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Abnormal intrinsic brain activity patterns in leukoaraiosis with and without cognitive impairment

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HIGHLIGHTS

- Leukoaraiosis and cognitive imapairment are both associated with altered spontaneous brain activity.
- Leukoaraiosis is related to ALFF increasing in IOG_R, Pcu_L, SFG_Orb_R and SOG_R.
- Decreasing ALFF in MTG_L is characteristic of cognitive impairment and may help its early detection.

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ABSTRACT

The amplitude of low frequency fluctuations (ALFF) from resting-state functional MRI (rs-fMRI) signals can be used to detect intrinsic spontaneous brain activity and provide valuable insights into the pathomechanism of neural disease. In this study, we recruited 56 patients who had been diagnosed as having mild to severe leukoaraiosis. According to the neuropsychological tests, they were subdivided into a leukoaraiosis with cognitive impairment group ($n = 28$) and a leukoaraiosis without cognitive impairment group ($n = 28$). 28 volunteers were included as normal controls. We found that the three groups showed significant differences in ALFF in the brain regions of the right inferior occipital gyrus (IOG_R), left middle temporal gyrus (MTG_L), left precuneus (Pcu_L), right superior frontal gyrus (SFG_R) and right superior occipital gyrus (SOG_R). Compared with normal controls, the leukoaraiosis without cognitive impairment group exhibited significantly increased ALFF in the IOG_R, Pcu_L, SFG_R and SOG_R. While compared with leukoaraiosis without cognitive impairment group, the leukoaraiosis with cognitive impairment group showed significantly decreased ALFF in IOG_R, MTG_L, Pcu_L and SOG_R. A close negative correlation was found between the ALFF values of the MTG_L and the Montreal Cognitive Assessment (MoCA) scores. Our data demonstrate that white matter integrity and cognitive impairment are associated with different amplitude fluctuations of rs-fMRI signals. Leukoaraiosis is related to ALFF increases in IOG_R, Pcu_L, SFG_Orb_R and SOG_R. Decreased ALFF in MTG_L is characteristic of cognitive impairment and may aid in its early detection.

1. Introduction

Leukoaraiosis is defined by areas in the cerebral white matter that appear hyper-intense on T2-weighted imaging and hypodense on computed tomography. It mostly reflects demyelination and axonal loss caused by chronic microvascular diseases and cerebral hypo-perfusion in elderly people [1]. The prevalence of MRI-detected leukoaraiosis in individuals over 60 years is higher than 30% and increases with age. It has been proven associated with cognitive impairment, although the exact mechanisms are not fully understood [2,3].

Resting-state functional MRI (rs-fMRI) has emerged in recent years as a new technology that has allowed researchers to detect intrinsic brain activity during rest [4]. The amplitude of low-frequency fluctuations (ALFF) was introduced to assess the amplitude of resting-state spontaneous brain activity by calculating the square root of the power spectrum (typically in a frequency range of 0.01–0.08 Hz) [5,6]. In a previous study, it was reported

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Table 1
Demographic and clinical data of the three groups.

	Normal control group	Leukoaraiosis without cognitive impairment group	Leukoaraiosis with cognitive impairment group	*F*	*p*
Gender (M/F)	14/16	16/12	13/15	0.848	0.655
Age (Y)	66.6 ± 4.6	67.9 ± 6.1	69.1 ± 6.9	1.316	0.274
Education (Y)	11.0 ± 4.2	10.1 ± 3.4	8.8 ± 3.9	2.227	0.114
MoCA	25.93 ± 1.80	25.71 ± 2.00	16.86 ± 4.79	76.845	<0.001
MMSE	28.10 ± 1.73	27.89 ± 1.57	23.39 ± 3.25	38.031	<0.001
Head motion	0.35 ± 0.26	0.34 ± 0.20	0.39 ± 0.25	0.241	0.787

Data are expressed as the range from min–max (mean ± SD). Abbreviations: MMSE – Mini-Mental State Examination; MoCA – Montreal Cognitive Assessment.

that subcortical ischemic vascular dementia (SIVD) patients exhibit a specific intrinsic pattern of ALFF. Compared with normal controls, SIVD patients showed ALFF changes in the brain regions of the bilateral precuneus, anterior cingulate cortex (ACC), left insula and hippocampus. Close correlations were found between the ALFF alteration of the left insula and Mini Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA) scores [7]. SIVD is caused by a restricted blood supply to the brain and subsequent lesions in the white matter and/or basal ganglia. Leukoaraiosis is common in clinical practice and is considered the primary pathology in SIVD. Clear evidence has proven that leukoaraiosis can lead to cognitive decline and plays a role in the etiology of cognitive impairment [8–11]. However, most of the literature examining the resting state brain activity of vascular impairment assumed the signal variation to be determined by cognitive impairment directly, whereas the contribution of leukoaraiosis has been ignored [12–15]. It is particularly important to investigate whether leukoaraiosis can influence the resting state signal. Therefore, the aims of this study were to compare ALFF alterations of the whole brain between leukoaraiosis patients with and without cognitive impairment to enhance our understanding of the pathomechanism of vascular cognitive impairment and to help in its early detection..

