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Changes in Cortical Thickness Are Associated with Cognitive Impairments in Patients with White Matter Lesions

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Abstract: White matter lesions (WMLs) are closely related with cognitive impairment and dementia. It has been hypothesized that cognitive impairment is related to cortical atrophy and cortical thickness network measurements in certain brain regions. We aimed to investigate the characteristics of cortical thickness in patients with WMLs and the relationship that these characteristics have with cognitive function. In this study, 76 WML patients and 37 healthy controls (HC) were enrolled and underwent a T1-weighted 3-D MRI scan using a 3.0-Tesla scanner. According to cognitive assessment results, the WML patients were divided into two subgroups, namely the WMLs with non-dementia vascular cognitive impairment (WML-VCIND) group and the WMLs with vascular dementia (WML-VaD) group. Cortical surface thickness was estimated using FreeSurfer software. The correlation between cognitive function and cortical thickness in WML patients was analyzed. We found that MoCA scores and executive function were significantly decreased in WML-VCIND and WML-VaD patients compared to the HC group ($P < 0.0001$). Significantly reduced cortical thickness in the left precentral, caudal middle frontal, rostral middle frontal, superior frontal, middle temporal, transverse temporal, insula, bilateral pars opercularis, and superior temporal regions was found in the WML-VaD group compared to the HC group ($P < 0.05$). The reduced cortical thickness of the above gyrus was positively correlated with executive function in WML patients. These cross-sectional results suggest that decreased cortex thickness in certain gyri in WML patients might lead to cognitive decline. The correlation between cortical thickness changes and cognitive function holds promise for understanding the underlying causes of cognitive impairment in WMLs.

Keywords: White Matter Lesions, Cognition, Cortical Thickness, Magnetic Resonance Imaging

1. Introduction

Cerebral white matter lesions (WMLs), also known as white matter hyperintensity (WMH), usually manifest as hyperintensity in paraventricular or deep white matter on fluid-attenuated inversion recovery (FLAIR) and T2-weighted magnetic resonance images (MRIs). WMLs are pathologically consistent with loss of myelin and axons, which are the common manifestation of cerebral small vessel disease [1]. WMLs are correlated with worse cognitive performance, with cognitive domains include attention, executive function, and information processing speed being affected first [2, 3]. Once cognitive decline occurs, it is often irreversible, which seriously harms the health of patients and consumes many medical resources. However, the mechanism of cognitive decline caused by white matter lesions is still unclear.

Studies have reported that WMLs are associated with structural atrophy of grey matter (GM), but the region of brain atrophy in WMLs and its association with cognitive impairment remain unclear. Clinical study has found that executive function decline is the early manifestation and main feature of cognitive impairment in WMLs patients [4]. Some WMLs patients show frontal lobe atrophy on MRI, which is related to executive function deficits [5]. These findings lead to a possible mechanism for the clinical symptoms of WMLs, that is, the thinning of linked cortex. In addition, subjects with heavier burden of WMLs have more severe cortical atrophy [6, 7]. By now, a few investigations have completed voxel-based morphometry, demonstrating that cognition in WMLs are related to GM changes [8, 9]. Cortical surface thickness analysis, characterized by the accurate localization of anatomical regions of the brain, plays an important role in brain morphology study. FreeSurfer is an automated software for the analysis and visualization of cortical segmentation and reconstruction using 3D magnetic resonance imaging [10]. At present, it is rare to use FreeSurfer technology to measure the thickness and volume of the cortex in the studies of WMLs, and few previous studies have analyzed the correlation between grey matter imaging parameters and the cognitive function of WMLs.

We aim to reveal the differences in cortical thickness in WMLs patients with various extent of cognitive decline and their relationship with cognitive function. In this study, FreeSurfer software was used to divide the cerebral cortex into 68 regions of interest (ROI). We measured the cortical thickness of WML patients with various degrees of cognitive impairment and compared it with HCs. We hypothesized that WML patients had reduced cortical thickness compared to HCs, and that the reduction in cortical thickness was severe with worsening cognitive impairment. We further aimed to study the characteristics of grey matter abnormalities in WML patients, and then investigate the correlation of brain regions with these grey matter abnormalities with cognitive function.

