Addiction severity modulates the precuneus involvement in internet gaming disorder: Functionality, morphology and effective connectivity

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ABSTRACT

Although higher precuneus activation has often been observed in subjects with addictions when facing addiction-relevant cues, the recruitment of the precuneus is not consistent across studies. Here, we examined the extent to which addiction severity may relate to precuneus involvement during cue reactivity in internet gaming disorder (IGD).

We recruited 65 subjects with IGD, collected brain responses when exposed to gaming cues and assessed brain structure. We correlated IGD severity with brain responses during a cue-craving task, precuneus volume, and connectivity with respect to inputs/outputs to/from the precuneus.

In the cue-craving task, IGD severity was positively correlated with precuneus activation when exposed to gaming cues. IGD severity was also positively correlated with the volume of precuneus and connectivity from the hippocampal gyrus to the precuneus. IGD severity was also negatively correlated with connectivity from the middle frontal gyrus to the precuneus.

In IGD, IGD severity relates to precuneus involvement with respect to functionality, morphology, and connectivity. The precuneus may act as a platform for integrating potential contradictory information between executive control and sub-cortical cravings.

1. Introduction

Individuals with Internet gaming disorder (IGD) are characterized by increased cravings to gaming cues and poorer executive function to control gaming motivations (Brand et al., 2016; Dong et al., 2017a, 2015a). Reward circuitry, which may involve dopaminergic and other neurotransmitter pathways, contributes importantly to motivated behaviors. It helps establish motivational values of extrinsic stimuli and links incentives to action (Cagniard et al., 2006; Dong et al., 2019b; Wise, 2004). Greater activation of brain regions implicated in reward processing (e.g., the ventral tegmental area, ventral striatum, ventromedial prefrontal cortex and amygdala) have been observed in IGD subjects when exposed to gaming cues (Cagniard et al., 2006; Dong et al., 2019b; Wise, 2004). On the other hand, regions involved in exerting cognitive control (e.g., the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (dLPFC), and parietal cortex) have been found observed to be less activated and less coherent in IGD subjects, suggesting poorer executive control abilities (Bae et al., 2017; Dong et al., 2015b). Poorer executive control over increased gaming-related craving may make it difficult for IGD subjects to stop problematic gaming behaviors (Brand et al., 2016; Dong et al., 2017a; Dong et al., 2015a; Zheng et al., 2019).

In addition to the aforementioned brain regions, the precuneus has been implicated in addiction-related studies, including in IGD. The
precuneus, located in the posteromedial portion of the parietal lobe, has widespread connections with higher association cortical region (such as the ACC, posterior cingulate cortex (PCC), and motor areas) and subcortical structures (such as the dorsolateral caudate nucleus and putamen) (Cavanna and Trimble, 2006). Most of these brain regions have demonstrated functional changes in addiction subjects and may relate to reward and executive-control circuitry. In addition, the precuneus has been implicated in self-centered, mental imagery strategies and successful episodic memory retrieval (Cavanna et al, 2006), and these functions may be relevant when encountering addiction-related cues. As an integrated hub of a putative exteroception network, researchers have proposed that the precuneus may be a vulnerable target in addictions (DeWitt et al., 2015).

As described above, the precuneus may serve as a relay to transform addiction-relevant cues information elicited by the visual system to systems involved in motivated behaviors and executive functions (Engelmann et al., 2012). Two meta-analyses have implicated the precuneus in cue presentation studies in alcohol-dependent (Schacht et al., 2013) and daily-tobacco-smoking (Engelmann et al., 2012) individuals. However, the involvement of the precuneus in addiction studies appears inconsistent, as sometimes it is observed but at other times not. A meta-analysis focusing on drug-related cue-reactivity found only two of the 13 alcohol-cue-elicited activations of the precuneus and measures of alcohol-use-disorder severity have been observed (Claus et al., 2013). These results suggest an important role for the precuneus in addictions: it may act as a cortical locus for neuroplastic changes related to disorder severity (Cavanna et al., 2006).

Based on the above, the seemingly inconsistent recruitment of the precuneus in IGD in cue-reactivity tasks may relate to disorder severity. Thus, the first goal of the current study was to test whether precuneus activation to gaming cues vs. neutral cues is correlated with disorder severity in IGD subjects. Additionally, we aimed to investigate whether such relationships extended beyond activation to morphological features. Thus, the second goal of the current study was to examine correlations between IGD severity and cortical thickness and volume of the precuneus in IGD subjects. Thus, we hypothesized that the precuneus is related with IGD severity, functionally and morphologically. Third, we examined the effect of disorder severity on effective connectivity (EC) measures involving the precuneus to examine the extent to which disorder severity may relate to precuneus-linked circuitry function.

