Original Paper

Neuro-degenerative Diseases

Neurodegener Dis 2015;15:322–330
DOI: 10.1159/000435918

Received: November 20, 2014
Accepted after revision: June 12, 2015
Published online: August 20, 2015

Breakdown of Sensorimotor Network Communication in Leukoaraiosis

Xia Wu[a, b] Youzhi Lai[b] Yumei Zhang[c] Li Yao[a, b] Xiaotong Wen[d]

[a]State Key Laboratory of Cognitive Neuroscience and Learning, [b]College of Information Science and Technology, Beijing Normal University, [c]Neurology Department, Beijing Tiantan Hospital Affiliated with Capital Medical University, and [d]Department of Psychology, Renmin University of China, Beijing, China

Key Words

Leukoaraiosis · Sensorimotor network · Sensory-motor integration · Resting-state fMRI · Functional connectivity

Abstract

Background: Leukoaraiosis (LA) patients may suffer from sensorimotor dysfunctions. The relationship between behavioral disturbances and changes in the sensorimotor network (SMN) has not been thoroughly elucidated. ***Objective:*** This study investigated the hypothesized breakdown of communication of SMN and its behavioral consequences in LA. ***Methods:*** Fluid-attenuated inversion recovery (FLAIR) images, resting-state functional magnetic resonance images (fMRI) and behavioral data were collected from 30 LA patients and 26 healthy individuals (normal controls, NC). The subjects were grouped according to LA severity, as indicated by their FLAIR images. Group independent component analysis was applied to the fMRI data to map the functional connectivity of SMN for NC and LA patients. A whole-brain, voxel-wise analysis was employed to investigate the functional connectivity alteration of SMN in LA. The relationships between LA severity, functional connectivity alteration of the SMN and behavioral clinical symptoms were examined by correlation analysis. ***Results:*** The right cingulate motor area (rCMA), left posterior insula and left ventral premotor area showed attenuated functional connectivity in the LA patients. The extent of the attenuation was related to the severity of the disease. Furthermore, the attenuation in the rCMA was associated with worse sensorimotor integration performance. ***Conclusions:*** These results suggest that LA impairs sensorimotor integration by interfering with the communication or coordination of these aforementioned regions related to the SMN.

Introduction

Leukoaraiosis (LA) is a type of white matter lesion frequently revealed as signal hyperintensities on T_2 magnetic resonance imaging (MRI) of aging individuals with vascular dementia [1, 2]. LA patients may suffer from cognitive dysfunctions and depression as well as a variety of behavioral deficits, such as disturbed micturition and gait, balance disorders and even disability in daily life [3, 4]. Sensorimotor disturbance is an early and the most pervasive symptom [5–7] and has become a research focus and a key issue for the clinical treatment of LA [8–12]. However, the relationship between the behavioral disturbances and certain cerebral changes in LA are unclear.

Dr. Xiaotong Wen
Department of Psychology, Renmin University of China
59 Zhongguancun Ave., Haidian
Beijing 100872 (China)
E-Mail wenxiaotong@gmail.com

Previous studies suggested that stenosis or occlusion of small cerebral vessels with acute or chronic ischemia plays a central role in the pathogenesis of LA [13]. Additionally, some evidence suggests that ischemic injury in LA may induce selective visible structural alterations limited to the cerebral white matter, while the gray matter regions generally remain intact [14, 15], indicating that functional deficits may be associated with the breakdown of the communication between the cortical regions rather than due to damage to these regions. A noninvasive method for examining this issue is functional connectivity analysis based on functional MRI (fMRI). To date, many LA studies assessing functional connectivity change have focused on alteration of the default-mode network and reveal that the abnormal functional connectivity caused by LA may be associated with several cognitive impairments [16, 17]. Investigation of impairment of the functional connectivity of the sensorimotor system and the behavioral consequences of this impairment is essential for understanding the neural substrates of sensorimotor dysfunction in LA [18], but research has rarely been conducted in this area. This study aimed to explore the neural substrates of sensorimotor dysfunction in LA by examining the functional connectivity change to the brain's sensorimotor network (SMN) and the behavioral consequences of this change.

The SMN is mainly composed of the pre- and post-central gyri extending from the superior bank of the Sylvian fissure to the medial wall of the interhemispheric fissure and supplementary motor area [19]. These areas are involved not only in lower-order motor functions but also in higher cognitive functions, such as sensorimotor transformations, action understanding and decisions regarding action execution; they interact and coordinate with each other to accomplish complex sensorimotor tasks [5]. Given the clinical symptoms and the structural alterations revealed by previous studies [20, 21], it was hypothesized that LA impairs sensorimotor functions by breaking down the communication and coordination of the SMN.

We tested this hypothesis in this study. Fluid-attenuated inversion recovery (FLAIR) images, resting-state fMRI data and behavioral data were collected from 30 LA patients and 26 healthy individuals (normal controls, NC). The subjects were grouped according to LA severity as indicated by their FLAIR images. Group independent component (IC) analysis was applied to the fMRI data to map the functional connectivity of the SMN for normal subjects and patients. A whole-brain, voxel-wise analysis was employed to investigate the functional connectivity alteration of the SMN in LA. The relationships between LA severity, functional connectivity alteration of the SMN and behavioral clinical symptoms were examined by correlation analysis.