2. Materials and Methods

Subjects

Initially, we enrolled 78 WML patients from the neurology clinics of the Beijing Tiantan Hospital, Capital Medical University, China, from January 2014 to December 2019. All subjects underwent clinical assessments such as age, gender, education level, vascular risk factors, and neuropsychological assessment. We excluded two patients from final data analysis because of head motion. Two radiologists assessed FLAIR MR images blinded to clinical data independently. Consensus diagnosis of WMLs were reached by them. We recruited patients meeting the following criteria: (a) age 50–85 years old; (b) white matter hyperintensities on FLAIR MR images. We also excluded patients with white matter lesions, cognitive impairment, aphasia and neurodegenerative disorders from other identified cause and general contraindications for undergoing MRI. In addition, we recruited 37 age-, gender-, and education levels-matched healthy control (HC) study subjects who without memory complaints. There were no abnormal findings on their MRI. The HC group's exclusion criteria were equivalent to WML patients' exclusion criteria.

Clinical cognitive assessment

Cognitive status of all subjects was assessed using the Beijing version of Montreal Cognitive Assessment (MoCA) [11] and the Clinical Dementia Rating (CDR) scale [12]. The tests were completed strictly according to the standard protocols under the supervision of a physician in a quiet room. The cut-off value of MoCA for cognitive impairment was < 26. If the subject had less than 12 years of education, one additional point was added to the raw MoCA score to compensate for lower educational level. Subjects were grouped based on the results of cognitive assessments. The WMLs-VCIND patients complied with the following criteria: 1) MoCA < 26; 2) CDR = 0.5. The WML-VaD complied with the following criteria: 1) MoCA < 26; 2) CDR ≥ 1. The HC complied with the following criteria: 1) MoCA ≥ 26; 2) CDR=0 and 3) MRI showing normal brain structure All participants were asked to complete a series of cognitive tasks. Cognitive assessments followed the LADIS protocol [13]. Global cognitive function was assessed with MoCA. Since cognitive impairment in WML patients is characterized by decreased executive function, according to the criteria of LADIS protocol, executive function was assessed with a composite measure of Stroop Colour and Word Test (SCWT), Trail-Making Test (TMT), Digit Symbol Substitution Test (DST), and Verbal Fluency Test (VFT).)

The Beijing Tiantan Hospital's Ethics Committee accepted this study protocol. Before enrolling, all participants or their legal representatives completed an informed consent form.

Image acquisition

Every subject in current study underwent standardized MRI scans that were performed on a 3.0T Siemens Magnetom Trio Tim scanner. We evaluated WML with assessment of T2-weighted FLAIR sequence. The image protocols were 1) high-resolution T1-weighted magnetization prepared rapid gradient recalled echo (256 slices, 1 mm thickness, inter- slice gap = 0.5 mm, matrix = 256 × 256, repetition time =2,300 ms, echo time = 3.28 ms, inversion time = 1200 ms, flip angle = 9°); 2) T2- weighted imaging protocol (axial spin echo sequence, 48 slices with 5 mm slice thickness, matrix = 256 × 256, field of view = 220 × 220 mm, repetition time = 4,500 ms, echo time = 84 ms); 3) fluid attenuated inversion recovery (FLAIR) imaging protocol (48 slices with 5 mm slice thickness, repetition time = 8,000 ms; echo time = 94 ms; inversion time = 2,200 ms; matrix = 256 × 256, field of view = 220 × 220 mm). All subjects were requested to remain awake, close their eyes, and relax. To prevent any motion artifacts, use rubber earplugs to decrease noise and foam cushions to steady the head.

Parcellation and cortical thickness analysis

All MRI data were saved offline in Digital Imaging and Communications in Medicine (DICOM) format and imported into the image processing workstation. The preprocessing pipeline contains format conversion, head motion correction and smoothing. Then, segment grey matter automatically

software based on surface area features under the Linux platform- FreeSurfer software (http://surfer.nmr.mgh.harvard.edu) was processed. The analysis workflow comprises non-brain tissue removing, intensity standardization and white and gray matter boundaries tessellating, segmentation of hemisphere total gray matter volume, smoothing, and segment the Desikan-Killiany atlas to finally generate a three-dimensional reconstruction map of the brain region. The technical process has been described in detail before [14].

Statistical analysis

The statistical analyses were done in SPSS 23. To allow for direct comparisons of neuropsychological test results for global cognition and executive function, we generated z scores. Executive functions = z scores of ((Stroop C-B) + (TMB-TMA) + symbol digit + verbal fluency)/4.

