Observational Study

Medicine®

OPEN

Abnormal functional connectivity density in patients with ischemic white matter lesions

An observational study

Ju-Rong Ding, PhD[a,*], Xin Ding, MD[b], Bo Hua, BS[a], Xingzhong Xiong, PhD[a], Qingsong Wang, MD[b,*], Huafu Chen, PhD[c]

Abstract

White matter lesions (WMLs) are frequently detected in elderly people. Previous structural and functional studies have demonstrated that WMLs are associated with cognitive and motor decline. However, the underlying mechanism of how WMLs lead to cognitive decline and motor disturbance remains unclear. We used functional connectivity density mapping (FCDM) to investigate changes in brain functional connectivity in 16 patients with ischemic WMLs and 13 controls. Both short- and long-range FCD maps were computed, and group comparisons were performed between the 2 groups. A correlation analysis was further performed between regions with altered FCD and cognitive test scores (Mini-Mental State Examination [MMSE] and Montreal Cognitive Assessment [MoCA]) in the patient group. We found that patients with ischemic WMLs showed reduced short-range FCD in the temporal cortex, primary motor cortex, and subcortical region, which may account for inadequate top-down attention, impaired motor, memory, and executive function associated with WMLs. The positive correlation between primary motor cortex and MoCA scores may provide evidence for the influences of cognitive function on behavioral performance. The inferior parietal cortex exhibited increased short-range FCD, reflecting a hyper bottom-up attention to compensate for the inadequate top-down attention for language comprehension and information retrieval in patients with WMLs. Moreover, the prefrontal and primary motor cortex showed increased long-range FCD and the former positively correlated with MoCA scores, which may suggest a strategy of cortical functional reorganization to compensate for motor and executive deficits. Our findings provide new insights into how WMLs cause cognitive and motor decline from cortical functional connectivity perspective.

Abbreviations: FCD = functional connectivity density, MFG = middle frontal gyrus, MMSE = Mini-Mental State Examination, MNI = Montreal Neurological Institute, MoCA = Montreal Cognitive Assessment, MRI = magnetic resonance imaging, PreCG = precentral gyrus, rs-fMRI = resting-state functional magnetic resonance imaging, WML = white matter lesion.

Keywords: aging, functional connectivity density mapping, functional magnetic resonance imaging, white matter lesions

1. Introduction

White matter lesions (WMLs) are frequently detected in elderly people,[1,2] which are easily visualized as white matter hyperintensity on T2-weighted magnetic resonance imaging (MRI) and hypodensity on computed tomography .[3] In populations over 65 years, the incidence of WMLs is higher than 30% and increases with age.[1,4] WMLs are not only strongly associated with age but also related to other risk factors, such as hypertension,[5,6] diabetes mellitus,[7] hyperlipidemia, and smoking.[8]

Recently, there is crescent evidence that impairments of cognitive function represent a key clinical finding of WMLs.[9] Results from neuropsychological and neuroimaging studies have reported that ischemic WMLs may lead to cognitive decline, especially on executive function,[10] memory,[11] and attention.[12] In addition, motor decline is also a common finding related to WMLs.[13,14] However, the underlying neural mechanism of how WMLs affect cognitive function and behavioral performance is not fully understood. According to the histopathological characteristics, WMLs may reflect ischemic tissue damage and correspond to loss of fibers,[15,16] which is likely to cause disconnection between cortical regions or between cortical-subcortical regions.[17] Since cognition and behavior are subserved by interconnected neural networks that allow parallel distributed processing,[18] disconnection of cortical networks resulting from ischemic WMLs may be detrimental to integration of brain function and cause cognitive impairments and motor dyspraxias.[17] Using resting-state functional magnetic resonance

Editor: Kavindra Nath.

Funding/support: This work was supported by the National Natural Science Foundation of China (No. 81401482), the Scientific Research Foundation of Sichuan University of Science and Engineering (No. 2014RC12), the Innovation Group Build Plan for the Universities in Sichuan (No. 13TD0017), and the Youth Science and Technology Innovation Group of Sichuan Provincial (No. 2015TD0022).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

The authors have no conflicts of interest to disclose.

[a] School of Automation and Electronic Information, Sichuan University of Science and Engineering, Zigong, [b] Department of Neurology, Chengdu Military General Hospital, [c] Key Laboratory for Neuroinformation of Ministry of Education, School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu, China.

[*] Correspondence: Ju-Rong Ding, School of Automation and Electronic Information, Sichuan University of Science and Engineering, Zigong, China (e-mail: jurongding@gmail.com); Qingsong Wang, Department of Neurology, Chengdu Military General Hospital, Chengdu, China (e-mail: happy174236@sina.com).

Medicine (2016) 95:36(e4625)

Received: 23 May 2016 / Received in final form: 21 July 2016 / Accepted: 27 July 2016

http://dx.doi.org/10.1097/MD.0000000000004625

imaging (rs-fMRI) technology, our recent work found that cognitive impairments are associated with special cortical dysfunction in patients with WMLs.[19] Overall, these studies suggest that specific cortical dysfunction or disconnection between cortical regions plays a vital role in cognitive changes associated with WMLs. Therefore, exploring functional connectivity between brain regions may aid to understand the underlying mechanism of how WMLs lead to cognitive decline and motor disturbance by cortical dysfunction.