Table 1. Demographic characteristics of participants

	NC	LA	p value
Gender, male/female	15/11	20/10	0.489
Age, years	54±9.13	58±6.88	0.101
Years of schooling	12±2.82	11.3±2.66	0.356

Pearson's χ^2 test was used for gender comparison and Student's t test for age and schooling comparison. Significance level was set at $p < 0.05$.

Table 2. Age, schooling and MoCA score of subgroups of different LA grades

	Age, years	Years of schooling	MoCA score
NC (n = 26)	54±9.13	12±2.82	27.2±2.11
LA grade 1 (n = 13)	57±7.01	11.2±2.12	24.9±2.23
LA grade 2 (n = 10)	59±4.52	11.3±2.37	21.8±4.09
LA grade 3 (n = 7)	60±6.57	11.3±2.66	20.9±4.12
p value[a]	p_{01} = 0.356 p_{12} = 0.283 p_{23} = 0.992	p_{01} = 0.452 p_{12} = 0.756 p_{23} = 0.879	p_{01} = 0.004 p_{12} = 0.029 p_{23} = 0.335

Comparisons between groups were performed for age, schooling and MoCA score using a Student's t test.

[a] Subscript numbers refer to LA grade, e.g. p_{01} denotes the significance of the difference between NC and LA grade 1, p_{12} denotes the significance of the difference between LA grade 1 and LA grade 2.

Methods

Subjects

Thirty LA patients (aged 58 ± 6.88 years; schooling of 11.3 ± 2.66 years; 10 females) and 26 age-matched NC (aged 54 ± 9.13 years; schooling of 12 ± 2.82 years; 11 females) participated in this study at the Tiantan Hospital, Beijing, China. There was no significant difference between NC and patients regarding the above demographic characteristics (table 1). The subjects were all right-handed, had no history of mental illness or brain disease other than vascular dementia, and no use of cognitive or antipsychotic medication such as cholinesterase inhibitors, NMDA receptor antagonists and tranquilizers. Written informed consent was obtained from every subject before the experiment, and the study was approved by the Institutional Review Board of the Tiantan Hospital. MRI was performed to ensure that the subjects had no clinically silent infarcts or lacunae in the brain. An expe-

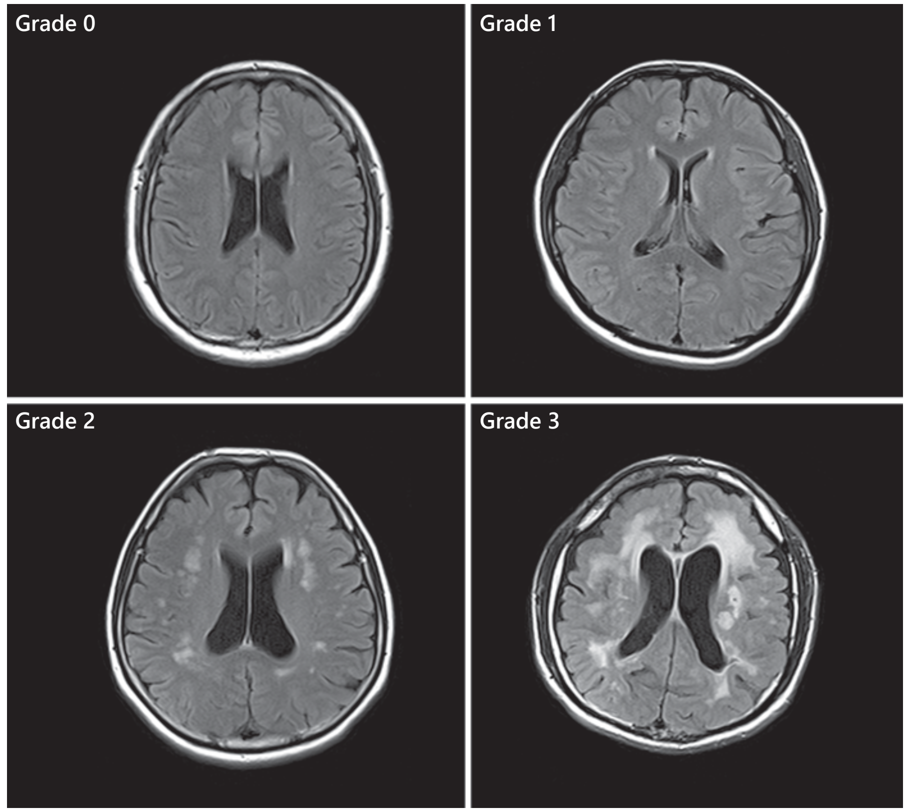

Fig. 1. Examples of FLAIR images of representative subjects with different LA grades. For subjects with grade 0, no periventricular white matter damage was identified, while for subjects with higher grades, damage was visible. The grade 0 image was from a subject in the NC group.

