MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2020; 26: e921874
DOI: 10.12659/MSM.921874

Received: 2019.12.03
Accepted: 2020.01.03
Published: 2020.01.15

Differential Influence of Location-Specific White-Matter Hyperintensities on Attention Subdomains Measured Using the Attention Network Test

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Data Interpretation D
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Source of support: This work was supported by the Anhui Province Key Laboratory of Cognition and Neuropsychiatric Disorders, China; the Collaborative Innovation Center for Neuropsychiatric Disorders and Mental Health, Anhui Province, China; the National Key Research and Development Program of China (2016YFC1300600); and the Projects of National Natural Science Foundation of China (91432301)

Background: Elderly people with white-matter hyperintensities (WMHs) typically show cognitive impairment. Attention, consisting of 3 independent component processes (alerting, orienting, and executive control), is crucial for cognitive functioning. Little is known about how WMHs interfere with these attention subdomains. In the present study, we sought to describe characteristics of attention deficits in patients with age-related WMHs and to assess whether the severity and location of lesions differentially affect specific attention subdomains using the attention network test (ANT), which is a computer-based paradigm tailored to accurately provide behavioral measures of the aforementioned subdomains.

Material/Methods: A total of 39 WMH patients and 39 age-, sex-, and education-matched controls underwent comprehensive neuropsychological and ANT evaluation. Brain magnetic resonance imaging (MRI) was performed to visualize severity of total and location-specific WMH lesions. Multiple linear regression analyses adjusted for possible confounders were performed.

Results: Compared with controls, WMH patients showed pronounced deficits in orienting and executive control efficiencies ($P<0.050$), but not alerting efficiency ($P=0.642$). As total WMH severity increased, efficiencies in the impaired subdomains significantly declined ($P<0.050$). In terms of lesion location, fronto-parietal type of periventricular WMH (PWMH) and deep WMH (DWMH) in the parietal lobe affected orienting efficiency, while all PWMH types and DWMH in the frontal, parietal, and temporal lobes affected executive control efficiency ($P<0.050$). Additional adjustment for other MRI lesions significantly changed the impact on orienting, but not on executive control efficiency.

Conclusions: Our results reveal specific attention deficits in patients with age-related WMH and may help clarify how the location of lesions influences their effects on attention subdomains.

MeSH Keywords: Attention • Executive Function • Leukoencephalopathies

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/921874

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Background

White-matter hyperintensity (WMH) of presumed vascular origin, also called leukoaraiosis or white-matter lesion, is the most common lesion in age-related cerebral small vascular disease (SVD). It commonly appears as bilateral and symmetrical hyperintense signals on T2-weighted images in white-matter areas, and is mainly a consequence of chronic hypoperfusion and breakdown of the blood-brain barrier [1]. WMH was historically considered silent because of its insidious onset and slow progression. Recent epidemiological studies taking advantage of the widespread use of magnetic resonance imaging (MRI) check-ups suggest that the prevalence of WMH is approximately 11–21% in adults around 65 years and up to 94% in the elderly [2]. Thus, the lesion has been extensively studied as a correlate of vascular changes in the ageing brain. Accumulating evidence from population-based data identifies the WMH as a major risk factor for stroke, all-cause mortality, and functional disturbance (e.g., gait and urinary impairment) [3–7]. Many elderly people frequently experience a spectrum of cognitive symptoms that can affect daily living, which highlights the importance of characterizing the impact of WMH on cognitive abilities. WMH lesions have been typically linked to deficits in information-processing speed and executive function arising from frontal-subcortical circuit dysfunction [8,9]. This implies a link between WMH and attention, since attention involves the allocation of limited cognitive resources for information processing and is essential for most types of cognitive functioning and social skills [10]. However, studies on WMH and attention have reported mixed results, which may reflect the difficulty of detecting mild cognitive defects using conventional neuropsychological scales and the masking of these defects by other clinical symptoms. These mixed results may also reflect differences in study populations, such as whether they have already manifested cognitive symptoms (e.g., mild cognitive impairment) or are high-risk populations with vascular risk factors or vascular disease [8]. Attention in many studies has been measured using the Stroop test and trail making test, which has the disadvantages that it involves subjective effects, mainly represents executive function, and is inappropriate for less-educated subjects [11]. Studies also tend to aggregate the attention function with other cognitive domains such as psychomotor speed or executive function using a composite score [8,12].

The present study examined attention specifically using an instrument that separates it from other processes: the attention network test (ANT) [13], based on attention network theory [14]. This theory, which integrates the findings of functional imaging and lesion studies, postulates that attention not simply represent a general property of the whole brain, but rather consists of 3 independent subdomains, each representing a different set of attentional processing networks. These attention subsystems include an alerting component, which produces and maintains optimal vigilance to detect upcoming stimuli; an orienting component, which selects high-priority information from numerous sensory inputs for further processing; and an executive control component, which resolves conflicts among numerous stimuli. This theory permits the use of attention as a model for exploring relationships between brain function and behavior. The computer-based ANT paradigm can effectively differentiate among the attention subdomains, allowing researchers to address whether attention dysfunction reflects a global deficit of cognitive abilities or selective impairment of specific attention subdomains. These attentional subdomains involve different anatomical regions of the brain, based on pharmacological, electrophysiological, and neuroimaging studies [15]. Generally speaking, the alerting system is associated with the thalamus and the parietal cortical networks in the right hemisphere. The orienting system interacts with the temporal-parietal junction and superior parietal lobe. The executive control system has been found to be related to the midline frontal areas and the prefrontal cortex, including the anterior cingulate, lateral prefrontal cortex, and the right inferior frontal gyrus. From the perspective of attention network theory, cognitive evaluation using the ANT has helped clarify the specific mechanisms of attention dysfunction in various neuropsychiatric disorders [16–18], but this literature has neglected WMH patients. Therefore, we sought to provide a comprehensive evaluation of attentional functioning measured by the ANT in conjunction with various neuropsychological tests among patients with age-related WMH. We hypothesized that WMH patients would show selective impairment of attention subdomains, and we wanted to examine whether lesion severity and location significantly affect the association between WMH and attention function as well as neuropsychological performance.

Material and Methods

Study participants

This case-control study involved consecutive inpatients or outpatients admitted to the Cerebrovascular Disease Clinic in the Department of Neurology at the First Affiliated Hospital of Anhui Medical University between June 2017 and June 2018, who were aged 50–85 years, right-handed, and diagnosed with ischemic WMH based on magnetic resonance imaging (MRI) (Fazekas score > 2) [19]. We followed the inclusion procedure of the LADIS (leukoaraiosis and disability) study [5]. The most frequent reasons for which patients were referred to our hospital were chronic symptoms (e.g., complaints related to cognitive status, gait, and mood), regular follow-up after a transient ischemic attack or clinical lacunar stroke syndrome, or unintentional findings on MRI or computed tomography (CT).

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For patients with clinical lacunar syndrome, cognitive testing was performed at least 3 months after stroke onset to avoid any acute effects of stroke on cognitive performance.

Patients were excluded if medical records, neuroimaging, and laboratory examinations indicated a non-vascular or hereditary form of leukoaraiosis, such as multiple sclerosis, CO poisoning, metabolic origin, vasculitis, cerebral autosomal dominant arteriopathy with subcortical infarcts, and leukoencephalopathy. We further excluded patients who declined to participate or who had been diagnosed with movement disorders, other diseases that severely affect cognitive function, or serious physical illnesses. Patients with comorbid anxiety or depression (Hamilton Anxiety Scale and Hamilton Depression Scale scores >7) were also excluded.

Control subjects were recruited during the same period from among patients who were seen at the same clinic for unrelated reasons and who showed no evidence of WMH, lacunar infarction, or the aforementioned diseases. Control subjects who were first admitted were matched to WMH patients for age, sex, years of education, and date of clinic visit. All controls were drawn from the same geographic regions as the patients. This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Anhui Medical University. All subjects signed an informed consent form before undergoing cognitive assessment.

MRI evaluation

All patients underwent MRI on a 3.0-T scanner (GE Signa HDxt, WI, USA). The imaging protocol included axial T1-weighted images (T1WI), axial T2-weighted images (T2WI) fast-spin echo (FSE), axial fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted imaging (DWI) sequences. The settings of FLAIR parameters were: TR/TE=8000–9000/140–200 millisecond, FOV=220×220 mm, slice thickness=5 mm, and pixel spacing=1.5 mm. The FSE T2WI images were obtained at TR/TE=3000–4500/80–150 millisecond, FOV=220×220 mm, slice thickness=5 mm, and pixel spacing=1.5 mm. Definitions of MRI lesions were based on the STRIVE guidelines [20]. WMH was defined as spotty or patchy changes in periventricular white matter or the centrum semiovale. T1WI presented as iso- or hypointense signals, and T2WI and FLAIR presented as hyperintense signals. The visual Fazekas scale rates total WMH burden in both the periventricular and subcortical regions on a 3-point scale [19]. We defined extensive WMHs as deep WHM (DWMH) with Fazekas scores 2–3 (confluent lesions) or periventricular WMH (PWMH) with Fazekas score 3 (irregular lesions extending into the deep white matter) [21]. To evaluate the location-specific effects of WMH on attention, the semiquantitative Scheltens scale was used to assess regional WMH burden separately in the periventricular and subcortical regions based on lesion size and number [22]. Specifically, PWMH was subdivided into 3 severity types: adjacent to anterior horns of the lateral ventricles (frontal caps), adjacent to posterior horns of the lateral ventricles (occipital caps), and along the lateral ventricles in the fronto-parietal regions (bands). We graded each PWMH type according to the following criteria: 0 point=none, 1 point=smooth halo (1–5 mm), and 2 points=large confluent lesions (5–10 mm). Subcortical DWMH was rated for each of frontal, temporal, parietal, and occipital WMHs as follows: 0 point=none; 1 point=size <4 mm and number <5; 2 points=size <4 mm and number >5; 3 points=4–10 mm and number <5; 4 points=size 4–10 mm and number >5; 5 points=size >10 mm and number >1; 6 points=confluent lesions. This scale also includes ratings for basal ganglia and infratentorial areas according to the criteria for DWMH. We analyzed the types of DWMH separately because recent international SVD guidelines suggest that lesions in the subcortical grey matter or brainstem should not be included in the category of SVD-related WMH [20].

Several other MRI features of SVD were also assessed in our study. Lacunes were defined as rounded or ovoid lesions of cerebrospinal fluid-like signal intensity with a diameter of 3–15 mm, generally with a surrounding rim of hyperintensity on the FLAIR sequence, and with no hyperintense signal on the DWI sequence. This definition accords with the STRIVE criteria and has been applied in previous studies [23,24]. Non-strategic lacunes were evaluated and counted in the basal ganglia, thalamus, internal or external capsule, or brain stem, and the number of lacunes was categorized as none, few (1–3), or many (>4) [5]. Enlarged perivascular space (EPVS) was defined as a lesion appearing as round (axial section) or linear-shaped (longitudinal section) with a diameter of no more than 3 mm and without a hyperintense rim. EPVS lesions were hyperintense signals on T2WI FSE, but usually were not visible on FLAIR; if visible on FLAIR, they were hypointensive signals on FLAIR and T1WI. The number of EPVS across the slide of basal ganglia was counted within the most affected hemisphere, and was graded into 3-point categories (0–10, 10–25, or >25) [25,26]. However, we could not determine EPVS scores for controls because they lacked the T2 FSE sequence. Cerebral atrophy was defined as ventricular and sulcal widening based on FLAIR or T1WI and reference brain MRI template of normal subjects. Enlargement of ventricles (deep) and sulcus (peripheral) was rated as absent, mild, moderate, or severe, using a 3-point scale [27]. Two trained raters (S.S.C. and W.P.), blinded to clinical data, assessed all MR images, and any disagreements were resolved through discussion with another professional neurologist when necessary. Interobserver reliability (Cohen kappa score) was determined through 2 evaluations of 11 scans (WMH, 0.72; high-grade EPVS, 0.84; lacune, 0.82; global atrophy, 0.66).

