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Research article

Abnormal cortical functional activity in patients with ischemic white matter lesions: A resting-state functional magnetic resonance imaging study

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HIGHLIGHTS

- We examine the relationship between WMLs and cognitive function using a ReHo method.
- Abnormal regions are related to memory, attention and executive and motor function.
- Altered regions in the DMN, FPCN and motor area correlate with cognitive test scores.
- The findings improve our understanding of pathophysiological mechanisms of WMLs.

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ABSTRACT

There is increasing evidence that white matter lesions (WMLs) are associated with cognitive impairments. The purpose of this study was to explore the relationship of WMLs with cognitive impairments from the aspect of cortical functional activity. Briefly, Sixteen patients with ischemic WMLs and 13 controls participated in this study. A regional homogeneity (ReHo) approach was used to investigate altered neural coherence in patients with ischemic WMLs during the resting state. A correlation analysis was further performed between regions with altered ReHo and cognitive test scores, including Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA), in the patient group. Finally, we found regions with altered ReHo values in patients with ischemic WMLs to be involved in default mode network (DMN), frontal-parietal control network (FPCN), dorsal attention network (DAN), motor network and right temporal cortex. Moreover, some altered regions belonging to DMN, FPCN and motor network were significantly correlated with cognitive test scores. Our results provide neuroimaging evidence for the impairments of memory, attention, executive and motor function in patients with ischemic WMLs. It is interesting to note that the decreased ReHo was mainly in the anterior brain regions, while increased ReHo in the posterior brain regions, which may indicate a failure down regulation of spontaneous activity in posterior regions. In summary, this study indicates an important role of specific cortical dysfunction in cognitive associated with WMLs.

Abbreviations: 3DFFE, 3D fast field echo; ACG, anterior cingulate gyrus; aMCG, anterior middle cingulate cortex; ANG, angular gyrus; BA, Brodmann's area; CUN, cuneus; DAN, dorsal attention network; DLPFC, dorsolateral prefrontal gyrus; DMN, default mode network; EPI, echo-planar-imaging; FDR, false discovery rate; FLAIR, fluid attenuated inversion recovery; FPCN, frontal-parietal control network; ING, insula; IPG, inferior parietal gyrus; KCC, Kendall's coefficient of concordance; MMSE, Mini-Mental State Examination; MNI, Montreal Neurologic Institute; MPFC, medial prefrontal cortex; MRI, magnetic resonance imaging; MTG, middle temporal gyrus; PCC, posterior cingulate cortex; PCUN, precuneus; PET, positron emission tomography; PoCG, postcentral gyrus; PreCG, precentral gyrus; ReHo, regional homogeneity; ROL, rolandic operculum; rs-fMRI, resting-state functional magnetic resonance imaging; SMA, supplementary motor area; SOG, superior occipital gyrus; SPM8, Statistical Parametric Mapping; SPG, superior parietal gyrus; STG, superior temporal gyrus; WMLs, white matter lesions.

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1. Introduction

White matter lesions (WMLs) are a common finding on magnetic resonance imaging (MRI) as white matter hyperintensities in elderly people older than 65 years [1,2]. The prevalence and severity of WMLs increases with advancing age [1,3]. WMLs are found to be a biomarker for long-term cerebrovascular disease and dementia [4].

There is growing evidence that WMLs are associated with clinical manifestations of cognitive impairments [4–6], including executive function [7], memory [8] and attention [9]. Moreover, motor decline is also a frequent finding associated with WMLs [10,11]. However, few studies have devoted their attention to the underlying mechanism of how WMLs influence cognitive function and behavioral performance. Nordahl et al. found that dysfunction of the prefrontal cortex caused by white matter degeneration might be a mechanism for the changes in memory function [8]. In addition, a positron emission tomography (PET) study revealed that WMLs had effects on metabolic activity of dorsolateral frontal cortex, which is related to executive function, memory and global cognitive function [12]. In our recent work, we found that cognitive impairments are associated with special cortical dysfunction in patients with WMLs using resting-state functional magnetic resonance imaging (rs-fMRI) [13]. In short, these studies suggest that dysfunction of specific cortical regions plays a vital role in cognitive impairments associated with WMLs. Therefore, investigating cortical functional activity may aid to better understand the relationship of WMLs with cognitive decline and motor disturbance.