Table 3. Means and standard deviations of MoCA subscores

	NC	LA grade 1	LA grade 2	LA grade 3
Visuospatial/executive	4.4±1.0	4.3±0.8	3.4±1.2	2.9±1.5
Naming	3±0	2.7±0.7	2.7±0.6	2.7±0.5
Delayed recall	3.7±1.2	2.3±1.6	1.9±1.3	1.7±0.9
Attention	5.5±0.7	5.4±0.8	4.7±1.5	5±1.2
Abstraction	1.6±0.5	1.9±0.8	1.2±0.9	0.9±0.6
Language	2.6±0.5	2±0.7	1.9±0.5	1.7±0.5
Orientation	5.9±0.3	6±0	5.8±0.4	5.4±0.7

rienced neuroradiologist at the hospital inspected the FLAIR scans and assigned each subject an LA grade according to the Fazekas scale of 0–3, with 0 denoting no lesion and 3 denoting a very severe lesion [22, 23]. The grading results showed that all 26 subjects in the NC group had a grade of 0. In the LA group, 13 subjects had a grade of 1, 10 had a grade of 2 and the remaining 7 subjects had a grade of 3 (table 2). Examples of the FLAIR images of representative subjects with different LA grades are shown in figure 1. No significant difference between subgroups was found in the demographic characteristics (i.e. age and schooling; table 2).

Each subject performed a Montreal Cognitive Assessment (MoCA) test to assess their cognitive performance. The test included alternating trail-making and visuoconstructional tasks, which assessed the visuospatial/executive ability of the subjects in relation to sensorimotor integration. Please see table 2 for the MoCA scores and table 3 for the MoCA subscores for each subject group.

Image Acquisition

All FLAIR images and fMRI data were acquired using a 3-tesla Siemens whole-body MRI system at the Tiantan Hospital. The subjects were instructed to rest and keep their eyes closed without thinking about anything in particular during the scan. Sedation was not used for any subjects. The resting-state functional scans were acquired with a T_2-weighted echo-planar imaging sequence (echo time 30 ms; repetition time 2,480 ms; flip angle 90°, 36 axial slices in each volume; field of view 256 × 256 mm^2; matrix size 64 × 64; slice thickness 3 mm; voxel size 3 × 3 × 4 mm^3). For each subject, 240 volumes were collected (9 min and 55 s). The FLAIR images were acquired using a spin-echo\inversion-recovery scanning sequence (slice thickness 5 mm; repetition time 8,000 ms; echo time 94 ms; inversion time 2,500 ms; percent phase field of view 87.5 mm; flip angle 150°; matrix size 256 × 224).

Image Preprocessing

Image preprocessing was performed using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm). For each subject, the first 10 volumes were discarded to eliminate the transient effects. The remaining 230 volumes were then preprocessed using slice-timing, motion correction, normalization to the Montreal

Neurological Institute template [24] and resampling into a 3 × 3 × 3 mm^3 per voxel resolution. Subjects with head motion exceeding 2 mm or 2° during scanning were excluded. In this study, no subject's head motion exceeded that range, so noone was excluded. The normalized data were smoothed by a Gaussian kernel with the full width set at a half maximum of 6 mm.

Group Functional Connectivity Analysis

A group functional connectivity analysis was performed using GIFT Toolbox (http://icatb.sourceforge.net) to identify the SMN for each group. The analysis procedure included principle component analysis, IC analysis separation and back-reconstruction [25, 26]. First, the data for each subject were dimension-reduced using principle component analysis. The optimal number of ICs was estimated as 44, based on the minimum description length method provided by GIFT Toolbox. Second, the data for all subjects were concatenated. Dimension reduction was performed again according to the optimal numbers determined by principle component analysis. The data were then decomposed using IC analysis based on the extended infomax algorithm. After IC analysis separation, the ICs corresponding to the SMN activity and its time courses for all subjects were used for back-reconstruction of the IC and time course of each subject [26].

To quantitatively determine the IC that best represented the SMN, an SMN template was developed based on a set of regions reported previously [19, 25], and the spatial correlation method was used to quantitatively evaluate how well the IC maps for each group matched the template [27]; the map that best matched was considered responsible for the SMN. The group IC maps were also double-checked by careful visual inspection. Finally, the component corresponding to the best-fit was designated as the SMN for each subject to yield the individual's map, which was also visually inspected as a third check. Each individual's map was Fisher-transformed to yield a z-map depicting the individual's SMN functional connectivity, namely, the individual functional connectivity map of the SMN. A one-sample Student's t test was then performed within each group to generate the SMN group functional connectivity map.

Selection of Regions of Interests with Altered Functional Connectivity in LA

To identify regions where functional connectivity was significantly altered in LA, we generated a resting-state functional connectivity difference map. In this analysis, we first generated a binary SMN mask for each group, using a threshold for the SMN group functional connectivity map of $p < 0.05$ (FWE-corrected). The union of the SMN masks of the LA and NC groups was defined as the explicit mask. Second, within the explicit mask, a voxel-wise two-sample t test was performed between the individual SMN map of the LA patients and those of the NC, in order to yield a resting-state functional connectivity difference map. The regions that showed significant differences between the 2 groups ($p < 0.05$, FDR-corrected) were selected as the regions of interest (ROIs) for the following analyses.