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Neuropsychological assessment

Trained examiners who were blinded to the clinical and categorization information of participants administered a well-established standardized battery of neuropsychological tests to determine a comprehensive cognitive profile. Tests included the Montreal Cognitive Assessment (MoCA), Digit Span (DS) subtest of the Wechsler Adult Intelligence Scale-Revised, Color Trial Test (part A and part B), Stroop color-word test, verbal fluency test (VFT), and episodic memory (Chinese auditory verb learning test) (Supplementary Table 1). These tests can measure patterns of cognitive impairment associated with SVD [28]. All subjects were informed of the test scores only after all data had been collected.

Attention network test

The ANT paradigm in our study included a full-feedback practice stage with 24 trials and triplicate 96-trial experimental stages without feedback [13]. During assessment, subjects adopted an appropriate sitting position at an approximate distance from the computer screen, with their right fingers placed on the left and right buttons in the keyboard. Subjects were instructed to respond quickly and accurately by pressing the corresponding button once they saw the arrow direction of the target stimulus, which randomly appeared at the top and bottom of the centrally located fixation point. The appearance of the target arrow varied according to 1 of 3 different types of stimuli: neutral, congruent, or incongruent. In the neutral condition, the target stimulus appeared as a single arrow flanked by 4 horizontal lines. In the congruent condition, the direction of the target arrow was the same as that of the remaining 4 arrows. In the incongruent condition, the target arrow was accompanied by pairs of opposite arrows in the sides. The presence of target stimuli was preceded by 1 of 4 cue conditions: no cue, central cue, double cue, and spatial cues. In the no cue condition, only the central fixation point appeared. In the central cue condition, there was an asterisk cue in the center. In the double cue condition, there were 2 cues simultaneously below and above the fixation point. These cues did not hint at the correct position of the target stimulus. In the spatial cue condition, the cue presented above or below the fixation point at which the target stimulus consistently appeared. The computer recorded reaction time (RT) and accuracy throughout the experiment.

In our study, the ANT experiment occurred in 4 stages. In the first stage, a "+" fixation point randomly appeared on the screen, with a duration of 400–1600 milliseconds (fixation phase). During the second stage, the cue stimulus appeared for a fixed duration of 100 milliseconds. In the third stage, the fixation point appeared on the screen for 400 milliseconds. In the fourth stage, the target stimulus appeared until the subject pressed a key in response. During this stage, the stimulus appeared for a maximum duration of 2700 milliseconds. If the subject's response time was shorter than that, the target stimulus disappeared after the subject pressed the key. Based on the duration and reaction time in the first stage, the computer adjusted the duration after the subject pressed the key for the target stimulus, in order to ensure a fixed experimental interval. Each run featured 48 experimental conditions: 2 directions for target stimuli ×4 types of cues ×3 flanker conditions ×2 target positions. The different experimental conditions were presented to subjects in a randomized sequence.

Efficiencies of different attention subdomains

We calculated the efficiency of the alerting, orienting, and executive components based on the RTs of various experimental conditions, as described previously [13]. The alerting efficiency was obtained by subtracting the mean RT under the double cue condition from the value under the no cue condition; the orienting efficiency, by subtracting the mean RT under the spatial cue condition from that under the central cue condition; and the executive control efficiency, by subtracting the mean RT under congruent conditions from that under incongruent conditions. Higher mean scores for alerting and orienting components indicate greater efficiency; conversely, higher mean scores for the executive control component indicate lower efficiency. We also calculated the overall mean RT and accuracy during the entire trial.

Statistical analysis

For analyses involving total WMH, we divided patients into mild or extensive WMH groups according to the aforementioned definitions because of the small sample assigned to each Fazekas score. For analyses involving regional WMH, we classified patients by lesion burden as none, mild, or extensive. The median Scheltens score was used to separate the mild and extensive groups. Inter-group differences in continuous variables were assessed for significance using the *t* test or the Mann-Whitney U test, and differences in categorical variables were assessed using the chi-square test. Alternatively, one-way ANOVA or Kruskal-Wallis tests were performed when appropriate. To control for multiple comparisons, post hoc comparisons with adjusted alpha level were conducted. Least square means and 95% confidence intervals were calculated for efficiencies of attention subdomains according to the categories of WMH burden. We applied multivariable linear regression models to assess the independent relationships of MRI lesions and neuropsychological tests with efficiencies on the 3 attention subdomains. Models were initially adjusted for age, sex, group, and years of education. Our analyses were further adjusted for MoCA and overall mean RT because of the influence of global cognition and mental flexibility on attention. We applied similar covariates

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Table 1. Demographic and neuropsychological characteristics of study participants.

Characteristics	WMH patients (n=39)	Extensive WMH (n=24)	Mild WMH (n=15)	Healthy control (n=39)	*P* value
Age (years), mean (SD)	69.23 (9.31)	69.92 (10.83)	68.13 (6.36)	68.26 (9.00)	0.754
Female, n (%)	19 (48.72)	11 (45.83)	8 (53.33)	17 (43.59)	0.794
Years of education, mean (SD)	8.54 (2.80)	8.12 (2.72)	9.20 (2.88)	8.90 (3.16)	0.480
Lacunes, n (%)					<0.001
None	19 (48.7)	10 (41.7)	9 (60.0)	39 (100)	
Few	14 (35.9)	10 (41.7)	4 (26.7)	0 (0)	
Many	6 (15.4)	4 (16.7)	2 (13.3)	0 (0)	
Global atrophy, n (%)*					0.166
None	6 (15.4)	2 (8.3)	4 (26.7)	11 (28.2)	
Mild	23 (59.0)	14 (58.3)	9 (60.0)	23 (59.0)	
Extensive	10 (25.6)	8 (33.3)	2 (13.3)	5 (12.8)	
Neuropsychological tests					
HAMA, median(IQR)	2.00 (1.00–3.00)	2.00 (1.00–2.00)	2.00 (1.00–3.00)	1.00 (1.00–2.00)	0.181
HAMD, median(IQR)	2.00 (1.00–2.50)#	2.00 (1.00–2.00)	2.00 (1.50–3.00)	2.00 (1.00–2.00)	0.167
MoCA, mean (SD)	21.69 (2.78)##	21.54 (2.75)	21.93 (2.91)	23.92 (2.79)	0.003
Digital span, median (IQR)					
DS-forward	8.00 (7.00–8.00)	8.00 (7.00–8.00)	8.00 (8.00–8.00)	8.00 (8.00–8.00)	0.123
DS-backward	5.00 (3.50–5.00)#	4.50 (3.00–5.00)	5.00 (4.50–5.00)	5.00 (5.00–6.00)	0.008
VFT, median (IQR)	14.00 (12.00–16.00)#	12.50 (10.00–15.25)	15.00 (15.00–16.00)	15.00 (14.00–16.00)	0.014
CAVLT, mean (SD)					
Immediate recall	9.26 (1.62)##	8.79 (1.56)	10.00 (1.46)	10.85 (1.37)	<0.001
Delayed recall	7.41 (1.58)##	6.96 (1.43)	8.13 (1.60)	8.92 (1.69)	<0.001
Recognition	6.51 (1.83)##	6.08 (1.74)	7.20 (1.82)	8.08 (1.92)	<0.001
SCWT (sec), mean (SD)@					
Stroop-dot test	23.10 (7.32)#	24.79 (7.42)	20.40 (6.52)	19.21 (6.22)	0.007
Stroop-word test	29.04 (8.51)#	31.15 (8.91)	25.66 (6.82)	24.15 (7.55)	0.004
Stroop-Interference test	42.71 (12.46)#	45.30 (12.94)	38.58 (10.79)	34.91 (10.62)	0.003
CTT(sec), mean(SD)@					
CTT-A	83.02 (19.03)##	84.63 (18.61)	80.45 (20.05)	61.05 (13.40)	<0.001
CTT-B	139.60 (29.12)##	143.55 (28.89)	133.29 (29.35)	99.26 (22.95)	<0.001

WMH – white matter hypertensity; HAMA – Hamilton Anxiety Scale; HAMD – Hamilton Depression Scale; MoCA – Montreal Cognitive Assessment; VFT – verbal fluency test; CAVLT – Chinese auditory verb learning test; SCWT – Stroop color-word test; CTT – color trial test; SD – standard deviation; IQR – interquartile range. * Mild global atrophy (0-6 score) was defined as total score of 1 and 2 on a rating scale, and extensive global atrophy was defined as a total score >2. # *P*<0.05 for WMH *vs.* control. ## *P*<0.001 for WMH *vs.* control. @ Higher score corresponded to lower performance unless otherwise noted.

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Table 2. Efficiencies in three attention subdomains in healthy controls and WMH patients stratified by severity(based on Fazekas scores).

	Adjusted means and 95% confidence interval (CI)*		Adjusted means and 95% CI across total WMH burden categories			P_{trend} value
	Healthy control (n=39)	WMH patients (n=39)	Healthy control (n=39)	Mild WMH (n=15)	Extensive WMH (n=24)	
Crude RT (ms)						
Alerting	26.42 (16.27, 36.56)	30.07 (19.93, 40.22)	26.27 (16.12, 36.43)	24.33 (8.69, 39.97)	33.89 (21.02, 46.76)	0.405
Orienting	65.30 (55.66, 74.93)	50.45 (40.81, 60.08)##	65.52 (55.99, 75.05)	59.59 (44.91, 74.27)	44.37 (32.29, 56.45)	0.014
Executive control	107.45 (95.46, 119.45)	145.88 (133.89, 157.87)@	107.16 (95.32, 118.99)	133.69 (115.47, 151.92)	153.98 (138.99, 168.98)	<0.001
Standardize-d RT#						
Alerting ratio	0.03 (0.02, 0.04)	0.04 (0.02, 0.05)	0.03 (0.02, 0.04)	0.03 (0.01, 0.05)	0.04 (0.02, 0.05)	0.417
Orienting ratio	0.08 (0.07, 0.09)	0.06 (0.05, 0.07)	0.08 (0.07, 0.09)	0.07 (0.06, 0.09)	0.06 (0.04, 0.07)	0.020
Executive control ratio	0.13 (0.11, 0.14)	0.16 (0.15, 0.18)@	0.13 (0.11, 0.14)	0.15 (0.13, 0.17)	0.17 (0.16, 0.19)	<0.001
Overall mean RT (ms)	833.30 (790.72, 875.88)	916.52 (873.94, 959.10)##	833.61 (791.37, 875.85)	877.73 (811.04, 944.43)	940.26 (887.51, 993.00)	0.004
Accuracy	0.95 (0.94, 0.97)	0.95 (0.93, 0.96)	0.95 (0.94, 0.97)	0.95 (0.93, 0.97)	0.94 (0.93, 0.96)	0.578

MoCA – Montreal Cognitive Assessment; RT – reaction time; ms – millisecond. * Values are least square means and 95% confidence intervals, adjusted for sex (male *vs.* female), age (continuous), years of education (continuous), MoCA score (continuous), and overall mean RT (continuous) when approximate. # The standardized ratio scores were the mean RT of each attention subdomain divided by participant's overall RT. ## $P<0.05$ for WMH patients *vs.* control. @ $P<0.001$ for WMH patients *vs.* control.

adjustment when analyzing the influence of MRI lesions on time-dependent neuropsychological tests. For analyses of ANT data, we additionally controlled for the accuracy of ANT performance. To describe the independent effect of each MRI lesion, other lesions were additionally included in the multivariable models. Subgroup analyses were used to explore whether our primary results varied with group, sex, age (<70 y *vs.* >70 y), or MoCA score (<24 *vs.* >24). Effect modification by prespecified covariates was estimated from the likelihood-ratio test of models with and without interaction terms. Receiver operating characteristic (ROC) analyses were used to determine the sensitivity and specificity of attention subdomain efficiency relative to other cognitive measures. To prove the reliability of results, we defined an alternative category of WMH burden using Fazekas scores in patients as follows: low burden (PWMH 1/DWMH 1, PWMH 1/DWMH 2, PWMH 2/DWMH 1), moderate burden (PWMH 1/DWMH 3, PWMH 2/DWMH 2, PWMH 2/DWMH 3, PWMH 3/DWMH 1, PWMH 3/DWMH 2), and high burden (PWMH 3/DWMH 3). A two-tailed $P<0.05$ was considered statistically significant. All analyses were carried out using R software (*http://www.R-project.org*).