The mean ± standard deviation (SD) and the median and the interquartile ranges were reported as the numeric parameters for skewed distributions. Normally distributed continuous variables were compared by 1-way analysis of variance (ANOVA), whereas the Kruskal-Wallis test was used for comparison of non-normally distributed variables. Categorical variables were compared by the Chi-square test (χ^2 test). Pearson's linear correlation coefficient was calculated to determine the associations between cognitive assessments and cortical thickness for WMLs patients. The level of significance was set at 0.05.

3. Results

3.1. Demographic and Clinical Characteristics

The HC group consisted of 37 individuals, while the WML group consisted of 76 patients. Demographic and clinical characteristics of study population according to three groups were listed in Table 1. Compared with HCs, WMLs patients showed a significantly older on age. (P<0.05).

3.2. Cognitive Function Measures in the Study Population

Neuropsychological assessment showed significant differences among the three groups. WML patients had lower MoCA scores than healthy controls, with the WML-VaD group having the lowest scores (p <0.0001). The same results were showed in the evaluation of executive function (p <0.0001). The cognitive function measures according to three groups were displayed in Table 2.

Table 1. *The baseline characteristics of WML and HC groups.*

Characteristics	HC (n=37)	WML-VCIND (n=42)	WML-VaD (n=34)	*p*
Age (years)	55.41±3.06	62.59±3.14	64.47±4.25	0.01[b]
Male, n (%)	18 (48.65)	20 (47.62)	17 (47.22)	0.31[a]
Years of education	12.17±1.72	11.05±2.56	11.31±2.01	0.82[b]
Hypertension	15 (40.54)	21 (50.00)	18 (52.94)	0.07[a]
Diabetes	6 (16.21)	8 (19.05)	7 (20.59)	0.11[a]
Hyperlipidemia	12 (32.43)	15 (35.71)	12 (35.29)	0.37[a]
Coronary heart disease	4 (10.81)	6 (14.29)	5 (14.71)	0.24[a]
Smoking	13 (35.13)	13 (30.95)	11 (32.35)	0.32[a]
Drinking	9 (24.32)	10 (23.81)	8 (23.53)	0.88[a]
BMI	23.99±2.17	24.52±2.59	24.31±2.47	0.39[b]

Categorical variables are expressed as number (percentage), and continuous ones as mean ± SD. HC, healthy controls; WML-VCIND, white matter lesion patients with non-dementia vascular cognitive impairment; WML-VaD, white matter lesion patients with vascular dementia; BMI, body mass index. [a] the P-value was obtained by chi squared (χ^2) test. [b] the P-value was obtained by ANOVA.

Table 2. *The baseline characteristics of WML and HC groups.*

Characteristics	HC (n=37)	WML-VCIND (n=42)	WML-VaD (n=34)	*p*
MoCA	27.51 ± 1.49	22.77 ± 2.92	17.18±3.83	<0.0001
z score	0.00 ± 2.14	0.00 ± 1.00	0.01 ± 1.01	<0.0001
EXECUTIVE FUNCTIONS				
SCWT- B (s)	43.85±1.21	73.10±3.50	87.51±10.75	<0.0001
SCWT- C (s)	64.91±7.06	69.91±3.08	94.59±7.14	<0.0001
TMT-A (s)	30.45 ± 1.01	36.05 ± 1.56	44.89 ± 1.97	<0.0001
TMT-B (s)	81.11±3.35	86.19±4.19	94.97±3.88	<0.0001
DST	47.90 ± 2.98	40.31 ± 3.78	33.94 ± 4.92	<0.0001
VFT	11.21±0.84	8.99±1.07	7.11±1.19	<0.0001
z scores	0.00 ± 2.18	−0.52 ± 2.49	−0.71 ± 2.11	<0.0001

Variables and z scores are shown as mean ± SD. HC, healthy controls; WML-VCIND, white matter lesion patients with non-dementia vascular cognitive impairment; WML-VaD, white matter lesion patients with vascular dementia; MoCA, Montreal Cognitive Assessment; SCWT, Stroop color and word test; TMT, trail-making test; DST, symbol-digital replacement task, VFT, verbal fluency test.

