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The Impact of Strategic White Matter Hyperintensity Lesion Location on Language

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ABSTRACT

Objective: *The impact of white matter hyperintensities (WMH) on language possibly depends on lesion location through disturbance of strategic white matter tracts. We examined the impact of WMH location on language in elderly Asians.* ***Design:*** *Cross-sectional.* ***Setting:*** *Population-based.* ***Participants:*** *Eight-hundred nineteen residents of Singapore, ages (≥65 years).* ***Measurements:*** *Clinical, cognitive and 3T magnetic resonance imaging assessments were performed on all participants. Language was assessed using the Modified Boston Naming Test (MBNT) and Verbal Fluency (VF). Hypothesis-free region-of-interest-based (ROI) analyses based on major white matter tracts were used to determine the association between WMH location and language. Conditional dependencies between the regional WMH volumes and language were examined using Bayesian-network analysis.* ***Results:*** *ROI-based analyses showed that WMH located within the anterior thalamic radiation (mean difference: −0.12, 95% confidence interval [CI]: −0.22; −0.02, p = 0.019) and uncinate fasciculus (mean difference: −0.09, 95% CI: −0.18; −0.01, p = 0.022) in the left hemisphere were significantly associated with worse VF but did not survive multiple testing. Conversely, WMH volume in the left cingulum of cingulate gyrus was significantly associated with MBNT performance (mean difference: −0.09, 95% CI: −0.17; −0.02, p = 0.016). Bayesian-network analyses confirmed the left cingulum of cingulate gyrus as a direct determinant of MBNT performance.* ***Conclusion:*** *Our findings identify the*

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left cingulum of cingulate gyrus as a strategic white matter tract for MBNT, suggesting that language − is sensitive to subcortical ischemic damage. Future studies on the role of sporadic ischemic lesions and vascular cognitive impairment should not only focus on total WMH volume but should also take WMH lesion location into account when addressing language. (Am J Geriatr Psychiatry 2020; ■■:■■–■■)

INTRODUCTION

Neuropsychological assessment plays a crucial role in detecting loss of cognitive functions and change in behavioral and functional state due to disruption in different neural networks and subnetworks caused by vascular damage.[1] Neuropsychological tests include tasks assessing domains considered to reflect "cortical function" for example, language and visuoconstruction and tasks that tap into domains that are especially sensitive to vascular damage in subcortical regions such as attention and visuomotor speed. Language in particular, has been suggested to be controlled not only by cortical regions (Broca's and Wernicke's area) but also the surrounding frontal cortex, underlying white matter, the insula, basal ganglia, and parts of the anterior superior temporal gyrus and inferior parietal lobe.[2,3] This implies that the deeper brain regions also participate in speech production and language. However, unequivocal evidence of how subcortical vascular injury disrupts language in a population-based setting is lacking.

Previous studies have demonstrated that subcortical vascular brain damage as manifested by white matter hyperintensities (WMH) located in the anterior thalamic radiation and forceps minor were related to worse performance in processing speed, executive functioning, and memory.[4–7] Such data is largely restricted to diseased population that is, memory clinic and patients diagnosed with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). So far, only two community-based studies have examined the effects of white matter damage with language domain.[8,9] One study consisting of a small sample (n = 220) has shown that the lower white matter diffusivity in posterior cingulum was associated with greater impairment in the language domain[8] whereas the other study (n = ~400) did not observe relationship between WMH loadings in any of the strategic white matter tracts and language performance.[9] Thus, it is possible that strategic location of WMH in specific white matter tracts will have a more substantial impact on language compared to lesions in the less critical parts of the white matter, but this requires more research.

Our objective is to investigate, to what extent language is affected by subcortical ischemic injury as manifested by WMH, and whether this depends on specific white matter tracts using advanced and robust statistical methods, including region of interest-based analysis, and Bayesian network analysis in a population-based setting. We hypothesize that strategic location of WMH is inversely associated with language performance.