Results

Demographic characteristics

Our study included a total of 39 WMH patients (mean [SD] age, 69.2 [9.3] years; 19 [48.7%] were women) and 39 control subjects (mean [SD] age, 68.3 [9.0] years; 17 [43.6%] were women). There were no significant differences between the groups in age or sex. Of the total patients, 15 (38.5%) had mild WMH lesion burden and 24 (61.5%) had extensive lesion burden. In addition, 51.3% of patients had lacunes. Among patients, 23 (59.0%) showed mild global atrophy and 10 (25.6%) showed extensive global atrophy; among control subjects, 23 (59.0%) showed mild global atrophy and 5 (12.8%) showed extensive atrophy (Table 1). The proportions of location-specific WMH lesions in patients are shown in Supplementary Figure 1. Extensive WMH lesions were observed mostly in the frontoparietal type (bands) of PWMH (61.5%) and DWMH in frontal (61.5%) and parietal lobes (66.7%).

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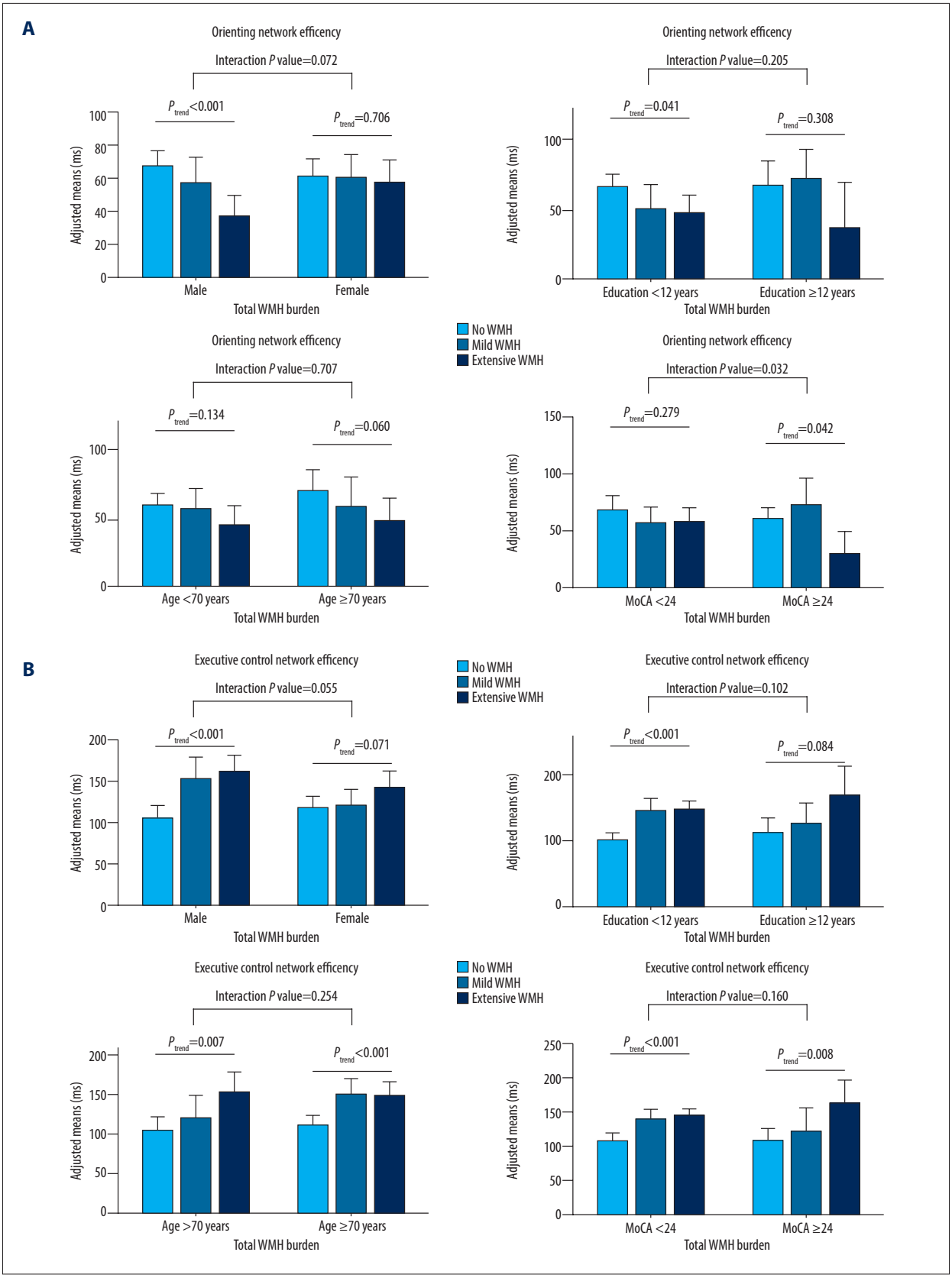

Figure 1. The changing trend of directional network and executive network efficiency was compared with the increase of WMH degree.

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Table 3. Effect of total WMH lesions on the efficiencies of attention subdomains estimated by multivariable linear regression models*.

Attention subdomains	WMH burden#					
	No (n=39)	Mild (n=15)		*P* value	Extensive (n=24)	*P* value
Alerting						
Unadjusted	Ref.	4.07	(–13.80, 21.95)	0.657	15.16 (–0.10, 30.43)	0.055
Adjusted	Ref.	–1.72	(–20.53,17.09)	0.858	8.83 (–8.22, 25.88)	0.314
Orienting						
Unadjusted	Ref.	–1.36	(–17.95,15.23)	0.873	–18.07 (–32.24, –3.90)	0.015
Adjusted	Ref.	–5.50	(–21.25,10.25)	0.496	–18.80 (–33.08, –4.52)	0.012
Executive control						
Unadjusted	Ref.	28.02	(7.52, 48.51)	0.009	50.57 (33.07, 68.08)	<0.001
Adjusted	Ref.	26.23	(4.56, 47.91)	0.021	45.18 (25.53, 64.83)	<0.001

Ref – reference; WMH – white matter hyperintensity. * Data indicated coefficient β and 95% confidence interval. Models were adjusted for age (continuous), sex, group, education (continuous), Montreal Cognitive Assessment (MoCA) score (continuous), overall mean reaction time (continuous) and accuracy (continuous). # WMH burden (score 0-6) was classified and rated according to the Fazekas scale.

Neuropsychological tests

The WMH and control groups did not differ significantly in HAMA, HAMD, DS-forward, or VFT (*P*>0.05; Table 1**)**.WMH patients displayed lower scores than controls on the MoCA (*P*<0.001), DS-backward (*P*=0.004), and delayed memory tests (P<0.001). The WMH group had significantly longer completion time than the control group in the Stroop dot test (P=0.014), Stroop word test (P=0.009), Stroop interference test (P=0.004), CTT-A (P<0.001), and CTT-B (P<0.001). As the WMH burden (based on Fazekas score) increased, there were marked differences on performance in most of the aforementioned tests among the 3 groups (all *P*<0.01). In the Stroop tests, differences were predominantly observed between patients with extensive WMH and controls (post hoc *P*<0.01). In the CTT-A test, patients with extensive or mild WMH had significantly longer completion times than controls (post hoc *P* <0.001).

Efficiencies of attention subdomains

WMH patients showed remarkably lower efficiency than control subjects in executive control (P<0.001) or orienting component (P=0.050; Table 2). The 2 groups did not differ significantly in alerting efficiency (P=0.642). The overall mean RT was longer in WMH patients (916.52 millisecond *vs.* 833.30 millisecond, *P*=0.012). A significant trend was observed toward reduced efficiency in orienting (P_{trend}=0.014) and executive control (P_{trend}<0.001) components with increasing WMH burden. For the orienting component, a difference was observed exclusively in the extensive WMH group (post hoc *P*=0.038). For the executive control component, patients with extensive or mild WMH showed significantly lower efficiency (extensive *vs.* control, *P*<0.001; mild *vs.* control, *P*=0.024; extensive *vs.* mild, *P*=0.121). No group differences were found for alerting efficiency (P=0.405). Furthermore, there was a significant interaction effect between WMH burden and MoCA score (<24 *vs.* >24) for orienting efficiency ($P_{interaction}$=0.032, Figure 1 and Supplementary Table 2).

Because the overall mean RT of the WMH group was significantly longer than that of the control group, we repeated the analysis using a standardized RT to exclude the influence of retardation of global information processing. We calculated a ratio score by dividing the mean RT of each attention subdomain by the participant's overall RT (Table 2). Consistent with the results above, the standardized RT of the executive control component was significantly different between the 2 groups (P<0.001), but the difference in orienting component was of borderline significance (P=0.080).

MRI lesions, efficiencies of attention subdomains, and neuropsychological performance

For ANT performance, the linear regression model controlling for covariates demonstrated that patients with highest total WMH burden had the lowest efficiencies of orienting (P=0.012) and executive control (P<0.001) relative to controls (Table 3). In terms of regional WMH lesions, patients with increased burden of DWMH in the parietal lobe (P=–15.06, 95%CI –29.02, –1.09, P=0.038) had significantly lower orienting efficiency, while all types of PWMH (frontal caps, occipital caps, and bands) and most types of DWMH (frontal, parietal, and temporal regions)

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Table 4. Effects of regional WMH lesions on the efficiencies of attention subdomains estimated by multivariable linear regression models*.