3.3. Cortical Thickness Analysis

The cortical thickness of the left precentral, caudal middle frontal, rostral middle frontal, superior frontal, middle temporal, transverse temporal, insula, bilateral pars opercularis, and superior temporal were significantly thinner in WML-VaD patients compared with HCs (all P < 0.05). The

cortical thickness of the left superior frontal cortex, pars opercularis, middle temporal cortex, transverse temporal cortex, insula, and bilateral superior temporal cortex were significantly thinner in WML-VCIND patients compared with healthy controls (all $P < 0.05$). WML-VaD patients had substantially lower cortical thickness in the left rostral middle frontal, right middle temporal, and bilateral superior temporal lobes as compared to WML-VCIND patients (all $P < 0.05$). Differences in cortical thickness among all participants were shown in Figure 1 and Table 3.

Table 3. *The differences in cortical thickness between WML and HC groups (controlled for age and intracranial volume).*

ROI	Cortical thickness (mm)		
	HC (n=37)	WML-VCIND (n=42)	WML-VaD (n=34)
L postcentral	1.93±0.05	1.85±0.21	1.73±0.15
R postcentral	1.85±0.26	1.82±0.18	1.75±0.06
L precentral	2.29±0.37	2.11±0.27	1.81±0.26*
R precentral	2.21±0.21	2.10±0.15	1.93±0.19
L paracentral	2.10±0.07	1.97±0.21	1.82±0.08
R paracentral	2.14±0.28	2.01±0.26	1.93±0.17
L frontal pole	2.75±0.19	2.51±0.19	2.49±0.07
R frontal pole	2.75±0.18	2.55±0.22	2.52±0.19
L lateral orbito frontal	2.61±0.15	2.49±0.33	2.38±0.37
R lateral orbito frontal	2.66±0.30	2.56±0.21	2.41±0.33
L medial orbito frontal	2.46±0.31	2.36±0.17	2.19±0.08
R medial orbito frontal	2.39±0.31	2.28±0.22	2.25±0.36
L caudal middle frontal	2.42±0.07	2.15±0.19	2.00±0.28*
R caudal middle frontal	2.31±0.28	2.19±0.24	2.12±0.23
L rostral middle frontal	2.22±0.18	2.18±0.21	2.02±0.15*†
R rostral middle frontal	2.18±0.26	2.10±0.24	2.07±0.17
L pars orbitalis	2.58±0.37	2.49±0.31	2.42±0.28
R pars orbitalis	2.59±0.31	2.52±0.33	2.45±0.31
L superior frontal	2.68±0.23	2.51±0.29#	2.34±0.18*
R superior frontal	2.54±0.33	2.46±0.31	2.38±0.28
L pars opercularis	2.37±0.19	2.23±0.14#	2.09±0.07*
R pars opercularis	2.32±0.21	2.21±0.17	2.05±0.26*
L pars triangularis	2.24±0.34	2.12±0.25	1.99±0.15
R pars triangularis	2.25±0.23	2.13±0.26	2.01±0.27
L entorhinal	3.39±0.27	3.22±0.35	3.09±0.37
R entorhinal	3.70±0.28	3.62±0.34	3.51±0.33
L parahippocampal	2.44±0.23	2.31±0.29	2.17±0.28
R parahippocampal	2.50±0.29	2.39±0.38	2.21±0.28
L Banks of the superior temporal sulcus	2.29±0.10	2.10±0.15	1.92±0.15
R Banks of the superior temporal sulcus	2.26±0.18	2.09±0.21	2.02±0.17
L superior temporal	2.58±0.23	2.41±0.14#	2.24±0.18*†
R superior temporal	2.61±0.31	2.44±0.21#	2.25±0.26*†
L middle temporal	2.83±0.19	2.63±0.18#	2.45±0.23*
R middle temporal	2.86±0.19	2.66±0.23	2.46±0.21†
L inferior temporal	2.80±0.37	2.71±0.35	2.59±0.31
R inferior temporal	2.81±0.18	2.72±0.37	2.63±0.32
L temporal pole	3.69±0.26	3.41±0.35	3.39±0.07
R temporal pole	3.63±0.28	3.34±0.32	3.35±0.28
L transverse temporal	2.13±0.19	1.94±0.20#	1.73±0.15*
R transverse temporal	2.06±0.19	1.85±0.17	1.71±0.21
L lateral occipital	2.11±0.18	2.05±0.25	1.99±0.37
R lateral occipital	2.09±0.19	2.03±0.22	1.96±0.19
L pericalcarine	1.42±0.07	1.37±0.11	1.35±0.15
R pericalcarine	1.43±0.26	1.39±0.21	1.35±0.07
L cuneus	1.65±0.15	1.62±0.11	1.60±0.05
R cuneus	1.70±0.07	1.67±0.17	1.63±0.15
L lingual	1.82±0.08	1.72±0.22	1.68±0.18
R lingual	1.82±0.07	1.76±0.21	1.72±0.26
L fusiform	2.64±0.26	2.48±0.39	2.37±0.23
R fusiform	2.63±0.15	2.45±0.38	2.34±0.36
L superior parietal	2.08±0.23	2.01±0.26	1.91±0.15
R superior parietal	2.02±0.19	1.99±0.25	1.95±0.16
L inferior parietal	2.25±0.19	2.14±0.31	1.99±0.29
R inferior parietal	2.29±0.31	2.17±0.28	1.96±0.17
L supramarginal	2.31±0.37	2.25±0.31	2.19±0.18

