



High white matter hyperintensity burden in strategic white matter tracts relates to worse global cognitive performance in community-dwelling individuals

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ABSTRACT

Background: White matter hyperintensities (WMH) are associated with cognitive impairment. The impact of WMH on cognitive domains (e.g. processing speed, executive functioning) depends on location. We determined whether the relevance of WMH location also applies to global cognitive functioning by testing if WMH in strategic white matter tracts are associated with global cognitive functioning independent of total WMH burden. **Methods:** We included 830 community-dwelling individuals. WMH volume within two a priori specified strategic white matter tracts (forceps minor and anterior thalamic radiation) were entered in a linear regression model with the Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE) as outcome variables and corrected for total WMH volume and other MRI markers for vascular injury and neurodegenerations (i.e. brain parenchymal fraction, and the presence of lacunes and microbleeds). **Results:** WMH in the forceps minor and left anterior thalamic radiation inversely correlated with MoCA, and WMH in the forceps minor inversely correlated with MMSE, independent of total WMH volume and other MRI markers. **Conclusion:** The impact of WMH on global cognitive functioning depends on location. Whether this reflects accumulated impairment in isolated cognitive domains or disruption of a network that is crucially involved in global cognitive performance remains to be determined.

1. Introduction

Small vessel disease (SVD) is an important cause of cognitive decline and dementia [1,2]. Yet, it is often difficult to determine to what extent white matter hyperintensities (WMH) are the cause of cognitive impairment in individual patients [3]. This is illustrated by the common observation in clinical practice that some patients with a high burden of WMH are cognitively impaired, whereas other patients with a similar WMH burden are not [3]. Recent lesion-symptom mapping studies (i.e.

studies in which the relation between WMH location and cognition is studied at the level of individual white matter tracts or individual voxels) have demonstrated that the impact of WMH on cognition depends on location and identified strategic white matter tracts where lesions have a larger impact on cognition than total WMH volume [4]. In some of these studies, the association between strategic WMH volume and cognition was independent of total WMH volume, which indicates that they are strategic in the sense that their impact goes beyond what is explained by total WMH burden. These previous studies have

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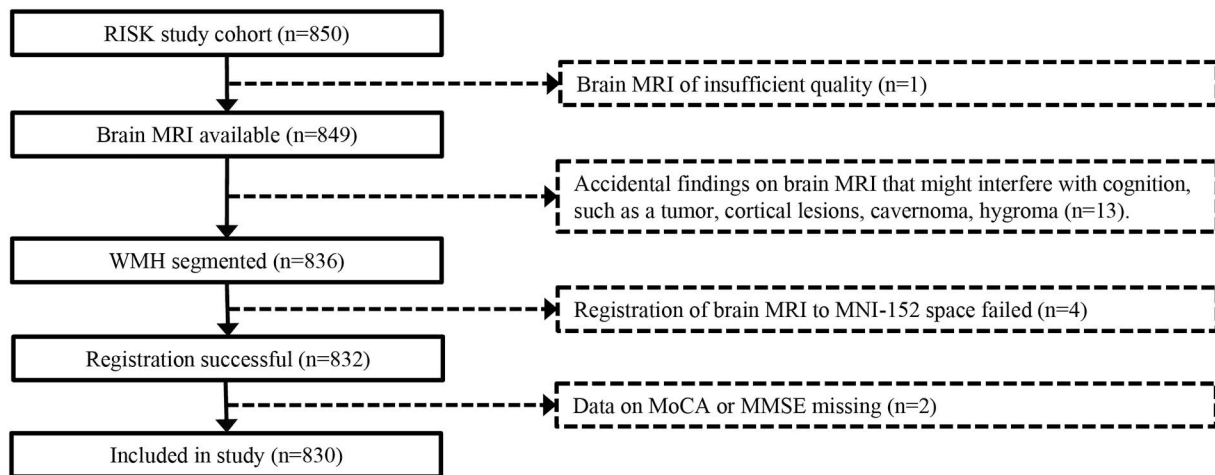


Fig. 1. Flowchart of the inclusion of patients.