	Alerting			Orienting			Executive control		
	No	Mild	Extensive	No	Mild	Extensive	No	Mild	Extensive
PWMH#									
Total (0-6 points) (N=39/19/20)##	Ref.	2.71 (−14.88, 20.30)	6.49 (−11.97, 24.95)	Ref.	−10.44 (−25.27, 4.40)	−16.61 (−32.18, −1.04)@	Ref.	34.93 (14.44, 55.43)@	40.09 (18.58, 61.60)@@
Frontal caps (0–2 points) (N=39/19/20)##	Ref.	6.94 (−10.75, 24.64)	1.63 (−16.68, 19.95)	Ref.	−11.36 (−26.34, 3.61)	−15.41 (−30.91, 0.09)	Ref.	38.82 (18.16, 59.48)@@	35.59 (14.21, 56.96)@
Occipital caps (0–2 points) (N=39/18/21)##	Ref.	−0.70 (−18.15, 16.75)	10.30 (−7.81, 28.41)	Ref.	−13.17 (−28.07, 1.73)	−13.38 (−28.84, 2.08)	Ref.	36.42 (15.89, 56.94)@@	38.30 (17.00, 59.60)@@
Bands (0–2 points) (N=39/15/24)##	Ref.	4.76 (−15.04, 24.55)	4.27 (−12.53, 21.06)	Ref.	−12.50 (−29.25, 4.24)	−13.70 (−27.91, 0.50)	Ref.	44.99 (22.09, 67.88)@@	32.93 (13.50, 52.36)@@
DWMH#									
Total (0–24 points) (N=39/20/19)##	Ref.	6.60 (−10.36, 23.55)	1.07 (−18.24, 20.38)	Ref.	−8.70 (−22.88, 5.47)	−20.42 (−36.57, −4.27)@	Ref.	36.99 (17.18, 56.79)@@	37.79 (15.23, 60.34)@
Frontal (0–6 points) (N=39/15/24)##	Ref.	9.48 (−9.14, 28.11)	0.43 (−16.97, 17.84)	Ref.	−14.78 (−30.62, 1.06)	−12.07 (−26.87, 2.73)	Ref.	42.49 (20.76, 64.23)@@	33.16 (12.85, 53.48)@
Parietal (0–6 points) (N=39/13/26)##	Ref.	−8.62 (−28.32, 11.07)	10.93 (−5.18, 27.04)	Ref.	−9.67 (−26.74, 7.40)	−15.06 (−29.02, −1.09)@	Ref.	36.03 (12.44, 59.61)@	37.93 (18.64, 57.22)@@
Occipital (0–6 points) (N=44/25/9)##	Ref.	21.07 (−8.31, 50.45)	24.81 (−9.29, 58.91)	Ref.	15.55 (−9.39, 40.48)	6.33 (−22.61, 35.27)	Ref.	−2.44 (−36.93, 32.05)	14.51 (−25.52, 54.54)
Temporal (0–6 points) (N=42/26/10)##	Ref.	−1.24 (−36.76, 34.28)	12.01 (−27.71, 51.73)	Ref.	−15.69 (−45.78, 14.40)	−11.27 (−44.91, 22.38)	Ref.	56.58 (17.11, 96.05)@	60.26 (16.12, 104.39)@

WMH – white matter hyperintensity; PWMH – periventricular white matter hyperintensity; DWMH – deep white matter hyperintensity. * Data indicated coefficient β and 95% confidence interval. Models were adjusted for age (continuous), sex, group, education (continuous), Montreal Cognitive Assessment (MoCA) score (continuous), overall mean reaction time (continuous) and accuracy (continuous). # For PWMH, mild and extensive total burden were respectively defined as Scheltens score of 3–4 points or 5–6 points, since patients in our study score between 3 to 6 points; mild or extensive regional burden were respectively defined as Scheltens score of 1 or 2 points. For DWMH, mild or extensive total burden was respectively defined as Scheltens score of 1–12 or 13–24 points; mild or extensive regional burden were respectively defined as Scheltens score of 1–3 points or 4–6 points, except in the case of occipital burden, where the corresponding score definitions were 1–2 or 3–4 points because the observed scores ranged from 0 to 4 points. ## Numbers in parentheses represent the sample size of each category (no *vs.* mild *vs.* extensive) for regional WMH lesions. @ $P<0.05$; @@ $P<0.001$.

were associated with significantly lower executive control efficiency (all P<0.01, Table 4). Additional adjustment for other MRI lesions, including lacunes and global atrophy, did not significantly attenuate the effects on executive control, but did substantially alter the relationships between all WMH lesions and orienting efficiency (all P>0.05, Supplementary Table 3). Similar results were observed for the independent impact of WMH lesions, especially frontal PWMH and DWMH in frontal and temporal lobes, on the standardized executive control efficiency (Supplementary Table 4). Furthermore, we found that the numbers of lacunes or existence of deep atrophy also had a significant effect on orienting efficiency, even after controlling for other MRI lesions (Supplementary Table 5). Meanwhile, the numbers of lacunes were significantly related to executive control efficiency (P=24.80, 95%CI 0.44, 49.16), but results became non-significant after further adjustment for lesions including

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Table 5. Associations between neuropsychological tests and the efficiencies of attention subdomains estimated by multivariable linear regression models*.

Neuropsychological tests	Alerting		Orienting		Executive control	
	Model I	Model II	Model I	Model II	Model I	Model II
Delayed recall memory	–4.18 (–9.32, 0.95)	–1.81 (–7.43, 3.82)	–1.02 (–5.95, 3.91)	0.67 (–4.10, 5.44)	–1.03 (–7.13, 5.08)	–0.42 (–7.00, 6.16)
VFT	–0.53 (–3.57, 2.50)	–0.88 (–3.99, 2.23)	2.22 (–0.60, 5.05)	0.57 (–2.06, 3.21)	–0.89 (–4.44, 2.66)	0.67 (–2.96, 4.30)
DS-backward	–3.09 (–10.59, 4.40)	–3.54 (–10.95,3.87)	6.51 (–0.44,13.46)	3.85 (–2.39,10.09)	–2.58 (–11.36,6.21)	0.22 (–8.47, 8.91)
Stroop-Interference	–0.24 (–0.94, 0.47)	–0.30 (–1.02, 0.41)	–0.21 (–0.87, 0.45)	0.10 (–0.50, 0.71)	0.43 (–0.38, 1.25)	0.10 (–0.74, 0.94)
Stroop $RT_{incongruent}$–$RT_{neutral}$	–1.35 (–2.6,–0.11)#	–1.14 (–2.37, 0.08)	–0.74 (–1.94, 0.46)	–0.40 (–1.46, 0.65)	0.61 (–0.88, 2.11)	0.45 (–1.00, 1.91)
CTT-A	–0.20 (–0.70, 0.30)	–0.31 (–0.81, 0.20)	–0.15 (–0.62, 0.32)	0.01 (–0.43, 0.44)	0.59 (0.02, 1.16)#	0.43 (–0.16, 1.01)
CTT-B	0.08 (–0.24, 0.39)	0.03 (–0.30, 0.36)	–0.23 (–0.52, 0.06)	–0.12 (–0.40, 0.16)	0.58 (0.24, 0.92)##	0.49 (0.13, 0.86)#
CTT-B-CTT-A	0.34 (–0.12, 0.81)	0.32 (–0.15, 0.79)	–0.39 (–0.82, 0.05)	–0.25 (–0.65, 0.14)	0.80 (0.28, 1.31)##	0.66 (0.13, 1.20)#

VFT – verbal flucency test; DS – digital span; CTT – color trial test. * Data indicated coefficient β and 95% confidence interval. Models were adjusted for age (continuous), sex, group, and education (continuous) in Model I and additional adjustment for Montreal Cognitive Assessment (MoCA) score (continuous), overall mean reaction time (continuous) and accuracy (continuous) in model II. # $P<0.05$; ## $P<0.01$.

WMH and global atrophy (Supplementary Table 5). For other neuropsychological tests, all regional WMH lesions were independently related to decline in recall memory in the fully adjusted model (Supplementary Table 6). All WMH lesions, but not occipital and temporal DWMH, were significantly associated with CTT performance. Only temporal DWMH showed an effect on the Stroop interference test ($P<0.05$). For other MRI lesions, the numbers of lacunes were significantly associated with poorer performance on the CTT-A test (Supplementary Table 7). These associations were not significant in the case of brain atrophy ($P>0.05$).

Exploratory analyses

We observed a significant decline in efficiency of the executive control component for every 1-unit increase in CTT-B score (P=0.49, 95%CI 0.13, 0.86; Table 5). In the subgroup analyses, we further found that age or education level significantly modified the associations between the efficiency of the executive control component and performance on CTT and Stroop interference (all $P_{interaction}<0.05$, Supplementary Figure 2). Other variables, including sex, group, and cognitive status (MoCA) did not appear to modify the aforementioned associations. The ROC curves showed that executive control efficiency discriminated WMH patients from controls (sensitivity 79.5%, specificity 94.9%) better than other neuropsychological markers of attention or memory (an important marker for dementia) (Supplementary Figure 3). Similar results were observed in subpopulations with different cognitive status and age (Supplementary Figure 4).

Additional analyses

In an analysis of another WMH burden category (none, low, moderate, or high), we found a similar and robust trend in the association between increased total WMH severity and decreased efficiency of executive control component (Supplementary Table 8).

Discussion

This cerebral SVD, mainly including WMH, is an important cause of cognitive decline and vascular cognitive impairment. While previous studies have shown associations between general neuropsychological functions and SVD pathologies, evidence linking these lesions to specific impairment of attention subdomains has generally been limited by the absence of definitive attention assessment. Our study is the first to addressed these unsolved issues by using the brief ANT assessment rather

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than only simple neuropsychological tests. The main finding in our study was that patients with age-related WMH had a selective impairment of the orienting or executive attention component, but the alerting component remained preserved. WMH severity was significantly associated with decline in the efficiencies of the 2 impaired subdomains, and these effects remained equally robust in various subgroups, except for the modifying effect of MoCA on orienting – mild WMH was weakly associated with orienting efficiency in patients with higher MoCA. Nevertheless, the effect of extensive WMH remained consistent regardless of MoCA category. Cognitive reserve may contribute to this phenomenon [29].

The differing cognitive profiles associated with different WMH locations have been studied [8,30], but the influence of WMH location on attention subdomains has never been reported. Notably, our study demonstrated specific correlations between regional WMH and attention subdomains. The PWMH and frontal, parietal, and temporal DWMH lesions may have a critical role in the observed impact on the executive control component, while the parietal WMH in DWMH appears to mainly affect the orienting efficiency.

We simultaneously investigated the independent impact of other MRI lesions, including lacunes and brain atrophy. The influence of WMH lesions on the executive control component of attention was independent of other SVD lesions, while the orienting effect disappeared after adjusting for other SVD lesions. The significant orienting effect in our population was attributed mainly to silent lacunar infarct and brain atrophy.

We followed standard procedures to evaluate neurocognitive disorder in the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5), and investigated the effects of WMH on domain-specific cognitive performance. Our results go one step further by demonstrating that cognitive deficits attributable to WMH lesions could extend to other subdomains apart from processing speed and executive function, which is consistent with a recent meta-analysis [12]. Furthermore, we found that memory deficit in WMH patients may be related to distributed WMH lesions, but not associated with the brain atrophy that commonly contributes to memory impairment in Alzheimer's disease. However, we caution that our study did not use a volumetric measurement to assess brain atrophy. Furthermore, we found that WMH lesions that were associated with decreased processing speed and executive function were located mainly in the frontal and parietal lobes. Among other SVD lesions, only lacunes were associated with lower processing speed. Our relatively small sample may have resulted in an underpowered interpretation. Importantly, neither slowed information processing nor impaired memory can account for the observed difference in efficiencies of attention subdomains.

The strengths of our study include sensitive attention assessment and comprehensive neuropsychological tests. We also were able to make adequate adjustments, even for global cognition and other MRI factors, reducing the risk of confounding. Despite a hospital-based design, our results may be applicable to other elderly samples, since we recruited consecutive patients with age-related WMH on neuroimaging who were admitted to the hospital due to clinically heterogeneous symptoms. We also explicitly assessed the influence of various lesions commonly observed in the ageing population.

The Stroop test and CTT have frequently been regarded as representative indicators of executive function. Our subgroup analyses suggest that impaired performance of executive function is associated with efficiency of executive control only in younger or more highly educated individuals. The results of these analyses should be considered preliminary because of the relatively small sample, which likely helps explain the broad confidence intervals for the effects estimates. Thus, the interpretation of these results should be conservative. Further research is needed to confirm whether age or education actually modifies the associations between executive function and the executive control component on the ANT test. The ageing and floor effects in traditional neuropsychological tests may explain why we observed these modifying effects. The ANT paradigm may help overcome these shortcomings. Indeed, our study provides evidence that the executive control efficiency may be a useful and stable marker, since it proved to be good at differentiating WMH subjects from controls across a broad range of age and cognitive status.