2. Methods

2.1. Ethics

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

2.2. Study overview

The current study includes three domains: correlations between IGD severity and brain responses in the cue-craving task; correlations
between IGD severity and morphological features; and, correlations between IGD severity and EC involving inputs/outputs to/from the precuneus (Fig. 1A).

2.3. Subject selection

We recruited 65 IGD subjects (33 males, 32 females) through posters and online advertisements (Table 1). The subjects who were categorized into the IGD group needed to meet two criteria: having scored > 50 on Young’s Internet Addiction Test (IAT) and met at least five of the nine DSM-5 diagnostic criteria for IGD (Petry et al., 2014) (Table 1). We only recruited subjects who regularly played League of Legends (LOL; Riot Games, Inc.) and played the game for at least 1 year.

All subjects also need to meet the following criteria: be right-handed; have a normal or corrected-to-normal vision; and, have no Axis-I psychiatric disorders as per assessment from a structured psychiatric interview (MINI) (Lecrubier et al., 1997). In addition, no subjects reported previous experience with gambling or illicit drugs (eg, cannabis and heroin).

2.4. The fMRI task

Magnetic resonance imaging (MRI) was conducted with a Siemens Trio 3 T scanner (Siemens, Erlangen, Germany). The cue-craving task has been described in our previous studies (Dong et al., 2017a; Dong et al., 2019a,b; Wang et al., 2017). All stimuli pictures we used were from the game 'League of Legends'. Briefly, in each trial, a fixation cross was presented first for 500 ms, and then a stimulus lasted for up to 4000 ms was presented with a response needed. In this period, participants were asked to identify whether there is a face in the picture, and select ‘yes’ or ‘no’ via button press (1, yes; 2, no; with counter-balancing the following black screen). The stimulus turned black after key-pressing, and the following black screen lasted for 4000 - the response time) ms. Then, another black screen jittered, ranging from 500 to 3500 ms. Next, the evaluation stage required subjects to evaluate the level of their craving on a scale from 1 (low) to 5 (high) for the relevant stimuli. After another jitter ranging from 500 to 3500 ms, the next trial ensued (Fig. 1B).

2.5. Stimuli materials

The task consisted of 60 pictures divided into two categories: gaming-related and typing-related pictures (neutral comparator images). Fifty percent of all pictures within each category contained a face, and the other half contained a hand. As shown in Fig. 1B, in gaming-related stimuli, somebody is displayed playing a game on a computer. In the typing-related pictures, the background imagery was similar except that somebody is typing rather than gaming. All pictures controlled for complexity and gender.

2.6. Structural MRI

Whole-brain T1-weighted MR images were collected via a T1-weighted three-dimensional spoiled gradient-recalled sequence in 384 s (176 slices, repetition time = 1700 ms, echo time = 3.93 ms, slice thickness = 1.0 mm, skip = 0 mm, flip angle = 15, inversion time = 1100 ms, field of view = 240 × 240 mm, in-plane resolution = 256 × 256). Head motions were minimized by filling the empty space around the subjects' heads with sponge and fixing their lower jaws with tape.

2.7. fMRI data analysis

The functional data were analyzed using standard steps proposed by SPM12 (http://www.fil.ion.ucl.ac.uk/spm) and Neuroelf (http://neuroelf.net), as described previously (Dong et al., 2017a; Dong et al., 2018b). Images were slice-aligned, reoriented, and realigned to the first volume, with T1-co-registered volumes used to correct for head movements. Images were then normalized to MNI space and spatially smoothed using a 6 mm full-width-half-maximum (FWHM) Gaussian kernel. No subjects were removed from analysis because of head motion (the exclusion criteria were 2 mm in directional movement or 2 degrees in rotational movement). A general linear model (GLM) was applied to identify BOLD (blood-oxygen-level-dependent) activation in relation to brain activities. Different types of trials (gaming-related, typing-related, incorrect or missed) were separately convolved with a canonical hemodynamic response function to form task regressors. The duration of each trial was 4000 ms. The GLMs also included the six head-movement parameters derived from the realignment stage, age, gaming history and response time. We focused analyses on voxels that were significantly activated for each event during the 'response' stage. Whole-brain correlation analyses were conducted using IGD severity (IAT, DSM-5, separately). The correlation results were corrected with Alphasim, p < .001, cluster size > 20 voxels.

