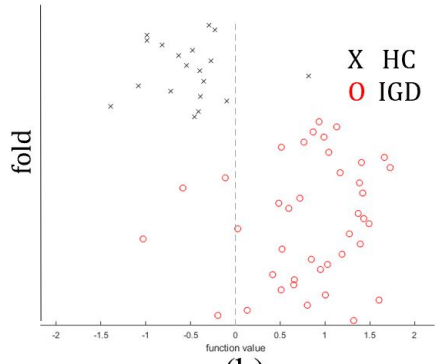
IGD = internet gaming disorder

Table 4. Brain regions contributing most to outcome prediction

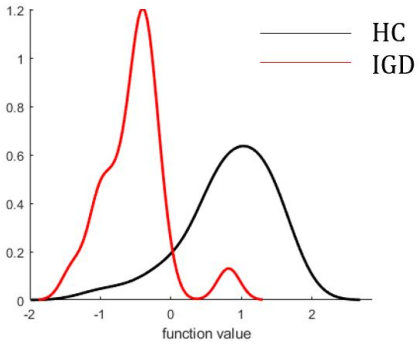
Brain regions	Hemisphere	Peak MNI(mm)			Cluster size
	L/R	X	Y	Z	
middle frontal gyrus	R	3	48	15	193
middle/superior frontal gyrus	R	24	45	45	254
superior frontal gyrus	R	12	0	78	218
supramarginal gyrus	R	57	-54	21	159
postcentral gyrus	L	-6	-36	78	577
cerebellum, anterior lobe	R	51	-66	-21	158
cerebellum, posterior lobe	R	9	-30	-51	487



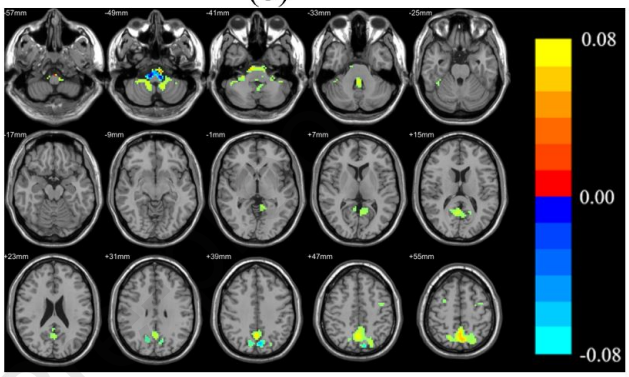
(a)



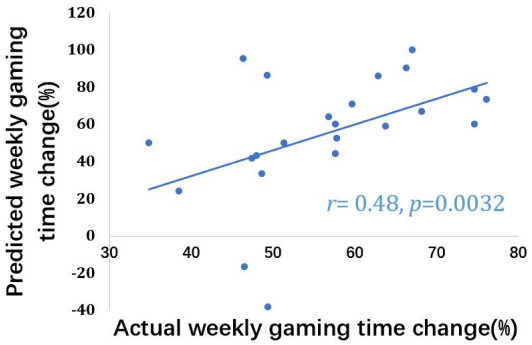
(b)



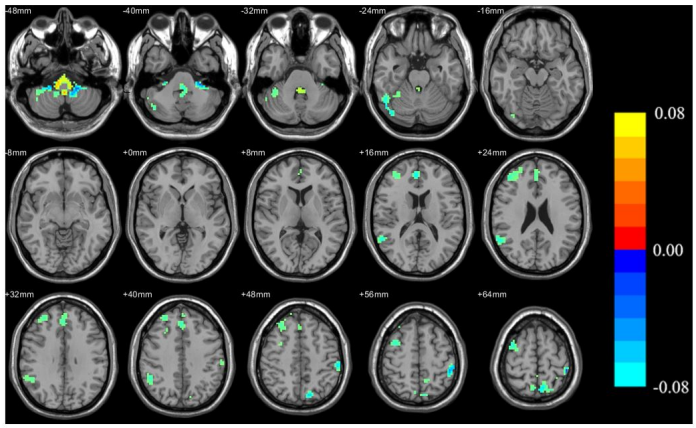
(c)



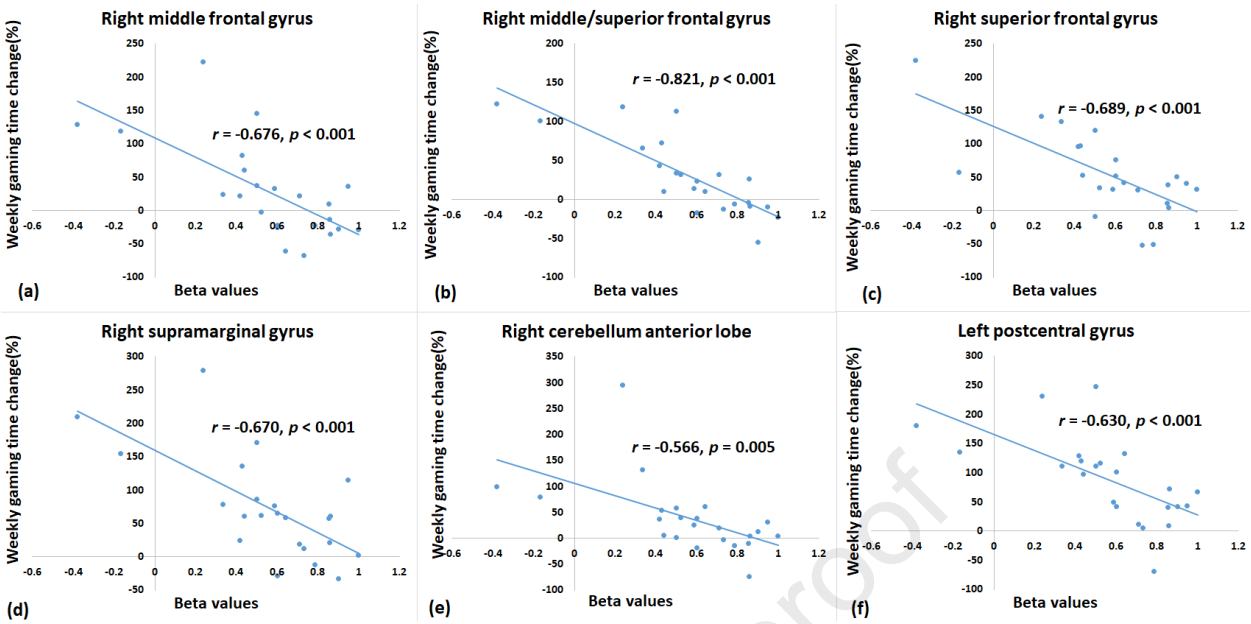
(d)



(a)



(b)



- The present study is the first to investigate the utility of MVPA in analyzing cue-reactivity data to classify individuals with IGD and statistically predict treatment outcomes.
- Cue-reactivity neural correlates could help identify IGD subjects.
- Cue-reactivity neural correlates could help predict CBI-related treatment outcomes.

Competing interests

The authors declared that there were no competing interests exist. Dr. Potenza has consulted for and advised Opiant Pharmaceuticals, Idorsia, AXA, Game Day Data and the Addiction Policy Forum; has received research support from the Mohegan Sun Casino, Connecticut Council on Problem Gambling and the National Center for Responsible Gaming; has participated in surveys, mailings or telephone consultations related to drug addiction, impulse control disorders or other health topics; and has consulted for law offices and gambling entities on issues related to impulse control or addictive disorders.