The patients in our study also showed a significant decline in efficiency of the orienting component. Consistently, another ANT study indicated that subcortical vascular patients with mild cognitive impairment (MCI), but not those with non-vascular MCI, showed a deficit in the orienting component but not in the other 2 components [31]. Cholinergic deficiency, regarded as the underlying mechanism of vascular cognitive impairment [32], significantly interferes with the ability to shift attention to a target (orienting effect) [33]. Our study and the aforementioned work by Fernandez appear to be the only published studies of WMH patients using theory-based attention assessment. However, the latter study did not quantify efficiency of the 3 attention components or determine the influence of detailed lesion features on ANT performance. In contrast, our study attempted to isolate the attention components using quantitative analysis and explored the effects of vascular pathologies on these attention subdomains.

The exact mechanism underlying the differential effects of spatial distribution of WMH lesions on attention is not clear. Previous evidence from functional MRI during ANT experiments in healthy individuals implicated the midline frontal areas, prefrontal cortex,

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and superior parietal lobe in the processing of executive control effect [33,34]. The significant correlation observed in our study between executive function and efficiency of executive control component may support the potential role of the frontal lobe again, since it participates in executive function [35]. Periventricular WMH affects multiple cognitive domains, mainly by impairing long association fibers traveling across frontal-subcortical circuits, while deep WMH causes distinct patterns of cognitive deficits in specific brain regions [30,36,37]. In our study, all types of PWMH lesion were indeed related to efficiency of the executive control component, and DWMH lesions influenced the attentional subdomain that was dependent on the location: lesions in frontal, parietal, and temporal lobes affected executive control, while lesions in the parietal lobe affected orienting. Moreover, the pathophysiological dysfunction of the brain networks interacting with the frontal cortex may help explain the selective pattern of attentional deficits. Structural MRI techniques have shown morphological alterations such as grey-matter volume and cortical thickness in bilateral parietal, dorsolateral prefrontal, and cingulate gyrus cortex far from WMH lesions, and these alterations arose as a consequence of disruption of white-matter tracts [38,39]. Functional MRI and electroencephalography of cerebral SVD patients [40] have shown impaired functional connectivity within and/or between the dorsal attention network, fronto-parietal control network, and other distributed intrinsic systems that support orienting and executive control [33,41]. The alerting component has been proposed to involve the thalamus and posterior parietal lobe in the right hemisphere and brainstem [33], but basal ganglia and infratentorial WMHs in our study were not significantly associated with attention subdomains (Supplementary Table 5). Moreover, our findings could have a biological plausibility. Our observation of an executive control defect in our patients may be related to the breakdown of ventral tegmental dopamine innervations, which was reported to be impaired in SVD patients [42]. Consistent with the well-established involvement of the temporal lobe in memory, our study found an association between temporal DWMH and delayed memory. We also found a significant relationship between DWMH lesions in the temporal region and efficiency of executive control component. Our results are consistent with the non-traditional view that the temporal lobe is involved in more than memory; a recent study suggested that the medial temporal lobe (MTL), consisting of the hippocampus and adjacent cortex, is also engaged in attentional and other cognitive processing [43]. These considerations should be validated in future work on the relationship of WMH lesions with attentional subdomains.

Our results should be interpreted with caution because of several limitations. One is selection bias caused by the cross-sectional, relatively small sample. Nevertheless, the results of this study provide some of the most extensive findings so far about connections between WMH and specific attentional subdomains, thereby laying the founding for future longitudinal studies. Computer-based paradigms such as the ANT test can be effective for detailed attentional assessment [31,44]. Second, lack of deeper analysis of cerebral microbleeds and EPVS may have led to overestimation of WMH effects. Nevertheless, only 11.5% of our patients had moderate and severe EPVS lesion (more than 10). In fact, the prevalence of microbleeds or EPVS may be relatively low in the Chinese population [45,46]. Regardless, these lesions are frequently reported to be only weakly associated with cognition [47,48]. Third, we assessed lesion characteristics using a visual/semi-automated rating scale rather than automated quantitative methods. Previous studies demonstrated good consistency between these 2 tools [49], and our method may be more appropriate and clinically convenient than volumetric algorithms in clinical settings. Finally, additional studies should explore the interaction of WMH with the pathology of Alzheimer's disease; although we did assess global atrophy in our study, none of our patients had been diagnosed with Alzheimer's disease or other dementia.

WMH lesions are often highly prevalent but progress asymptomatically into dementia [2,50], highlighting the need for cognitive screening of high-risk populations to ensure timely treatment. Our study shows that WMH patients, even those with mild lesions, have selective impairment in the executive control subdomain of attention. This impairment may be useful as an end-point in clinical cognitive studies. It may be feasible to combine the ANT task with other neuropsychological tests to provide more details about the behavioral phenotype. Future longitudinal studies could explore the possibility that combining the ANT with CTT can allow researchers to determine the effect of treatment on WMH lesions.

Conclusions

Our results reveal specific attention deficits in patients with age-related WMH and may help clarify how the location of lesions influences their effects on attention subdomains, and may assist in the recognition and treatment of early cognitive impairment in patients with leukoencephalopathy.

Conflicts of interest

None.

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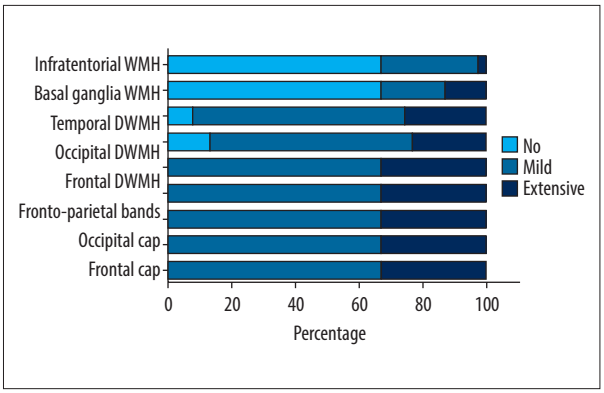
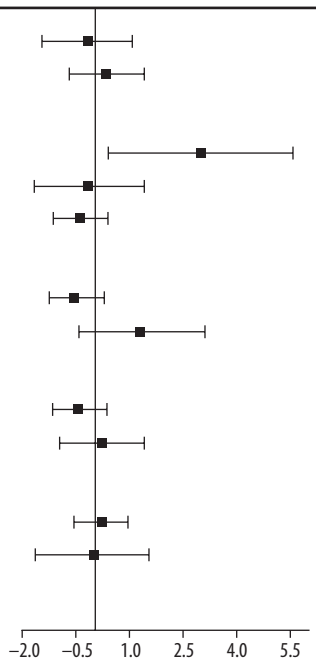
Supplementary Data



Supplementary Figure 1. Percentage of white-matter hyperintensity lesion burden by specific location.

A

Subgroups		N	Mean (SD)	β (95% CI)	*P* value for interaction
Gender	Male	42	39.85 (11.92)	−0.19 (−1.44, 1.07)	0.485
	Female	36	37.60 (12.48)	0.33 (−0.70, 1.37)	
Age category	60 years	13	34.51 (9.64)	3.00 (0.41, 5.80)	0.007
	60–70 years	27	33.71 (10.06)	−0.13 (−1.86, 1.40)	
	≥70 years	38	43.91 (12.41)	0.36 (−1.11, 0.39)	
Educatory	<12 years	47	39.72 (12.82)	−0.52 (−1.27, 0.22)	0.021
	≥12 years	31	37.44 (11.47)	1.31 (−0.43, 3.05)	
Group	Control	38	34.91 (10.82)	−0.42 (−1.17, 0.33)	0.376
	WMH	39	42.71 (12.46)	0.20 (−0.99, 1.39)	
MoCA	<24	38	41.07 (12.24)	0.16 (−0.58, 0.90)	0.824
	≥24	40	36.66 (11.83)	−0.02 (−1.60, 1.56)	



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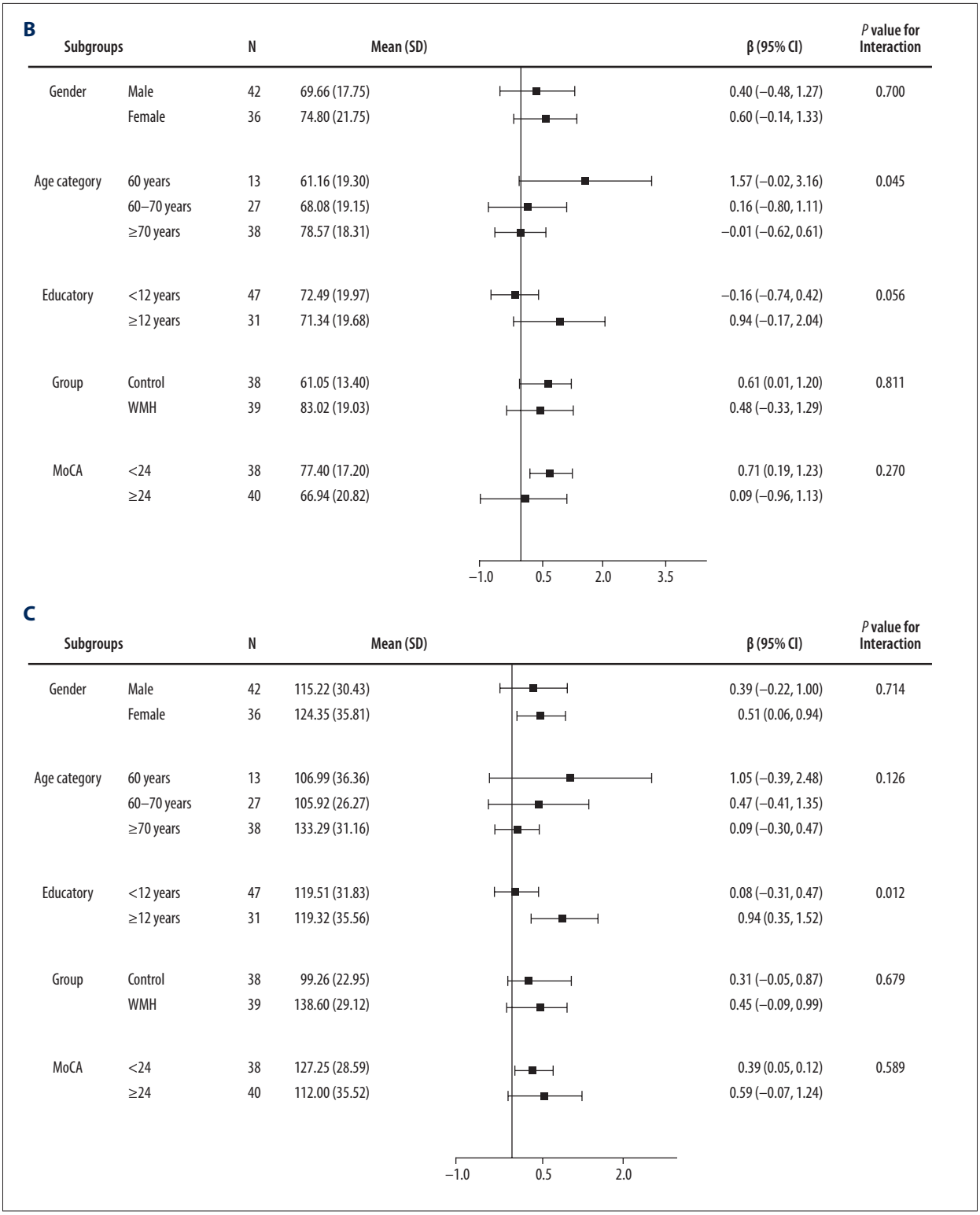

Supplementary Figure 2. (**A–C**) Relationship between neuropsychological performance and efficiency of the executive control component in exploratory subgroups.