Resting-state functional connectivity measured from rs-fMRI data can be used to explore the intrinsic organization of functional brain network.[20] In recent, Tomasi and Volkow[21] proposed a functional connectivity density mapping (FCDM) method that measures the number of functional connections of a given voxel with others. Compared with simple voxelwise functional connectivity analyses, FCDM is an ultrafast method and can locate functional hubs, which are densely connected and play more important roles in the information processing, with high sensitivity and discrimination among short- and long-range functional connectivity density (FCD) hubs.[22,23] Thus, investigating FCD changes associated with WMLs can clearly exhibit change in importance of a voxel in information processing, which may facilitate our understanding of the neural mechanism of cognitive and motor decline related to WMLs. In this study, we employed this data-driven method based on rs-fMRI data to investigate abnormal functional connectivity in patients with ischemic WMLs. We aimed to find FCD changes associated with WMLs, and further explore the relationship between the regions with FCD changes and cognitive performance. Here, we speculate that FCD changes are mainly in brain regions related to cognitive and motor function.

2. Materials and methods

2.1. Participants

Sixteen patients (7 males, age range: 49–72 years) who were diagnosed clinically with ischemic WMLs were recruited from Department of Neurology, Chengdu Military General Hospital, Chengdu, China. All participants were right-handed and underwent a comprehensive clinical examination by 2 experienced neurologists, including medical history, physical, and neurological assessments. All participants were required to undergo laboratory examinations, including a routine blood test, blood chemistry test, vitamin B12/foliate measurement, human immunodeficiency virus infection screening, syphilis serology, and thyroid functioning tests. 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 WML of 25 mm or more according to a modification of the Fazekas ischemia criteria.[16] Patients were excluded 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. Additionally, the patients with disorders that might impact their current cognitive state, including metabolic encephalopathy, human immunodeficiency virus infection, 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 neuropsychological tests evaluated in the present study included: Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). The comparison group consisted of 16 controls (8 males, age range: 54–71 years) with no WMLs on MRI. The control subjects had no neurologic or psychiatric disorders and exhibited no deficits on the neuropsychological test.

This study was approved by the medical ethics committee of Chengdu Military General Hospital. Before experimentation, written informed consents were obtained from all participants.

2.2. Image acquisition

Experiments were performed on a 3.0-T Philips MR scanner (Philips Medical System, Best, Netherlands). Foam padding and ear plugs were used to minimize head motion and scanner noise. Functional images were collected using an echo-planar-imaging sequence for a total of 230 volumes (repetition time/echo time = 2000/30 ms, flip angle = 90°, field of view = $192 \times 192\,mm^2$, matrix = 64×64, voxel size = $3 \times 3 \times 3\,mm^3$, without gap, 35 axial slices). During data acquisition, subjects were instructed to keep their eyes closed, relax, and move as little as possible. For each subject, a set of high-resolution T1-weighted anatomical images were also acquired in sagittal orientation using a 3D fast field echo sequence (repetition time/echo time = 2500/2.0 ms, flip angle = 30°, matrix = 192×256, slice thickness = 1 mm, without gap, voxel size = $1 \times 1 \times 1\,mm^3$). Data from 1 control subject was discarded due to uncompleted functional images.

2.3. Image preprocessing

Functional images preprocessing were carried out using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm). The 1st 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 1st volume for head-motion correction. Any participant who had a maximum displacement in any of the cardinal directions (x, y, z) larger than 2.0 mm or a maximum spin (x, y, z) less than 2.0° was excluded. Consequently, 2 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 spatially normalized to the Montreal Neurological Institute EPI template. Since previous studies have shown that functional connectivity analysis is sensitive to gross head motion effects,[24,25] we further calculated the mean absolute displacement of each brain volume compared with the previous one.[25] The largest mean displacement of all subjects was less than 0.2 mm, and no significant group differences ($P = 0.1793$) were found in mean displacement between patients (0.0674 ± 0.0451) and controls (0.0489 ± 0.0192) using 2-sample t tests. For each subject, the time series of all voxels from brain gray matter were extracted and corrected using a linear regression process to remove several spurious sources of variances, including 6 head realignment parameters and averaged signals from ventricles and white matter. Subsequently, the residuals of these regressions were temporally band-pass-filtered (0.01–0.08 Hz) to reduce the effects of low-frequency drift and high-frequency noise.[26,27]

2.4. Short- and long-range FCD

The preprocessed image data underwent FCD mapping to compute the strength of the local FCD and global FCD at voxel-wise spatial resolution, a detailed description can be seen in Tomasi and

Volkow.[21] Pearson correlation was used to calculate the functional connections, and 2 voxels were considered functionally connected if their correlation coefficient R was larger than a given threshold. Here, the correlation threshold T was set to 0.425, corresponding to $P<0.05$, family-wise error-corrected. This correlation threshold was used to minimize false positive connections across all subjects. For a given voxel, the global FCD was defined as the number of functional connections between this voxel and all other voxels in the brain. The calculation was repeated for all voxels in the brain using a parallel C-language algorithm.[23] The local FCD at a given voxel x_i was computed as the number of elements in the local functional connectivity cluster using a "growing" algorithm. Specifically, given a voxel x_i, a voxel x_j was added to the list of voxels functionally connected with x_i only if it was adjacent to a voxel that was linked to x_i by a continuous path of functionally connected voxels and $R_{ij}>T$. This calculation was repeated for all voxels that were adjacent to voxels that belonged to the list of voxel functionally connected to x_i in an iterative manner until no new voxels could be added to the list. Then, the calculation was initiated for the other voxels in the brain.[23] The short-range FCD is equal to the local FCD, since the local FCD mainly reflects functional connectivity of the local cluster. The long-range FCD is defined as global FCD-local FCD because the global FCD included both local and distal functional connections.[22,23] The short- and long-range FCD maps were spatially smoothed by convolution with an isotropic Gaussian kernel (FWHM = 8 mm). To reduce individual overall differences in the strength of FCD, short- and long-range FCD distributions were scaled by the mean value of each subject.[28]

Table 1

Demographic and clinical characteristics.

