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FEATURED ARTICLE

Strategic white matter hyperintensity locations for cognitive impairment: A multicenter lesion-symptom mapping study in 3525 memory clinic patients

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Abstract

Introduction: Impact of white matter hyperintensities (WMH) on cognition likely depends on lesion location, but a comprehensive map of strategic locations is lacking. We aimed to identify these locations in a large multicenter study.

Methods: Individual patient data (n = 3525) from 11 memory clinic cohorts were harmonized. We determined the association of WMH location with attention and executive functioning, information processing speed, language, and verbal memory performance using voxel-based and region of interest tract-based analyses.

Results: WMH in the left and right anterior thalamic radiation, forceps major, and left inferior fronto-occipital fasciculus were significantly related to domain-specific impairment, independent of total WMH volume and atrophy. A strategic WMH score based on these tracts inversely correlated with performance in all domains.

Discussion: The data show that the impact of WMH on cognition is location-dependent, primarily involving four strategic white matter tracts. Evaluation of WMH location may support diagnosing vascular cognitive impairment.

KEYWORDS
cognitive impairment, lesion symptom mapping, location, memory clinic patients, white matter hyperintensities

Highlights

- We analyzed white matter hyperintensities (WMH) in 3525 memory clinic patients from 11 cohorts
- The impact of WMH on cognition depends on location
- We identified four strategic white matter tracts
- A single strategic WMH score was derived from these four strategic tracts
- The strategic WMH score was an independent determinant of four cognitive domains

1 | INTRODUCTION

Small vessel disease (SVD) is a major cause of cognitive decline and dementia. White matter hyperintensities (WMH) are the most common MRI manifestation of SVD.[1–3] A dose-dependent relation between WMH volume and cognitive impairment has been firmly established at a group level.[2,4,5] Yet, in clinical practice, the usefulness of WMH burden to explain cognitive deficits in individual patients is limited, due to considerable intersubject variability.[1,2,6] For example, some people with a high WMH burden are cognitively unimpaired, whereas others with a relatively low WMH burden have marked deficits. This can create diagnostic uncertainty.

There is emerging evidence from studies in community-dwelling individuals, memory clinic patients, and patients with CADASIL that WMH location is an important determinant of cognitive impact.[6–9] These findings align with the concept that disruption of strategic white matter tracts is a key mechanism through which subcortical vascular damage affects cognition.[2,6] Taking WMH location into account is particularly relevant in patients with cognitive symptoms attending a memory clinic. These patients typically present with different degrees of cognitive impairment, affecting different domains, and variable burden of WMH, often making it difficult to determine the extent to which WMH contributes to the cognitive symptoms. One study among nearly 200 memory clinic patients demonstrated that WMH in the anterior thalamic radiation and forceps minor were inversely associated with executive functioning, visuomotor speed, and memory, after controlling for total WMH volume.[7] However, despite the substantial sample size, lesion coverage was still limited, that is, in large parts of the white matter lesions occurred in too few patients to be included in the analysis. This reflects the typical features of WMH distribution in this setting. In most patients, only a small fraction of the total white matter is affected by WMH, with different WMH locations between patients. Consequently, a substantial fraction of WMH occurs in locations that are relatively rarely affected across patients.

In order to obtain insight into the role of strategic WMH across the entire brain in cognitive impairment and dementia, a comprehensive, large multicenter study including thousands of patients is needed to address white matter locations that are affected more rarely and increase statistical power.[10] We included memory clinic patients from 11 cohorts through the Meta VCI Map consortium[10] in order to identify WMH locations strategic for cognitive impairment through a large scale tract-based lesion-symptom mapping study.

RESEARCH IN CONTEXT

1. **Systematic review**: We used PubMed to identify publications describing the relation between white matter hyperintensity (WMH) location and cognition.
2. **Interpretation**: Prior studies have suggested that the cognitive impact of WMH depends on location, but studies in memory clinic patients were limited in terms of sample size and lesion coverage. Our results, based on a comprehensive analysis of WMH location in 3525 memory clinic patients from 11 cohorts, provide clear evidence that the cognitive impact of WMH indeed depends on location, and identified four strategic white matter tracts. A strategic WMH score was developed that is inversely associated with all cognitive domains, independent of WMH volume.
3. **Future directions**: WMH location may be used as a biomarker to diagnose SVD-related cognitive impairment more accurately. Future steps required for implementation include external validation and the development of fully automated MR image processing. The prognostic value of WMH location should also be explored.