ROI	Cortical thickness (mm)		
	HC (n=37)	WML-VCIND (n=42)	WML-VaD (n=34)
R supramarginal	2.35±0.36	2.29±0.26	2.21±0.28
L precuneus	2.14±0.23	2.04±0.28	1.93±0.15
R precuneus	2.17±0.19	2.07±0.27	1.91±0.17
L insula	2.85±0.26	2.69±0.28[#]	2.50±0.18[*]
R insula	2.77±0.33	2.67±0.33	2.58±0.23
L rostral anterior cingulate	2.69±0.19	2.57±0.27	2.45±0.07
R rostral anterior cingulate	2.65±0.28	2.59±0.22	2.46±0.21
L posterior cingulate	2.29±0.31	2.19±0.28	2.13±0.26
R posterior cingulate	2.33±0.36	2.28±0.21	2.26±0.28
L caudal anterior cingulate	2.45±0.30	2.39±0.34	2.24±0.32
R caudal anterior cingulate	2.47±0.31	2.41±0.29	2.31±0.33
L isthmus cingulate	2.28±0.37	2.12±0.24	2.06±0.23
R isthmus cingulate	2.26±0.33	2.18±0.17	2.13±0.20

HC, healthy controls; WML, white matter lesions; WML-VaD, WML and vascular dementia; WML-VCIND, WML and non-dementia vascular cognitive impairment. ROI, region of interest; L, left; R, right;

[#] P < 0.05 post hoc result for WML-VCIND vs. HC.

[*] P < 0.05 post hoc result for WML-VaD vs. HC.

[†] P < 0.05 post hoc result for WML-VaD vs. WML-VCIND.

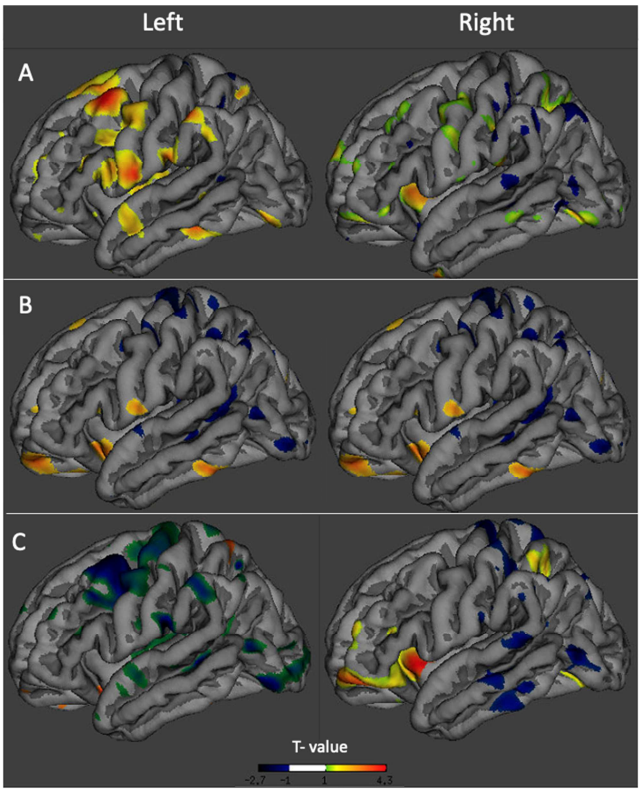

Figure 1. *Differences in cortical thickness between HCs and patients with WMLs. Group comparisons were performed using QDEC implemented in FreeSurfer. (A) WML-VaD patients versus HCs (P < 0.05); (B) WML-VCIND patients versus HCs (P < 0.05); (C) WML-VCIND patients versus WML-VaD patients (P < 0.05).*