used detailed neuropsychological tests and focused on isolated cognitive functions or domains such as executive functioning, processing speed and memory as outcome measures. Detailed neuropsychological tests have the advantage of being able to isolate specific cognitive processes in order to identify their neural correlates. As of yet, no studies have determined whether WMH location is associated with global cognitive functioning, measured with for example the Montreal Cognitive Assessment (MoCA) or Mini-Mental State Examination (MMSE), which are both validated cognitive screening tools, available in many languages, frequently used, and easily administered [5,6]. Though both the MoCA and MMSE provide a score for global cognitive functioning by capturing multiple cognitive domains, a notable difference is that the MoCA includes more executive tasks than the MMSE such as the clock drawing test, which is particularly relevant in the current study as executive functioning tends to be disproportionately affected in SVD [7–9]. One might expect that, because the cognitive impact of WMH on specific cognitive domains depends on location, the same would hold true for a cognitive test that captures all of these domains, either because of accumulated impairment in isolated domains or disruption of an underlying network that is crucially involved in global cognitive performance. On the other hand, if each specific domain depends on a unique set of strategic tracts (which is to some extent indeed the case [4]), it is also conceivable that the lesion location-specific effects for each domain might be neutralized when using a cognitive test that captures multiple cognitive domains and that only total WMH volume remains relevant.

The aim of this study was to test the hypothesis that the impact of WMH on global cognitive functioning depends on location, by determining whether WMH in strategic tracts are associated with global cognitive impairment, independent of total WMH volume in a large community-based cohort. Global cognitive functioning was assessed with the MoCA as well as the MMSE. The tracts that were specifically evaluated were the forceps minor and left and right anterior thalamic radiation, because these tracts have been consistently associated with SVD-related cognitive decline in multiple individual cognitive domains (executive functioning, speed and memory) and clinical settings (healthy individuals, memory clinic cohorts with sporadic SVD and CADASIL) [4].

2. Methods

Approval was given by the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee for the study [10]. The methods were carried out in accordance with the relevant guidelines and regulations.

2.1. Participants

Healthy community-dwelling individuals were recruited from the community-based cohort of the CU-RISK Study (The Chinese University of Hong Kong - Risk Index for Subclinical brain lesions in Hong Kong) [10]. The recruitment procedure has been previously described [10]. Participants were recruited by advertisement of the study in local community centers and word-of-mouth in the local community network. Inclusion criteria were 1) age ≥ 65 ; 2) functional independence as defined by a score of 20 on the 20-point Barthel Index [11] and < 2 on the Lawton's Instrumental of Daily Living Scale (IADL) [12]; 3) Cantonese-speaking, 4) sufficient sensorimotor and language competency for cognitive testing; and 5) written informed consent given. Exclusion criteria were 1) history of clinical stroke or transient ischemic attack ascertained by medical records on the Clinical Management System of the Hospital Authority, which is the public healthcare provider in Hong Kong that covers $\geq 90\%$ local inpatient service; 2) self-reported history of neurological or psychiatric conditions affecting cognitive functions; 3) dementia determined by the cutoff values of the published Chinese Mini-mental state examinations (locally validated education-adjusted cut-off were as follows: < 18 for illiterate subjects, < 20 for those with 1 to 2 years of schooling, and < 22 for those with more than 2 years of schooling [6]) or medical history; 4) evidence of brain tumors, large cerebral infarcts (i.e. infarcts ≥ 20 mm in diameter), cortical infarcts, or hydrocephalus on MRI, which were rated by a radiologist and neurologist. This resulted in the inclusion of 830 individuals (a flowchart is provided as Fig. 1).

2.2. Neuropsychological assessment

Trained research assistants administered the Hong Kong version of the MoCA and MMSE according to standardized procedures [5,6,10].

2.3. Scan protocol and image processing

Brain MRI was acquired using a 3.0-T scanner (Achieva 3.0 T X-series, Philips Medical System, Best, the Netherlands) for all participants [13]. Because the scan protocol was updated during the inclusion of participants, two scan protocols were used (the sequences relevant for this study are provided in Table 1 and were previously described [13]). WMH segmentations of FLAIR sequences were performed using a semi-automated method. Automated WMH segmentations were first performed on all FLAIR sequences using a built-in tool [14] of the automatic brain quantification software AccuBrain® (BrainNow Medical Technology Limited, Hong Kong SAR). To guarantee sufficient precision of the WMH segmentations for the quantification of regional WMH

Table 1
Brain MRI protocol.