Regional homogeneity (ReHo) measures the functional coherence of a given voxel with its nearest neighbors and can effectively evaluate resting-state brain activities [14]. This method assumes that brain activity is more likely to occur in clusters than in a signal voxel. Thus, ReHo provides an approach for using fMRI to investigate local connectivity and may be useful for revealing the complexity of human brain function [15]. Until now, ReHo analysis has been widely used to investigate the cortical functional activity and reveal the pathophysiological changes in the resting state in neurologic and psychiatric disorders, such as epilepsy [16], autism spectrum disorders [17], Alzheimer's disease [15,18], depression [19], anxiety disorder and Parkinson's disease [20]. Thus, this method may be helpful to understand the underlying mechanism of cognitive and motor deficits in patients with WMLs, since it can reflect the temporal homogeneity of neural activity.

We hypothesized that the ReHo value would be different between patients with ischemic WMLs and control subjects, particularly in brain regions associated with cognitive and motor function. In the present study, we employed ReHo analysis to investigate differences in cortical activity between patients with ischemic WMLs and the control subjects. Furthermore, correlation analyses of the ReHo value with clinical variables i.e., Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) were carried out in the patient group to evaluate the relationship between the cortical activity and the cognitive abilities associated with WMLs.

2. Materials and methods

2.1. Participants

This study was approved by the medical ethics committee of Chengdu Military General Hospital, Chengdu, China. All participants gave their written informed consent after the experimental procedure had been clearly explained. Finally, a total of 16 patients (7 males, age range: 49–72 years) who were diagnosed clinically with ischemic WMLs and 16 controls (CN; 8 males, age range: 54–71 years) with no WMLs on MRI were recruited, same with those in our recently published paper [21]. All participants underwent a comprehensive clinical examination by two experienced neurologists, including medical history, physical, and neurological assessments. Patients with ischemic WMLs were determined by T2-weighted MRI images, defined as a cap or a band of 10 mm or more and a deep white matter lesion of 25 mm or more according to a modification of the Fazekas ischemia criteria [22]. We excluded patients if they had psychiatric or neurological disorders that might cause cognitive impairment, such as stroke, schizophrenia, epilepsy, severe head trauma, encephalitis and brain tumors, or neurodegenerative diseases such as Parkinson's disease. In addition, the patients with disorders that might impact their current cognitive state, including metabolic encephalopathy, thyroid disease, syphilis, alcoholic encephalopathy and severe depression, were excluded. We also excluded the patients who did not undergo MRI and neuropsychological test due to aphasia, hearing or visual impairment and sensory disorders. The control subjects did not have any neurologic or psychiatric disorders and showed no deficits on the neuropsychological test. The neuropsychological tests evaluated in this study included: Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). All participants were right-handed.

2.2. Imaging data acquisition

All imaging data were collected on a 3.0-T Philips MR scanner (Philips Medical System, Best, Netherlands). Tight but comfortable foam padding was used to minimize head motion, and ear plugs were used to reduce scanner noise. Conventional MRI scans included transverse fluid attenuated inversion recovery (FLAIR), T1-weighted and T2-weighted images. Resting-state functional images were acquired using an echo-planar-imaging (EPI) sequence with the following parameters: TR/TE = 2000/30 ms, flip angle = 90°, FOV = 192 × 192 mm^2, matrix = 64 × 64, slice thickness = 3 mm, without gap, 35 axial slices, voxel size = 3 × 3 × 3 mm^3, and a total of 230 vols for each subject. Subjects were instructed to keep their eyes closed, relax and move as little as possible. Additionally, high-resolution T1-weighted anatomical images were acquired in sagittal orientation from each subject using a 3D fast field echo (3DFFE) sequence with the following parameters: TR/TE = 2500/2.0 ms, flip angle = 30°, matrix = 192 × 256, slice thickness = 1 mm, without gap, voxel size = 1 × 1 × 1 mm^3.Data from one control subject was discarded due to uncompleted functional images.

2.3. Image preprocessing

All preprocessing steps were carried out using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm). The first 10 volumes of each functional time series were discarded to ensure steady-state longitudinal magnetization and stabilization of participant status. The remaining 220 consecutive volumes were first corrected for the temporal difference in acquisition among different slices, and then realigned to the first volume for head-motion correction. Only participants with head motion less than 2.0 mm in the x, y or z direction and less than 2.0° rotation about each axis were included. Then, two control subjects were excluded from the further analyses. Totally, 16 patients (7 males, age range: 49–72 years) and 13 controls (6 males, age range: 54–70 years) remained. Next, the functional images were realigned with the corresponding T1-volume and warped into a standard stereotaxic space at a resolution of 3 × 3 × 3 mm^3, using the Montreal Neurological Institute (MNI) EPI template. Subsequently, the functional images were temporally band-pass-filtered (0.01–0.08 Hz) to reduce the effects of low-