MATERIAL AND METHODS

Study Sample

The Epidemiology of Dementia In Singapore (EDIS) is a subsample of the Singapore Epidemiology of Eye Disease (SEED) study, a large population-based study of three major ethnic cohorts: Chinese (Singapore Chinese Eye Study [SCES]), Malay (Singapore Malay Eye Study [SiMES-2]), and Indians (Singapore Indian Eye Study [SINDI-2]).[10] A similar protocol was employed for recruitment and assessment of study participants for all the three ethnicities. As part of the first phase of the EDIS study, participants who were 60 years or older underwent cognitive screening using the Abbreviated Mental Test (AMT) and a self-report of progressive forgetfulness. Screen positives were defined based on the education-based cut-offs on AMT. A cut-off score of AMT less than or equal to 6, was given to participants with up to 6 years of formal education, or a score of less than or equal to 8 among those with more than 6 years of formal education; or if the caregiver confirmed progressive forgetfulness (PFQ).[11,12] Subsequently, these screen-positive persons (n = 1,598) were invited to

participate in the second phase of the EDIS study. All the participants underwent an extensive clinical and neuropsychological evaluation, along with 3T magnetic resonance imaging (MRI). Of the 1,598 participants, 957 eventually agreed to participate in phase-II (overall response rate 60%) and hence were included in the present study. Recruitment took place from August 8, 2010 to July 24, 2015. The main exclusion criteria were individuals who did not give consent to participate in the second phase and those who were screened negative on AMT and PFQ.

Individuals with no MRI images (n = 93), cortical infarcts (n = 24), poor quality images (n = 10), and dementia (n = 6) were excluded.

Ethics approval was obtained from the Singapore Eye Research Institute, and National Healthcare Group Domain-Specific Review Board (ID no: 2009/00628). The study followed the tenets of Helsinki. Written informed consent was taken prior to subjects' recruitment into the study.

Neuroimaging

MRI was performed on a 3T Siemens Magnetom Trio Tim scanner, using a 32-channel head coil, at the Clinical Imaging Research Centre of the National University of Singapore. The standardized protocol included 3D T1-weighted imaging ($1.0 \times 1.0 \times 1.0$ mm^3 voxels, repetition time, TR = 2300 ms, time to echo, TE = 1.9 ms, inversion time (TI), 900 ms, flip angle 9°, matrix = $256 \times 256 \times 180$ mm^3), 2D multislice T2-weighted ($1.0 \times 1.0 \times 3.0$ mm^3 voxels, TR = 3000 ms, TE = 10.1 ms, matrix = 247×256) and 2D multislice fluid-attenuated inversion recovery (FLAIR) images ($1.0 \times 1.0 \times 3.0$ mm^3; TR = 9000 ms; TE = 82 ms; TI 2500 ms, matrix = 232×256). Lacunes were graded on FLAIR and T2 sequences using the STandards for ReportIng Vascular changes on nEuroimaging (STRIVE) criteria,[13] and were defined as lesions involving the subcortical regions, 3−15 mm in diameter, with low signal on T1-weighted image and FLAIR, a high signal on T2-weighted image, and a hyperintense rim with a center following cerebrospinal fluid intensity on FLAIR.

WMH Segmentation

WMH together with brain tissue volumes of the whole brain were quantified by automatic segmentation using the FLAIR and T1 sequences as described previously.[14] Briefly, a k-nearest-neighbor brain tissue technique was used to classify voxels into cerebrospinal fluid, gray matter, normal appearing white matter, and WMH, and volume (mL) was calculated from these measurements. Default settings with k = 5 and probability threshold of 0.7 were used for the WMH segmentation in the present study. Results were visually checked and manually corrected for segmentation quality by the same grader (SH) who visually graded lacunes.

Generation of Lesion Maps

Registration of T1 images to a 1-mm MNI-152 (Montreal Neurological Institute) template was performed using RegLSM[15,16] (https://metavcimap.org/) with a linear registration followed by a nonlinear registration. Visual checks of the results of the registration process were performed for all participants. After quality control of T1 images in MNI space, the warp fields were used to co-register the corresponding WMH maps to the 1-mm MNI template.[5] The total WMH volume after registration to MNI space was calculated for all participants. Five scans were excluded due to failed WMH registration.