Characteristics	Patients with WMLs (n = 16)	CN (n = 13)	*P*
Age, years	49–72 (61.6 ± 6.1)	54–70 (60.2 ± 4.7)	0.5235*
Gender (male/female)	7/9	6/7	>0.9999†
Education, years	6–15 (8.5 ± 2.8)	6–12 (8.5 ± 1.9)	0.8881‡
Vascular risk factors			
Hypertension	7 (43.8%)	4 (30.8%)	0.7021†
Diabetes mellitus	2 (12.5%)	2 (15.4%)	>0.9999†
Hyperlipidemia	6 (37.5%)	3 (23.1%)	0.4543†
Current smoker	1 (6.3%)	1 (7.7%)	>0.9999†
MMSE	16–30 (23.7 ± 3.9)	27–29 (28 ± 0.8)	0.0006*
MoCA	10–24 (18.3 ± 4.1)	26–29 (27.2 ± 0.9)	<0.0001*

Data were expressed as the range from min–max (mean ± SD). CN = controls, MMSE = Mini-Mental State Examination, MoCA = Montreal Cognitive Assessment, SD = standard deviation, WML = white matter lesion.

* *P*-value was obtained using the 2-sample, 2-tailed *t* test.

† *P*-value was obtained using the 2-tailed Fisher exact test.

‡ *P*-value was obtained using the 2-tailed Mann–Whitney *U* test.

2.5. Statistical analysis

Statistical analysis was carried out using SPM8 software. One-way analysis of covariance with 3 covariates (age, gender, and mean displacement) was applied to map group differences in short- and long-range FCD, respectively. The statistical significance of group comparison was set at $|t|>2.79969$ (individual voxel threshold of $P<0.005$, df = (1,27) and minimum cluster size of 40 voxels,

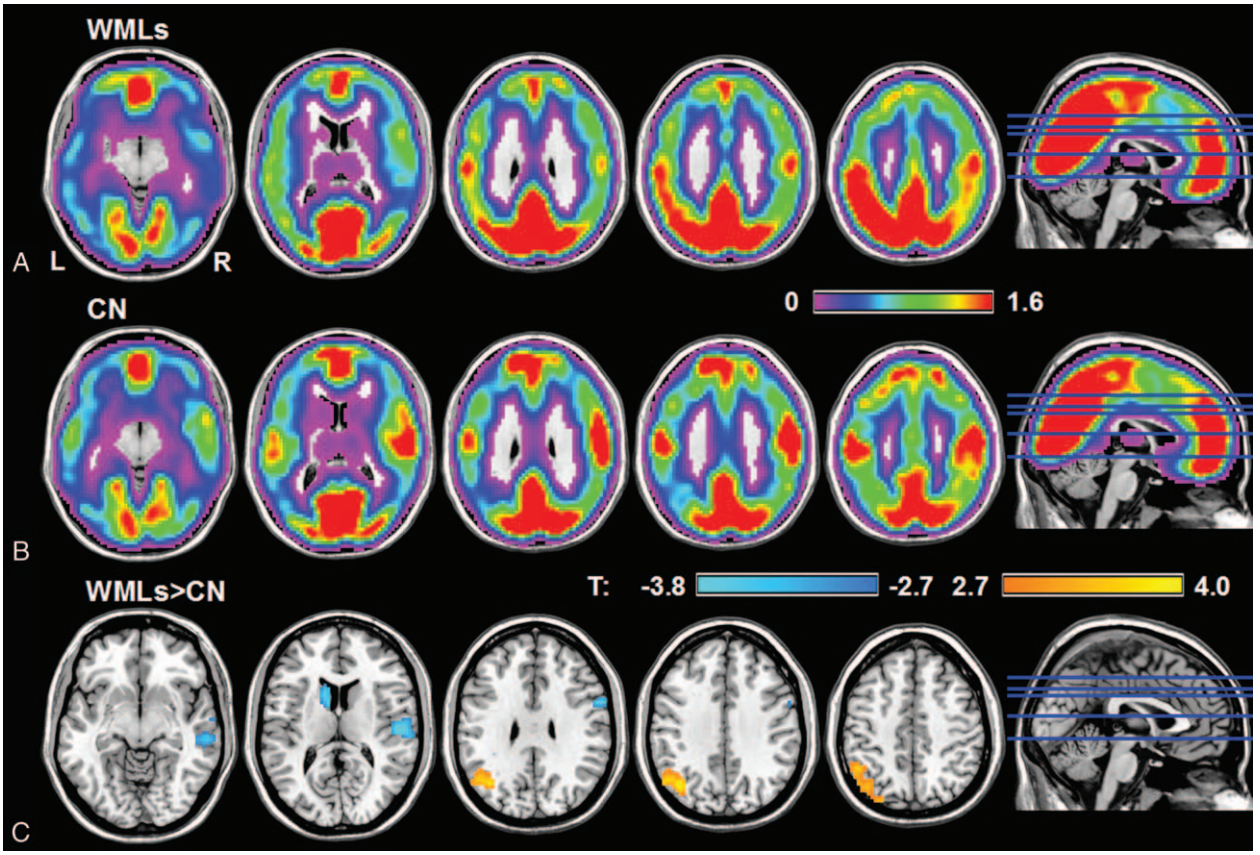

Figure 1. Distribution of short-range FCD within groups and statistical differences between groups ($P<0.05$, AlphaSim corrected). CN = controls, FCD = functional connectivity density, L = left, R = right, WML = white matter lesion.

corresponding to a corrected $P<0.05$. This correction was confined within the brain gray matter and determined by the Monte Carlo simulations performed by the AlphaSim program in the REST toolkit (http://sourceforge.net/projects/resting-fmri).

