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Altered spontaneous activity in the default-mode network and cognitive decline in chronic subcortical stroke

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ABSTRACT

Background and purpose: The resting-state functional connectivity (rsFC) has been reported to be impaired in the default-mode network (DMN) in stroke patients. However, it remains unclear whether the regional homogeneity (ReHo) of spontaneous activity and gray matter volume (GMV) are also altered in the DMN in these patients. Here we investigated ReHo, rsFC and GMV changes in the DMN and their functional correlations in stroke patients.
Methods: Eighteen patients with chronic subcortical stroke and 20 healthy controls underwent multi-modality MRI examinations to extract the DMN and to calculate the ReHo, rsFC and GMV. The ReHo difference in the DMN was compared between groups and brain regions with significant group differences in ReHo were extracted to calculate rsFC and GMV of these regions. Correlations of the cognitive or depressive scores with the imaging indices of the DMN that exhibit group differences were also investigated in stroke patients.
Results: Compared with healthy controls, patients with stroke exhibited decreased ReHo in the posterior cingulate cortex (PCC) and decreased rsFC between the PCC and anterior cingulate cortex (ACC). There were no significant volumetric differences in the PCC or the whole DMN between the two groups. The ReHo (not the rsFC) of the PCC was correlated with cognitive decline even after controlling for depressive scores. Neither ReHo nor rsFC of the PCC was correlated with depressive severity in these patients.
Conclusions: These findings suggest that both regional spontaneous activity and their interactions are impaired in stroke patients and that the reduced ReHo of the PCC may underlie post-stroke cognitive decline.

1. Introduction

More than one-third of patients with stroke will experience cognitive decline, which adversely affects outcome [1]. The default-mode network (DMN), an important resting-state functional network of the brain [2], has been associated with cognitive and emotional processing [3,4]. The resting-state functional connectivity (rsFC) that is operationally defined as the temporal correlations between spatially remote neurophysiological processes [5], has been extensively used to investigate functional alterations of the DMN under different conditions. The cognitive decline has been associated with the rsFC impairment of the DMN in ischemic stroke patients with variously located lesions [6]. However, little is known whether the regional spontaneous activity of the DMN is also damaged in patients with subcortical infarction.

The regional homogeneity (ReHo) was proposed by Zang and colleagues, which measures resting-state regional brain spontaneous activity [7]. Voxel-based ReHo analysis can rapidly map the level of regional activity across the whole brain of an individual [8] and has been applied to evaluate the efficiency of rehabilitative therapies following stroke [9]. Nevertheless, the alteration of the ReHo in the DMN and association between the ReHo and cognitive decline in these patients remain unclear. Previous studies have found that the rsFC impairment of the DMN is also related to depressive symptoms in patients with stroke [10], whereas no researchers have considered the two factors in a single study. Functional impairment may be secondary to the structural damage, however, structural alternation of the DMN in the subcortical infarction patients is unknown.

In the present study, we recruited a homogeneous group of chronic first-ever stroke patients with infarction restricting to the internal capsule and neighboring regions and exhibiting good recovery in global motor function. First, we investigated ReHo changes in the DMN in these patients. Second, we explored the rsFC and structural changes in the brain regions with significant ReHo changes in stroke patients. Finally, we explored correlations between the altered imaging indices and cognitive or depressive scores in the patient group. Through these analyses, we aimed to clarify the functional alteration patterns of the DMN, its underlying mechanisms, and its functional implications in subcortical stroke patients.

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2. Materials and methods

2.1. Subjects

The experimental protocol was approved by the Medical Research Ethics Committee of Tianjin Medical University, and written informed consent was obtained from all participants. The inclusion criteria were: (1) first-onset ischemic stroke; (2) single lesion restricting to the internal capsule and neighboring regions; (3) right-handed before the stroke; (4) amount of time post-stroke onset >6 months to ensure patients at a stable chronic stage; and (5) with good recovery of global motor function, upper extremity Fugl-Meyer Assessment (UE_FMA) of >60 and whole extremity Fugl-Meyer Assessment (WE_FMA) of >90. The exclusion criteria were: (1) recurrent stroke which is defined based on both clinical history and MRI evaluation; (2) any other brain disorders or abnormalities that could be identified by medical history or imaging examinations; (3) the lacunes and microbleeds were excluded based on T1-, T2-, and diffusion-weighted images; (4) severe white matter hyperintensity manifesting as a Fazekas [11] scale score >1; (5) and a history of drug dependency or psychiatric disorders. According to these criteria, 18 patients (14 males; mean age: 55.7 ± 7.9 years) were included in this study. Twenty healthy subjects (11 males; mean age: 56.0 ± 6.1 years) were also recruited as controls. The cognitive function was assessed by the Montreal Cognitive Assessment (MoCA), the motor function was assessed by the Fugl-Meyer Assessment (FMA), and the depressive symptom severity was assessed by the Beck Depression Inventory (BDI).