Language Assessment

Neuropsychological tests were administered in the participant's habitual language to avoid variance due to insufficient language proficiency. Language was assessed using the Modified Boston Naming Test (MBNT)[17] and Verbal Fluency (VF).[18] MBNT consisted of 15 line drawings of objects of graded difficulty, ranging from very common objects (e.g., a tree) to less familiar objects such as an abacus. Score was given for every spontaneous correct response within 20 seconds. VF consisted of naming items within a particular category such as fruits and animals in a given time (60 seconds).[19] Both tests were administered to every participant and were scored separately.

For each participant, raw scores of each test for language was first transformed to standardized Z-scores using the mean and standard deviation (SD) of that test in this study. Subsequently, for each participant a mean Z-score for language was calculated by averaging the Z-scores of the two individual tests.

Statistical Analyses

The association between three ethnicities and language performance was determined using linear regression models adjusting for age, sex, and education. In order to identify strategic white matter tracts in which WMHs are associated with cognitive function, we performed the following hypothesis − free analyses: Region of interest (ROI)-based analyses based on the association between WMH volumes within specific white matter tracts and language performance and, Bayesian network analysis between language domain and regional volume of WMH for each white matter tract.

ROI-Based Analyses

For the ROI-based analyses, 10 regions of interest were created using a probabilistic white matter tract atlas with a probability threshold of 10%.[20] As there were very few WMH voxels in parahippocampal white matter, this tract was removed from further analysis leaving nine white matter tracts for ROI-based analyses. The regional WMH volumes within these 10 white matter tracts were entered as independent variables in a linear regression model, with the z-scores of language domain, VF and MBNT as outcomes, adjusting for age, sex, spoken language (Mandarin, Malay, or Tamil), education and presence of lacunes as covariates. The models were further adjusted for total normalized WMH volume (i.e., WMH volume after registration to the MNI-152 template) to determine the independent effects of strategic WMH on language. Correction for multiple comparisons (within 18 white matter tracts including left and right and three outcomes) was performed using the Bonferroni method with a significance level set at 0.05/18*3∼0.00093.

Bayesian Network Analysis

We analyzed Bayesian networks of conditional dependencies between language Z scores, VF, MBNT, age, sex, education, and regional WMH volumes for each white matter tract on left and right to reveal the major determinants for language domain impairment. Gaussian linear Bayesian network analysis for continuous data was applied using the Learning Bayesian Networks. The network structure was learned using a Semi-Interleaved Hiton Parents and Children (SI-HITON-PC) constraint-based algorithm, with a nonparametric conditional independence test based on mutual information (i.e., sequential Monte Carlo permutation test; 500 permutations; alpha = 0.05). This analysis was done with the bnlearn package (version 4.4) within the R software package (version 3.5.1).[21] The applied algorithm in the Bayesian network analysis (a constraint-based learning algorithm) requires no multiple testing adjustment, because these algorithms are largely self-adjusting in that respect.[22] The analyses were carried out without prespecified directionality with the following two exceptions: for biologically relevant structure-function dependencies where WMH impacted language and not vice versa, language was used as the dependent variable and WMH volume as an independent variable. Similarly, age, sex, and education were used as independent variables. The robustness of the final strategic network to sampling variability was confirmed using a bootstrapping approach and the strength of each arc was calculated as a relative frequency of the arc appearance in 1,000 networks obtained through resampling. Bootstrap replications were performed to investigate the robustness of the observed relationships between WMH volumes in white matter tracts and cognitive performance and expressed as the relative frequency in which the arcs (i.e., the connections between the variables) appeared in the reconstructed network. Good confidence was indicated by an arc frequency of 50% and higher in accordance with previous applications of this method in the literature.[23] The level of significance was set to 5% and all tests were two-sided.