2.8. Data analysis: structure

Cortical reconstruction was performed using the FreeSurfer software package (Version 5.3.0, http://surfer.nmr.mgh.harvard.edu) based on procedures described in previous publications (Dale et al., 1999; Fischl and Dale, 2000; Fischl et al., 1999). Before the analysis of the cortical thickness, we visually checked the quality of raw data and used the TkMedit command (https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/TroubleshootingDataV6.0) to modify errors. None of the subjects' scanned images were excluded due to excessive distortions or artifacts.

Vertex-wise general linear modeling using FreeSurfer's statistical tools Query, Design, and Estimate were used to examine cortical thickness based on the Desikan–Killiany atlas (Desikan et al., 2006). Age was entered as a covariate. Subjects' cortical volume/thickness data were smoothed with a 10 mm FWHM Gaussian kernel. A surface-based whole-brain analysis was performed by fitting a generalized linear model (GLM) at each surface vertex to correlate cortical volume and the IAT and DSM scores in the IGD group, with age, gender and intracranial volume serving as covariates of no interest. A statistical threshold of p < .05 was used for the correction of imaging results.

Besides the whole-brain correlations, we also conducted an ROI analysis. We took the left and right precuneus as ROIs, and extracted their cortical volume/thickness indexes, and correlated these with IGD severity (IAT score) to calculate correlation coefficients, separately. The average cortical volume and thickness of the precuneus were estimated using 3D brain structural images with the FreeSurfer v5.2.0 software (http://surfer.nmr.mgh.harvard.edu) according to the Brodmann area. Pearson correlation was conducted between the volumes, thickness of the precuneus and the IAT and DSM-5 scores in IGD subjects.

### Table 1

Demographic information of IGD subjects in the current study.

<table>
<thead>
<tr>
<th>Demographic information</th>
<th>IGD</th>
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<tbody>
<tr>
<td>Age (Mean ± SD)</td>
<td>20.74 ± 1.95</td>
</tr>
<tr>
<td>Education (years) (Mean ± SD)</td>
<td>14.16 ± 1.84</td>
</tr>
<tr>
<td>IAT score (Mean ± SD)</td>
<td>64.06 ± 10.58</td>
</tr>
<tr>
<td>DSM-5 score (Mean ± SD)</td>
<td>5.81 ± 1.11</td>
</tr>
<tr>
<td>Gaming history (years) (Mean ± SD)</td>
<td>3.78 ± 0.57</td>
</tr>
<tr>
<td>Game playing per week (hours) (Mean ± SD)</td>
<td>21.41 ± 5.22</td>
</tr>
</tbody>
</table>

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

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**Demographic information IGD**

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2.9. Data analysis: effective connectivity

Effective connectivity refers to the influence that one brain region may exert over another and was evaluated through Granger causality analysis (GCA) in the current study. GCA, as compared to dynamic causal modeling (DCM), only requires the predefining of ROIs and can be applied directly to detect coupling between the ROI and other regions, without prior knowledge of the connections between regions (Deshpande et al., 2010). In the current study, we took the peaks of the clusters that showed significant correlations with IAT in the cue-craving task (left precuneus: \(-12, -72, 39\); Right precuneus: \(12, -72, 42\)) as the central points to create the spheres with 6 mm radii (approximately 33 voxels per sphere). For each subject, the time series in the ROIs and the rest of the voxels in the whole brain were extracted. Several nuisance covariates including six rigid body head motion parameters, white matter, and cerebrospinal fluid signals, were regressed through linear regressions to remove sources of spurious variances.

Residual-based voxel-wise GCA on the precuneus was performed through DynamicBC (http://guorongwu.weebly.com/software.html), a MATLAB-based toolbox. We explored the effective connectivity between seeds (left and right precuneus) and all other brain regions in each subject. The input and output brain maps were generated separately for each brain region in each subject. The order of the autoregressive model was set to 1 according to the Schwartz criterion. The coefficients of the models were calculated using a standard least squares optimization. The GCA maps were spatially smoothed by convolution with an isotropic Gaussian kernel (FWHM = 4 mm). We extracted these parameters of effective connectivity between the precuneus and surviving brain regions, and correlated these with IGD severity (IAT) to find which may be affected by IGD severity.

3. Results

Behavioral performance, cue-elicited brain activations (gaming cues vs. neutral cues), and brain features correlated with DSM-5-related severity are in the supplementary materials.

3.1. Correlations between IGD severity and brain responses during a cue-craving task

Whole-brain correlations were performed between brain activations when exposed to gaming cues vs. neutral cues against IGD severity (IAT score). First, brain regions that activated during gaming cues versus typing cues were analyzed (Fig. 2A; Supplementary Table 1). Greater activations were found in the precuneus when correlating with IAT scores (bilateral precuneus; Fig. 2B). No negative correlations were found.

