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ORIGINAL ARTICLE

Cortical Thinning Mediates the Correlation between Periventricular White Matter Hyperintensities and Cognitive Impairments

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ABSTRACT

Introduction: Previous studies showed that white matter lesions (WMLs) were an important risk factor for cognitive impairment, but the mechanisms whereby WMLs induced cognitive impairment have not been clarified. We hypothesised that the correlation between WMLs and cognitive impairments would be mediated by cortical thinning.

Methods: Patients with periventricular white matter hyperintensities (PWMHs) on MRI were selected as research subjects. We investigated the contributions of PWMHs to several domains of cognitive impairment and the topography of cortical thinning and then investigated the relationship among diffusion tensor imaging (DTI) measurements, cortical thinning, and cognitive impairments. Participants included 16 stroke- and dementia-free subjects with PWMHs on magnetic resonance imaging (MRI) and 20 healthy control subjects. All participants underwent an examination of cognition, cortical thickness, and a DTI scan.

Results: After accounting for age, sex, years of education, and treatable cardiovascular risk factors related to cognitive performance, DTI measurements of periventricular WMLs were associated with cognitive impairment in executive function and verbal fluency and with cortical thinning in the frontal pole, orbitofrontal cortex, superior and middle frontal gyri, superior and middle temporal gyri, insula, lingual gyrus, and cuneus. Cortical thinning, but not PWMH, was independently associated with cognitive impairment.

Conclusion: Our results suggest that the correlation between PWMHs and cognitive impairments is mediated by cortical thinning.

INTRODUCTION

White matter hyperintensities (WMHs), which are commonly observed on MRI scans of elderly people, have been found to increase in prevalence and severity with age [1, 2]. WMHs have been associated with cognitive dysfunction in patients with mild cognitive impairment or dementia, and they have also been identified as a risk factor for dementia [3-6].

The relationships between WMH, cortical thickness, and cognitive impairments in stroke- and dementia-free subjects are uncertain. Although WMHs may tend to be associated with cognition, the independent

associations of PWMHs with cognition are inconsistent among studies. In a longitudinal cohort study of normal elderly patients, PWMHs were associated with the level of cognitive impairment [3, 5, 7], whereas some reports demonstrate that PWMHs are not associated with levels of cognitive decline, especially when cortical volume loss is accounted for [8, 9].

Previous studies of WMHs, cortical thickness and cognitive impairment have not separately evaluated the stroke- and dementia-free subjects. Furthermore, analyses regarding the association of PWMHs with cognitive function and cortical thickness have not excluded the effect of other WMHs. In addition, WMH measurements have been limited by the use of conventional structural MRI techniques such as T2-weighted and fluid-attenuated inversion recovery (FLAIR) images and did not include DTI. Conventional structural MRI techniques provide little information about the severity of the underlying pathological changes [10]. DTI is a quantitative MRI technique that measures the directionality and mobility of water diffusion in tissue and provides increased sensitivity to detect the structural integrity of white matter fibres [11,12]. Fractional anisotropy (FA) is a measurement of the diffusion consistency in all directions [13].

The present study evaluated PWMH with magnetic resonance DTI, the topography of cortical thinning with surface based morphometry, and cognitive impairment with neuropsychological tests. We investigated the relationships among these variables to test our hypothesis that the correlation between PWMH and cognitive impairments is mediated by cortical thinning.

METHOD

Participants

Sixteen stroke- and dementia-free subjects with PWMH on MRI and 20 healthy control subjects were included in our study. All subjects were required to be within the age range of 50 to 75 years and underwent a comprehensive clinical examination including medical history, physical and neurological assessment, and brain MRI. Patients with PWMH were evaluated with conventional structural MRI techniques such as T1-weighted, T2-weighted, and FLAIR images. Periventricular regions were defined as regions between 3 mm and 13 mm from the ventricular surface [13]. All participants with disorders that could have confounded their current cognitive state, such as metabolic encephalopathy, thyroid disease, or syphilis, were excluded. Participants who had current or past somatic, psychiatric, or neurological disorders that could have caused the cognitive impairment, such as stroke, schizophrenia, epilepsy, severe head trauma, encephalitis, brain tumours, alcohol abuse, severe depression, or neurodegenerative diseases such as Parkinson's disease, were excluded. Control subjects showed no WMH on MRI imaging, had no neurological disorders, and showed no deficits on the neuropsychological test battery.