2. Subjects and methods

2.1. Subjects

The study was approved by the Medical Ethics Committee of our hospital, and all subjects gave their informed consent. Fifty-six patients who had been diagnosed as having mild to severe leukoaraiosis were recruited from the neurology department of our hospital (Table 1). All of the patients underwent laboratory examinations and conventional MRI or CT, and disease histories were collected from knowledgeable informants. The patients all had subcortical white matter hyperintensity on T2-weighted images and were diagnosed with ischemic brain diseases, including chronic cerebral circulation insufficiency or subcortical arteriosclerotic encephalopathy. The exclusion criteria were cerebral hemorrhage, cortical or subcortical infarcts, specific causes of white matter lesions (e.g., multiple sclerosis, sarcoidosis, or brain irradiation), neurodegenerative disease or normal pressure hydrocephalus. Patients with severe depression [Hamilton Depression Rating Scale >18], severe claustrophobia, or contraindications to MRI were also excluded. All patients completed a formal neuropsychological assessment comprising the following tests: MMSE, MoCA, Clinical Dementia Rating (CDR), Verbal and Categorical Fluency Test, Figural Recognition Test, Auditory Verbal Learning Test and Boston Naming Test. According to the neuropsychological tests, the 56 patients were subdivided based on cognitive status into a leukoaraiosis with cognitive impairment group ($n = 28$) and a leukoaraiosis without cognitive impairment group ($n = 28$). Twenty-eight volunteers with no known nervous system disease were recruited as the healthy controls. None of them had vascular risk factors, cognitive complaints, or psychiatric illness. All of the participants were right-handed.

2.2. MR image acquisition

All of the subjects were scanned using a 3T MRI scanner (MAGNETOM Trio Tim System; Siemens, Erlangen, Germany) with a 12-channel head coil. First, a transverse fluid-attenuated inversion recovery (FLAIR) sequence (TR = 9000 ms, TE = 93 ms, TI = 2500 ms, flip angle = 130°, matrix = 256 × 256, thickness = 4.0 mm, voxel size = 0.9 × 0.9 × 4 mm^3) and T1-weighted sequence (TR = 200 ms, TE = 2.78 ms, flip angle = 70°, matrix = 384 × 384, thickness = 4.0 mm, voxel size = 0.7 × 0.6 × 5 mm^3) were scanned. Next, resting-state functional images were acquired using an echo-planar imaging (EPI) sequence with the following parameters: TR = 2000 ms, TE = 30 ms, flip angle = 90°, matrix = 64 × 64, thickness = 3 mm, voxel size = 3.5 × 3.5 × 3.0 mm^3, time points = 240. Finally, structural images were acquired using a magnetization-prepared rapid gradient echo (MPRAGE) sequence with the following parameters: TR = 1900 ms, TE = 2.52 ms, TI = 900 ms, flip angle = 9°, matrix = 256×256, thickness = 1.0 mm, voxel size = 1 × 1 × 1 mm^3.

2.3. Image processing and analysis

The voxel-based morphometry 8 (VBM8) toolbox (http://dbm.neuro.uni-jena.de/vbm.html) was used for structural data analysis. All of the structural images were corrected for bias-field inhomogeneity, registered using linear (12-parameter affine) and nonlinear transformations. The brain tissues were classified as gray matter, white matter and cerebrospinal fluid [16]. The gray matter volume of each subject was used as a covariate in the group analysis of functional images. Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm) and Data Processing Assistant for Resting-State fMRI (DPARSF, http://rest.restfmri.net) software were used for functional image analysis [17]. The first five images of each functional time series were discarded, and the remaining were corrected for the within-scan acquisition time differences between slices and realigned to the first volume. Subjects with a more than 2 mm displacement or 2° head rotation were excluded. The group differences of head motion were examined using two-sample t-tests according to the mean framewise displacement (FD) Jenkinson measurement. All functional data were normalized to the Montreal Neurological Institute (MNI) space and smoothed with 6-mm FWHM. The six head motion parameters were regressed to avoid the confounding effect of head motion on ALFF.

ALFF calculation was performed using REST software (www.restfmri.net). After linear-trend removal, the time series of all functional images were transformed to the frequency domain using a fast Fourier transform (FFT). The square root of the power spectrum was computed and averaged across a predefined frequency of 0.01- to 0.08-Hz bands, which were selected as physiologically meaningful. The other frequency bands were discarded because they mainly reflected low-frequency drift, WM signals or high-frequency physiological noises. To reduce the global effects of variability among different subjects, the ALFF value of each voxel was divided by the global mean ALFF value to obtain the relative ALFF value of the whole brain.