3.2. Correlations between IGD severity and cortical thickness and volume

Whole-brain correlations showed that the precuneus and the anterior cingulate cortex were significantly correlated with IGD severity (Fig. 3A; Table 2).

When we extracted the whole precuneus (not limited to the surviving brain region in the whole-brain correlation) and examined correlations with IGD severity, the cortical volume in the left precuneus was positively correlated with IAT scores (Fig. 3B). Similar relationships were found for DSM-5 scores (Supplementary fig. 2).

3.3. Effective connectivity results

When individuals are exposed to gaming cues, the current results suggest that the precuneus receives input from higher association cortical regions, including the superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, and inferior temporal gyrus, as well as from subcortical brain regions, including the parahippocampal gyrus and the thalamus. The output sources from the precuneus include the middle frontal gyrus, superior frontal gyrus, and inferior temporal gyrus. Most of these regions are higher association cortical regions (Supplementary fig. 3).

When correlating IGD severity (IAT score) with the EC results (input/output from precuneus), positive correlations were found between IAT scores and input from the parahippocampal gyrus to the precuneus (\(r = 0.296, p = .017\)) (Fig. 4A). At the same time, a negative correlation was observed between IGD severity and input from the medial frontal gyrus to the precuneus (\(r = -0.313, p = .011\)) (Fig. 4B). No correlations were found with EC output results.

4. Discussion

4.1. IGD severity relates to precuneus activation in a cue-craving task

This study aimed to identify how IGD severity was related to precuneus activation, morphology and EC. Our hypotheses that precuneus structure and function would relate to IGD severity (as operationalized by IAT or DSM scores) were largely supported. Implications are discussed below.

The precuneus is an important component of the default-mode network (DMN), and it has been suggested that the precuneus may be involved in wide-ranging cognitive processes (Bruner et al., 2015; Gusnard et al., 2001). The precuneus is implicated across multiple addictions (Grant et al., 1996; McClernon et al., 2009) and using different tasks, including cue-reactivity (Cavanna and Trimble, 2006), self-centered mental imagery (Buckner and Carroll, 2007) and others. Increased neural response to drug cues in the precuneus has been associated with symptoms of addiction, such as risky decision-making and problems related to substance use (Clas et al., 2011; Schacht et al., 2013). Studies have also shown greater activation in the precuneus during exposure to tobacco cues (vs. neutral cues), and that subjective craving levels correlated with precuneus activation (Brody et al., 2007). In the current study, the activation of precuneus was positively correlated with IGD severity, suggesting that the more severe the condition, the greater the precuneus activated when exposed to gaming cues.

As the precuneus has been implicated in episodic memory retrieval (Cavanna and Trimble, 2006), the precuneus features during cue-reactivity may represent processes of subjective craving. One explanation might relate to habitual responses. The precuneus involvement in drug cue reactivity may be sub-serving a habitual response to the cues in individuals with more severe IGD. To extrapolate to addictions more generally, this suggests that when seeking of addictive substances or behaviors, the goal-directed and habit systems operate in parallel, with habitual processes being more dominant when facing addictive stimuli. While this notion is currently speculative, future studies should examine this possibility and how it may relate to developing better interventions for IGD specifically and addictions more generally.

4.2. IGD severity relates to precuneus volume

Cortical volume is largely determined by the number of radial columns perpendicular to the pial surface, and cortical thickness is largely determined by horizontal layers in cortical columns (Bruner et al., 2015; Rakic, 2009). These two indexes may provide a reliable quantification on individual differences in cortical volumes. In the current study, the results revealed that cortical volume was positively correlated with IGD severity. Thus, the results suggest that the IGD is related to morphological aspects of the precuneus, perhaps in the number of radial columns in the precuneus. As we described in ‘Introduction’ section, the precuneus has been implicated in self-centered, mental imagery strategies and successful episodic memory retrieval (Cavanna and Trimble, 2006; Moscovitch et al., 2006), thus, an alternative explanation on this issue might be that gaming cues activated relevant craving experience, and conversely, the craving experience further
Fig. 2. Correlations between IGD severity and brain response in the cue-craving task.
A: Brain features when comparing gaming cues to typing ones in all subjects.
B: Bilateral precuneus activation correlated with IAT score in all subjects.
4.3 IGD severity relates to effective connectivity inputs into the precuneus from executive control and reward system