For each patient, the mean FCD of each cluster with significant group differences was extracted. A correlation analysis was then performed to test the association between FCD and cognitive test scores (MMSE scores and MoCA scores) in patients with ischemic WMLs.

3. Results

3.1. Demographic and clinical characteristics

The demographics and clinical characteristics of the participants are summarized in Table 1. There were no significant differences between the 2 groups in age, gender, educational level, and vascular risk factors. Compared with the control group, patients with ischemic WMLs showed significantly lower MMSE and MoCA scores, which indicated obvious cognitive impairment in the patient group.

3.2. Spatial distribution of the FCD

As shown in Figs. 1 and 2, the 2 groups exhibited similar FCD spatial distributions. The high short-range FCD was mainly distributed in the bilateral precuneus, cuneus, medial prefrontal cortex, occipital cortex, parietal cortex, and postcentral gyrus (Fig. 1A and B). The long-range FCD was also high in the bilateral posterior cingulate/precuneus, median cingulate gyrus, occipital cortex, parietal cortex, angular, middle temporal gyrus, and medial and dorsolateral prefrontal cortex (Fig. 2A and B). These regions with high FCD, namely brain hubs, are consistent with previous studies.[21,28]

3.3. Group comparisons

Figure 1C shows the short-range FCD differences between the 2 groups ($P<0.05$, AlphaSim corrected). Compared with the controls, the patients exhibited significantly decreased short-range FCD in the left caudate nucleus, the right middle and superior temporal gyrus, rolandic operculum, and precentral gyrus (PreCG); and increased short-range FCD in the left angular gyrus and inferior parietal gyrus. The details of the brain regions with significant short-range FCD differences are shown in Table 2.

As seen in Fig. 2C, the patients showed significantly increased long-range FCD mainly in the right PreCG and middle frontal gyrus (MFG, $P<0.05$, AlphaSim corrected). No significantly decreased long-range FCD was found in this study. The details of the brain regions with significant long-range FCD differences are shown in Table 3.

3.4. Correlation with cognitive performances

We performed Spearman correlations between the abnormal regions and cognitive test scores (MMSE and MoCA scores) in

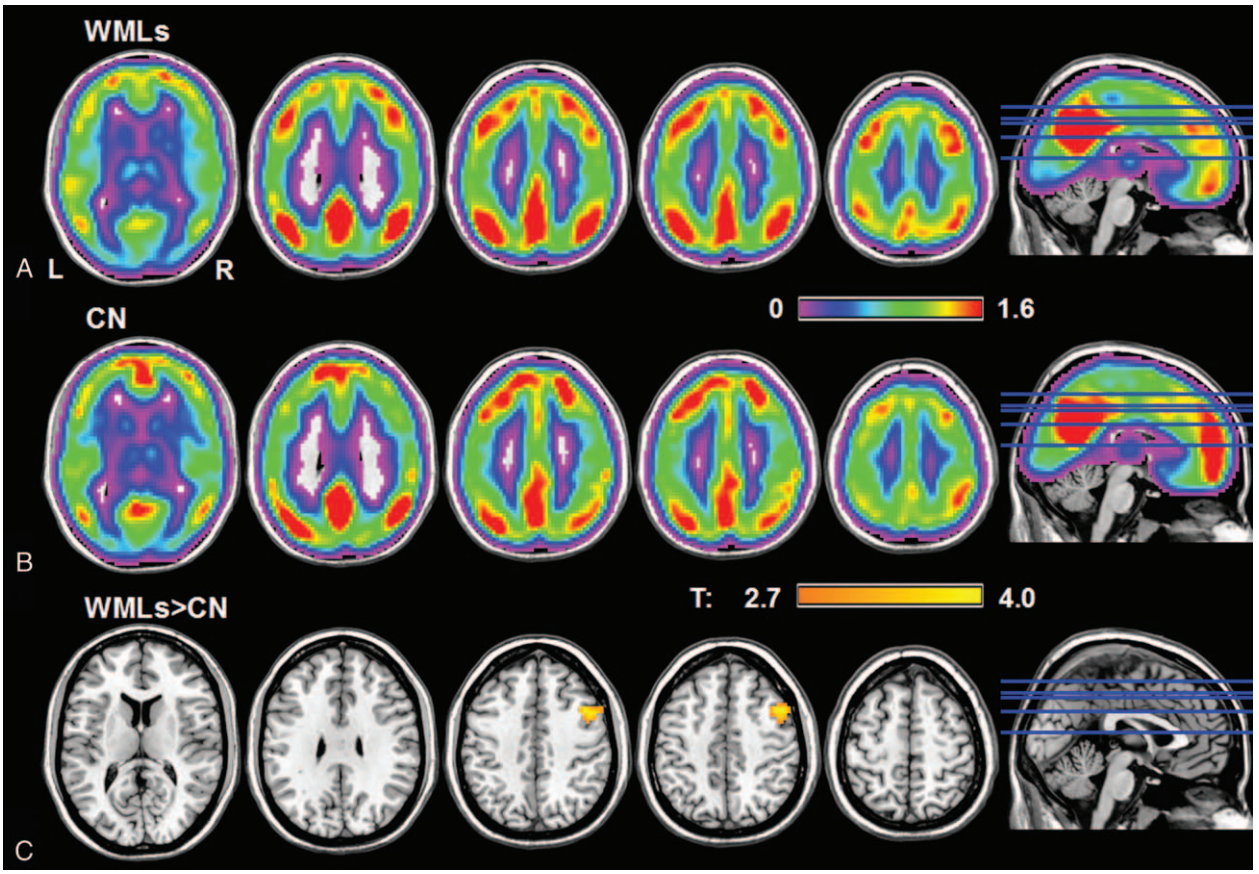

Figure 2. Distribution of long-range FCD within groups and the statistical differences between groups ($P<0.05$, AlphaSim corrected). CN=controls, FCD=functional connectivity density, L=left, R=right, WML=white matter lesion.

