Altered cingulate functional circuits in adolescents with Internet addiction disorder revealed by resting-state fMRI

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Introduction Internet addiction disorder (IAD), a serious mental health issue around the world, has attracted considerable attention from the public and scientific community [1-3]. Convergent evidences through the neuroimaging literature demonstrated that the cingulate is related to IAD. In this study, we used resting-state functional connectivity (rsFC) to investigate the cingulate functional circuits in adolescents with IAD.

Materials and Methods *Subjects:* Fourteen IAD subjects (two females; mean age: 17.1±2.7) and Fifteen age, gender, and years of education matched normal controls (two females, mean age: 17.9±2.5) participated in this study. IAD subjects met the criteria by Beard and Wolf [4]. Six questionnaires were used to assess the behavioral features, namely the Young's Internet Addiction Scale (YIAS), Strengths and Difficulties Questionnaire (SDQ), Time Management Disposition Scale (TMDS), Barrett impulsiveness scale (BIS), the Screen for Child Anxiety Related Emotional Disorders (SCARED) and Family Assessment Device (FAD). *Image acquisition:* Rs-fMRI scans were performed by a 3.0 Tesla Phillips scanner with the following parameters: TR/TE: 2,000/30ms; flip angle: 90°; matrix: 64×64; FOV: 23 cm×23 cm; slice thickness: 4 mm without gap. Each run contained 220 volumes. *Data preprocessing:* For each subject, the first 10 volumes were discarded and the remaining 210 volumes were corrected for acquisition time delay, realigned for head motion, normalized to the MNI space, re-sampled to a 3mm isotropic voxel, smoothed with a 6-mm FWHM Gaussian kernel. After removing the WM and CSF signals, the time series were band-pass filtered temporally (0.01-0.08 Hz). *Subregions of cingulate:* The entire cingulate was divided into seven subregions (Fig. 1), which are subcallosal anterior cingulated cortex (sACC), rostral ACC (oACC), dorsal ACC (dACC), middle cingulate cortex (MCC), dorsal PCC (dPCC), ventral PCC (vPCC), and the retrosplenial cortex (RSC) [4]. *Functional connectivity analysis:* For each subject, a cross-correlation coefficient map for each subregion was calculated and converted to a z-value map. Then the z-value maps were entered into the two-sample t test with age and gender as covariates to evaluate group-between rsFC differences. A corrected threshold of p_{alpha}<0.05 was considered significantly. Step-wise multiple regression analyses were performed to check whether the rsFC are correlated with the behavioral scores.

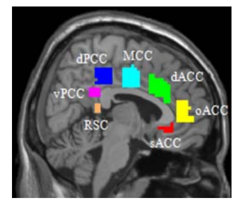

Fig.1: Seven subregions of the cingulate

Results Consistent with those reported by Yu et al [5] and Hong et al [6], we found that each cingulate subregion showed a region-specific rsFC map. The spatial pattern of the rsFC map for each cingulate subregion appeared to be similar in the IAD subjects and the normal controls. However, statistical comparisons revealed that the IAD individuals had significant changes in connectivity strength for every cingulate subregion except the RSC (Fig. 2). The sACC show decreased FC in the caudate. The oACC show reduced FC in the thalamus and MCC. The dACC show decreased FC in the bilateral inferior frontal gyrus, bilateral caudate, right insula, right thalamus, right supplementary motor area (SMA) and right dACC while increased FC in the right precuneus. The MCC show increased FC in the left SMA. The dPCC show decreased FC in the right thalamus, left parahippocampal gyrus (PHG), and right angular gyrus while increased FC in the left dACC and bilateral MCC. The vPCC show decreased FC in the bilateral precuneus and right superior frontal gyrus (SFG). Moreover, we found that the rsFC between dPCC and PHG negatively correlated with SCARED (r=-0.720, *p*=0.004; Fig. 3A), and the rsFC between vPCC and SFG negatively correlated with YIAS (r=-0.548, *p*=0.043; Fig. 3B).

Discussion In this study, we identified seven resting-state functional networks associated with cingulate subregions (sACC, oACC, dACC, MCC, dPCC, vPCC and RSC) based on rsFC. These functional networks involve multiple cortical, subcortical, insula, parietal regions that are known to engage in emotional generation and processing, executive attention, decision making, and cognitive control. We found that IAD shows altered connectivity strength for every cingulate subregion except the RSC. Moreover, the SCARED was inversely associated with the strength of the coherent activity between dPCC and PHG, and YIAS was negatively related with the strength of the rsFC between vPCC and SFG. These findings suggest that rsFC may be used as a qualified biomarker to understand the underlying neural mechanisms or to evaluate the effectiveness of specific early interventions in IAD.

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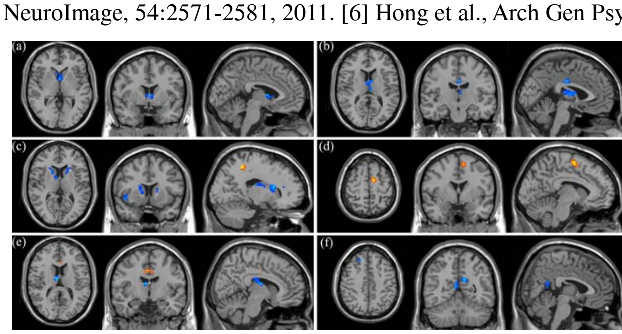

Fig. 2: Significant rsFC differences between IAD and controls. (a) sACC, (b) oACC, (c) dACC, (d) MCC, (e) dPCC, (f) vPCC, and (g) RSC. Hot and cold colors indicate rsFC increases and decreases in IAD when compared with controls.

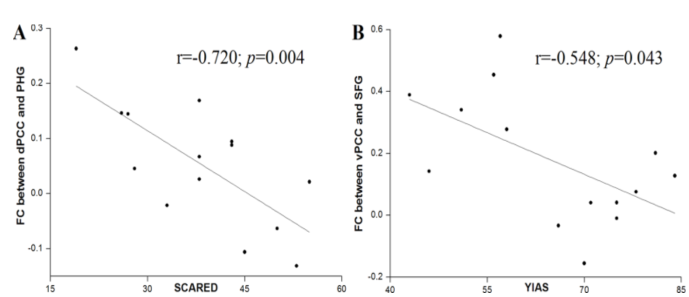

Fig. 3: Correlation analysis between rsFC and behavioral measures within the IAD. rsFC between the dPCC and PHG was negatively correlated with SCARED (A), and rsFC between the vPCC and SFG was negatively correlated with YIAS (B).