Correlation Analysis between LA Symptoms and Changes in Functional Connectivity

For each individual's SMN map, the functional connectivity index of a ROI was calculated by averaging the z-values of the voxels in that ROI. The Spearman rank partial-correlation analysis was performed to assess the relationship between LA grade and functional connectivity index across all subjects with adjustment for age as a controlling random variable [28]. The same correlation analysis was performed between the ROI functional connectivity index and the MoCA subscore of the visuospatial/executive ability test, which included 1 task of alternating trail-making and 2 visuoconstructional tasks, including drawing a clock and a 3-dimensional cube. The subscore reflected the sensorimotor integration ability. A relationship was identified only when the correlation was significant ($p < 0.05$, after FWE correction). Although the other 7 MoCA subscores (i.e. for naming, attention, language, memory, abstraction, delayed recall and orientation) were not the focus of this study, the relationship between each subscore and the functional connectivity change of the SMN was also tested for validation. Additionally, correlations between MoCA score/subscore and LA grade were also examined.

Results

Functional Connectivity of SMN in the NC and LA Groups

The functional connectivity map of the SMN in the LA and NC groups (fig. 2) both included the pre- and post-central gyri extending from the superior bank of the Sylvian fissure to the medial wall of the interhemispheric fissure and the supplementary motor area and cingulate motor area (CMA) [19]. Differences between the up-threshold maps of both NC and LA patients were notable by visual inspection. For the LA group, the functional connectivity strength was weaker and the map was more diffuse than that of the NC group.

ROIs with Functional Connectivity Alteration in LA Group

Comparing the SMN map of the NC with that of the LA group (LA < NC, see Methods section for more details), we found that LA patients had significantly decreased functional connectivity in the right CMA (rCMA), left posterior insula (LPI) and left ventral premotor area (LPMV; FDR $p < 0.05$; fig. 3; table 4). These clusters were selected as the ROIs for the following analyses. No significant cluster was found using reverse contrast (LA > NC).

Relationship between Functional Connectivity and LA Severity

For each ROI, we examined the relationship between LA grade and functional connectivity using the Spearman rank partial-correlation analysis across subjects (fig. 4).

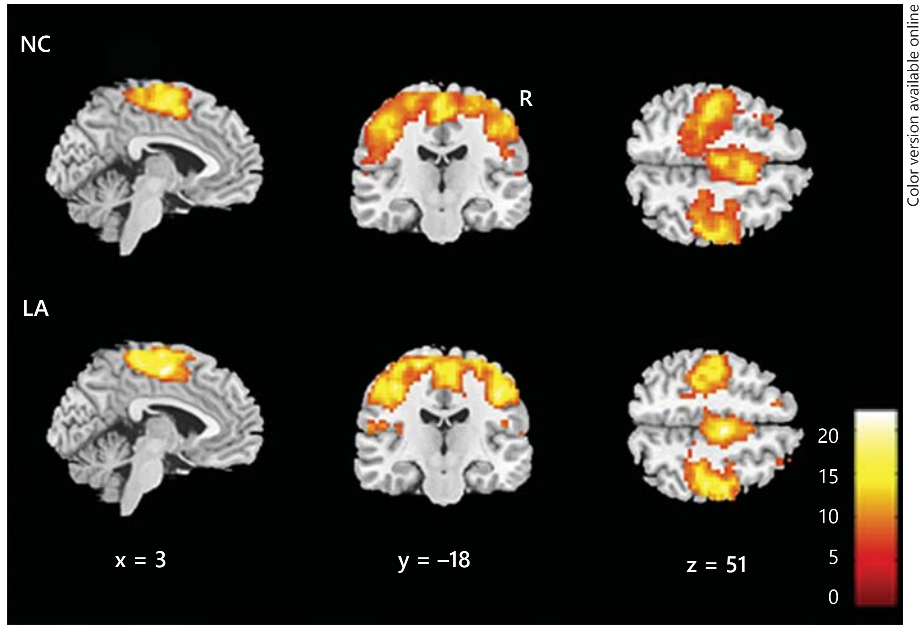

Fig. 2. Functional connectivity map of SMN in the LA and NC groups (one-sample t test; $p < 0.05$; FWE-corrected). R = Right hemisphere.