Sequence		Protocol 1 (n = 787)	Protocol 2 (n = 44)
3D T1	TR (ms)	7.49	6.49
	TE (ms)	3.46	3.112
	Reconstructed voxelsize (mm)	$0.60 \times 1.04 \times 1.04$	$1.2 \times 1.0 \times 1.0$
	Acquisition matrix	228×227	256×256
3D FLAIR	TR (ms)	8000	–
	TE (ms)	328.6	–
	TI (ms)	2400	–
	Reconstructed voxelsize (mm)	$0.55 \times 0.44 \times 0.44$	–
2D FLAIR	Acquisition matrix	208×208	–
	TR (ms)	–	11,000
	TE (ms)	–	125
	TI (ms)	–	2800
SWI	Reconstructed voxelsize (mm)	–	$0.33 \times 0.33 \times 5.5$
	Acquisition matrix	–	352×234
	TR (ms)	16.85	–
	TE (ms)	23.84	–
T2	Reconstructed voxelsize (mm)	$0.45 \times 0.45 \times 1.0$	–
	Acquisition matrix	–	–
	TR (ms)	–	2366.86
	TE (ms)	–	80
	Reconstructed voxelsize (mm)	–	$5.5 \times 0.22 \times 0.22$
	Acquisition matrix	–	512×385

volumes, a manual correction was generally required. To enable manual correction of the WMH segmentations, the 3D FLAIR sequences ($n = 787$, acquired with > 200 transversal slices with a slice thickness of 0.55 mm, see scan protocol 1 in Table 1) and the corresponding WMH lesion masks were downsampled to transversal slices with a slice thickness of 5 mm. For scan protocol 2 ($n = 44$), the 2D FLAIR sequences were acquired with a transversal slice thickness of 5.5 mm (with 25 slices in total), and image downsampling was therefore not required. All 830 automated WMH segmentations were subsequently checked and manually corrected by experienced raters (JMB and BYKL). Next, the WMH lesion maps were registered to standard space using a previously described tailor-made software [15,16]. The downsampled FLAIR sequences were first registered to the corresponding high-resolution 3D T1 sequence with a linear registration. The high-resolution T1 sequence was subsequently transformed to the T1 1-mm T1 MNI-152 (Montreal Neurological Institute) template [17], with a linear registration followed by a non-linear registration. Considering that most of the included patients were elderly subjects, an age-specific MRI template [18] was used as an intermediate step before the final registration to MNI-152 space in order to improve the quality of the registration by providing a better match between patient and template. The resulting transformations were combined into a single transformation that was subsequently used to transform the corresponding lesion maps to the MNI-152 template [15]. The final registration results of all cases were visually checked and 4 participants were excluded because the registration results were of insufficient quality. The WMH maps in MNI-space were used to calculate total normalized WMH volume and WMH volume in the forceps minor and anterior thalamic radiation using a probabilistic white matter tract atlas that was thresholded at 10% (see Fig. 2 for an illustration of these tracts) [19]. WMH volumes were calculated by multiplying voxel volume (in all cases 1 mm³) with binary lesion status (i.e., 1 when the voxel is lesioned, 0 when the voxel is not lesioned) and dividing the result by 1000, so that volume was expressed in milliliters. The presence of lacunes (scored by JMB) and microbleeds (scored by ZW) were scored by experienced raters using FLAIR, T1, and either T2*-weighted or T2 sequences in accordance with the internationally established STRIVE Criteria [20]. All raters were blinded to the clinical data during the segmentation and rating process. Total brain volume and intracranial volume were quantified using the Statistical Parametric Mapping 12b unified segmentation approach [21] and used to compute the brain parenchymal fraction (BPF; (brain

volume/intracranial volume)) as a measure of brain atrophy (lower brain tissue volume, higher ventricular volume and higher peripheral cerebrospinal fluid volume correspond with lower BPF).

2.4. Statistics

To answer our main research question, a hypothesis-driven region of interest-based lesion-symptom mapping approach was used, focusing on two white matter tracts: the forceps minor and anterior thalamic radiation. These were selected because they have previously been

