Coupling between the Salience Network and Default-mode Network Predicts Task-induced Deactivation through Regional Glutamate and GABA Concentrations

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Introduction

Efficient behavior involves the coordination of multiple brain networks[1]. Among these networks, the salience network (SN) has been proposed to play a critical role in dynamical control of activity in other networks[2]. While the default mode network (DMN) is thought to be engaged in internally oriented thoughts that need to be suppressed in order to perform tasks demanding intensive external attention. The variation in task-induced DMN deactivation has been shown to correlate with behavioral performance across subjects[3,4]. It has also been demonstrated recently that the coordinative actions of resting glutamate and GABA concentrations in the posterior cingulate cortex (PCC, a core node in the DMN) predicted the DMN deactivation induced by a working memory (WM) task[5]. In addition, drug modulated functional connectivity change between the SN and DMN was found to correlate with WM-induced PCC deactivation in cigarette smokers[6]. However, an experimental quantification of the relationships among the task-induced regional activation (or deactivation), functional connectivity related to the region, and regional neurotransmitter concentrations has not been well conducted. In this study, we tested two hypotheses 1) the coupling strength between the SN and DMN at resting state predicts task-induced DMN deactivation; and 2) regional balance of the excitation and inhibition mediates the relationship between the SN-DMN coupling and the task-induced deactivation in DMN.

Methods

Subjects and Experiment Design. Twenty-four healthy volunteers (14 male; age: 34±8.6) participated in the study. All subjects underwent a high-resolution anatomical scan, an 8 min eyes-closed resting fMRI scan, a resting state MRS scans with a voxel placed in the PCC, and a 12 min block-design fMRI scan during which subjects performed an n-back working memory (WM) task under four loads: 0-, 1-, 2-, and 3-back (0b, 1b, 2b, and 3b)[6].

Data Acquisition. All MRI and MRS scans were acquired on a Siemens 3T Trio scanner. The resting and task fMRI scans were acquired using a single-shot GE EPI sequence. GABA-edited MR spectra were acquired from a 2.4×3.2×3.6 cm^3 volume using the MEGA-PRESS method[7] and glutamate concentration from the same volume was obtained using a PRESS sequence[8]. The anatomical scan was acquired with a T1-weighted 3D MPRAGE.

Data Processing and Analyses. Slice-timing correction, motion correction, 6-mm spatial smoothing, and quadratic detrending were performed for all fMRI data. Additional band-pass filtering and nusance parameters (due to motion, WM, and CSF fluctuations) regression were performed on the resting data. GLM model was constructed to obtain the activation maps during the 1b, 2b, and 3b WM condition versus the vigilant 0b condition. The repeated-measures ANOVA was then conducted to obtain the group activation map of the WM effects. The activation map was thresholded ($p_{corrected}$<0.01) and the deactivated PCC region was extracted as the seed region in the rsFC analysis. The WM-induced deactivation in the PCC was assessed by the average signal percentage change. The MRS data were quantified using LCModel[9] and the concentrations were referenced to the unsuppressed water concentration.