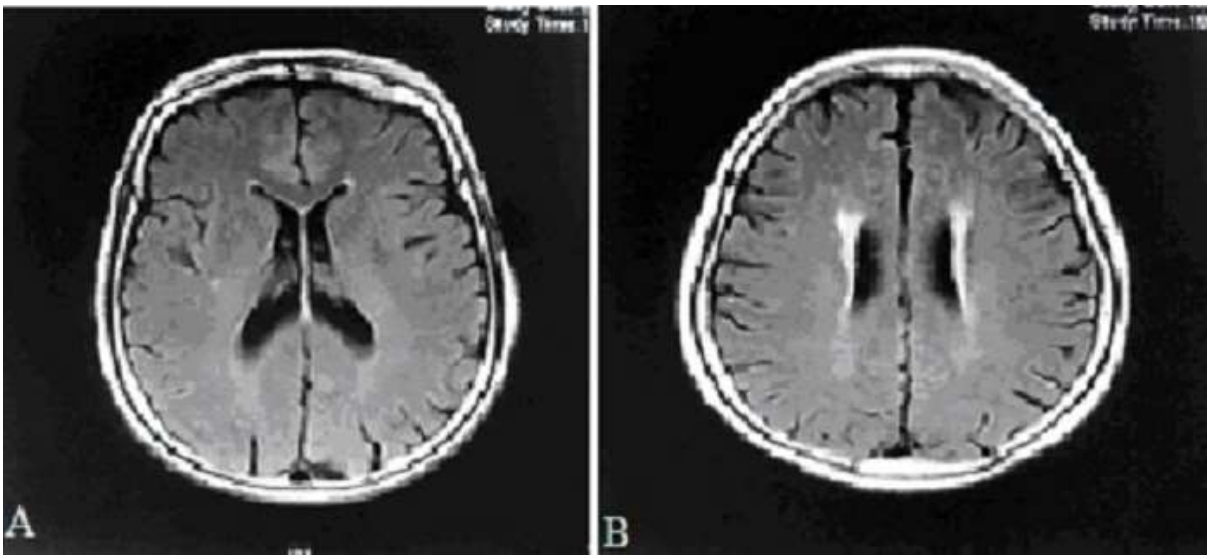

Fig.1: Illustration of patients and controls in CT images.

A: controls=shows a participant with no white matter hyperintensities on MRI imaging. B: PWMHs=shows a participant with periventricular hyperintensities

This study was approved by the ethics committees of the Third Military Medical University and the Xin-Qiao Hospital affiliated with the university. Written informed consent was obtained from all participants.

Acquisition of MR images

Images were acquired with a 3.0-Tesla GE Excite MRI system (GE, Milwaukee, WI, USA). We performed routine whole brain MRI scans for every

subject, including axial T1-weighted MRI (acquisition matrix = 320×320, TR = 5600 ms, TE = 2.46 ms, slice thickness = 5 mm), axial T2-weighted MRI (acquisition matrix=320×320, TR=5600 ms, TE = 90 ms, slice thickness = 5 mm), and axial FLAIR (acquisition matrix = 320×320, TR = 9000 ms, TI = 2250 ms, TE = 85 ms, slice thickness = 5 mm).

DTI measurement and analysis

Post-processing of the DTI data was performed on a GE workstation (FuncTool, Advantage Workstation 4.2, GE, Medical System, Milwaukee, WI). This system uses automatic correction of the echo planar imaging (EPI) distortion by scaling, deskewing, and translating to align each image with the reference image (b= 0) and to minimise the mismatch between diffusion and reference images. The fractional anisotropy (FA) maps were computed and displayed along with a b = 0 reference map. We measured the FA at different locations of white matter using ROI-based analysis. The neuroradiologist responsible for the placement of regions of interests (ROIs) was blind to the clinical diagnosis of all the participants. We placed 12 ovoid ROIs in the white matter regions on two slices that included the temporal subcortical white matter (SCWM) adjacent to the temporal horns, the genu and splenium of the corpus callosum, the anterior SCWM, the anterior periventricular white matter (PVWM), and the posterior SCWM and PVWM (see Fig. 1). The non-midline regions were measured on both sides. The size of the ROIs was 8–12 voxels, measuring 1.878 mm×1.875 mm×5 mm each [14].