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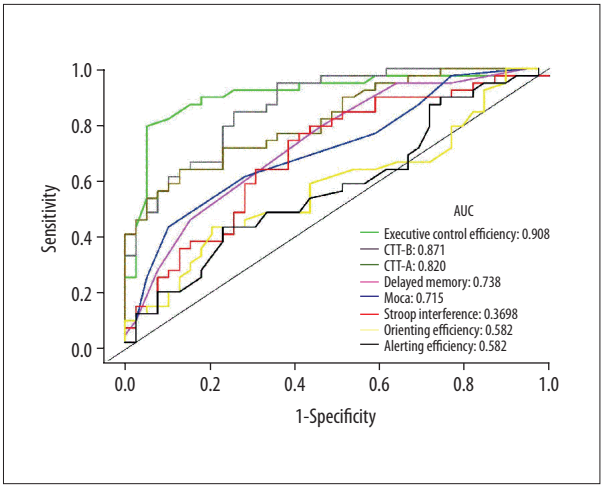
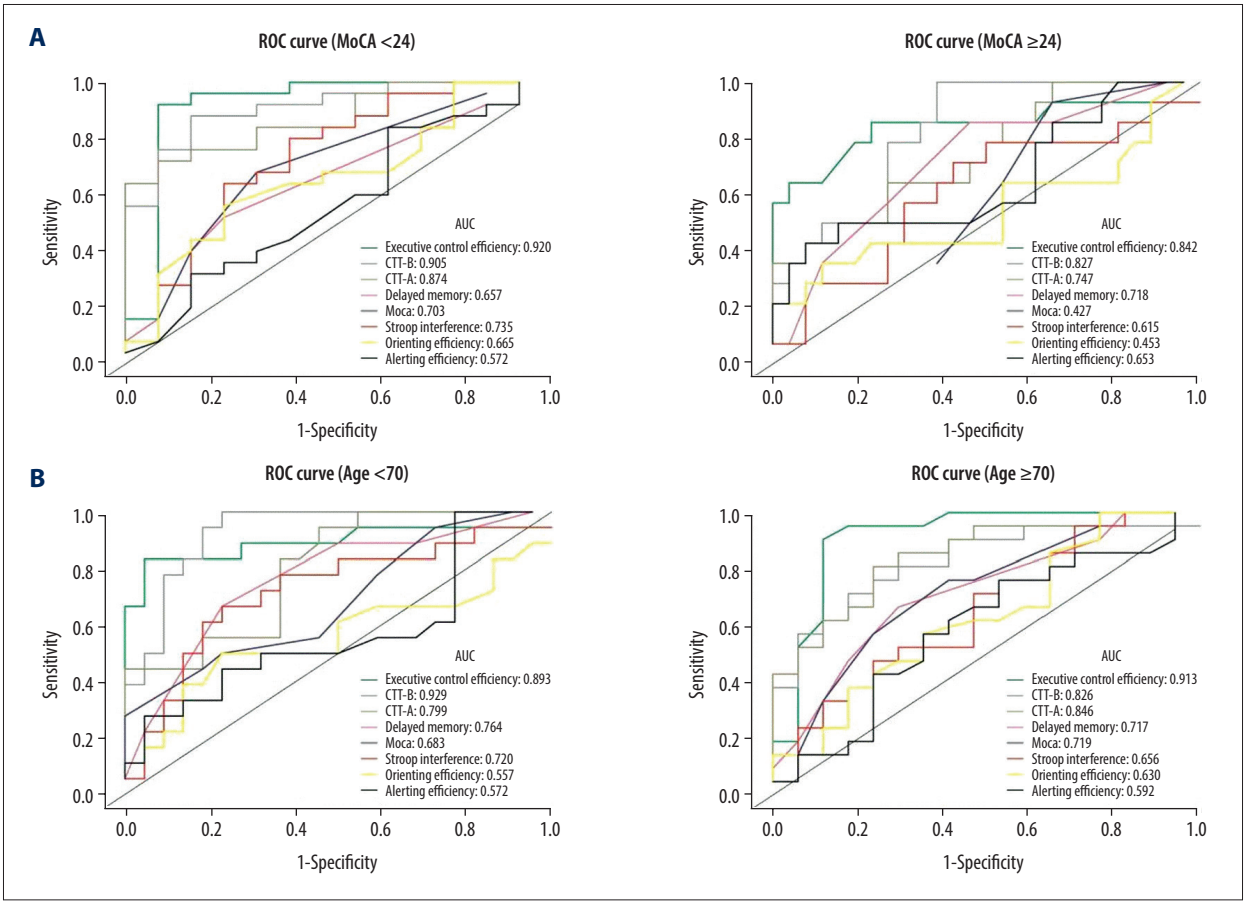


Supplementary Figure 3. Receiver operating characteristic curves showing the sensitivity and specificity of efficiencies of attention subdomains on the ANT paradigm or other neuropsychological tests in all participants.



Supplementary Figure 4. Receiver operating characteristic curves showing the sensitivity and specificity of efficiencies of attention subdomains on the ANT paradigm or other neuropsychological tests in participants stratified by cognitive status (Panel A) and age categories (Panel B).

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Supplementary Table 1. Detailed characteristics of the neuropsychological battery.

Test name	Completion time	Cognitive domains	Administration methods	Measures of performance
MoCA	15 min	Global cognition	Subdomains of visuospatial skill, executive function, memory, naming, attention, abstract reasoning, and orientation	A total score of 0 to 30 points, with higher scores indicating better performance
HAMA and HAMD	5 min	Anxiety and depression	Include 14 and 17 items of mental and somatic symptoms, respectively	A total of score >7 was regarded as existence of symptoms
Digital span	5 min	Working memory and general attention	Repeat increasingly long strings of digits directly (DS-forward) or in reverse order (DS-backward)	The highest number of digits in the sequence that the subject correctly repeated
VFT	2 min	General frontal function, language	Word in a specific semantic category of animals within one minute	Total number of animals correctly spoken by the subject
CAVLT	45 min	Episodic memory	Immediate memory, delayed memory (30 min after the learning stage)	The total number correctly recalled by the subject
SCWT	5 min	Attention, executive function (response inhibition)	Quickly and accurately say the color (red, green, yellow, and blue) of the dot (Stroop Dot test), word (Stroop Word test) or color-word (Stroop Interference test)	Longer completion time corresponds to worse performance
CTT	8 min	Information processing speed, executive function	Quickly and accurately connect circles containing numbers in an ascending order (CTT-A) and connect circles containing numbers in an ascending order accompanied by alternation between different circle colors (CTT-B)	Llonger completion time and/or higher number of errors correspond to worse performance

MoCA – Montreal Cognitive Assessment; HAMA – Hamilton Anxiety Scale; HAMD – Hamilton Depression Scale; VFT – verbal fluency test; CAVLT – Chinese auditory verb learning test; SCWT – Stroop color-word test; CTT – color trial test

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Supplementary Table 2. Subgroup analyses of the relationship between total WMH burden and efficiencies of orienting and executive control components*.

	Orienting efficiency				Executive control efficiency			
	No WMH	Mild WMH	Extensive WMH	*P* value interaction#	No WMH	Mild WMH	Extensive WMH	*P* value interaction#
Sex				0.072				0.055
Male (n=42)	Ref.	−10.51 (−29.86,8.84)	−29.93 (−45.94,−13.91)@		Ref.	47.29 (15.26,79.32)##	56.27 (29.76,82.79)@	
Female (n=36)	Ref.	−0.95 (−18.86,16.96)	−3.63 (−22.34,15.08)		Ref.	2.75 (−23.34,28.84)	26.77 (−0.49,54.02)	
Education				0.205				0.102
<12 y (n=47)	Ref.	−14.46 (−35.55,6.62)	−17.32 (−33.31,−1.33)##		Ref.	44.94 (22.46,67.42)§	45.94 (28.90,62.99)@	
≥12 y (n=31)	Ref.	3.89 (−23.32,31.09)	−30.23 (−70.69,10.22)		Ref.	13.13 (−25.70,51.95)	57.94 (0.20,115.67)	
Age				0.707				0.254
<70 y (n=40)	Ref.	−2.60 (−20.08,14.87)	−13.39 (−30.12,3.35)		Ref.	15.71 (−18.40,49.83)	47.66 (14.99,80.33)##	
≥70 y (n=38)	Ref.	−12.45 (−38.42,13.53)	−22.33 (−45.16,0.50)		Ref.	41.54 (17.85,65.23)##	40.91 (20.08,61.73)@	
MoCA				0.032			0.032	0.032
<24 (n=38)	Ref.	−11.59 (−31.35,8.18)	−10.39 (−28.12,7.34)		Ref.	32.23 (13.35,51.10)@	37.33 (20.40,54.26)@	
≥24 (n=40)	Ref.	11.60 (−15.14,38.34)	−30.74 (−53.97,−7.51)##		Ref.	7.80 (−34.81,50.40)	56.08 (19.07,93.10)##	

MoCA – Montreal Cognitive Assessment; Ref. – reference; WMH – white matter hyperintensity.
* Data indicated coefficient β and 95% confidence intervals; models were adjusted for age (continuous), sex, group, education (continuous), MoCA score (continuous), overall mean reaction time (continuous) and accuracy (continuous) except for the variable of stratification.
# *P* values for interaction were calculated from the log likelihood ratio test between multivariate linear regression models with and without interaction terms, in which total WMH burden was treated as a categorical variable.
P<0.05; @ *P*<0.001.

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Supplementary Table 3. Independent effects of WMH lesions on efficiencies of attention subdomains after further adjustment for other MRI lesions*.