3.4. Correlation Between Cortical Thickness and Cognitive Impairment

We performed a correlation analysis between cognitive assessments and brain regions with reduced cortical thickness in WML patients. MoCA score was positively correlated with thickness of left caudal middle frontal, rostral middle frontal, superior frontal, pars opercularis, transverse temporal, insula and bilateral superior temporal gyrus. (P < 0.05). Executive function was shown to be significantly positively linked with regional cortical thickness (all P < 0.05) (Table 4).

Table 4. *Correlations between cortical thickness and cognitive function in WML patients (controlled for age and intracranial volume, n = 76).*

ROI	MoCA correlation	EF correlation
L precentral	0.202	0.295[*]
L caudal middle frontal	0.374[*]	0.677[**]
L rostral middle frontal	0.369[*]	0.501[**]
L superior frontal	0.344[*]	0.603[**]
L pars opercularis	0.289[*]	0.441[*]
R pars opercularis	0.255	0.396[*]
L superior temporal	0.372[*]	0.478[**]
R superior temporal	0.358[*]	0.421[*]
L middle temporal	0.196	0.338[*]
L transverse temporal	0.321[*]	0.367[*]
L insula	0.339[*]	0.384[*]

ROI, region of interest; L, left; R, right; MoCA, Beijing version of Montreal Cognitive Assessment; EF, executive function.

*P < 0.05.

**P < 0.01.

4. Discussion

In current study, the cerebral cortex thickness of WML patients was measured using MRI-based FreeSurfer technology and compared with HCs. Certain cerebral cortex thicknesses in WML patients were found to be significantly thinner than those in HCs, according to this study. In WML patients, a decrease in cortical thickness was closely associated with cognitive impairment.

WMLs are prevalent in older population and aggravate with age. In current study, we also revealed that the WML group's average age was above 60 years old [15]. In this study, we found no significant differences between WML patients and healthy controls in factors such as gender, education level, and risk of cerebrovascular disease, largely eliminated the influence of possible confounding factors on cognitive

assessment. The Previous studies have found that MoCA is more sensitive than MMSE in the assessment of vascular cognitive impairment [16]. WML typically affects the cognitive domains in terms of executive function, attention, and delayed recall. Competencies related to executive function, such as inhibitory control, working memory, cognitive flexibility, were assessed by calculating composite measures of SCWT, TMT, DST, VFT and generating Z-scores. These functional deficits are more consistent with the characteristics of cognitive impairment in patients with WMLs [17]. Our study indicated that patients with WMLs had varying degrees of global cognitive and executive dysfunction, which was more severe in patients with WML-VaD.

The mechanism underlying the cognition impairment in WMLs is still unclear. One possible mechanism is cortex thinning. This mechanism has recently been confirmed in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) [18, 19]. A study on imaging markers of cerebral small vessel disease (SVD) found that the burden of SVD was associated with reduced cortical thickness in widespread brain regions [20]. A voxel-based morphometry study also found that WMLs were related to local cortical atrophy [21]. Another possible mechanism is that WMLs may disrupt cortical network connections, resulting in cognitive impairment. However, research on the correlation between cerebral cortex thickness and cognitive impairment in WMLs is very limited. This study used cortical segmentation techniques to analyze the correlation between thickness in various cortex regions and cognitive status in patients with WMLs, which was of great significance for demonstrating the correlations among WMLs, cortical morphology, and possibly accompanying cognitive decline and dementia.