DTI was conducted using an EPI sequence with TR/TE = 6000 ms/90 ms, 25 uniformly distributed gradient directions, a b-value of 1000 s/mm², and number of excitations (NEX) = 2. Contiguous axial slices were acquired with 5 mm slice thickness, 240 mm×240 mm field of view, and 128×128 matrix. The slices were positioned to run parallel to the posterior commissural and anterior commissural planes (Fig.2).

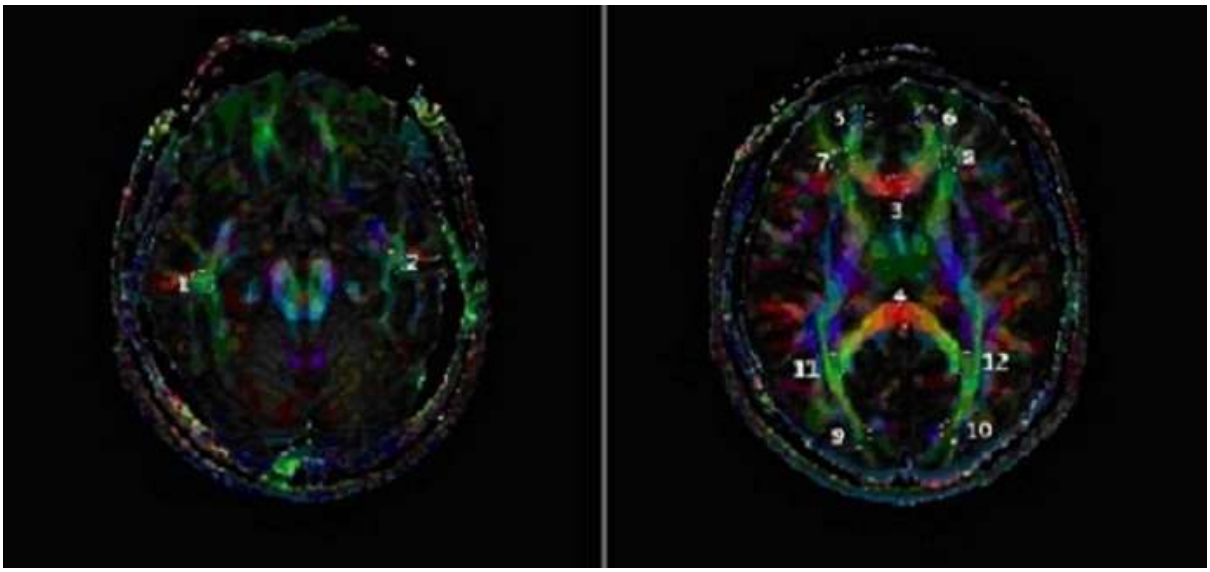

Fig.2: Illustration of the ROIs selection in FA maps.

Twelve ROIs were selected. Brain regions are indicated as: 1 and 2 = Right and left temporal subcortical white Matter(SCWM), 3 and 4 = genu and splenium of corpus callosum,5 and 6 = right and left anterior medial SCWM, 9 and 10 = right and left posterior SCWM, 7 and 8 = right and left anterior periventricular white matter (PVWM), and 11 and 12 = right and left posterior PVWM.

Cortical thickness analysis

The automatic cortical thickness analysis of the magnetic resonance images was processed by the standard Montreal Neurological Institute anatomic pipeline [15]. First, intensity-based non-uniformities, which resulted from the inhomogeneities in the magnetic field, were corrected with the N3 algorithm and the brain tissue was classified into grey matter, white matter, and cerebrospinal fluid using a 3D stereotaxic brain mask and the intensity-normalised stereotaxic environment for classification of tissues (INSECT) algorithm[16]. Next, the brain was automatically divided into two separate hemispheres, and the inner and outer surfaces of the cortex were automatically extracted using the constrained Laplacian-based automated segmentation with proximities (CLASP) algorithm. The CLASP algorithm extracts the boundaries of the cortex by using a dense polygon mesh that is first expanded inside the white matter and then fitted into the surface between the white matter and the inner surface of the cortex. The outer surface of the cortex is detected by expanding the polygon mesh further into the surface between the grey matter and cerebrospinal fluid. Cortical thickness was defined as the Euclidean distance be-

tween the linked vertices of the outer and inner surfaces. Finally, the cortical thickness maps were smoothened using a surface-based 20 mm WHM diffusion kernel that has been demonstrated to increase the signal-to-noise ratio and the statistical power [17].