Table 2

Statistical significance of short-range functional connectivity density differences between patients with ischemic white matter lesions and controls.

Anatomical region	BA	MNI (x,y,z)*	Voxels	t†
Short-range FCD increased regions				
Angular gyrus, L	7/39	−39,−66,36	196	4.21
Inferior parietal gyrus, L	7/40	−51,−51,48	70	3.52
Short-range FCD decreased regions				
Middle temporal gyrus, R	20/21	63,−9,−15	126	−3.90
Superior temporal gyrus, R	22/48	54,−18,12	65	−3.94
Rolandic operculum, R	48	54,−18,15	53	−3.86
Caudate nucleus, L	–	−9,9,15	45	−3.91
Precentral gyrus, R	6	60,6,30	38	−3.68

BA = Brodmann area, FCD = functional connectivity density, L = left, MNI = Montreal Neurological Institute, R = right.
* Indicates coordinates of peak locations in the MNI space.
† Indicates the statistical value of peak voxel showing short-range FCD differences between the 2 groups. Positive *t* value represents increased short-range FCD, and negative *t* value represents decreased short-range FCD.

Table 3

Statistical significance of long-range functional connectivity density differences between patients with ischemic white matter lesions and controls.

Anatomical region	BA	MNI (x,y,z)*	Voxels	t†
Long-range FCD increased regions				
Middle frontal gyrus, R	9/44	45,12,45	50	4.27
Precentral gyrus, R	6	48,9,42	49	3.80

BA = Brodmann area, FCD = functional connectivity density, MNI = Montreal Neurological Institute, R = right.
* Indicates coordinates of peak locations in the MNI space.
† Indicates the statistical value of peak voxel showing long-range FCD differences between the 2 groups. Positive *t* value represents increased long-range FCD.

the patient group after removing potential outliers.[29] As seen in Fig. 3, the short-range FCD in the right PreCG and the long-range FCD in the right MFG showed positive correlations with MoCA scores, respectively ($P < 0.05$). No significant correlation was found between regions with altered FCD and MMSE scores.

4. Discussion

The present study employed a voxel-wise data-driven method to explore map changes in brain functional connectivity in patients with ischemic WMLs. The regions with altered FCD in patients with ischemic WMLs were mainly involved in cortical regions, including the temporal, inferior parietal, prefrontal and primary motor cortex, and subcortical regions such as caudate nucleus. In addition, regions in the prefrontal and motor cortex were correlated with cognitive test scores. The FCD changes in these regions represent an alteration of total number of functional connections between these regions and all other voxels in the whole brain, which reflect an alteration of information processing in these regions. Thus, our findings provide new insights into how WMLs affect cognitive function and behavioral performance.

4.1. Altered short-range FCD

WMLs probably diminish the efficiency of neural transmission and, consequently, functionally reduce cortical connectivity.[30] In the present study, we found regions with reduced number of short-range connections were mainly involved in temporal cortex (the right middle temporal gyrus, superior temporal gyrus, and rolandic operculum), subcortical region (the left caudate nucleus), and primary motor cortex (the right PreCG).

The middle temporal gyrus is part of extended dorsal attention system and is associated with top-down orienting of attention.[31,32] As a critical node of the brain's language network, the posterior middle temporal gyrus subserves the retrieval of lexical syntactic information as well as subsequent selection and integration of this information.[33,34] The activation of this region in response to ambiguous sentences may reflect demanding top-down processing for sentence comprehension,[35] and damage to this region is strongly associated with language comprehension and semantic deficits.[36] In addition, the superior temporal gyrus and rolandic operculum are also involved in speech and language recognition.[37] Recently, the right superior temporal gyrus and rolandic operculum showed altered gray matter volume in children who stutter relative to fluent children, indicating widespread anatomic abnormalities throughout the cortical network for speech motor control.[38] Furthermore, the right superior temporal gyrus is implicated in social cognition, as well as in processing and integrating different types of information to give appropriate response to the surrounding world.[39,40] Our results of reduced FCD in these regions may reflect insufficient top-down attention for language comprehension and information integration, which probably provide evidence from cortical functional connectivity perspective for previous finding of impaired ability in verbal fluency and information retrieval in patients with WMLs.[41]

The caudate nucleus, a critical structure of basal ganglia, has a primary role in behavioral and cognitive functions.[42,43] Animal lesion experiments suggest that the caudate nucleus contributes to body and limbs posture as well as the speed and accuracy of directed movements.[44] Moreover, the caudate nucleus is thought to mediate executive and emotional function, and lesions of this region will lead to executive function deficits and