RESULTS

Characteristics of the study population are shown in Table 1. The mean age of the participants was 70.2 years and 54% were women. The median WMH was 2.33 mL and the prevalence of lacunes in this sample was 17%. Chinese performed better on language domain and MBNT whereas Malay and Indian had lower scores on language domain and MBNT (Table 2); no differences in VF performance were found among the three ethnicities.

TABLE 1. Characteristics of the Study Sample

Demographics Characteristics	Study Sample (n = 819)
Age, mean (SD)	70.2 (6.6)
Women, no. (%)	442 (54)
Education (years), mean (SD)	5.9 (4.54)
Right handedness, no. (%)	814 (99)
Vascular risk factors	
Hypertension, no. (%)	657 (80.2)
Hyperlipidemia, no. (%)	614 (75)
Diabetes, no. (%)	306 (37.4)
Smoking, no. (%)	211 (25.8)
MRI markers	
Lacunes, no (%)	139 (17)
White matter hyperintensities volume, mL, median (IQR)	2.33 (0-61.8)
Microbleeds, no. (%)	278 (34.5)
Language tests	
Modified Boston Naming Test, mean (SD)	13.20 (1.69)
Animal naming, mean (SD)	12.87 (3.90)
Food naming, mean (SD)	14.28 (4.26)

Bold values represent p <0.05.

ROI-Based Analyses

Total WMH volume was significantly associated with worse performance on language (mean difference in z-scores per SD increase in WMH volume: −0.14, 95% CI: −0.19; −0.07, p <0.001, degrees of freedom (df): 1, F statistic: 15.9) as well as VF (mean difference in z-scores per SD increase in WMH volume: −0.13, −0.19; −0.06, p <0.001, df: 1, F statistic: 14.4) and MBNT (mean difference in z-scores per SD increase in WMH volume: −0.08, 95%CI: −0.15; −0.02, p <0.001, df: 1, F statistic: 5.77). Table 3 shows the association between strategic white matter tracts in which WMH volume were associated with language domain and its specific subtests. Upon adjusting for age, sex, spoken language, education, presence of lacunes and total WMH volume, WMH in left anterior thalamic tract, and uncinatefasiculus were significantly associated with worse performance on VF whilst the left cingulum of cingulate gyrus was associated with the MBNT (Table 3). After applying Bonferroni correction to the WMH-corrected models, none of the associations reached revised statistical significance. These associations did not differ when the analysis was stratified by language spoken among the participants (Table 4).

Bayesian Network Analyses

To account for the multicollinearities and interactions between variables in the previous step on linear

TABLE 2. AssociationBetween Ethnicities and Language With Its Specific Subtests

	Language		Verbal Fluency		Modified Boston Naming Test	
Ethnicities	**Mean (SD)**	**β (95% CI)[a], p Value**	**Mean (SD)**	**β (95% CI)[a],p Value**	**Mean (SD)**	**β (95% CI)[a],p Value**
Chinese	0.09 (0.92)	**0.18 (0.05; 0.30), F = 7.6, p = 0.006**	0.31 (0.92)	−0.05 (−0.18; 0.08), F = 0.55, p = 0.458	−0.06 (1.0)	**0.49 (0.37; 0.62), F = 58.8, p =<0.001**
Malay	−0.21 (0.99)	**−0.13 (−0.26; −0.00), F = 3.9, p = 0.047**	−0.23 (1.0)	−0.06 (−0.19; 0.07), F = 0.89, p = 0.346	−0.14 (0.96)	**−0.19 (−0.32; -0.06), F = 7.9, p = 0.005**
Indian	0.13 (1.05)	−0.06 (−0.19; 0.08), F = 0.69, p = 0.406	−0.07 (1.11)	0.12 (−0.02; 0.26), F = 3.04, p = 0.081	0.22 (1.0)	**−0.34 (−0.47; −0.20), F=24.3, p =<0.001**

Bold values represent p <0.05.
[a]All models adjusted for age, sex, and education. For the F test, the degrees of freedom (df) is 1.