Cortical thickness calculations were performed in each subject's native space, rather than using Talairach space, due to limitations in linear stereotaxic normalisation. Intracranial volume was included as a covariate to control for the brain size effect in statistical analyses. The cortical thickness was calculated in the native space through applying an inverse transformation matrix to the cortical surfaces and reconstructing in the native space [18].

Neuropsychological tests

All subjects underwent an extensive neuropsychological battery. The tests assess five cognitive domains: attention, executive function, language, memory, and visuospatial skills. The Montreal Cognitive Assessment (MOCA) was used to assess global cognitive function. Attention abilities were examined with the digit span test (DST)[19]. Executive function was assessed with the trail making test (TMT) [20]. Language was measured with the verbal fluency test (VFT) [21]. Visuospatial skills were evaluated with the clock drawing test (CDT) [22]. Memory was tested with the auditory verbal learning test (AVLT) [23].

Statistical analysis

Data analyses were performed using the statistical software package SPSS 13.0 for Windows (SPSS, Chicago, IL, USA). Descriptive statistics were run for neuropsychological tests, DTI measurements, and clinical and demographic data. Continuous variables were tested for normality with the Kolmogorov-Smirnov test. The mean (standard deviation) or the median (interquartile range) was used to express the participants' characteristics for continuous variables. Categorical variables were expressed as frequencies and/or percentages. Categorical variables were evaluated with the Chi-squared test or the Fisher's exact test as appropriate. Continuous variables were analysed with Student's t-test for independent samples or the Mann-Whitney test as appropriate.

Associations of clinical and demographic variables with cognitive function were measured using Pearson or Spearman rank correlation coefficients to clarify potential confounding variables that might influence the association of the DTI measurements with cognitive function.

Pearson correlations were calculated to examine the associations between the DTI measurements and cortical thickness. To correlate cortical thickness with multiple ROIs, a stepwise linear regression was performed to identify the contribution of each related ROI. For each regression, we controlled the effects of age, sex, years of education, and treatable cardiovascular risk factors related to cognitive performance.

To explore the relationships among PWMH, cortical thickness, and cognitive performance, we performed a multiple linear regression analysis, after controlling for age, sex, years of education, treatable cardiovascular risk factors. In Model 1, we entered PWMH as the predictor and the results of the cognitive tests as outcomes. In Model 2, we entered cortical thickness as the predictor (instead of PWMH as in Model 1). In Model 3, we used both PWMH and cortical thickness as predictors.

RESULTS

Demographic and Clinical Data

The demographics and relevant clinical information, including mean age, sex, years of education, MOCA scores and cardiovascular risk factors, are listed in table 1. There were no significant differences between groups for dyslipidaemia, diabetes mellitus, or current smoker status. patients with PWMHs (64.26±2.58) were older than the controls (60.47±3.56) .Hypertension was more frequent in participants with PWMHs (50.0 %) versus healthy controls (40.0%). The PWMH subjects had significantly lower MOCA scores compared to the controls. Participants with PWMH had fewer years of education (median 8 years) versus controls (median 10 years). The proportion of males was higher in participants with PWMH (43.8%) versus controls (30%) (Table 1).

Table 1: Demographic and clinical data

	PWMHS (n=16)	controls (n=20)	P
Age(years) [1]	64.26(2.58)	60.47(3.56)	0.02
Sex (% female)[2]	9 (56.2)	14(70)	0.04
Education(years)[3]	8(6.25-10.25)	10(6-12)	0.04
MOCA[3]	22(21-23)	25(24-26)	0.03
Vascular risk factors			
Hypertension (%)[2]	8(50.0)	8(40.0)	0.02
Dyslipidemia (%)[2]	10(62.5)	12(60)	0.68
Diabetes mellitus (%)[2]	3 (18.8)	4(20.0)	0.28
Current smoker (%)[2]	3(18.8)	4(20.0)	0.28

Note. PVHS = periventricular hyperintensities; MOCA = Montreal cognitive assessment. Values are means (standard deviations) in Student's t-test or medians (interquartile range) in Mann-Whitney test for continuous variables. Values are n (%) for categorical variables in chi-square test and Fisher's exact test. p shows statistical comparison between participants with periventricular white matter lesions and no white matter lesions.
1.Student's t-test; 2.Chi-square test; 3.Mann-Whitney test;
4.Fisher's exact test; * $p < 0.05$.