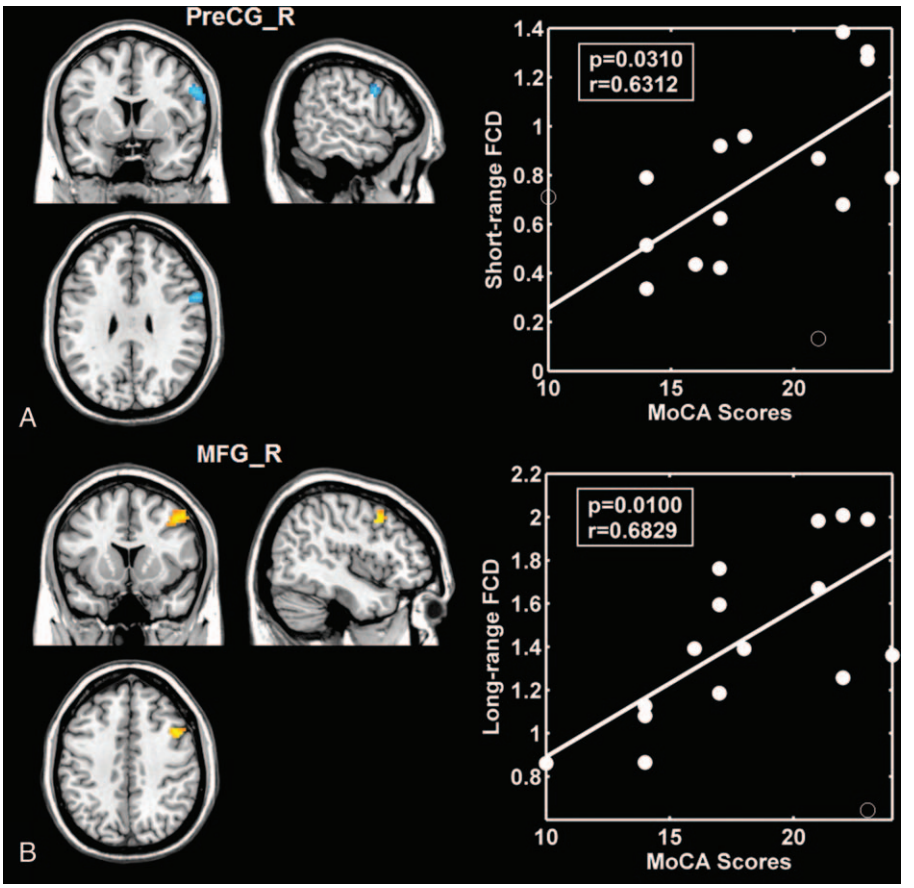

Figure 3. Correlations between regions with altered short- and long-range FCD and MoCA scores in patients with ischemic WMLs ($P < 0.05$). Spearman correlations were calculated over the data after removing outliers marked by circles. FCD = functional connectivity density, MFG = middle frontal gyrus, MoCA = Montreal Cognitive Assessment, PreCG = precentral gyrus, R = right, WML = white matter lesion.

inappropriate behavior.[42,45] Lewis et al[46] found that the decreased activity in the caudate nucleus was related to memory impairment in patients with Parkinson disease. Thus, the reduced FCD in the left caudate nucleus may account for gait disturbance, memory, and executive decline in patients with WMLs.[10,11,47]

The PreCG, also referred to as primary motor cortex, is involved in executing voluntary movements. In the present study, the reduced FCD in this region may explain gait disturbance in patients with WMLs, supporting the speculation of previous study that gait disturbance may be attributed to the disruptions in motor network.[47] Together with the result of caudate nucleus, our finding further supports that the basal ganglia-cortical loops play a vital role in gait impairment in patients with WMLs.[48] Besides, the short-range FCD in the right PreCG was positively correlated with MoCA scores, suggesting that the poorer the cognitive function is, the less local connections the right PreCG has, and the more serious the gait impairment in patients with WMLs is. This result is in favor of previous finding that balance and gait speed are affected by cognitive function.[49]

In addition, we found that the left inferior parietal cortex, including angular gyrus and inferior parietal gyrus, showed increased number of short-range connections in patients with WMLs. Previous studies have suggested that the inferior parietal cortex is part of a bottom-up attentional subsystem that mediates the automatic attentional resources to task-related information, especially information in episodic memory.[50,51] The activity of the inferior parietal cortex, particularly in the left hemisphere, is related to episodic memory retrieval,[50,52] and the left angular gyrus is consistently found to be involved in semantic and conceptual processing.[36,53] Our findings of increased number of local functional connections in the left inferior parietal cortex reflect a hyper bottom-up attention for memory retrieval and semantic processing, which may compensate for the insufficient top-down attention for language comprehension and information retrieval in patients with WMLs.

4.2. Increased long-range FCD

In the present study, regions with increased long-range FCD in patients with ischemic WMLs included the right PreCG and MFG. Results from animal and human studies have proved that the cerebral cortex possess structural and functional plasticity.[54,55] After a cortical injury, such as stroke, the cerebral cortex is capable of significant reorganization,[55] especially cortical areas distant from the injury.[56] It is interesting that the right PreCG showed both reduced short-range FCD and increased long-range FCD in this study. However, the specific locations were different. We suggest that the increased long-range FCD in the right precentral gyrus may reflect a strategy of cortical functional reorganization to compensate for local disruptions in motor cortex by recruiting more distant areas.[55,57] Since the frontal-subcortical circuits (the prefrontal cortex and caudate

nucleus) play an important role in executive function,[45] we speculate that the increased distant connections in the right MFG may represent a compensatory response to the reduced local connections in the caudate nucleus for executive decline in the patients with WMLs. Moreover, the positive correlation between long-range FCD in the MFG and MoCA scores indicates that the greater the compensation is, the better the cognitive function is, which may also provide evidence for our speculation.