TABLE 3. Association Between White Matter HyperintensitiesVolume Within 10 White Matter Tracts Separate for Left and Right Hemisphere With Language and Its Specific Tests (Verbal Fluency and Modified Boston Naming Test)

White Matter Tracts	Language β (95% CI)[a], p Value	Verbal Fluency β (95% CI)[a], p Value	Modified Boston Naming Test β (95% CI)[a], p Value
Anterior thalamic radiation, Left	−0.06 (−0.16; 0.04), F = 1.45, p = 0.229	**−0.12 (−0.22; −0.02), F = 5.53, p = 0.019**	0.07 (−0.03; 0.17), F = 1.93, p = 0.166
Anterior thalamic radiation, Right	0.05 (−0.05; 0.14), F = 0.78, p = 0.354	0.02 (−0.08; 0.12), F = 0.09, p = 0.743	0.08 (−0.02; 0.17), F = 2.15, p = 0.126
Corticospinal tract, Left	0.00 (−0.07; 0.08), F = 0.00, p = 0.934	0.02 (−0.06; 0.09), F = 0.27, p = 0.596	−0.03 (−0.10; 0.05), F = 0.63, p = 0.458
Corticospinal tract, Right	0.07 (−0.01; 0.15), F = 2.69, p = 0.103	0.08 (−0.00; 0.17), F = 3.51, p = 0.062	0.02 (−0.07; 0.10), F = 0.19, p = 0.676
Cingulum of cingulate gyrus, Left	−0.07 (−0.14; 0.01), F = 3.19, p = 0.067	−0.04 (−0.11; 0.04), F = 0.95, p = 0.321	**−0.09 (−0.17; −0.02), F = 5.51, p = 0.016**
Cingulum of cingulate gyrus, Right	−0.05 (−0.11; 0.01), F = 2.21, p = 0.115	−0.03 (−0.09; 0.03), F = 1.07, p = 0.286	−0.05 (−0.11; 0.01), F = 2.42, p= 0.090
Inferior fronto-occipital fasciculus, Left	−0.03 (−0.12; 0.07), F = 0.26, p = 0.593	−0.12 (−0.33; 0.10), F = 1.11, p = 0.299	0.03 (−0.07; 0.13), F = 0.49, p = 0.510
Inferior fronto-occipital fasciculus, Right	−0.01 (−0.14; 0.12), F = 0.00, p = 0.877	0.00 (−0.22; 0.22), F = 0.00, p 0 .985	−0.03 (−0.16; 0.10), F = 0.05, p = 0.692
Inferior longitudinal fasciculus, Left	0.02 (−0.06; 0.10), F = 0.22, p = 0.649	0.04 (−0.04; 0.13), F = 0.95, p = 0.331	−0.03 (−0.11; 0.06), F = 0.44, p = 0.501
Inferior longitudinal fasciculus, Right	−0.00 (−0.07; 0.07), F = 0.00, p = 0.952	0.02 (−0.06; 0.09), F = 0.19, p = 0.681	−0.03 (−0.48; 0.19), F = 0.53, p = 0.389
Uncinate fasciculus, Left	−0.03 (−0.11; 0.04), F = 0.72, p = 0.390	**−0.09 (−0.18; −0.01), F = 5.24, p = 0.022**	0.08 (−0.00; 0.17), F = 4.37, p = 0.051
Uncinate fasciculus, Right	0.04 (−0.04; 0.12), F = 0.89, p = 0.359	0.03 (−0.06; 0.11), F = 0.47, p = 0.500	0.04 (−0.05; 0.12), F = 0.89, p = 0.370
Superior longitudinal fasciculus, Left	0.05 (−0.03; 0.14), F = 1.76, p = 0.231	0.07 (−0.02; 0.16), F = 2.38, p = 0.116	0.02 (−0.07; 0.11), F = 0.09, p = 0.662
Superior longitudinal fasciculus, Right	0.05 (−0.04; 0.13), F = 1.98, p = 0.265	0.05 (−0.05; 0.15), F = 1.05, p=0.293	0.08 (−0.02; 0.17), F = 1.96, p = 0.128
Temporal part of superior longitudinal fasciculus, Left	0.05 (−0.03; 0.14), F = 1.28, p = 0.243	0.07 (−0.02; 0.16), F = 2.60, p = 0.102	−0.01 (−0.09; 0.08), F = 0.07, p = 0.879
Temporal part of superior longitudinal fasciculus, Right	0.19 (−0.04; 0.13), F = 1.18, p = 0.333	0.02 (−0.07; 0.11), F = 0.24, p = 0.615	0.07 (−0.01; 0.16), F = 2.56, p = 0.100
Forceps major	0.02 (−0.06; 0.11), F = 0.42, p = 0.552	0.03 (−0.05; 0.18), F = 0.64, p = 0.436	−0.00 (−0.08; 0.08), F = 0.00, p = 0.985
Forceps minor	−0.05 (−0.13; 0.04), F = 1.18, p = 0.255	−0.07 (−0.16; 0.02), F = 2.43, p = 0.115	0.01 (−0.08; 0.09), F = 0.08, p = 0.851