Table 2: Performance of cognitive function tests

		PWMHS (n=16)	Controls (n=20)	P
Executive function	Trail making test(TMT)	88.0(33.2)	51.2(12.5)	0.001*
Attention	Digit span test(DST)	5.0(0.8)	5.5(0.5)	0.04*
Language	Verbal fluency test(VFT)	23.6(5.6)	37.8(6.7)	0.003*
Visuospatial skills	Clock design test(CDT)	3.5(0.8)	3.0(0.7)	0.02*
Memory	Auditory verbal learning test(AVLT)	6.9(2.2)	8.1(1.7)	0.27

Note. Data are presented as mean (standard deviation); Values are means (standard deviations) in Student's t-test; p shows statistical comparison between participants with periventricular white matter lesions and no white matter lesions.
* $p < 0.05$.

Table 3: Performance of fraction anisotropy of region-of-interest

	PWMHS (n=16)	controls (n=20)	P
Diffusion tensor measurements in periventricular white matter			
Anterior right	0.31(0.06)	0.39(0.07)	0.01*
Anterior left	0.31(0.06)	0.40(0.06)	0.01*
Posterior right	0.45(0.08)	0.48(0.07)	0.04*
Posterior left	0.44(0.07)	0.48(0.08)	0.03*
Diffusion tensor measurements in subcortical white matter			
Anterior right	0.43(0.07)	0.44(0.06)	0.24
Anterior left	0.48(0.05)	0.47(0.08)	0.32
Posterior right	0.43(0.08)	0.44(0.05)	0.48
Posterior left	0.42(0.06)	0.43(0.04)	0.38
Temporal right	0.45(0.05)	0.46(0.07)	0.56
Temporal left	0.49(0.06)	0.48(0.05)	0.61
Diffusion tensor measurements in corpus callosum			
Genu	0.69(0.07)	0.79(0.06)	0.03*
Splenium	0.74(0.06)	0.74(0.06)	0.26

Note. FA, fraction anisotropy (standard deviation); Values are means (standard deviations) in Student's t-test; p shows statistical comparison between participants with periventricular white matter lesions and no white matter lesions.
* $p < 0.05$.

Table 4: Brain regions demonstrating statistically significant difference in cortical thickness in comparisons PVHS<C

Anatomical location	side	PWMHs<Cs			Max t	P
		MNI coordinates				
		x	y	z		
Frontal						
Frontal pole	Left	-6	60	-21	2.93	0.001
	Right	7	62	-19	2.66	0.001
Orbitofrontal	Left	-4	24	-26	4,12	0.001
	Right	5	26	-28	4.02	0.001
Superior frontal gyrus	Left	-9	-30	11	4.08	0.01
	Right	6	-16	2	3.74	0.01
Middle frontal gyrus	Left	-25	-25	30	3.29	0.001
	Right	25	-11	24	3.98	0.001
Temporal						
Superior temporal gyrus	Left	-44	-30	11	4.97	0.01
	Right	66	-16	3	4.36	0.01
Middle temporal gyrus	Left	-61	-25	-5	4.34	0.01
	Right	65	-11	-16	4.20	0.01
Insula	Left	-36	-16	5	4.78	0.01
	Right	38	-8	-9	5.69	0.01
Occipital						
Lingual	Left	-16	-54	6	3.05	0.01
	Right	12	-57	-3	2.95	0.01
Cuneus	Left	-12	-78	12	2.91	0.01
	Right	9	-86	-19	2.95	0.01

Note. PVHS = periventricular hyperintensities; C= Healthy controls, MNI =Montreal Neurological Institute. MNI coordinates are based on a standard brain template defined by using multiple MRI scans of normal controls. The coordinates x, y and z refer to the anatomical location, indicating standard stereotactic space as defined by Talairach and Tournoux . In this table, the reported voxels are $p < 0.01$ or $p < 0.001$(FDRcorrected) as indicated; FDR threshold values of significance were 1.8921 on the left,and 2.0032 on the right hemisphere.

Cognitive function

Comparing the cognitive tests between patients with PWMH and the controls showed significant decline in attention, visuospatial skills, language, executive function (all P values<0.05) (Table 2).

DTI measurement

The DTI measurements showed a significant group effect with decreased FA in the genu of the corpus callosum and in the bilateral anterior and posterior PVWM (all P values < 0.05) (Table 3).