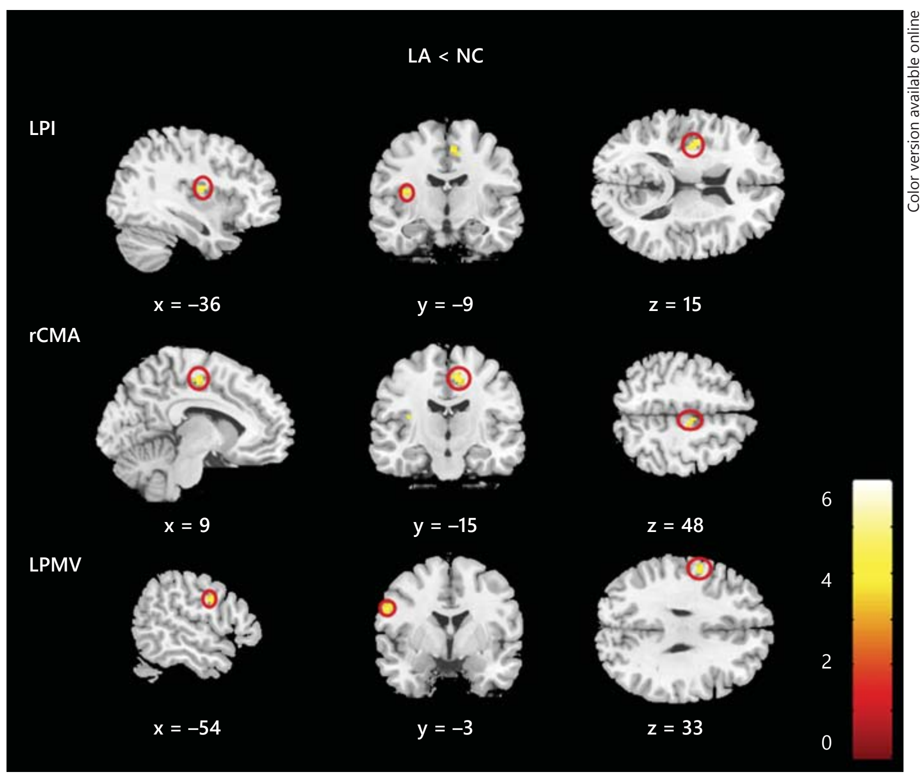

Fig. 3. Regions show the decreased functional connectivity index of SMN in LA patients (LA < NC; two-sample t test; FDR $p < 0.05$).

The results showed that the functional connectivity index in the rCMA, LPI and LPMV were negatively correlated with LA grade (CMA: $r = -0.485$, $p < 0.001$; LPI: $r = -0.536$, $p < 0.0001$; LPMV: $r = -0.454$, $p < 0.002$; all data underwent FWE correction).

Relationship between Functional Connectivity and Sensorimotor Integration Performance

Using the Spearman rank partial-correlation analysis across the LA patients, we found a significant correlation only between the rCMA functional connectivity index

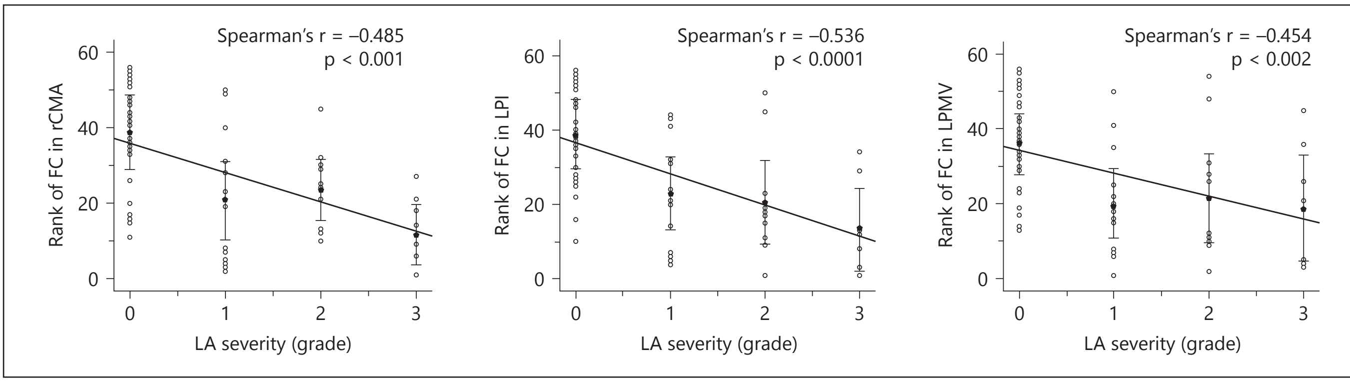

Fig. 4. Relationship between LA severity and ROI functional connectivity (FC) rank. The Spearman rank partial-correlation coefficient (r) and statistical significance (p value, FWE-corrected) are presented. Mean functional connectivity rank and error bars for each group are superimposed. The solid spot is the mean rank of the functional connectivity.

Table 4. Regions demonstrating reduced functional connectivity of SMN in LA

Brain region	Cluster size, voxels	BA	T	p_{FDR}	MNI coordinates		
					x	y	z
LPI	13	13	4.79	0.038	–42	–6	15
rCMA	18	6	4.60	0.041	6	–15	51
LPMV	15	6	4.39	0.041	–54	–3	33

LA < NC; Two-sample t test; FDR p < 0.05. BA = Brodmann area; MNI = Montreal Neurological Institute.

and the MoCA subscore of the visuospatial/executive test ($r = 0.43$, $p < 0.01$, FWE corrected; fig. 5). Overall, the weaker functional connectivity of the rCMA was associated with worse sensorimotor integration performance in the LA group. No correlation was found between functional connectivity and the other 7 MoCA subscores.

Relationship between LA Severity and Behavioral Performance

We calculated the partial Spearman correlations between LA grade and MoCA score/subscores. All of them, except the attention score, were significantly correlated with LA grade and all correlations were negative (table 5).

Discussion

By applying group ICA to the resting-state fMRI data, we obtained the functional connectivity map of the SMN [29]. Based on the SMN map, we identified the ROIs with significantly changed functional connectivity in the LA group. Then, for the defined ROI, the relationships between functional connectivity change, LA severity and behavioral performance were examined. We reported 3 main results. First, functional connectivity was significantly attenuated in the rCMA, LPI, and LPMV in LA patients. Second, for these regions, severe LA was associated with more attenuated functional connectivity of the SMN. Third, the weaker functional connectivity of the SMN in these regions was associated with worse performance on the MoCA visuospatial/executive test, indicating that the decreased functional connectivity in the LA-affected regions may cause impaired visuospatial-motor integration [30, 31].