Bold values represent p <0.05.

[a] All models adjusted for age, sex, spoken language, education, lacunes and total white matter hyperintensities volume. p Values reported are not Bonferroni corrected. For the F test, the degrees of freedom (df) is 1.

regression, we performed Bayesian network analyses to identify a strategic network of major white matter tracts relevant for language and its subtests taking into account age and sex. We found that the left cingulum of the cingulate gyrus was directly linked with the MBNT (Fig. 1). A detailed network analysis of left cingulum and other white matter tracts with MBNT are shown in supplemental digital content 1. The strength of the arc between the left cingulum of the cingulate gyrus and the MBNT obtained by bootstrapping was 51% reflecting a good confidence interval. No direct connections between WMH in specific tracts and verbal fluency or the composite language domain were found.

DISCUSSION

This study identified strategic white matter tracts in which WMH are associated with worse performance in language in a population-based setting. More specifically, the left cingulum of the cingulate gyrus was identified as a strategic white matter tract for the MBNT. This suggests that the language is sensitive to ischemic damage in a larger subcortical network than was previously thought.

Previous studies have shown that the total WMH volume only explains a limited proportion of interindividual variability in cognitive functioning and that

TABLE 4. Association BetweenWhite Matter HyperintensitiesVolume Within Three White Matter Tracts With Verbal Fluency and Modified Boston Naming Test (Tracts Significant From Table 3)

	Verbal Fluency			
White Matter Tracts	**English** β **(95% CI)[a], p Value**	**Mandarin** β **(95% CI)[a], p Value**	**Chinese Dialect** β **(95% CI)[a], p Value**	**Malay** β **(95% CI)[a], p Value**	**Tamil** β **(95% CI)[a], p Value**
Anterior thalamic radiation, Left	−0.23 (−0.48; 0.01), F = 3.54, p = 0.061	−0.06 (−0.34; 0.21), F = 0.21, p = 0.651	−0.16 (−0.66; 0.34), F = 0.40, p = 0.529	−0.12 (−0.28; 0.04), F = 2.20, p = 0.139	−0.11 (−0.48; 0.26), F = 0.33, p = 0.569
Uncinate fasciculus, Left	**−0.18 (−0.34; -0.01), F = 4.39, p = 0.037**	−0.16 (−0.38; 0.07), F = 1.86, p = 0.174	−0.48 (−1.76; 0.81), F = 0.56, p = 0.459	−0.05 (−0.18; 0.09), F = 0.44, p = 0.507	0.05 (−0.21; 0.31), F = 0.14, p = 0.710
	Modified Boston Naming Test				
	English β **(95% CI)[a], p Value**	**Mandarin** β **(95% CI)[a], p Value**	**Chinese Dialect** β **(95% CI)[a], p Value**	**Malay** β **(95% CI)[a], p Value**	**Tamil** β **(95% CI)[a], p Value**
Cingulum of cingulate gyrus, Left	**−0.20 (−0.37; −0.04), F = 5.77, p = 0.017**	**0.28 (0.03; 0.54), F = 4.68, p = 0.032**	**−0.41 (−0.72; -0.09), F = 6.89, p = 0.012**	**−0.13 (−0.25; -0.01), F = 4.51, p = 0.035**	−0.01 (−0.28; 0.26), F = 0.00, p = 0.949