	Alerting			Orienting			Executive control		
	No	Mild	Extensive	No	Mild	Extensive	No	Mild	Extensive
Total WMH	Ref.	–0.93 (–21.43, 19.56)	10.96 (–9.93, 31.86)	Ref.	0.84 (–15.61, 17.29)	–9.56 (–26.33, 7.21)	Ref.	20.04 (–3.14, 43.22)	35.27 (11.64, 58.90) @@
PWMH#									
Total (0–6 points) (N=39/19/20)##	Ref.	2.69 (–17.36, 22.75)	7.73 (–14.10, 29.56)	Ref.	–3.05 (–19.19, 13.09)	–5.72 (–23.29, 11.85)	Ref.	24.98 (2.24, 47.72)@	30.71 (5.96, 55.47)@
Frontal caps (0–2 points) (N=39/19/20)##	Ref.	6.47 (–13.30, 26.25)	2.06 (–20.14, 24.25)	Ref.	–3.64 (–19.56, 12.28)	–5.00 (–22.86, 12.86)	Ref.	30.36 (7.97, 52.74)@@	22.53 (–2.58, 47.64)
Occipital caps (0–2 points) (N=39/18/21)##	Ref.	–0.67 (–20.32, 18.98)	13.04 (–8.68, 34.76)	Ref.	–5.68 (–21.67, 10.30)	–1.85 (–19.52, 15.81)	Ref.	27.02 (4.44, 49.59)@	27.87 (2.92, 52.83)@
Bands (0–2 points) (N=39/15/24)##	Ref.	4.82 (–17.45, 27.10)	4.76 (–15.11, 24.62)	Ref.	–5.29 (–23.20, 12.61)	–3.45 (–19.41, 12.52)	Ref.	34.74 (9.67, 59.81)@@	22.72 (0.37, 45.08)@
DWMH#									
Total (0–24 points) (N=39/20/19)##	Ref.	5.89 (–13.10, 24.87)	1.57 (–22.97, 26.12)	Ref.	–1.72 (–16.88, 13.43)	–11.23 (–30.82, 8.36)	Ref.	29.09 (7.59, 50.60)@	22.32 (–5.48, 50.12)
Frontal (0–6 points) (N=39/15/24)##	Ref.	8.88 (–11.97, 29.73)	0.68 (–20.18, 21.53)	Ref.	–6.17 (–22.98, 10.65)	–2.15 (–18.97, 14.67)	Ref.	33.76 (10.21, 57.31)@@	20.95 (–2.60, 44.50)
Parietal (0-6 points) (N=39/13/26)##	Ref.	–8.23 (–29.84, 13.38)	12.88 (–6.36, 32.12)	Ref.	–2.35 (–20.25, 15.55)	–5.29 (–21.22, 10.65)	Ref.	27.41 (2.15, 52.67)@	27.33 (4.83, 49.82)@
Occipital (0–6 points) (N=44/25/9)##	Ref.	25.91 (–5.89, 57.71)	33.62 (–4.80, 72.05)	Ref.	5.13 (–20.78, 31.04)	–7.32 (–38.63, 23.99)	Ref.	3.68 (–32.78, 40.15)	22.50 (–21.57, 66.56)
Temporal (0–6 points) (N=42/26/10)##	Ref.	–2.27 (–39.42, 34.89)	14.09 (–27.48, 55.65)	Ref.	–11.19 (–41.27, 18.89)	–4.61 (–38.26, 29.04)	Ref.	55.54 (15.10, 95.97)@@	55.79 (10.55, 101.02)@

WMH – white matter hyperintensity; PWMH – periventricular white matter hyperintensity; DWMH – deep white matter hyperintensity.
* Data indicated coefficient β and 95% confidence intervals; Models were adjusted for age (continuous), sex, group, education (continuous), Montreal Cognitive Assessment (MoCA) score (continuous), overall mean reaction time (continuous), accuracy (continuous), number of lacunes (no *vs.* few *vs.* many), and global atrophy (no *vs.* mild *vs.* extensive).
# For PWMH, mild or extensive total burden was respectively defined as a Scheltens score of 3–4 or 5–6 points, since patients in our study scored between 3 to 6 points. Mild or extensive regional burden was respectively defined as a Scheltens score of 1 or 2 points. For DWMH, mild or extensive total burden was respectively defined as a Scheltens score of 1–12 or 13-24 points. Mild or extensive regional burden was respectively defined as a Scheltens score of 1–3 or 4–6 points, except in the case of occipital burden, where the corresponding score definitions were 1–2 or 3–4 points because the observed scores ranged from 0 to 4 points.
Numbers in parentheses represent the sample size in each category for regional WMH lesions (no *vs.* mild *vs.* extensive).
@ $P<0.05$; @@ $P<0.01$.

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Supplementary Table 4. Effects of WMH lesions on standardized efficiencies of attention subdomains estimated by multivariable linear regression models*.

	Standardized Alerting			Standardized Orienting			Standardized Executive control		
	No	Mild	Extensive	No	Mild	Extensive	No	Mild	Extensive
Total WMH	Ref.	0.000	0.012	Ref.	0.002	–0.011	Ref.	0.013	0.027
		(–0.023, 0.024)	(–0.011, 0.036)		(–0.016, 0.020)	(–0.029, 0.008)		(–0.015, 0.040)	(–0.001, 0.055)
PWMH#									
Total (N=39/19/20)##	Ref.	0.003 (–0.020, 0.026)	0.010 (–0.014, 0.035)	Ref.	–0.004 (–0.021, 0.014)	–0.005 (–0.024, 0.014)	Ref.	0.019 (–0.008, 0.046)	0.020 (–0.009, 0.050)
Frontal caps (N=39/19/20)##	Ref.	0.007 (–0.016, 0.029)	0.005 (–0.020, 0.030)	Ref.	–0.003 (–0.021, 0.015)	–0.006 (–0.025, 0.014)	Ref.	0.026 (0.000, 0.053)@	0.009 (–0.020, 0.038)
Occipital caps (N=39/18/21)##	Ref.	0.000 (–0.022, 0.023)	0.014 (–0.010, 0.039)	Ref.	–0.006 (–0.023, 0.012)	–0.002 (–0.021, 0.017)	Ref.	0.020 (–0.007, 0.047)	0.019 (–0.011, 0.048)
Bands (N=39/15/24)##	Ref.	0.007 (–0.018, 0.032)	0.005 (–0.017, 0.028)	Ref.	–0.008 (–0.027, 0.012)	–0.002 (–0.019, 0.016)	Ref.	0.029 (–0.001, 0.059)	0.013 (–0.013, 0.040)
DWMH#									
Total (N=39/20/19)##	Ref.	0.007 (–0.015, 0.028)	0.004 (–0.023, 0.032)	Ref.	–0.002 (–0.018, 0.015)	–0.011 (–0.032, 0.010)	Ref.	0.024 (–0.002, 0.049)	0.008 (–0.024, 0.041)
Frontal (N=39/15/24)##	Ref.	0.009 (–0.014, 0.033)	0.003 (–0.020, 0.027)	Ref.	–0.005 (–0.024, 0.013)	–0.003 (–0.021, 0.016)	Ref.	0.029 (0.001, 0.057)@	0.010 (–0.017, 0.038)
Parietal (N=39/13/26)##	Ref.	–0.008 (–0.032, 0.017)	0.015 (–0.007, 0.037)	Ref.	–0.002 (–0.021, 0.018)	–0.006 (–0.023, 0.012)	Ref.	0.017 (–0.013, 0.047)	0.021 (–0.006, 0.048)
Occipital (N=44/25/9)##	Ref.	0.028 (–0.008, 0.064)	0.037 (–0.006, 0.080)	Ref.	–0.001 (–0.030, 0.027)	–0.011 (–0.045, 0.023)	Ref.	0.004 (–0.040, 0.048)	0.012 (–0.040, 0.065)
Temporal (N=42/26/10)##	Ref.	0.005 (–0.037, 0.047)	0.019 (–0.028, 0.066)	Ref.	–0.015 (–0.048, 0.019)	–0.008 (–0.045, 0.029)	Ref.	0.067 (0.019, 0.115)@@	0.059 (0.006, 0.113)@

WMH – white matter hyperintensity; Ref. – reference; PWMH – periventricular white matter hyperintensity; DWMH – deep white matter hyperintensity.

* Data indicated coefficient β and 95% confidence intervals. Models were adjusted for age (continuous), sex, group, education (continuous), Montreal Cognitive Assessment (MoCA) score (continuous), accuracy (continuous), number of Lacunes (no *vs.* few *vs.* many), and global atrophy (no *vs.* mild *vs.* extensive).

For PWMH, mild or extensive total burden was respectively defined as a Scheltens score of 3–4 or 5–6 points, since observed scores ranged from 3 to 6 points; mild or extensive regional burden was respectively defined as a Scheltens score of 1 or 2 points. For DWMH, mild or extensive total burden was respectively defined as a Scheltens score of 1–12 or 13–24 points; mild or extensive regional burden was respectively defined as a Scheltens score of 1–3 or 4–6 points, except in the case of occipital burden, where the corresponding score definitions were 1–2 or 3–4 points because the observed scores ranged from 0 to 4 points.

Numbers in parentheses represent the sample size of each category for regional WMH lesions (no vs. mild vs. extensive).

@ $P<0.05$; @@ $P<0.01$.

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Supplementary Table 5. Effects of other MRI lesions on efficiencies of attention subdomains estimated by multivariable linear regression models*.

MRI lesions	Alerting		Orienting		Executive control	
	Model I	Model II	Model I	Model II	Model I	Model II
Basal ganglia WMH						
No (n=51)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Mild (n=17)	11.88 (–11.40, 35.16)	12.90 (–11.13, 36.94)	0.54 (–21.67, 22.75)	2.98 (–19.66, 25.62)	–18.32 (–45.58, 8.94)	–20.89 (–48.44, 6.66)
Extensive (n=10)	10.51 (–14.98, 36.01)	10.06 (–16.87, 37.00)	–7.42 (–31.74, 16.91)	–2.48 (–27.85, 22.88)	–20.97 (–50.82, 8.89)	–26.42 (–57.29, 4.45)
Infratentorial WMH#						
No (n=69)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes (n=9)	3.18 (–20.82, 27.18)	1.27 (–24.12, 26.66)	–0.34 (–23.15, 22.46)	3.76 (–19.97, 27.48)	–3.04 (–31.42, 25.34)	–8.21 (–37.73, 21.31)
Lacune presence						
No (n=58)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes (n=20)	0.35 (–18.97, 19.67)	–1.93 (–21.85, 17.99)	–19.24 (–34.94, –3.54)@	–17.63 (–33.77, –1.49)@	21.88 (–0.04, 43.80)	18.69 (–3.87, 41.26)
Lacune burden						
No (n=58)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Few (n=14)	1.73 (–19.78, 23.23)	–1.56 (–24.00, 20.88)	–15.29 (–32.64, 2.06)	–13.06 (–31.07, 4.95)	24.80 (0.44, 49.16)@	21.42 (–3.95, 46.80)
Many (n=6)	–2.69 (–30.81, 25.43)	–2.69 (–31.71, 26.32)	–27.99 (–50.67, –5.30)@	–27.18 (–50.46, –3.89)@	15.43 (–16.42, 47.28)	12.98 (–19.83, 45.79)
Global atrophy##						
No (n=17)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Mild (n=46)	0.54 (–17.30, 18.38)	–0.40 (–18.71, 17.91)	–5.90 (–20.96, 9.17)	–4.68 (–19.37, 10.01)	–3.85 (–24.68, 16.97)	–3.86 (–24.56, 16.84)
Extensive (n=15)	–4.99 (–28.70, 18.72)	–7.06 (–32.30, 18.18)	–3.94 (–23.96, 16.08)	0.48 (–19.77, 20.74)	–1.16 (–28.84, 26.51)	–1.86 (–30.39, 26.68)
Deep atrophy##						
No (n=36)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Mild (n=24)	0.35 (–16.40, 17.10)	–3.89 (–21.91, 14.14)	–16.45 (–30.12, –2.78)@	–15.28 (–29.35, –1.20)@	6.24 (–13.30, 25.78)	2.38 (–18.10, 22.86)
Extensive (n=18)	–6.54 (–26.18, 13.09)	–11.79 (–33.66, 10.08)	–5.53 (–21.55, 10.49)	–2.79 (–19.86, 14.28)	0.21 (–22.69, 23.11)	–2.79 (–27.63, 22.05)
Peripheral atrophy##						
No (n=24)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Mild (n=26)	11.14 (–6.27, 28.56)	11.19 (–6.60, 28.98)	3.99 (–10.98, 18.96)	4.46 (–10.08, 19.00)	–16.93 (–37.16, 3.29)	–16.13 (–36.14, 3.89)
Extensive (n=28)	–0.27 (–18.00, 17.45)	–1.03 (–19.40, 17.34)	1.79 (–13.44, 17.02)	4.26 (–10.76, 19.28)	–14.50 (–35.08, 6.08)	–15.56 (–36.23, 5.11)

* Data indicated coefficient β and 95% confidence intervals. Models are adjusted for age (continuous), sex, group, education (continuous), Montreal Cognitive Assessment (MoCA) score (continuous), overall mean reaction time (continuous) and accuracy (continuous) in Model I and additional adjustment for various MRI lesions including total WMH burden (no *vs.* mild *vs.* extensive), number of lacunes (no *vs.* few *vs.* many, for atrophy analysis), and global atrophy (no *vs.* mild *vs.*extensive, for lacune analysis).

