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Investigating the role of GABA in posterior cingulate cortex during resting state

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Introduction

The role of neurotransmitters in the activity of resting state networks has been gaining attention and has become a field of research with magnetic resonance spectroscopy (MRS) being one of the key techniques. The MRS technique permits the measurement of γ-aminobutyric acid (GABA) and glutamate levels, the central biochemical constituents of the excitation-inhibition balance in vivo. The inhibitory effects of GABA in the brain have been largely investigated in relation to the activity of resting state networks in functional magnetic resonance imaging (fMRI)[1,2]. Based on evidence showing the importance of posterior cingulate cortex (PCC) during resting state, as well as the modulatory functions of GABA, we hypothesize that GABA concentration in the PCC measured by MRS has a direct relationship with the response of some areas in the default-mode network (DMN).

Methods

Data were recorded from 20 healthy male volunteers (mean age 25.4, SD 3.7) in a 3 T Siemens Magnetom Trio scanner. Written, informed consent was obtained from all subjects and the study was approved by the local Ethics Committee. The study was conducted according to the Declaration of Helsinki. During the scanner procedure the subjects were requested to close their eyes and relax. Functional images were acquired using a T2*-weighted EPI sequence (TR = 2.2 s, TE = 30 ms, field-of-view = 200 mm, slice thickness = 3 mm and number of slices = 36). The functional time series consisted of 165 volumes. Anatomical images were acquired for every subject. Single voxel spectra were consecutively measured by the means of PRESS (TE1 = 14 ms, TE = 105 ms, TR = 2.5 s, NA = 128, 25 mm 25 mm 25 mm voxel size, RF pulse centred at 2.4 ppm, 16 step phase cycling). B0 field was shimmed by running FASTESTMAP[3] iteratively. The position of the voxel was set to the PCC and always confirmed by a trained operator.

The spectra were analysed with LCModel version 6.3-0I[4] using a GAMMA simulated basis set[5]. GABA ratio (GABA / Cr+PCr) was extracted and used as covariant in the fMRI resting state data analysis.

Analysis of functional data was carried out in MELODIC (Multivariate Exploratory Linear Decomposition into Independent Components) Version 3.10, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Temporal concatenation ICA was performed across all functional datasets from each subject using automatic dimensionality estimation. The DMN was identified by visual inspection and comparison to previously published data[6,7].

Finally, the dual regression algorithm[8] was applied in order to identify the individual contribution of every subject to the DMN using the GABA ratio in the PCC as a covariant in the second stage of dual regression analysis within the framework of general linear model. Here, the subject-specific GABA ratio was tested for linear relationship with the subject-specific z-values of the IC representing the DMN using nonparametric permutation testing (10000 permutations). This resulted in spatial maps characterizing the voxels with signal intensities that had a linear relationship (slope) with GABA ratio. The maps were thresholded and controlled for family-wise error rate at $p < 0.05$.

Results

The voxel-wise statistical maps, generated by the permutation test of dual regression, exhibited a cluster in the right putamen with significant values ($p < 0.05$) where the signal intensity of the DMN had a negative linear relationship with GABA ratio measured in the PCC. The point of lowest p value ($p = 0.0002$) was located in the right putamen (MNI coordinates x = 26, y = 10, z = 4) according to the Harvard-Oxford Subcortical Structural Atlas (Figure 1).

Conclusion

Our data show that the activity of right putamen in the DMN during resting state has a negative linear relationship with the GABA ratio measured in the PCC. These findings highlight the role of PCC and GABA in motor inhibition, which is an inherent condition that characterises resting state.

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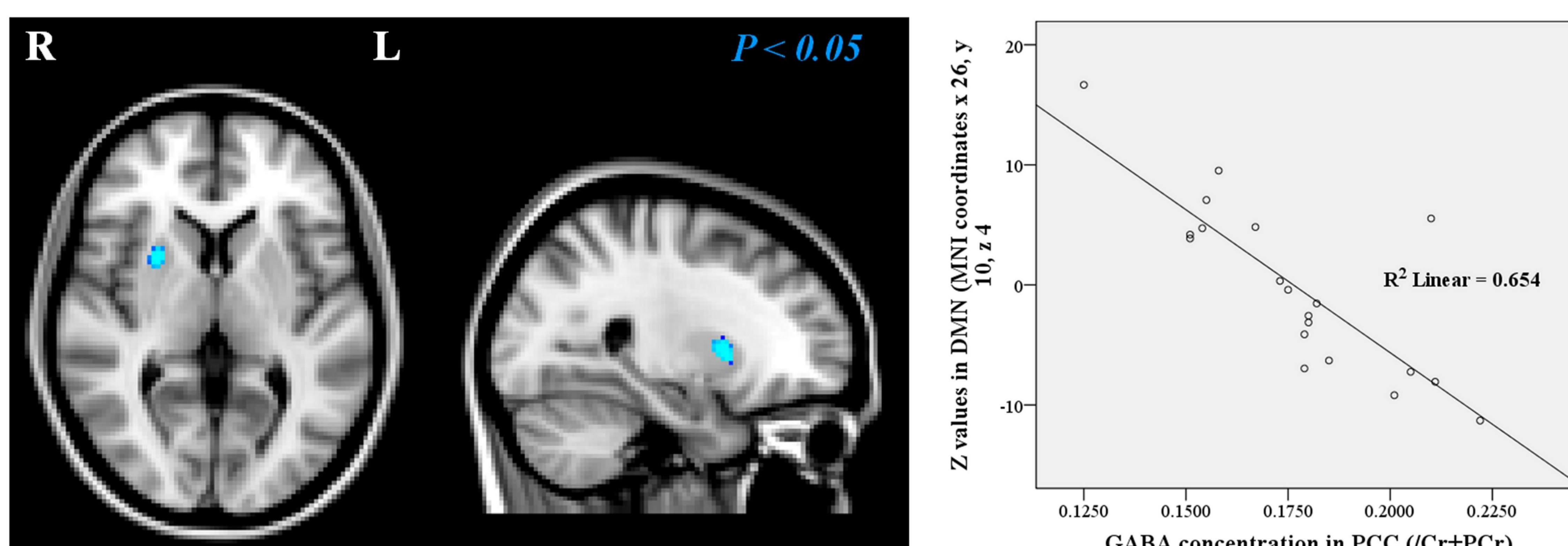
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Figure 1. Voxel-wise statistical maps with the inclusion of the GABA ratio measured in the PCC and generated by the dual regression analysis of the DMN. Significant voxels thresholded at p < 0.05. The point of lowest p value (p = 0.0002) was located in MNI coordinates x = 26, y = 10, z = 4.