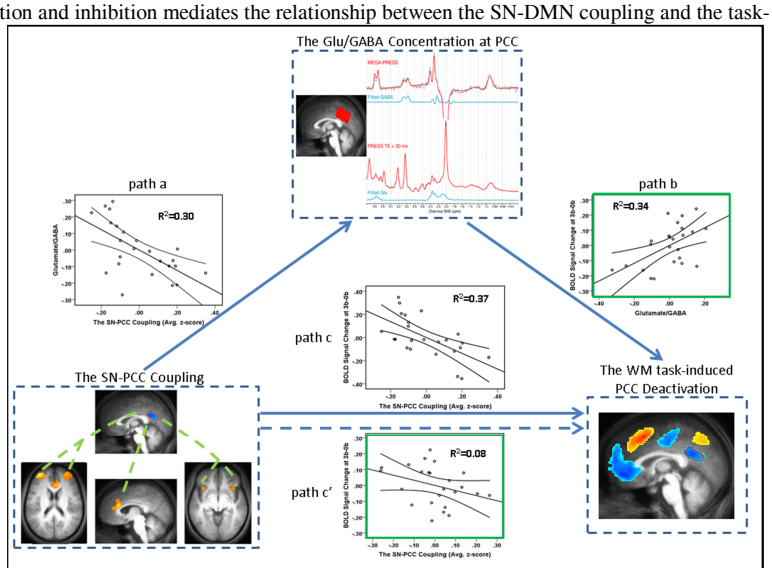

Fig.1 Mediation analysis of the relationship among the SN-PCC coupling, regional excitation and inhibition balance $R_{Glu/GABA}$ in the PCC, and the working memory task-induced PCC deactivation.

Statistical Analyses. Voxel-wise regression analysis of the PCC rsFC map was performed against the PCC deactivation at 3b-0b, controlling for age. To identify the brain regions in the SN whose rsFC strengths with the PCC were correlated with the PCC deactivation, the regression map was thresholded at $p_{uncorrected}$<0.05 combined with a cluster threshold of 40 voxels and was then masked by the SN map. The resting SN-PCC coupling strength was evaluated by averaging the CC values between these SN regions and the PCC seed region. To investigate the relationship among the SN-PCC between-network coupling, neurotransmitter concentrations, and the PCC deactivation, mediation analyses using Sobel test were conducted to test whether the local balance of excitation and inhibition (expressed as the glutamate/GABA ratio $R_{Glu/GABA}$) acted as a mediator in the prediction of PCC deactivation by the resting SN-PCC coupling.

Results

The SN regions, whose rsFC with the PCC predicted the PCC deactivation, included bilateral anterior insula (AI), dorsal ACC, and bilateral DLPFC (the SN-PCC coupling in Fig.1). The resting SN-PCC connectivity was negatively correlated with the PCC deactivation (p = 0.001) (path ***c*** in Fig.1). The local balance of excitation and inhibition ($R_{Glu/GABA}$) in the PCC showed negative association with the resting SN-PCC coupling (p = 0.002) (path ***a*** in Fig.1), whereas the balance positively predicted the WM task-induced deactivation in the PCC (p = 0.01), after controlling for the SN-PCC coupling (path ***b*** in Fig.1). The mediation analysis showed that the relationship between the SN-PCC connectivity and PCC deactivation was completely mediated by the local balance of the excitation and inhibition $R_{Glu/GABA}$ (p = 0.03) at 3b, since the direct effect of SN-PCC coupling on PCC deactivation is not significant after controling $R_{Glu/GABA}$ (p = 0.13, path ***c'*** in Fig.1). The reverse mediation model, i.e. that the SN-PCC connectivity mediates the relationship between the PCC $R_{Glu/GABA}$ and PCC deactivation, did not yield a significant mediation effect at 3b (p=0.16).

Discussion

We found that the connectivity strength between the SN and the PCC is associated with the local balance of excitation and inhibition ($R_{Glu/GABA}$) in the PCC, both of which predict the WM task-induced PCC deactivation. The negative correlation between the SN-PCC coupling and the $R_{Glu/GABA}$ indicates that the more negative the SN-PCC coupling, the higher/lower glutamate/GABA level was observed in the PCC. We speculate that following the glutamatergic signal projection from the key SN regions to the PCC, the local signal might relay through feedforward inhibition microcircuit in the PCC, i.e. the presynaptic glutamatergic neuron excites an inhibitory interneuron and that interneuron then inhibits the downstream neurons, leading to decreased baseline activity in the PCC. The balance of these two neurotransmitters is therefore modulated by the SN-PCC connectivity strength.

The negative association between the resting SN-PCC connection and the PCC deactivation suggested that the more the subject attends to the internal processes during the rest, the more the PCC will have to suppress the spontaneous activities while performing demanding cognitive tasks. However, the direct effects of the SN-PCC coupling on the PCC deactivation were significantly reduced when the local neurotransmitter concentrations were added in the prediction model. This suggested that the projections from the SN key regions to the PCC are related to signaling inhibition, thereby increasing the GABA concentration and/or decreasing the glutamate concentration, lead to further decreased activity in the PCC.

References

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