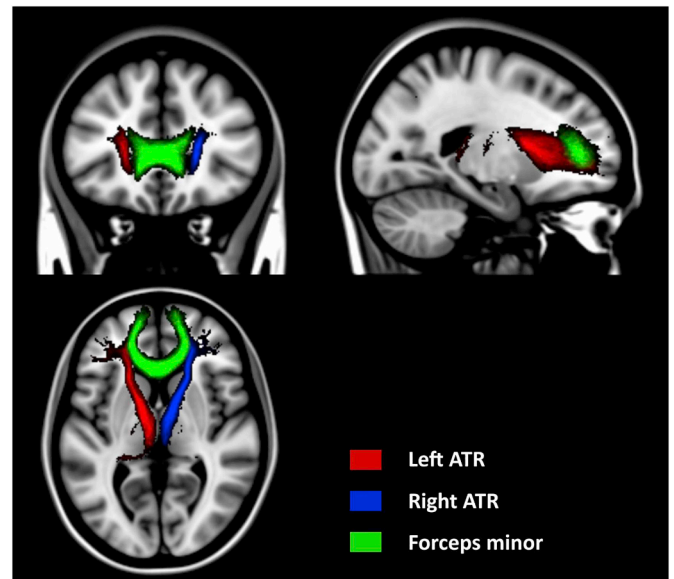


Fig. 2. Illustration of the anterior thalamic radiation (ATR) and forceps minor. These regions of interest for the ATR and forceps minor were based on a previously published probabilistic anatomical atlas [19], thresholded at a probability of 10% and used to calculate regional WMH volumes. The anterior thalamic radiation connects the anterior and mediodorsal thalamic nuclei with the anterior cingulate and prefrontal cortex and runs through the anterior limb of the internal capsule [32]. The forceps minor consists of fibers connect both frontal lobes and run through the genu of the corpus callosum.

Table 2
Characteristics of the study cohort.

	Study cohort (n = 830)
Demographic characteristics	
Age, mean (SD)	71.8 (5.1)
Male, n (%)	322 (38.8)
Education in years, mean (SD)	7.9 (4.9)
Vascular risk factors, n (%)	
Hypertension	509 (61.3)
Hyperlipidemia	256 (30.8)
Current smoker	29 (3.5)
Diabetes Mellitus	197 (23.7)
Brain MRI characteristics	
Individuals with lacunes, n (%)	54 (6.5)
Lacune number, median (range)	0 (0–6)
Individuals with microbleeds, n (%) ^a	177 (21.9)
Microbleed number, median (range) ^a	0 (0–109)
BPF, mean (SD) ^b	0.74 (0.06)
WMH volumes in ml, median (IQR)	
Total WMH volume	4.00 (6.40)
WMH volume forceps minor	0.16 (0.23)
WMH volume left ATR	0.22 (0.38)
WMH volume right ATR	0.32 (0.46)
Cognitive testing	
MoCA, mean (SD)	22.5 (3.9)
MMSE, mean (SD)	27.0 (2.3)

IQR: interquartile range.

^a Data missing in 21 cases.

^b Data missing in 2 cases.

consistently associated with SVD-related impairment in several cognitive domains [4]. Strategic WMH volumes were correlated with the MMSE and MoCA and corrected for age, sex, education, and total WMH volume using a stepwise linear regression model. To determine whether correlations between strategic WMH volumes are independent of other MRI markers for vascular injury and neurodegeneration, the regression models were additionally corrected for brain parenchymal fraction, the presence of lacunes (i.e. dichotomized variable, ≥ 1 lacunes versus 0 lacunes), and the presence and microbleeds (i.e. dichotomized variable, ≥ 1 microbleeds versus 0 microbleeds). This final regression model was also corrected for MRI protocol. Standardized beta coefficients (β) with 95% confidence intervals (95%CI) and incremental explained variance (ΔR^2) are reported for the regression models. The residuals of the regression analyses were inspected to ensure that the assumption of normality was met in all cases.

3. Results

The clinical and imaging characteristics of the study cohort are shown in Table 2. The WMH distribution map is shown in Fig. 3.

In the linear regression analysis (Table 3), age, sex, and education explained 39.4% of variance in MoCA ($p < .001$) and 25.6% of variance in MMSE ($p < .001$). When total WMH volume was added, the

models for MoCA (β -0.029, 95% CI -0.084 to 0.025, $p = .292$) and MMSE (β -0.016, 95% CI -0.077 to 0.044, $p = .593$) did not significantly improve. After correction for age, sex, education and total WMH volume, there was a statistically significant correlation between MoCA and WMH volume in the forceps minor (β -0.120, 95% CI -0.221 to -0.019, $p = .019$), and the left anterior thalamic radiation (β -0.116, 95% CI -0.226 to -0.007, $p = .038$) (Table 3). WMH volume in the right anterior thalamic radiation did not significantly correlate with MoCA. After correction for age, sex, education and total WMH volume, WMH volume in the forceps minor correlated with MMSE (β -0.132, 95%CI -0.244 to -0.021, $p = .020$), whereas WMH volume in the anterior thalamic radiation did not. After additional correction for other MRI markers for vascular injury and neurodegeneration (brain parenchymal fraction, presence of lacunes and microbleeds) and scan protocol, the correlations between WMH volume in the forceps minor (β -0.116, 95% CI -0.218 to -0.015, $p = .024$) and the left anterior thalamic radiation (β -0.113, 95% CI -0.222 to -0.003, $p = .043$) and total MoCA and the correlation between WMH volume in the forceps minor (β -0.144, 95% CI -0.257 to -0.031, $p = .012$) and MMSE remained statistically significant.