In our study, patients with WML-VCIND showed reduced thickness of cortex in the superior frontal gyrus, pars opercularis, superior temporal gyrus, middle temporal gyrus, transverse temporal gyrus and insula compared with HCs. In addition to the above-mentioned regions, patients with WML-VaD showed reduced thickness of cortex in the precentral gyrus, caudal middle frontal gyrus, and rostral middle frontal gyrus compared with the HCs. The functions of the superior frontal gyrus are behavioural inhibition, behavioural decision-making, and regulation of motivation, learning, and attention. The pars opercularis establishes the connection among stimulation, response, and processing. The insula is an important cerebral cortex region for attention transition. The superior temporal gyrus, middle temporal gyrus, and transverse temporal gyrus are involved in the formation of attentional networks, representing the ability of selective attentional/inhibitory control to focus attention on processing stimuli from the environment [22]. The precentral gyrus and middle frontal gyrus are mainly responsible for the visual control of movement and the cognitive processing of the spatial attributes of things, reflecting the ability of working memory [23]. The above-mentioned gyri are regions of reduced cortical thickness in WML and vascular dementia patients, which play a crucial part in information process and memory management. Previous related studies have demonstrated that frontal [24] and insular [25] atrophy in patients with subcortical vascular dementia. It should be noted that WMLs were linked to frontal atrophy, which could lead to executive dysfunction and global cognitive deficits [26]. In addition, a meta-analysis showed that progression of white matter hyperintensities was associated with even worse cognitive functioning, most pronounced in attention and executive functioning [27]. Our research revealed that patients with WMLs exhibited reduced cortical thickness in certain regions. Therefore, detecting structural abnormalities could be used as a powerful biomarker to assess cognitive manifestations at different levels in patients with WMLs.

Furtherly, we analyzed the function of brain regions with reduced cortical thickness and their association with cognitive status in patients with WMLs. We found that cortical thinning in certain brain regions was positively correlated with global cognition and executive function, indicating that WML were related to specific grey matter atrophy and led to cognitive dysfunction. It has been proposed that the frontal lobe represents executive function [21]. Frontal lobe lesions can lead to executive function impairment [28]. Most researchers now assume that executive dysfunction is caused by a functional disruption of the frontal-subcortical network [29]. White matter fibre tracts connecting the insula, frontal, and temporal lobes play a crucial role in information processing and integration, which are the core features of cognitive dysfunction. White matter fibre lesions can result in grey matter atrophy or disconnection of neural circuits, leading to cognitive dysfunction. This study demonstrated that executive function impairment in WML patients was related to the thinning of certain regions in the frontal, temporal, and insular cortex. This finding adds to our knowledge of the link between white matter damage, grey matter atrophy, and cognitive dysfunction. The effect of WMLs on cognitive function may be mediated by cortical thickness. In addition, it has been observed that the proportion of patients with vascular cognitive impairment (VCI) may develop into Alzheimer's disease (AD) every year is 12% to 15% [30]. One of the most important issues in the clinical management of WML patients is to determine or predict whether VCI progresses to AD. Cortical thickness analysis, as an objective technical means, can provide potential quantitative imaging measurements for assessing the progression and prognosis of VCI in patients with WML. Our research demonstrated that cortical thickness could be applied as an imaging feature for diagnosing and monitoring the cognitive function of WMLs.

There were limitations to this study. First, the statistical power was low due to the limited sample. Second, our study was based on cross-sectional data, and the contribution of predicting disease progression was limited. Longitudinal studies with larger dataset and longer follow-up, which further investigate the mechanism of cognitive dysfunction in WMLs, should be carried out. Third, this study did not involve WML patients with normal cognition. Fourth, this study only evaluated cortical thickness but not cortical volume. The classification of WML patients with normal cognition and

examination of the volume of WML load should be included. More research into the relationship between white matter and grey matter structural changes is needed.

5. Conclusion

In summary, we investigated a group of WMLs and suggested that the cortical thickness of certain brain regions was reduced, and this change was closely related to cognitive impairment, especially the cognitive domain of executive function. Our study provided some evidence that grey matter alterations in WMLs were related to cognition. Individual structural changes in different WMLs subgroups indicated the order of cortical involvement as the disease progresses. Our current study provided supporting evidence that the mechanism of cognitive impairment in WML patients might be related to cortical atrophy. Further in-depth longitudinal studies are needed to gain insight into understand of the imaging, pathological, and molecular evolution characteristics of the cortex of WMLs over time as well as their impact on cognitive function. The study provided cortical thickness as an imaging marker to evaluate and monitor the cognitive function of WMLs patients.

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Conflicts of Interest

The authors declare no conflict of interest.

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