Some limitations should be considered when interpreting the findings of the present study. First, our sample size was relatively small. Despite the small numbers of participants, statistically significant alterations in FCD were found. A large sample size in further studies is needed to confirm and extend this study. Second, as an exploratory study, only a single threshold was selected to calculate FCD maps. Future study may choose a range of thresholds to test the stability of the results. Finally, previous studies have found that the short- and long-range FCD are sensitive to normal aging and gender.[23,58] However, this has less influence on the understanding of our findings, since there were no significant age and gender differences between the 2 groups (see Table 1). Moreover, the age and gender were further regressed out as covariates during statistical analysis.

5. Conclusions

In summary, we investigated the changes in brain FCD in patients with ischemic WMLs. The regions with reduced short-range FCD were involved in temporal cortex, primary motor cortex, and subcortical region, indicating inadequate top-down attention, impaired motor, memory, and executive function in patients with ischemic WMLs. The increased short-range FCD in the inferior parietal cortex reflects a hyper bottom-up attention, which may compensate for the inadequate top-down attention for language comprehension and information retrieval in patients with WMLs. Moreover, the regions with increased long-range FCD were found in the prefrontal and primary motor cortex, which may reflect a strategy of cortical functional reorganization to compensate for motor and executive deficits by recruiting distant brain areas. This study provides new knowledge to understand how WMLs cause cognitive and motor decline from cortical functional connectivity perspective.

References

[1] Longstreth WTJr, Manolio TA, Arnold A, et al. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. Stroke 1996;27: 1274–82.

[2] Ylikoski A, Erkinjuntti T, Raininko R, et al. White matter hyperintensities on MRI in the neurologically nondiseased elderly. Analysis of cohorts of consecutive subjects aged 55 to 85 years living at home. Stroke 1995;26:1171–7.

[3] Hachinski VC, Potter P, Merskey H. Leuko-araiosis. Arch Neurol 1987; 44:21–3.

[4] Breteler MM, van Swieten JC, Bots ML, et al. Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: the Rotterdam Study. Neurology 1994;44:1246–52.

[5] Verhaaren BF, Vernooij MW, de Boer R, et al. High blood pressure and cerebral white matter lesion progression in the general population. Hypertension 2013;61:1354–9.

[6] van Swieten JC, Geyskes GG, Derix MM, et al. Hypertension in the elderly is associated with white matter lesions and cognitive decline. Ann Neurol 1991;30:825–30.

[7] Fazekas F, Niederkorn K, Schmidt R, et al. White matter signal abnormalities in normal individuals: correlation with carotid ultrasonography, cerebral blood flow measurements, and cerebrovascular risk factors. Stroke 1988;19:1285–8.

[8] O'Brien JT. Vascular cognitive impairment. Am J Geriatr Psychiatry 2006;14:724–33.

[9] Pantoni L, Poggesi A, Inzitari D. The relation between white-matter lesions and cognition. Curr Opin Neurol 2007;20:390–7.

[10] Kramer JH, Reed BR, Mungas D, et al. Executive dysfunction in subcortical ischaemic vascular disease. J Neurol Neurosurg Psychiatry 2002;72:217–20.

[11] Nordahl CW, Ranganath C, Yonelinas AP, et al. White matter changes compromise prefrontal cortex function in healthy elderly individuals. J Cogn Neurosci 2006;18:418–29.

[12] Viana-Baptista M, Bugalho P, Jordao C, et al. Cognitive function correlates with frontal white matter apparent diffusion coefficients in patients with leukoaraiosis. J Neurol 2008;255:360–6.

[13] Silbert LC, Nelson C, Howieson DB, et al. Impact of white matter hyperintensity volume progression on rate of cognitive and motor decline. Neurology 2008;71:108–13.

[14] Viana-Baptista M, Bugalho P, Jordao C, et al. Motor dysfunction correlates with frontal white matter ischemic changes in patients with leukoaraiosis. J Aging Res 2011;2011:950341.

[15] Meyer JS, Kawamura J, Terayama Y. White matter lesions in the elderly. J Neurol Sci 1992;110:1–7.

[16] Fazekas F, Kleinert R, Offenbacher H, et al. Pathologic correlates of incidental MRI white matter signal hyperintensities. Neurology 1993;43: 1683–9.

[17] Kim KW, MacFall JR, Payne ME. Classification of white matter lesions on magnetic resonance imaging in elderly persons. Biol Psychiatry 2008;64:273–80.

[18] Mesulam MM. Large-scale neurocognitive networks and distributed processing for attention, language, and memory. Ann Neurol 1990; 28:597–613.

[19] Ding X, Wu J, Zhou Z, et al. Specific locations within the white matter and cortex are involved in the cognitive impairments associated with periventricular white matter lesions (PWMLs). Behav Brain Res 2015; 289:9–18.

[20] van den Heuvel MP, Hulshoff Pol HE. Exploring the brain network: a review on resting-state fMRI functional connectivity. Eur Neuropsychopharmacol 2010;20:519–34.

[21] Tomasi D, Volkow ND. Functional connectivity density mapping. Proc Natl Acad Sci U S A 2010;107:9885–90.

[22] Tomasi D, Volkow ND. Abnormal functional connectivity in children with attention-deficit/hyperactivity disorder. Biol Psychiatry 2012;71: 443–50.

[23] Tomasi D, Volkow ND. Aging and functional brain networks. Mol Psychiatry 2012;17:471549-458.

[24] Power JD, Barnes KA, Snyder AZ, et al. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. NeuroImage 2012;59:2142–54.

[25] Van Dijk KR, Sabuncu MR, Buckner RL. The influence of head motion on intrinsic functional connectivity MRI. Neuroimage 2012;59: 431–8.