4. Discussion

Our findings demonstrate that the impact of WMH on global cognitive functioning, as measured with MoCA and MMSE, depends on location. WMH volume in the left anterior thalamic radiation and forceps minor was inversely correlated with MoCA, independent of total WMH volume and other MRI markers for vascular injury and neurodegeneration. WMH volume in the forceps minor was inversely associated with MMSE, also independent of total WMH volume and of other MRI markers for vascular injury and neurodegeneration. Thus, our results indicate that the previously demonstrated role of strategically located WMH in SVD-related cognitive decline [4] also applies when using MoCA and MMSE, which are widely used and validated cognitive screening tools, instead of detailed neuropsychological testing of specific cognitive domains.

It should be noted that the MoCA has been shown to be more sensitive than the MMSE for detecting cognitive decline [22]. For example, a recent study in patients with SVD and mild cognitive impairment found an association between white matter microstructural damage and MoCA, but not MMSE [23], and other studies found a higher sensitivity of the MoCA for detecting cognitive impairment in patients with vascular dementia [24], Parkinson's disease [25], and Alzheimer's Disease [22,26] when compared with the MMSE. We cannot entirely rule out the possibility that the correlations between strategic WMH and total MoCA and MMSE are driven by a decline in specific cognitive domains. Alternatively, it is conceivable that some strategic regions form a crucial part of a central network that is involved in many cognitive functions. This latter notion is in line with evidence that single strategic infarcts can cause dementia and that infarcts and WMH in strategic tracts can cause impairment in multiple cognitive domains including executive functioning, processing speed, memory and language

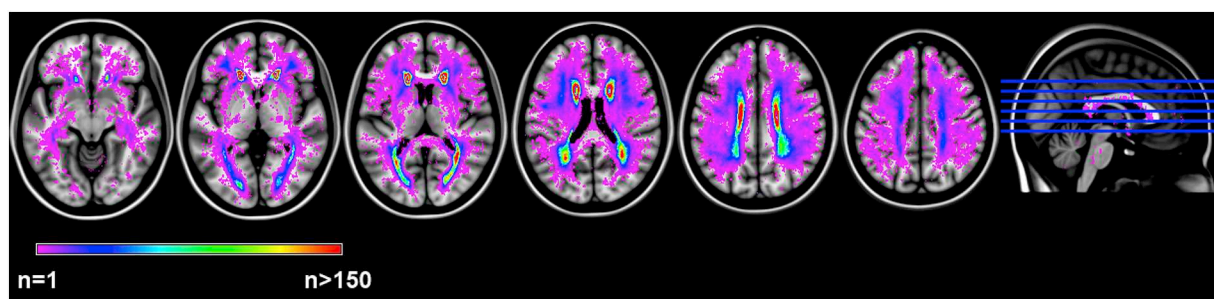


Fig. 3. WMH distribution map: lesion overlay of all 830 subjects showing the number of patients with a WMH for each voxel.

Table 3
Results of stepwise linear regression models: strategic WMH volumes and MoCA and MMSE.

Independent variables	Dependent variable: MoCA			Dependent variable: MMSE		
	ΔR^2	Beta (95%CI)	p-value	ΔR^2	Beta (95%CI)	p-value
Model 1: age, sex, education	0.394	–	< 0.001	0.256	–	< 0.001
Model 2: model 1 + total WMH volume	0.001	-0.029 (–0.084 to 0.025)	0.292	0.000	-0.016 (–0.077 to 0.044)	0.593
Model 3a: Model 2 + WMH volume forceps minor	0.004	-0.120 (–0.221 to –0.019)	0.019*	0.005	-0.132 (–0.244 to –0.021)	0.020*
Model 3b: Model 2 + WMH volume left ATR	0.003	-0.116 (–0.226 to –0.007)	0.038*	0.001	0.040 (–0.082 to 0.161)	0.521
Model 3c: Model 2 + WMH volume right ATR	0.001	–0.058 (–0.155 to 0.040)	0.244	0.002	–0.076 (–0.184 to 0.032)	0.168

Linear regression model 1 includes the independent variables age, sex and education. Model 2 includes the same independent variables as model 1 with the addition of the variable total WMH volume. Models 3 a-c additionally include WMH volume in a specific white matter tract and show the standardized regression coefficient and additional explained variance in cognition on top of age, sex, education, and total WMH volume (i.e. on top of the variables included in model 2). *Statistically significant, $p < .05$. ATR: anterior thalamic radiation.