Cortical thickness measurement

Comparing the cortical mantle between patients with PWMH and the controls showed significant cortical thinning throughout the lateral and medial frontal lobes and temporal lobes. In the bilateral frontal lobes, the most significant amount of thinning was apparent in the dorsolateral prefrontal gyrus, the medial frontal gyrus, the superior and middle frontal gyri and the orbitofrontal gyrus. In the bilateral temporal lobes, cortical thinning was detected in the superior and middle temporal gyri and insula. In the bilateral occipital lobes, cortical thinning was displayed in the lingual and cuneus gyri (all P values < 0.05) (Table 4).

Correlation analyses

Associations of demographic and clinical variables with cognitive tests: To clarify other potential confounding variables that might influence the correlation between the DTI measurements and cognitive function, we evaluated the associations between cognitive function and clinical and demographic variables. We found that age was inversely related to executive function; years of education was positively related to attention, language, and visuospatial skills; and women had lower scores than men on attention and language. Additionally, we found that participants with hypertension had lower language scores (all P values < 0.05) (Table 5).

Associations of DTI measurements with cognitive tests: The FA of both anterior (right β =0.445, P=0.002 and left β=0.452 P=0.001) and posterior (right β =0.534 P=0.003 and left β=0.511 P=0.002) PVWM was significantly associated with executive function. FA of both posterior PVWM (right β=0.514 P=0.002 and left β=0.462 P=0.001) was also significantly associated with language. All of the statistical analyses were controlled for the confounding factors of age, sex, years of education, and treatable cardiovascular risk factors (Table 6, Model 1).

Associations of cortical thickness with cognitive tests: The cortical thickness (CTH) in the dorsolateral prefrontal gyrus (left β=0.664; p=0.001 and right β=0.616; p=0.001), the medial frontal gyrus (left β=0.581; p=0.001 and right β=0.563; p=0.001), the superior (left β=0.517; p = 0.003 and right β=0.442; p=0.004)and middle frontal gyri (left β=0.431; p=0.006 and right β=0.374; p=0.008), the orbitofrontal gyrus (left β=0.416;p = 0.027 and right β= 0.445; p= 0.031), the superior (left β=0.332; p=0.005 and right β=0.296;p=0.004) and middle temporal gyri (left β=0.412; p = 0.003 and right β=0.352; p=0.007), the insula (left β=0.342; p=0.036 and right β=0.296; p=0.041) and the lingual (left β=0.292; p=0.045 and right β=0.286; p= 0.039) and cuneus gyri (left β=0.223; p=0.035 and right β=0.216; p=0.040) of the bilateral hemisphere was correlated with executive function. The CTH in the middle frontal gyrus (left β=0.312; p=0.001 and right β=0.266; p= 0.001), the superior (left β=0.302; p=0.012 and right β=0.276; p=0.021) and middle temporal gyri (left β=0.282; p=0.025 and right β=0.246; p=0.021), and the lingual (left β=0.182; p=0.034 and right β=0.166; p=0.041) and cuneus gyri (left β=0.132; p=0.045 and right β=0.126; p=0.031) of the bilateral hemisphere was correlated with language. All of the statistical analyses were controlled for the confounding factors of age, sex, years of education, and treatable cardiovascular risk factors (Table 7, Model 2).

Associations among DTI measurements, cortical thickness and cognitive tests: DTI measurements were no longer associated with the cognitive tests after we added cortical thickness as a predictor (Model 3). The CTH in the dorsolateral prefrontal gyrus (left β=0.554; p=0.001 and right β=0.506; p=0.001); the medial frontal gyrus (left β=0.4581; p=0.001 and right β=0.443; p=0.002); the superior (left β=0.412; p = 0.004 and right β=0.382; p=0.006) and middle frontal gyri (left β=0.381; p=0.016 and right β=0.334; p=0.017); the orbitofrontal gyrus (left β=0.316; p = 0.032 and right β= 0.295; p= 0.041); the superior (left β=0.232; p=0.015 and right β=0.216; p=0.024) and middle temporal gyri (left β=0.312; p = 0.033 and right β=0.282; p=0.027); the insula (left β=0.242; p=0.037 and right β=0.226; p=0.039) and the lingual (left β=0.232; p=0.048 and right β=0.218; p= 0.032) and cuneus gyri (left β=0.123; p=0.038 and right β=0.116; p=0.044) of the bilateral hemisphere had an independent influence on executive function. The CTH in the middle frontal gyrus (left β=0.272; p=0.001 and right β=0.246; p= 0.002), the superior (left β=0.282; p=0.016 and right β=0.256; p=0.028) and middle temporal gyri (left β=0.263; p=0.035 and right β=0.216; p=0.031), and the lingual (left β=0.162; p=0.038 and right β=0.154; p=0.042) and cuneus gyri (left β=0.112; p=0.035 and right β=0.106; p=0.021) of the bilateral hemisphere predicted language. All of the statistical analyses were controlled for the confounding factors of age, sex, years of education, and treatable cardiovascular risk factors (Table 8, Model 3).