[26] Foerster BU, Tomasi D, Caparelli EC. Magnetic field shift due to mechanical vibration in functional magnetic resonance imaging. Magn Reson Med 2005;54:1261–7.

[27] Cordes D, Haughton VM, Arfanakis K, et al. Frequencies contributing to functional connectivity in the cerebral cortex in "resting-state" data. AJNR Am J Neuroradiol 2001;22:1326–33.

[28] Ding J, An D, Liao W, et al. Abnormal functional connectivity density in psychogenic non-epileptic seizures. Epilepsy Res 2014;108:1184–94.

[29] Schwarzkopf DS, De Haas B, Rees G. Better ways to improve standards in brain-behavior correlation analysis. Front Hum Neurosci 2012;6:200.

[30] Reed BR, Eberling JL, Mungas D, et al. Effects of white matter lesions and lacunes on cortical function. Arch Neurol 2004;61:1545–50.

[31] Gao W, Lin W. Frontal parietal control network regulates the anti-correlated default and dorsal attention networks. Hum Brain Mapp 2012;33:192–202.

[32] Fox MD, Corbetta M, Snyder AZ, et al. Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. Proc Natl Acad Sci U S A 2006;103:10046–51.

[33] Acheson DJ, Hagoort P. Stimulating the brain's language network: syntactic ambiguity resolution after TMS to the inferior frontal gyrus and middle temporal gyrus. J Cogn Neurosci 2013;25:1664–77.

[34] Snijders TM, Vosse T, Kempen G, et al. Retrieval and unification of syntactic structure in sentence comprehension: an FMRI study using word-category ambiguity. Cereb Cortex 2009;19:1493–503.

[35] Rodd JM, Johnsrude IS, Davis MH. Dissociating frontotemporal contributions to semantic ambiguity resolution in spoken sentences. Cereb Cortex 2012;22:1761–73.
[36] Binder JR, Desai RH, Graves WW, et al. Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. Cereb Cortex 2009;19:2767–96.
[37] Bigler ED, Mortensen S, Neeley ES, et al. Superior temporal gyrus, language function, and autism. Dev Neuropsychol 2007;31:217–38.
[38] Beal DS, Gracco VL, Brettschneider J, et al. A voxel-based morphometry (VBM) analysis of regional grey and white matter volume abnormalities within the speech production network of children who stutter. Cortex 2013;49:2151–61.
[39] Allison T, Puce A, McCarthy G. Social perception from visual cues: role of the STS region. Trends Cogn Sci 2000;4:267–78.
[40] Zilbovicius M, Meresse I, Chabane N, et al. Autism, the superior temporal sulcus and social perception. Trends Neurosci 2006;29: 359–66.
[41] Bolandzadeh N, Davis JC, Tam R, et al. The association between cognitive function and white matter lesion location in older adults: a systematic review. BMC Neurol 2012;12:126.
[42] Mendez MF, Adams NL, Lewandowski KS. Neurobehavioral changes associated with caudate lesions. Neurology 1989;39:349–54.
[43] Narumoto J, Matsushima N, Oka S, et al. Neurobehavioral changes associated with bilateral caudate nucleus infarctions. Psychiatry Clin Neurosci 2005;59:109–10.
[44] Villablanca JR. Why do we have a caudate nucleus? Acta Neurobiol Exp 2010;70:95–105.
[45] Cummings JL. Frontal-subcortical circuits and human behavior. Arch Neurol 1993;50:873–80.
[46] Lewis SJ, Dove A, Robbins TW, et al. Cognitive impairments in early Parkinson's disease are accompanied by reductions in activity in frontostriatal neural circuitry. J Neurosci 2003;23:6351–6.
[47] Xiong YY, Mok V. Age-related white matter changes. J Aging Res 2011; 2011:617927.
[48] Iseki K, Hanakawa T, Hashikawa K, et al. Gait disturbance associated with white matter changes: a gait analysis and blood flow study. Neuroimage 2010;49:1659–66.
[49] Starr JM, Leaper SA, Murray AD, et al. Brain white matter lesions detected by magnetic resonance [correction of resosnance] imaging are associated with balance and gait speed. J Neurol Neurosurg Psychiatry 2003;74:94–8.
[50] Cabeza R, Ciaramelli E, Olson IR, et al. The parietal cortex and episodic memory: an attentional account. Nat Rev Neurosci 2008;9:613–25.
[51] Ciaramelli E, Grady CL, Moscovitch M. Top-down and bottom-up attention to memory: a hypothesis (AtoM) on the role of the posterior parietal cortex in memory retrieval. Neuropsychologia 2008;46: 1828–51.
[52] Vilberg KL, Rugg MD. Memory retrieval and the parietal cortex: a review of evidence from a dual-process perspective. Neuropsychologia 2008;46:1787–99.
[53] Seghier ML. The angular gyrus: multiple functions and multiple subdivisions. Neuroscientist 2013;19:43–61.
[54] Buonomano DV, Merzenich MM. Cortical plasticity: from synapses to maps. Ann Rev Neurosci 1998;21:149–86.
[55] Nudo RJ, Wise BM, SiFuentes F, et al. Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. Science 1996;272:1791–4.
[56] Dancause N, Barbay S, Frost SB, et al. Extensive cortical rewiring after brain injury. J Neurosci 2005;25:10167–79.
[57] Chollet F, DiPiero V, Wise RJ, et al. The functional anatomy of motor recovery after stroke in humans: a study with positron emission tomography. Ann Neurol 1991;29:63–71.
[58] Tomasi D, Volkow ND. Gender differences in brain functional connectivity density. Hum Brain Mapp 2012;33:849–60.