Reduced Communication between SMN Regions

The group IC map of the SMN that we selected was highly consistent with the previously proposed SMN spatial pattern [19]. The functional connectivity maps of the SMN that we obtained were also consistent with the activation map of the supplemetary motor area identified us-

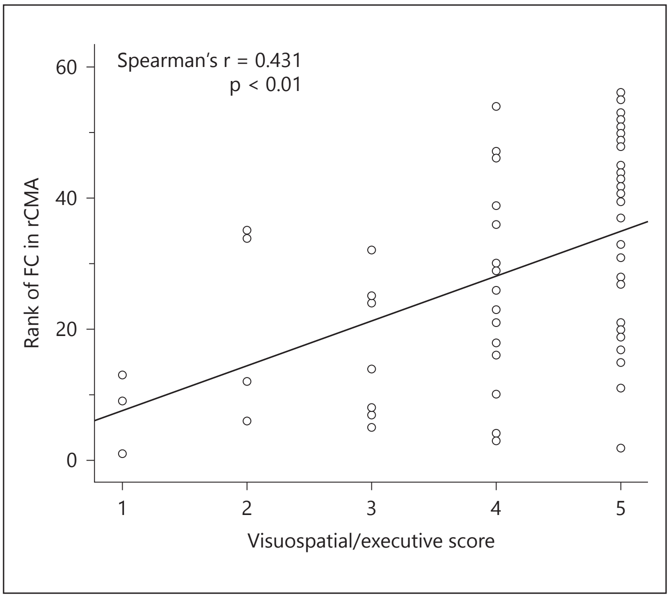

Fig. 5. Relationship between behavioral performance and functional connectivity rank of rCMA. The Spearman rank partial-correlation coefficient (r) and statistical significance (p value, FWE-corrected) are presented.

Table 5. Correlation between LA severity and MoCA score/subscores

	LA grade	
	Spearman's r	p value
MoCA	–0.6391	<0.0001
Visuospatial/executive	–0.3940	0.0029
Naming	–0.3308	0.0136
Delayed recall	–0.5503	<0.0001
Attention	–0.2117	0.1208
Abstraction	–0.3267	0.0149
Language	–0.5347	<0.0001
Orientation	–0.3885	0.0034

ing bimanual motor tasks [29]. The SMN map for the LA group was weaker and more diffuse than that of the NC group, indicating attenuated coordination of the postulated SMN regions in the LA group.

CMA activities are thought to be important for multiple behavioral factors, ranging from the retrieval and processing of associative visual signals to the planning and execution of instructions [32]. Previous anatomical studies have revealed that the CMA receives input from a variety of sensory association and limbic areas, including the amygdala, parahippocampal gyrus, parietal association cortex, temporal pole, insular cortex and claustrum, and the connections between these areas are implicated in the perceptual and limbic information processing that occurs in the CMA [32–34]. The CMA also has output to the primary motor cortex and premotor areas, including the PMV [35]. The neurons in the PMV are primarily involved in receiving visuospatial signals and specifying the spatial location of the target to be reached [36]. The LPI is reciprocally connected to the primary and secondary sensory cortices and receives input from the ventral posterior inferior thalamus nucleus, which conveys input from the spine [37, 38]. Given the above information, the connections between the rCMA, LPMV and LPI appeared to be particularly dedicated to sensorimotor transformation and integration in close collaboration. In our study, the decreased functional connectivity values in the rCMA, LPMV and LPI indicated that communication between them was impaired by LA-related damage [39]. According to our correlation results of functional connectivity and LA severity, impairment in functional connectivity is positively correlated with the extent of ischemic injury in LA. Overall, structural damage to the periventricular white matter (fig. 1) leads to breakdown of the connections between regions important for sensorimotor integration.

Behavioral Consequences of Functional Connectivity Decline in CMA

Although some anatomical studies regarding CMA connections have been conducted [40], the functional role of CMA remains unclear. Based on the established anatomical connectivity, some researchers hypothesize that CMA is a pivotal area for gathering sensory information that originates from multiple brain areas like the frontoparietal association and the limbic areas, and for delivering the specific intention for action to the premotor and parietal areas [35]. Our results showed a significant positive correlation between the rCMA functional connectivity index and the subscore of the visuospatial/executive ability test. In other words, if rCMA activity related to SMN communication is disturbed by LA, the sensorimotor integration performance of patients is impaired. The visuospatial/executive ability test includes the following tasks: trail-making, drawing a clock and drawing a 3-dimensional cube. These tasks demand sensorimotor integration [41, 42], including transforming sensory coordinates to motor coordinates, efference copy and internal modeling. The SMN regions have to cooperate closely to accomplish these tasks. The results of this study were consistent with the theory that decreased connectivity in sensorimotor integration regions plays a role in the etiology of movement disorders [43], suggesting a central role for CMA in SMN communication.

In this study, the observed functional connectivity decrease in the CMA of LA patients was lateralized to the right hemisphere. Previous studies observed a mild right lateralization of the visuomotor integration network for the connections with the superior temporal cortex and the occipital cortex [44]. The hemispheric asymmetry in our results agreed with those previous findings and also suggested a role for the rCMA in sensorimotor integration, which is impaired by LA.