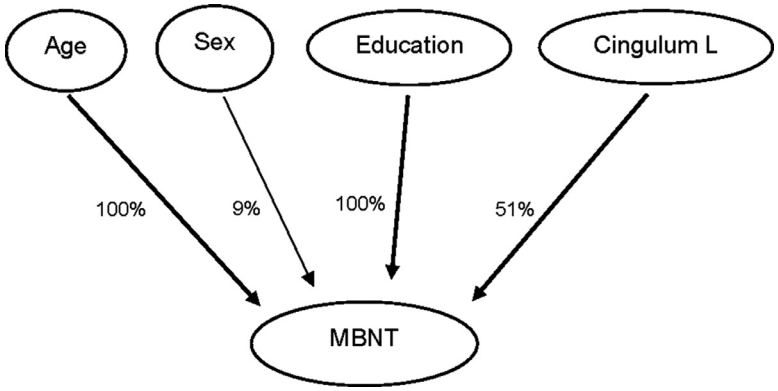
Bold values represent p <0.05.
[a] All models adjusted for age, sex, education, lacunes and total white matter hyperintensities volume. For the F test, the degrees of freedom (df) is 1.

location of WMH might be more relevant to study the effects of WMH on cognition.[6] This has been reported in studies on CADASIL patients,[4,23] clinically manifest arterial disease,[5] memory clinic patients,[6] and community-based cohorts.[24,25] However, these studies have been largely focused on vascular cognitive impairment domains which include impairment in executive function, processing speed and memory whereas the effects of WMH on language has been less studied. Earlier lesion studies have suggested that the language deficits extend beyond the traditional cortical areas such as Broca's area and involve surrounding frontal cortex, white matter, insula, and basal ganglia.[26–28] Interestingly, an MR study involving imaging of Broca's aphasic patients showed that the actual surface lesion (Broca's area) which was attributed to all aspects of speech deficits in these patients, extended significantly into the medial location of the brain involving subcortical white matter and deep gray nuclei.[2]

A more recent study only reported an association between gray matter atrophy with language impairment but did not find a link with WMH volumes.[9] As such, our study adds further to the previous findings by reporting an association between the strategic location of WMH in white matter tracts and language subtasks suggesting that strategic ischemic lesions within white matter tracts are better predictors of language impairment than total lesion volume. Interestingly, regional WMH volume in left cingulum was associated with the MBNT, thus reflecting that different language subtasks maybe impaired by different strategic white matter tracts. This was also corroborated in earlier literature where relationship between location and extent of ischemic lesion was examined using CT scan in cases with verbal stereotypes and nonfluent Broca's aphasia. It was suggested that the extent of the lesion involved medial subcallosal fasciculus which contained projections from the cingulate gyrus and supplementary motor area to caudate nucleus, was extensive enough to interrupt a large number of white matter connections.[29] Interestingly, the language spoken by the participants did not affect performance on language tasks suggesting that these associations are least affected by spoken languages.