[4,27,28]. These previous studies have thus far mainly highlighted the thalamus, caudate nucleus, anterior thalamic radiation and forceps minor as strategic regions that form a central subcortical network that relays information required for many cognitive processes, though it is likely that future studies will continue to expand this strategic network for vascular cognitive impairment [4]. This mechanism for the profound cognitive impact of strategic infarcts is illustrated by observations from functional connectivity studies showing that thalamic lesions can interrupt both the default mode network and the central executive network [29,30].

A strength of the current study is that we performed a straightforward hypothesis-driven analysis in which the relation between WMH volume in two white matter tracts known to be strategic for SVD-related cognitive decline in several specific cognitive domains was related to global cognitive functioning. This hypothesis-driven approach was used for two reasons. First, there was sufficient evidence from previous studies to focus on the two aforementioned white matter tracts (though these studies used other, more detailed neuropsychological tests as outcome measures) and this approach limits the chance of making a type I error. Second, the limited WMH burden and asymptomatic status of the participants means that even with 830 subject, there was insufficient power to perform a hypothesis-free analysis including all white matter regions in the brain. We could therefore not determine which other white matter regions might be crucially involved in SVD-related global cognitive decline. Thus, this hypothesis-driven approach was most suited for this study aimed at proving the concept that the previously demonstrated role of strategically located WMH in SVD-cognitive impairment also applies when using MoCA or MMSE as an outcome measure.

It should be noted that the effect sizes regarding the impact of brain MRI markers on MoCA were small. Demographics explained 39.4% of variance, whereas WMH volumes explained only an additional 0.5%. The small role of brain MRI markers compared to demographics in explaining variance in MoCA and MMSE can be explained by the fact that the study cohort consisted of non-demented community-dwelling individuals. The variance in cognition explained by pathology on brain MRI tends to be higher in memory clinic cohorts [28]. Furthermore, the WMH distribution map (Fig. 3) shows that even in this cohort of 830 subjects, many white matter regions were lesioned in only a few individuals. This means that in order to study the cognitive impact of WMH anywhere in the white matter, including less frequently affected regions, multicenter studies including thousands of subjects are needed. As mentioned in the methods, the automated WMH segmentation was performed on the high resolution 3D FLAIR images, but the manual corrections were performed on downsampled images with a transversal slice thickness of 5 mm. Downsampling for manual correction was necessary for the project to be feasible, resulting in decreased precision of the WMH segmentations and the corresponding lesion maps in MNI space. A decrease in precision might introduce more noise in the data when lesions located just outside a white matter tract would be

wrongfully included within the tract-based region of interest and vice versa, potentially resulting in a lower sensitivity of our region of interest-based analyses. Another limitation of the current study is that WMH represent a heterogeneous group of underlying pathologies and etiologies (see Wardlaw et al. 2015 [31] for a review) and we were unable to distinguish between these etiologies as this would require additional biomarkers (e.g. cerebrospinal fluid markers or more advanced brain imaging techniques). Thus, though we can conclude that the cognitive impact of WMH depends on location, we could not determine whether and to what extent this is influenced by the underlying etiology and histopathological changes in the white matter.

5. Conclusion

In community-dwelling individuals, WMH in strategic white matter tracts, i.e. the forceps minor and left anterior thalamic radiation, are associated with global cognitive functioning as measured with MoCA and MMSE, independent of total WMH volume. Thus, the previously demonstrated role of lesion location in the cognitive impact of WMH not only applies to isolated cognitive domains such as executive functioning, but also to global cognitive functioning. The role of strategic WMH in global cognitive impairment might reflect either an impairment in specific underlying cognitive domains or a disruption of strategic connections that have a more widespread impact on multiple cognitive functions.

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Declaration of Competing Interest

The author(s) declare no competing interests.

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