2.2. MR data acquisition

MR images were acquired using a 3.0 Tesla MR scanner (Signa Excite HDx; GE Healthcare, Milwaukee, WI, USA). Tight but comfortable foam padding was used to minimize head movement, and earplugs were used to reduce scanner noise. Resting-state fMRI data were obtained using a Gradient-Echo Single-Shot Echo-Planar Imaging sequence (GRE-SS-EPI) with the following imaging parameters: repetition time (TR)/echo time (TE) = 2000/30 ms; field of view (FOV) = 240 mm × 240 mm; matrix = 64 × 64; flip angle (FA) = 90°; slice thickness = 3 mm; 1 mm gap; 38 interleaved transversal slices; and 180 volumes. During the resting-state fMRI scans, all subjects were instructed to keep their eyes closed, to stay as still as possible, to think of nothing in particular, and to not fall asleep. Sagittal 3D T1-weighted images were acquired by a brain volume (BRAVO) sequence (TR/TE = 8.1/3.1 ms; inversion time = 450 ms; FA = 13°; FOV = 256 mm × 256 mm; matrix = 256 × 256; slice thickness = 1 mm, no gap; and 176 slices).

2.3. Image preprocessing

The resting-state fMRI data were preprocessed using Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm). The first 10 volumes from each subject were discarded to allow the signal to reach equilibrium and the participants to adapt to the scanning noise. The remaining 170 volumes were corrected for acquisition time delay between slices. Then, head motion parameters were estimated; none of the 38 subjects had a maximum displacement of >2 mm or a maximum rotation of >2.0°. In this step, the framewise displacement (FD) was also calculated to characterize the instantaneous head motion of each volume. The remaining data set was spatially normalized to the Montreal Neurological Institute (MNI) EPI template and resampled into $3 \times 3 \times 3$ mm^3 voxels. Thereafter, some nuisance variables were regressed out from the fMRI data, including the averaged signals of the ventricular, white matter, and the whole brain, and six head parameters. Because recent studies have found that signal spike caused by motion may also significantly contaminate the final resting-state fMRI results even after regressing out the realignment parameters, in this experiment, we also regressed out the spike volumes by generating an individual vector when the FD of specific volume exceeded 0.5. Next, a band-pass frequency filter (0.01–0.08 Hz) was applied to reduce low-frequency drift and high-frequency noise [12]. Finally, the filtered BOLD images were spatially smoothed using an isotropic Gaussian kernel of 8 mm × 8 mm × 8 mm full width at half maximum (FWHM).

2.4. Extraction of the DMN

Fox and colleagues [13] described task-negative core regions located in the left lateral parietal cortex (LPC) (peak MNI coordinates: −45, −67, 36), medial prefrontal cortex (MPFC) (peak MNI coordinates: −1, 47, −4), and posterior cingulate cortex/precuneus (PCC/Pcu) (peak MNI coordinates: −5, −49, 40). These core regions were defined as a sphere with a radius of 6 mm which centered at these MNI coordinates, and then we performed the seed-based rsFC analysis in total subjects (n = 38). Multiple comparisons were corrected by the false discovery rate (FDR) method with $P < 0.05$. Finally, we extracted the overlapping brain regions of these rsFC analyses to define the DMN (Fig. 1).

2.5. ReHo analysis

We used Kendall's coefficient concordance (KCC) to measure regional homogeneity of a given voxel with its nearest 26 neighbor voxels in a voxel-wise manner. The unsmoothed fMRI data were used to calculate the ReHo; and then the ReHo maps were spatially smoothed with an isotropic Gaussian kernel of FWHM = 8 mm. Finally, a general linear model (GLM) was used to voxel-wisely compare group differences in ReHo within the DMN using age and sex and years of education as nuisance variables. A corrected threshold of $P < 0.05$ was derived from a combined threshold of $P < 0.001$ for each voxel and a cluster size >9 voxels which was determined by the AlphaSim program. We used Cohen's d to describe the effect size (ES) of each comparison. To explore the effects of cognitive impairment on the DMN, stroke patients were divided into two subgroups by MoCA score, which was widely used and recognized as one of the best screening tests for cognitive deficits [14,15]. The cognitive impairment subgroup was defined by a MoCA score of <26. ReHo differences among the three groups were compared using analysis of

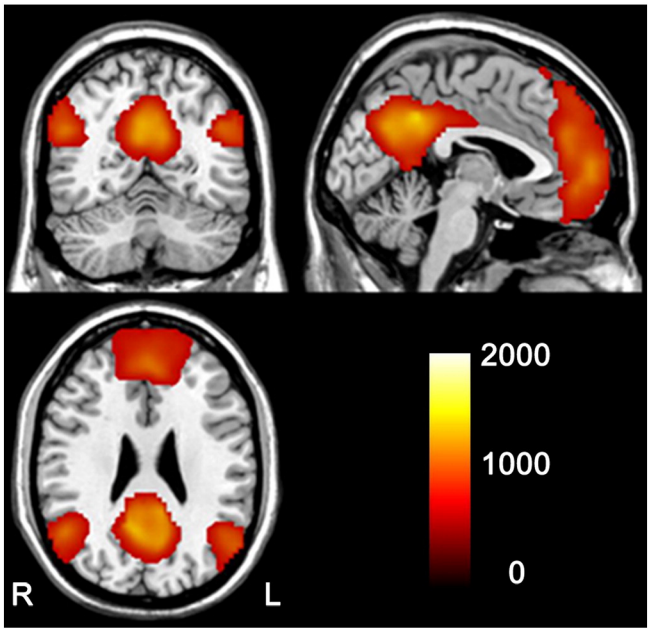

Fig. 1. Default-mode network. Default-mode network is shown on structural images.

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