Our analysis shows that visuospatial/executive ability was not the only function affected by LA. The MoCA total score and most of the other subscores were also negatively correlated with LA severity (table 5). These results were also consistent with the previous reports that LA may be related to multiple functional declines [3, 4]. However, only the visuospatial/executive score (trail-making and visuoconstruction) was significantly correlated with the functional connectivity index for the CMA of the SMN (fig. 5), indicating a relationship between the specific observed behavioral decline and alteration to that particular brain functional network.

Methodology Considerations and Limitations

Some of the methods utilized in this study require improvement, and the study results require confirmation in future studies. First, the correlation analysis was performed across subjects, and LA patients were in different stages at the same time points. A longitudinal study that follows subjects from before the presentation of LA and through its different stages may provide further insights into how an individual's SMN communication is gradually disrupted as LA develops. Second, in order to further explore the functional significance of the SMN regions like the CMA and the interference in their functions by LA, fiber tracking techniques, such as diffusion-tensor imaging, may be an option in future studies.

Conclusions

Our results suggest that LA interferes with the communication and coordination of several brain regions in the SMN, including the rCMA, LPI and LPMV, which are essential for sensorimotor integration. The breakdown of communication between these regions is associated with degraded behavioral performance.

Acknowledgements

This work was supported by International Cooperation and Exchange of the National Natural Science Foundation of China (61210001), the general Program of National Natural Science Foundation of China (61222113), Program for New Century Excellent Talents in University (NCET-12-0056), the Fundamental Research Funds for Central Universities, the Youth Program of National Natural Science Foundation of China (31400973), Funds for Scientific Research of Renmin University of China (14XNLF11), The Key Program of the National Social Sciences Program Fundation (13&ZD155).

Disclosure Statement

The authors declare that they have no conflicts of interest.

References

1 Bowler J: The concept of vascular cognitive impairment. J Neurol Sci 2002;203:11–15.

2 Román GC, Royall DR: Executive control function: a rational basis for the diagnosis of vascular dementia. Alzheimer Dis Assoc Disord 1999;13:S69–S80.

3 Wu Z, Song B, Gao Y, Fang H, Xu Y: Leukoaraiosis and stroke. Life Sci J 2014;11:383–387.

4 Jokinen H, Schmidt R, Ropele S, Fazekas F, Gouw AA, Barkhof F, Scheltens P, Madureira S, Verdelho A, Ferro JM, Wallin A, Poggesi A, Inzitari D, Pantoni L, Erkinjuntti T, Group LS: Diffusion changes predict cognitive and functional outcome: the LADIS study. Ann Neurol 2013;73:576–583.

5 Rizzolatti G, Luppino G: The cortical motor system. Neuron 2001;31:889–901.

6 Kalinosky BT, Schindler-Ivens S, Schmit BD: White matter structural connectivity is associated with sensorimotor function in stroke survivors. NeuroImage Clin 2013;2:767–781.

7 Cárdenas-Morales L, Volz LJ, Michely J, Rehme AK, Pool E-M, Nettekoven C, Eickhoff SB, Fink GR, Grefkes C: Network connectivity and individual responses to brain stimulation in the human motor system. Cereb Cortex 2014;24:1697–1707.

8 O'Sullivan M, Morris R, Huckstep B, Jones D, Williams S, Markus H: Diffusion tensor MRI correlates with executive dysfunction in patients with ischaemic leukoaraiosis. J Neurol Neurosurg Psychiatry 2004;75:441–447.

9 Szolnoki Z, Kondacs A, Mandi Y, Somogyvari F: A genetic variant in cytoskeleton motors amplifies susceptibility to leukoaraiosis in hypertensive smokers: gene-environmental interactions behind vascular white matter demyelinization. J Mol Neurosci 2007;33:173–179.

10 Viana-Baptista M, Bugalho P, Jordão C, Ribeiro O, Esperança-Pina JA, Ferro J: Motor dysfunction correlates with frontal white matter ischemic changes in patients with leukoaraiosis. J Aging Res 2011;2011:950341.

