Abnormal Neural Activity in Treatment-Resistant Depression: a Resting-State fMRI Study

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INTRODUCTION:

Treatment resistant depression (TRD) represents a large proportion of patients with depressive disorder that leads to major social cost [1]. However, to date the underlying neurobiological mechanisms of TRD are poorly understood. Resting-state fMRI (rfMRI) has been widely used in investigating mental illnesses due to its advantage in revealing abnormalities of intrinsic neuronal activity. Thus in the present study, we performed a rfMRI study on patients with clinically defined TRD with age/sex-matched healthy controls. Our fMRI data were analyzed using a recently developed functional data analytical approach [2], namely Regional Homogeneity (ReHo), in which a Kendall's coefficient of concordance (KCC) was used to calculate the similarity of the time series of a given voxel and its neighboring voxels. We aim to investigate whether the functional abnormalities can be identified in patients with TRD using the ReHo analysis of the rfMRI data.

MATERIALS and METHODS:

Twenty-two patients were recruited from the Mental Health Center of the university hospital, and all of them were diagnosed as major depressive disorder in accordance with the DSM-IV criteria. The definition of TRD was consistent with previously published studies [3]. Disease severity was assessed using the 17-item Hamilton Rating Scale for Depression (HRSD). The exclusion criteria included those with other major psychiatric and neurological disorders, younger than 18 or older than 60, or scored less than 18 using HRSD. All patients and 23 age/sex-matched control subjects underwent MRI scan on a 3T GE scanner. Functional images were acquired using an EPI sequence and the parameters were: TR/TE = 2000/30 ms, FOV = 24 cm^2, data matrix = 64 x 64, 30 contiguous slices / volume, slice thickness = 5 mm and number of volumes = 2900. All subjects were reviewed without abnormalities on conventional MRI. So the functional data were pre-processed using SPM2, including steps of motion correction, within-subject registration, slice timing, normalization and time series detrending. A temporal band-pass filtering (0.01 Hz < f < 0.08 Hz) was performed to reduce the influence by the respiratory and cardiac rhythms. ReHo analysis was carried out using an in-house software REST (http://resting-fmri.sourceforge.net). ReHo maps were generated by calculating the Kendall's coefficient of each voxel with its 26 neighboring voxels. For normalization, each map was divided by its mean ReHo value. Finally, voxel-wised group comparison was made using two-sample t-test and a correlation analysis was also conducted between the individual whole brain ReHo maps of TRD patients and their HRSD score. The study was approved by the local ethics committee, and informed consents were obtained from all participants.

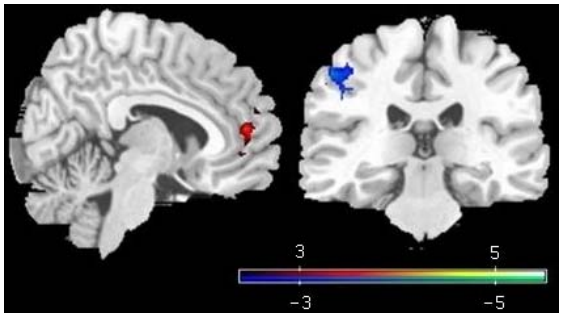

Fig.1 Regional increase (left, in red) and decrease (right, in blue) of ReHo values in TRD group compared with controls.

RESULTS:

Compared to control group, when statistical threshold was set at cluster level $p < 0.05$, corrected, with a cluster extent of 50 voxels, the TRD group showed increased ReHo in the right medial frontal gyrus and anterior cingulate cortex (ACC) and decreased ReHo in right inferior parietal lobule (IPL) (Fig.1). A significant negative correlation (cluster level $p < 0.001$, uncorrected, cluster extent of 50 voxels) was found in the ACC area between HRSD score and ReHo value (Fig.2).

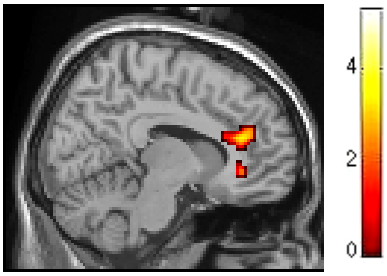

Fig.2 Significant correlation between ReHo values of TRD patients and their HRSD scores was found in ACC (regions in red).

DISCUSSION and CONCLUSION:

Agree with earlier studies using PET and fMRI techniques [4-6], we observed two brain regions, namely ACC and IPL, which are closely related to major depressive disorder in the present study. In particular, the ACC has been implicated as the crucial area which may predict antidepressant treatment effects [4]. Although the underlying neurobiological basis of ReHo changes requires further clarification, our results suggested the usefulness of ReHo in detecting unpredicted hemodynamic responses in r-fMRI experiments in patients with TRD. Future longitudinal studies utilizing r-fMRI in combination of ReHo analysis would provide further insight into the psycho-pathological mechanisms of TRD and hence to facilitate the optimization of antidepressant treatment.

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