Moreover, Bayesian network analysis identified the left cingulum as a relevant structure contributing to worse performance on language. Limited data support the role of the cingulum in executive function

FIGURE 1. Bayesian network analysis for strategic white matter hyperintensities with Modified Boston Naming Test. The left cingulum of the cingulate gyrus, age, sex, and education has a direct connection to the Modified Boston Naming Test. Bold black arrows indicate confidence level above 50% and numbers indicate the confidence level of the arcs as determined by 1,000 bootstrap replications.



and processing speed but less so for language.[30] One study involving diffusion tensor imaging employed an ROI approach to study the contribution of anterior and posterior cingulum fractional anisotropy and mean diffusivity to attention/executive function, language, memory, and visuo-spatial function in a group of 220 cognitive healthy older adults. They found that fractional anisotropy differences in the anterior cingulum correlate with differences in attention/executive and memory performance, while fractional anisotropy in the posterior dorsal cingulum appeared to contribute to all four cognitive domains.[8,31] Thus, our data extends knowledge by demonstrating a strategic role of WMH within the cingulum with the MBNT. Our findings strengthen the concept that the cingulate circuits play an important role in vascular cognitive impairment-related subcortical ischemic lesions.

Interestingly, the cingulum network identified by Bayesian analysis primarily involved the left hemisphere which is in line with the previous studies where white matter integrity in relation to cognition showed predominance in the left hemisphere.[23] Even though, there was no specific asymmetry of WMH distribution in the included sample, the verbal and naming tasks are predominantly controlled by the left hemisphere.[23] The lack of association between lesions in longitudinal tracts and language might be due to a relatively low WMH burden in these tracts. This may explain why the total burden of WMH explained only a small proportion of variance in cognition.

Limitations of the present study include first, participants were recruited based on cognitive screening, meaning the study population is enriched with persons with cognitive impairment. This enrichment increases the statistical power for detecting associations between WMH lesions and cognition but may limit the generalizability to a community-based setting. Second, the cross-sectional design of the present study limits the temporal relationship between WMH volume and cognition. Third, there might be an overlap between the tests of language and processing speed as well as executive functioning. Fourth, we did not consider microstructural changes in the white matter tracts, which may influence our results. Fifth, the Bayesian network analysis showed association between WMH in cingulum and the MBNT which was not corroborated in linear regression analysis after applying multiple testing correction, thus providing less strong evidence for such association. Finally, even though ROI-based analysis showed between WMH in the left cingulum and the MBNT, and the left anterior thalamic radiation and uncinate fasciculus and VF, these associations did not survive testing. Moreover, as the size of these standardized coefficients are small, they may lack clinical meaning but remain of possible theoretical interest. Strengths of the study include a large population-based setting, usage of Bayesian network analysis, which deals well with multicollinearity providing intuitive representation of the complex relationships. Confidence in the

involvement of the cingulum network was further confirmed by bootstrapping the white matter networks in Bayesian analysis.

CONCLUSION

This study demonstrated an association between WMH in the left cingulum and the MBNT. Our findings support the concept that WMH located in these strategic white matter tracts specifically left cingulum disrupt language and suggest that the subcortical network involved in language production is larger than was previously thought. Future studies on the role of sporadic ischemic lesions and vascular cognitive impairment should not only focus on total WMH volume but should also take WMH lesion location into account when addressing language. Longitudinal studies are needed to determine whether WMH volumes in strategic white matter tracts predict future (domain-specific) cognitive decline.

AUTHOR CONTRIBUTIONS

Saima Hilal: Conceptualization, Methodology, Formal analysis, Writing- Original draft preparation, Project administration, Funding acquisition. **J. Matthijs Biesbroek:** Conceptualization, Methodology, Formal analysis, Writing - Review & Editing. **Henri Vrooman:** Software, Methodology, Formal analysis. **Eddie Chong**: Methodology, Writing- Reviewing and Editing. **Hugo J. Kuijf:** Software, Methodology, Formal analysis. **NarayanaswamyVenketasubramanian:** Supervision. **Ching-Yu Cheng:** Supervision. **Tien Yin Wong:** Supervision. **Geert Jan Biessels:** Conceptualization, Supervision, Writing- Reviewing and Editing. **Christopher Chen:** Conceptualization, Supervision, Writing- Reviewing and Editing. All authors approve final version of the manuscript.

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SUPPLEMENTARY MATERIALS

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