11 Baezner H, Blahak C, Poggesi A, Pantoni L, Inzitari D, Chabriat H, Erkinjuntti T, Fazekas F, Ferro J, Langhorne P: Association of gait and balance disorders with age-related white matter changes: the LADIS study. Neurology 2008;70:935–942.
12 Kaski D, Dominguez RO, Allum JH, Bronstein AM: Improving gait and balance in patients with leukoaraiosis using transcranial direct current stimulation and physical training: an exploratory study. Neurorehabil Neural Repair 2013;27:864–871.
13 Schmidt R, Petrovic K, Ropele S, Enzinger C, Fazekas F: Progression of leukoaraiosis and cognition. Stroke 2007;38:2619–2625.
14 Pantoni L, Garcia JH: Pathogenesis of leukoaraiosis: a review. Stroke 1997;28:652–659.
15 Group LS: 2001–2011: A decade of the LADIS (leukoaraiosis and disability) study: what have we learned about white matter changes and small-vessel disease? Cerebrovasc Dis 2011;32:577–588.
16 Yi L, Wang J, Jia L, Zhao Z, Lu J, Li K, Jia J, He Y, Jiang C, Han Y: Structural and functional changes in subcortical vascular mild cognitive impairment: a combined voxel-based morphometry and resting-state fMRI study. PLoS One 2012;7:e44758.
17 Sun Y-W, Qin L-D, Zhou Y, Xu Q, Qian L-J, Tao J, Xu J-R: Abnormal functional connectivity in patients with vascular cognitive impairment, no dementia: a resting-state functional magnetic resonance imaging study. Behav Brain Res 2011;223:388–394.
18 Wu T, Wang L, Chen Y, Zhao C, Li K, Chan P: Changes of functional connectivity of the motor network in the resting state in Parkinson's disease. Neurosci Lett 2009;460:6–10.
19 Beckmann CF, DeLuca M, Devlin JT, Smith SM: Investigations into resting-state connectivity using independent component analysis. Philos Trans R Soc Lond B Biol Sci 2005;360:1001–1013.
20 Liston R, Mickelborough J, Bene J, Tallis R: A new classification of higher level gait disorders in patients with cerebral multi-infarct states. Age Ageing 2003;32:252–258.
21 Carboncini MC, Volterrani D, Bonfiglio L, Barsotti G, Della Porta M, Mariani G, Rossi B: Higher level gait disorders in subcortical chronic vascular encephalopathy: a single photon emission computed tomography study. Age Ageing 2009;38:302–307.
22 Wahlund L, Barkhof F, Fazekas F, Bronge L, Augustin M, Sjögren M, Wallin A, Ader H, Leys D, Pantoni L: A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke 2001;32:1318–1322.
23 Fazekas F, Chawluk JB, Alavi A, Hurtig H, Zimmerman R: MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. Am J Roentgenol 1987;149:351–356.
24 Friston K, Ashburner J, Frith CD, Poline JB, Heather JD, Frackowiak RS: Spatial registration and normalization of images. Hum Brain Mapp 1995;3:165–189.
25 Li R, Chen K, Fleisher AS, Reiman EM, Yao L, Wu X: Large-scale directional connections among multi resting-state neural networks in human brain: a functional mri and bayesian network modeling study. NeuroImage 2011;56:1035–1042.
26 Calhoun V, Adali T, Pearlson G, Pekar J: A method for making group inferences from functional MRI data using independent component analysis. Hum Brain Mapp 2001;14:140–151.
27 Wen X: Exploring resting-state functional connectivity with total interdependence. NeuroImage 2012;60:1587–1595.
28 Grueter BE, Schulz UG: Age-related cerebral white matter disease (leukoaraiosis): a review. Postgrad Med J 2011;88:79–87.
29 Biswal B, Zerrin Yetkin F, Haughton VM, Hyde JS: Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med 1995;34:537–541.
30 Amiez C, Petrides M: Neuroimaging evidence of the anatomo-functional organization of the human cingulate motor areas. Cereb Cortex 2014;24:563–578.
31 Rizzolatti G, Fogassi L, Gallese V: Motor and cognitive functions of the ventral premotor cortex. Curr Opin Neurobiol 2002;12:149–154.
32 Hoshi E, Sawamura H, Tanji J: Neurons in the rostral cingulate motor area monitor multiple phases of visuomotor behavior with modest parametric selectivity. J Neurophysiol 2005;94:640–656.
33 Lloyd D, Morrison I, Roberts N: Role for human posterior parietal cortex in visual processing of aversive objects in peripersonal space. J Neurophysiol 2006;95:205–214.
34 Morecraft RJ, Cipolloni PB, Stilwell-Morecraft KS, Gedney MT, Pandya DN: Cytoarchitecture and cortical connections of the posterior cingulate and adjacent somatosensory fields in the rhesus monkey. J Comp Neurol 2004;469:37–69.
35 Shima K, Tanji J: Role for cingulate motor area cells in voluntary movement selection based on reward. Science 1998;282:1335–1338.
36 Hoshi E, Tanji J: Functional specialization in dorsal and ventral premotor areas. Prog Brain Res 2004;143:507–511.
37 Nakamae T, Narumoto J, Sakai Y, Nishida S, Yamada K, Kubota M, Miyata J, Fukui K: Reduced cortical thickness in non-medicated patients with obsessive-compulsive disorder. Prog Neuropsychopharmacol Biol Psychiatry 2012;37:90–95.
38 Mesulam M, Mufson EJ: Insula of the old world monkey. III: Efferent cortical output and comments on function. J Comp Neurol 1982;212:38–52.
39 Kawamura J, Meyer JS, Terayama Y, Weathers S: Leukoaraiosis correlates with cerebral hypoperfusion in vascular dementia. Stroke 1991;22:609–614.
40 Takada M, Tokuno H, Hamada I, Inase M, Ito Y, Imanishi M, Hasegawa N, Akazawa T, Hatanaka N, Nambu A: Organization of inputs from cingulate motor areas to basal ganglia in macaque monkey. Eur J Neurosci 2001;14:1633–1650.
41 Olson RA, Chhanabhai T, McKenzie M: Feasibility study of the Montreal Cognitive Assessment (MoCA) in patients with brain metastases. Support Care Cancer 2008;16:1273–1278.
42 Bates S, Wolbers T: How cognitive aging affects multisensory integration of navigational cues. Neurobiol Aging 2014;35:2761–2769.
43 Abbruzzese G, Berardelli A: Sensorimotor integration in movement disorders. Movement Disord 2003;18:231–240.
44 Cauda F, D'Agata F, Sacco K, Duca S, Geminiani G, Vercelli A: Functional connectivity of the insula in the resting brain. Neuroimage 2011;55:8–23.