Table 5: Association of demographic and clinical variables with cognitive domains

	EF	Attention	Language	VS
Age	0.02(0.81)	-0.08(0.43)	0.04(0.62)	-0.07(0.48)
Sex	0.01(0.98)	2.12(0.03)*	1.97(0.04)*	0.06(0.85)
Education	0.02(0.87)	0.44(0.01)*	0.42(0.01)*	0.32(0.01)*
Hypertension	0.56(0.48)	1.26(0.17)	2.15(0.02)*	1.68(0.88)

Note. EF=Executive Functioning; VS= Visuospatial Skills; Education = years of education; Hypertension = arterial hypertension; Values are Pearson correlation coefficients (p value) in age. Values are Spearman rank correlation coefficients (p value) in years of education. Values are Student's t (p value) in sex and in the treatable cardiovascular risk factors; * Confounding factor (p<0.05).

Table 6: Multivariate linear regression for association of diffusion tensor with cognitive domains (Model 1)

		EF	Attention	Language	VS
Diffusion tensor measurements in periventricular white matter	Anterior L/R	*/*	⊥	⊥	⊥
	Posterior L/R	*/*	⊥	*/*	⊥
Diffusion tensor measurements in subcortical white matter	Anterior L/R	⊥	⊥	⊥	⊥
	Posterior L/R	⊥	⊥	⊥	⊥
	Temporal L/R	⊥	⊥	⊥	⊥
Diffusion tensor measurements in corpus callosum	Genu	⊥	⊥	⊥	⊥
	Splenium	⊥	⊥	⊥	⊥

Note. EF=Executive Functioning; VS= Visuospatial Skills; Values are Pearson correlation coefficients; *For all subjects; Pearson correlation analysis. We controlled age, sex, years of education, and treatable cardiovascular risk factors related to cognitive performance; * p< 0.05.

Table 7: Multivariate linear regression for the association of regional brain cortical thickness with cognitive domains (Model 2)

Cortical thickness		EF	Attention	Language	VS
Frontal	Frontal pole L/R	*/*	⊥	⊥	⊥
	Orbitofrontal L/R	*/*	⊥	⊥	⊥
	Superior frontal gyrus L/R	*/*	⊥	⊥	⊥
	Middle frontal gyrus L/R	*/*	⊥	*/*	⊥
Temporal	Superior temporal gyrus L/R	*/*	⊥	*/*	⊥
	Middle temporal gyrus L/R	*/*	⊥	*/*	⊥
	Insula L/R	*/*	⊥	⊥	⊥
Occipital	Lingual L/R	*/*	⊥	*/*	⊥
	Cuneus L/R	*/*	⊥	*/*	⊥

Note. EF=Executive Functioning; VS= Visuospatial Skills; Values are Pearson correlation coefficients; *For all subjects; Pearson correlation analysis. We controlled age, sex, years of education, treatable cardiovascular risk factors related to cognitive performance/ and intracranial volume on cortical thickness; * p < 0.05.

Table 8: Multivariate linear regression for the relationship among fraction anisotropy of region-of-interest, regional brain cortical thickness and cognitive domains (Model 3)