The EC results provide a possible explanation for the role of the precuneus in IGD. The precuneus represents an important hub for information input and output, and its input sources include higher association cortical and sub-cortical brain regions, whereas it mostly outputs to higher association cortical brain regions. When correlating input/output indexes with IGD severity, that IGD severity (IAT score) was positively correlated with input from the parahippocampal gyrus to the precuneus. The parahippocampal gyrus may contribute to craving through integration of contextual memory information (Chambers et al., 2003). According to the psychophysiology meanings of functional connectivity among these brain regions (Havlicek et al., 2015; Stephan et al., 2010), higher values in contextual-memory-to-precuneus connectivity in people when exposed to gaming cues suggest the information from regions encoding prior experiences to the precuneus are stronger. Thus, the correlation between IGD severity and the value from parahippocampal gyrus to precuneus suggests the more severe the disorder, the more that contextual memory cues may be contributing to cue-elicited craving responses in IGD. As such, targeting the disengagement of these processes in treatments may be an effective means to promote recovery, and this currently speculative notion warrants further direct examination.

A significant negative correlation was observed between IGD severity and the EC from the medial frontal gyrus to the precuneus. As part of the prefrontal cortex, the medial frontal gyrus may contribute to various executive functions, including inhibition, attention control, and decision-making (Koechlin, 2016; Werchan and Amso, 2017). The medial frontal gyrus has shown relatively decreased activation in IGD subjects, which may suggest impaired executive control ability (Koob and Volkow, 2016; Meng et al., 2015). Also according to the psychophysiology meaning of the functional connectivities among these brain regions (Havlicek et al., 2015; Stephan et al., 2010), the decreased EC from the medial frontal gyrus to the precuneus when exposed to gaming cues suggests executive control input into the precuneus may be weaker. The negative correlation between IGD severity and the connectivity suggest that the more severe the IGD, the less executive control input into the precuneus may exist when exposed to gaming cues.

When considering these two correlations together, we can posit a trade-off between source inputs from prefrontal brain regions to precuneus (which may represent the rational aspect of our executive control) and input from the subcortical parahippocampal gyrus to the precuneus (which may contribute to motivational drive). This combination may lead to decreased executive control over craving, leading to persistence of problematic gaming.

4.4 Limitations

The study has multiple limitations. First, it is cross-sectional. As such, directionality of the relationships cannot be determined (for example, whether IGD severity exerts an impact on precuneus structure and function or whether precuneus structure and function leads to...
Fig. 4. Correlations between IGD severity and effective connectivity (EC) with regions that input into the precuneus. IGD severity was positively correlated with EC from the left parahippocampal gyrus to precuneus (A) and negatively correlated with EC from the medial frontal gyrus to the precuneus (B). The positive or negative results indicate increased or decreased connectivity when comparing gaming-related cues to typing-related cues, respectively.
changes in IGD severity). As such, future longitudinal studies are needed. Second, the sample included young adults from China. The extent to which the findings may extend to other age groups from other jurisdictions warrants examination.

5. Conclusions

The current study found that the IGD severity relates to the features of the precuneus from three aspects. First, IGD severity relates to precuneus activations when exposed to gaming cues. Second, IGD severity is positively correlated with the brain volume of the precuneus. Third, IGD severity modulates EC input precuneus from executive control and contextual memory regions. Taken together, the precuneus may act as a hub for information originating from executive control and motivational drive networks, and this feature could be indexed functionally and morphologically. This conclusion providing a potential brain mechanism by which cue exposure may lead to persistence of gaming in IGD.

Ethical statement

The authors declare that they have no conflict of interest. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee. This work does not contain any studies with animals performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee. This work does not contain any studies with animals. Informed consent was obtained from all participants included in the study.

All authors contributed to and had approved the final manuscript. Neither the entire paper nor any part of its content has been published or has been accepted elsewhere. It is not being submitted to any other journal.

Contributors

Guangheng Dong designed the task and wrote the first draft of the manuscript; Min Wang analyzed the task state data and the EC data, Ziliang Wang analyzed the structural data and prepared relevant figures, tables; Hui Zheng, Min Wang, Ziliang Wang and Xiaoxia Du collected the data. Marc Potenza contributed to editing, interpretation and revision processes. All authors contributed to and have approved the final manuscript.

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All authors reported no biomedical financial interests or other conflicts of interest with respect to the content of this manuscript. Dr. Potenza has consulted for legal and gambling entities on issues related to addictive disorders.

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Declaration of Competing Interest

All authors reported no biomedical financial interests or other conflicts of interest with respect to the content of this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2019.109829.

References


8