Infratentorial WMH was divided into binary variable because of the limited sample.

Mild global atrophy was defined as a total score of 1–3; extensive global atrophy, 3–6; mild deep or peripheral atrophy, 1; and extensive deep or peripheral atrophy, 2–3 (since few subjects scored 3).

@ $P<0.05$.

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Supplementary Table 6. Covariate-adjusted associations of neuropsychological performance with WMH lesion characteristics*.

	Delayed recall memory		Stroop-Interference		CTT-A		CTT-B	
	Mild	Extensive	Mild	Extensive	Mild	Extensive	Mild	Extensive
Total WMH	−0.46 (−1.29, 0.37)	−1.34 (−2.17, −0.51)@	3.13 (−3.59, 9.84)	7.73 (0.92, 14.53)@	14.36 (5.19, 23.54)@	14.12 (4.81, 23.42)@	26.25 (11.92, 40.57)@@	29.06 (14.54, 43.58)@@
PWMH#								
Total (N=39/19/20)##	−0.67 (−1.49, 0.15)	−1.18 (−2.05, −0.32)@	5.59 (−1.02, 12.19)	5.06 (−2.06, 12.18)	17.15 (8.39, 25.92)@@	10.30 (0.86, 19.75)@	28.79 (14.87, 42.70)@@	26.03 (11.05, 41.01)@
Frontal caps (N=39/19/20)##	−0.70 (−1.51, 0.11)	−1.19 (−2.08, −0.31)@	5.12 (−1.37, 11.61)	5.76 (−1.54, 13.05)	11.42 (2.83, 20.01)@	18.81 (9.15, 28.46)@@	24.51 (10.95, 38.06)@@	32.63 (17.40, 47.86)@@
Occipital caps (N=39/18/21)##	−0.78 (−1.60, 0.03)	−1.07 (−1.96, −0.18)@	6.15 (−0.36, 12.66)	4.17 (−3.05, 11.38)	16.78 (8.11, 25.45)@@	10.37 (0.76, 19.98)@	28.01 (14.27, 41.76)@@	27.01 (11.78, 42.24)@@
Bands (N=39/15/24)##	−0.60 (−1.51, 0.31)	−1.07 (−1.87, −0.28)@	3.44 (−3.84, 10.73)	6.50 (0.07, 12.93)	19.03 (9.34, 28.71)@@	11.40 (2.86, 19.95)@	34.28 (19.08, 49.48)@@	23.66 (10.26, 37.06)@
DWMH#								
Total (N=39/20/19)##	−0.65 (−1.41, 0.11)	−1.53 (−2.48, −0.57)@	4.53 (−1.68, 10.74)	7.71 (−0.28, 15.71)	13.38 (4.99, 21.76)@	16.69 (5.89, 27.49)@	26.36 (13.25, 39.48)@@	31.16 (14.28, 48.04)@@
Frontal (N=39/15/24)##	−0.44 (−1.28, 0.40)	−1.30 (−2.11, −0.49)@	4.42 (−2.46, 11.30)	6.27 (−0.55, 13.09)	13.11 (3.83, 22.38)@	15.34 (6.14, 24.54)@	24.88 (10.42, 39.35)@	30.26 (15.91, 44.60)@@
Parietal (N=39/13/26)##	−0.74 (−1.65, 0.16)	−1.00 (−1.81, −0.19)@	3.75 (−3.52, 11.02)	6.37 (−0.11, 12.86)	19.13 (9.50, 28.76)@@	11.17 (2.57, 19.76)@	30.76 (15.43, 46.09)@@	25.64 (11.96, 39.31)@@
Occipital (N=44/25/9)##	−1.63 (−2.90, −0.37)@	−1.94 (−3.44, −0.43)@	−0.79 (−11.30, 9.72)	3.65 (−9.18, 16.48)	3.73 (−10.37, 17.82)	10.44 (−6.77, 27.66)	7.54 (−14.03, 29.11)	24.79 (−1.55, 51.13)
Temporal (N=42/26/10)##	−1.24 (−2.73, 0.25)	−1.89 (−3.52, −0.27)@	8.66 (−3.05, 20.36)	16.62 (3.64, 29.59)@	−8.23 (−24.37, 7.91)	1.98 (−15.91, 19.88)	4.12 (−20.83, 29.06)	23.02 (−4.65, 50.68)

Abbreviations: WMH, white matter hyperintensity; PWMH, periventricular white matter hyperintensity; DWMH, deep white matter hyperintensity.

* Data were expressed as coefficient β (95% confidence interval) with "no" WMH category as the reference. Models were adjusted for age (continuous), sex, group, education (continuous), Montreal Cognitive Assessment (MoCA) score (continuous), overall mean reaction time (continuous, only for Stroop-Interference and CTT), number of Lacunes (no vs. few vs. many), and global atrophy (no vs. mild vs. extensive).

For PWMH, mild or extensive total burden was respectively defined as a Scheltens score of 3–4 or 5–6 points (since observed scores ranged from 3 to 6 points); mild or extensive regional burden was respectively defined as a Scheltens score of 1 or 2 points. For DWMH, mild or extensive total burden was respectively defined as a Scheltens score of 1–12 or 13–24 points; mild or extensive regional burden was respectively defined as a Scheltens score of 1–3 or 4–6 points, except in the case of occipital burden, where the corresponding score definitions were 1–2 or 3–4 points because the observed scores ranged from 0 to 4 points.

Numbers in parentheses represent the sample size of each category for regional WMH lesions (no *vs.* mild *vs.* extensive).

@ $P<0.05$; @@ $P<0.001$.

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Supplementary Table 7. Covariate-adjusted associations of neuropsychological performance with other MRI lesion characteristics*.

	Delayed recall memory	Stroop-Interference	CTT-A	CTT-B
Basal ganglia WMH				
No (n=51)	Ref.	Ref.	Ref.	Ref.
Mild (n=17)	–0.12 (–1.08, 0.84)	–5.50 (–13.39, 2.39)	–5.50 (–16.19, 5.19)	–10.05 (–26.77, 6.68)
Extensive (n=10)	–0.36 (–1.47, 0.75)	–0.39 (–9.11, 8.32)	–6.92 (–18.73, 4.90)	–3.83(–22.31, 14.65)
Infratentorial WMH#				
No (n=69)	Ref.	Ref.	Ref.	Ref.
Yes (n=9)	–0.47 (–1.51, 0.58)	4.22 (–4.06, 12.50)	5.79 (–5.38, 16.95)	–2.92(–20.48, 14.65)
Lacune presence				
No (n=58)	Ref.	Ref.	Ref.	Ref.
Yes (n=20)	0.07 (–0.73, 0.87)	–0.98 (–7.46, 5.51)	8.98 (0.07, 17.88)	12.08 (–1.78, 25.93)
Lacune burden				
No (n=58)	Ref.	Ref.	Ref.	Ref.
Few (n=14)	–0.10 (–0.99, 0.78)	–1.34 (–8.58, 5.90)	10.89 (1.00, 20.79)@	13.94 (–1.51, 29.38)
Many (n=6)	0.49 (–0.69, 1.66)	–0.18 (–9.69, 9.34)	4.75 (–8.25, 17.75)	7.97(–12.33, 28.26)
Global atrophy##				
No (n=17)	Ref.	Ref.	Ref.	Ref.
Mild (n=46)	0.61 (–0.12, 1.34)	–3.38 (–9.38, 2.63)	1.15 (–7.06, 9.35)	7.72 (–5.08, 20.52)
Extensive (n=15)	–0.21 (–1.21, 0.79)	–1.50 (–9.77, 6.78)	–1.36 (–12.67, 9.95)	2.63(–15.02, 20.29)
Deep atrophy##				
No (n=36)	Ref.	Ref.	Ref.	Ref.
Mild (n=24)	0.28 (–0.45, 1.00)	0.84 (–5.00, 6.69)	–0.92 (–9.00, 7.16)	6.36 (–6.32, 19.03)
Extensive (n=18)	–0.74 (–1.60, 0.12)	5.78 (–1.34, 12.90)	–2.23 (–12.07, 7.61)	2.71(–12.72, 18.15)
Peripheral atrophy##				
No (n=24)	Ref.	Ref.	Ref.	Ref.
Mild (n=26)	0.57 (–0.17, 1.32)	–0.16 (–6.04, 5.72)	–0.93 (–9.04, 7.18)	4.09 (–8.67, 16.85)
Extensive (n=28)	0.43 (–0.35, 1.21)	–4.00 (–10.07, 2.07)	–1.92 (–10.29, 6.45)	0.45(–12.73, 13.62)

* Values were the regression coefficient β (95% confidence interval) calculated by multivariate linear regression analysis, adjusted for age (continuous), sex, group, education (continuous), Montreal Cognitive Assessment (MoCA) score (continuous), overall mean reaction time (continuous, only for Stroop-Interference and CTT), total WMH burden (no *vs.* mild *vs.* extensive), number of lacunes (no *vs.* few *vs.* many, only for atrophy analysis), and global atrophy (no *vs.* mild *vs.* extensive, only for lacune analysis)

Infratentorial WMH was treated as a binary variable because of the small sample.

Mild global atrophy was defined as total score of 1-3; extensive global atrophy, 4-6; mild deep or peripheral atrophy, 1; and extensive deep or peripheral atrophy, 2-3 (since few subjects scored 3).

@ $P<0.05$.

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Supplementary Table 8. Adjusted association of total WMH lesions with efficiencies of attention subdomains based on additional analysis using an alternative categorization of total WMH severity*.

Attention subdomains	WMH burden#							
	No (n=39)	Low (n=16)		Moderate (n=11)		High (n=12)	
Alerting							
Unadjusted	Ref.	3.64	(–13.89, 21.18)	17.93	(–2.23, 38.10)	14.12	(–5.38, 33.62)
Model I	Ref.	–2.34	(–20.99, 16.31)	9.16	(–12.09, 30.41)	10.12	(–11.41, 31.65)
Model II	Ref.	–1.36	(–22.14, 19.42)	10.75	(–12.59, 34.10)	13.62	(–14.08, 41.33)
Orienting							
Unadjusted	Ref.	–6.32	(–22.89, 10.26)	–14.87	(–33.93, 4.18)	–15.78	(–34.20, 2.65)
Model I	Ref.	–8.50	(–24.28, 7.28)	–20.65	(–38.63, –2.67)#	–12.68	(–30.90, 5.54)
Model II	Ref.	0.92	(–15.53, 17.36)	–14.67	(–33.15, 3.81)	6.78	(–15.15, 28.71)
Executive control							
Unadjusted	Ref.	39.59	(18.92, 60.27)##	43.46	(19.69, 67.24)##	43.53	(20.54, 66.52)##
Model I	Ref.	35.78	(13.93, 57.62)#	44.71	(19.81, 69.60)#	31.43	(6.20, 56.65)#
Model II	Ref.	25.04	(1.59, 48.49)#	35.80	(9.45, 62.15)#	10.47	(–20.80, 41.73)

* Data were expressed as regression coefficient β and 95% confidence interval. For the multivariable analyses, data were adjusted for age (continuous), sex, group, education (continuous), Montreal Cognitive Assessment (MoCA) score (continuous), overall mean reaction time (continuous) and accuracy (continuous) in Model I. Data were adjusted for the same variables in Model II, as well as number of lacunes (no *vs.* few *vs.* many) and global atrophy
(no *vs.* mild *vs.* extensive).
# $P<0.05$; ## $P<0.001$.

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