		EF	Attention	language	VS
Diffusion tensor measurements in periventricular white matter	Anterior L/R	*/*	⊥	⊥	⊥
	Posterior L/R	*/*	⊥	*/*	⊥
Diffusion tensor measurements in corpus callosum	Genu	⊥	⊥	⊥	⊥
	Splenium	⊥	⊥	⊥	⊥
Diffusion tensor measurements in subcortical white matter	Anterior L/R	⊥	⊥	⊥	⊥
	Posterior L/R	⊥	⊥	⊥	⊥
	Temporal L/R	⊥	⊥	⊥	⊥
Cortical thickness					
Frontal	Frontal pole L/R	*/*	⊥	⊥	⊥
	Orbitofrontal L/R	*/*	⊥	⊥	⊥
	Superior frontal gyrus L/R	*/*	⊥	⊥	⊥
	Middle frontal gyrus L/R	*/*	⊥	*/*	⊥
Temporal	Superior temporal gyrus L/R	*/*	⊥	*/*	⊥
	Middle temporal gyrus L/R	*/*	⊥	*/*	⊥
	Insula L/R	*/*	⊥	⊥	⊥
Occipital	Lingual L/R	*/*	⊥	*/*	⊥
	Cuneus L/R	*/*	⊥	*/*	⊥

Note. EF=Executive Functioning; VS= Visuospatial Skills; We controlled age, sex, years of education, and treatable cardiovascular risk factors related to cognitive performance in all types of model. Model 1 = relationship between fraction anisotropy of region-of-interest and cognitive domains; Model 2 = relationship among fraction anisotropy of region-of-interest, regional brain cortical thickness and cognitive domains; * p < 0.05.

DISCUSSION

Three major findings were noted in the present study. First, patients with PWMH had lower scores for language and executive function. Next, decreased FA values of PVWM were significantly associated with cortical thinning in the dorsolateral prefrontal gyrus, the medial frontal gyrus, the superior and middle frontal gyri, the orbitofrontal gyrus, the superior and middle temporal gyrus, the insula and the lingual and cuneus gyri. Finally, our study results support the hypothesis that PWMHs were associated with cortical thinning, which accounts for the language and executive dysfunctions in these patients.

We found that the decreased FA values of the frontal and parietal PVWM were associated with executive function and verbal fluency impairments after adjusting for age, sex, years of education, and treatable cardiovascular risk factors. Previous conventional MRI studies suggested the association of periventricular WMLs with executive function and verbal fluency impairments [24]. Moreover, a recent DTI-related study also showed that executive function and verbal fluency performance were associated with white matter changes in the frontal and parietal PVWM [25].

In the present study, the typical finding for the subjects with PWMH compared to the controls was wide cortical thinning located bilaterally in the lateral and medial frontal lobes, temporal lobes and occipital lobes. This finding is consistent with previous research showing that PWMH is negatively correlated with cortical thickness in the frontal and perisylvian regions [26]. Previous studies have shown that WMLs are associated with cortical thinning [27]. WMLs cause cortical thinning through several mechanisms. Denervation correlated with loss of white matter connections may result in secondary changes in the cortex [28]. Alternatively, cortical hypoperfusion or microinfarcts, which are not detected by current neuroimaging but are associated with WMLs, can also lead to cortical thinning. On the other hand, cortical neuronal loss may induce downstream axonal loss and demyelination, resulting in WMLs [29].

More importantly, we showed that the associations between PWMH and cognitive performance were lost when cortical thickness was added into the models. These findings suggest that the correlation between cognitive impairment and WMLs is mediated by cortical atrophy. This finding is consistent with previous research showing that WMHs do not correlate significantly with levels of cognitive impairment, especially when grey matter loss is accounted for [28]. Recent studies examining patients with age-related confluent WMLs also showed that cognitive impairment with confluent WMLs was directly related to frontal atrophy and that such atrophy is in turn related to WML severity [30]. In contrast, several previous studies found that both PWMH and frontal thinning were independently associated with executive dysfunction [26, 31-33]. There may be several explanations for this discrepancy. First, our study used samples with mild cognitive impairment and healthy controls, while the previous study compared patients with Alzheimer's disease and subcortical vascular dementia. Second, samples were limited to patients with PWMH on MRI in our study, while the previous studies included diffuse WMLs.

This study has a number of limitations. First, the number of participants is low, possibly giving rise to Type II errors. Future work with larger numbers of patients with PWMH and controls is necessary and may provide more information. Second, we used only brief cognitive measures. Future studies should employ more extensive cognitive performance batteries. Finally, although we performed the ROI-based approach extremely carefully, the normal problems of manual ROI methods (which include limitations to circumscribing tissue and structural boundaries) could not be absolutely excluded.

In conclusion, our study suggests that the domains of cognitive impairment affected in patients with PWMH are executive function and verbal fluency, but these associations are mediated by cortical thinning.

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