2 | METHODS

2.1 | Study design and participants

We pooled and harmonized individual patient data from 11 memory clinic cohorts: Austria (n = 1, PRODEM[11]), Canada (n = 2; Brain IMPACT,[12] FAVR[12]), Germany (n = 1; VASCAMY), the Netherlands (n = 3; ACE, TRACE-VCI,[13] UMCC), Singapore (n = 1; Harmonization[7]), the UK (n = 1; YOAD[14]), and the USA (n = 2; ADNI[15] (http://adni.loni.usc.edu), AUCD[16]). Cohort specific in- and exclusion criteria are described in Table S1. Eligible cohorts were identified through the Meta VCI Map consortium data index of member cohorts, according to the following criteria: (1) patients evaluated at an outpatient clinic because of cognitive symptoms; (2) availability of MRI with T1 and either FLAIR or T2 images; and (3) availability of neuropsychological data. Patients with any degree of symptom severity (i.e., subjective cognitive impairment, mild cognitive impairment, dementia) and either vascular, neurodegenerative, or mixed etiology were included. Patients diagnosed with apparent non-vascular and non-neurodegenerative causes of cognitive decline (e.g., excessive alcohol consumption, brain tumor, trauma, multiple sclerosis, psychiatric disorder) or monogenic disorders (e.g., CADASIL or presenilin mutations), were excluded. Mixed etiologies and psychiatric comorbidity were allowed.

We further excluded patients without data on age, sex, and level of education, and patients with >6 months between cognitive assessment and brain MRI. A flowchart of cohort and patient inclusion is provided in Figure S1.

Central data processing and analysis were performed at the University Medical Center Utrecht (Utrecht, the Netherlands). For all cohorts, ethical and institutional approval was obtained as required by local regulations, including informed consent, to allow data acquisition and data sharing. The background and organization of the Meta VCI Map consortium is described in the design paper[10] and on the consortium website https://metavcimap.org.

2.2 | Cognitive data harmonization

Ten cohorts provided data on individual neuropsychological tests, which were assigned to four cognitive domains: (1) attention and executive functioning; (2) information processing speed; (3) language; (4) verbal memory. One cohort (AUCD) provided cognitive domain scores. An overview of the used neuropsychological tests and categorization across the four different cognitive domains is provided in Table S2. All neuropsychological test results were norm-referenced, either using local normative data or a local healthy control group, and corrected for age, sex, and education on an individual participant basis. An overview of the normative data per cohort is provided in Table S3. The mean of the norm-referenced z-scores on individual tests was calculated to obtain cognitive domain z-scores. Further details on neuropsychological test protocols, quality checks, and the harmonization procedure are provided in the supplements.

2.3 | Lesion data harmonization

WMH segmentations were provided by 10 participating centers; for one cohort (ACE) the WMH segmentations were performed in Utrecht. Details on WMH segmentation procedures are described in the supplements. WMH maps were registered to the 1×1×1 mm resolution Montreal Neurological Institute (MNI)-152 brain template for spatial normalization.[17] Two cohorts (AUCD, ADNI) shared WMH maps that were already registered to MNI space. For the remaining cohorts, WMH maps were registered to the MNI template centrally using RegLSM.[18] The registration results were visually inspected to ensure that the procedure was successful and patients with failed registrations were excluded. All image processing steps were performed blinded to cognitive performance. A detailed description of the registration procedure quality checks of the imaging data is described in the supplements.

2.4 | Statistical analyses

Statistical analyses were performed using two complementary approaches: voxel-based and region of interest (ROI)-based analyses. Voxel-based lesion-symptom mapping (VLSM) probes every supratentorial white matter voxel that is affected by WMH in at least five subjects in an assumption-free manner, resulting in very high spatial resolution. In the ROI-based analysisi the total number of voxels with WMH within 20 specific white matter tracts is added up and related to cognition, whichs has the advantage that it is directed by the functional anatomy of the brain, has higher statistical power than VLSM, and that it also takes voxels into account that are affected in less than five subjects. Further considerations regarding these methods are provided in the supplements.

For the VLSM analyses, the norm-referenced z-scores for all cognitive domains were first corrected for total normalized WMH volume using linear regression. Voxels that were damaged in less than five individuals were excluded from the analyses to prevent bias. Correction for multiple testing was performed by applying a false discovery rate (FDR) with $q < 0.01$. All VLSM analyses were done in Python (https://github.com/Meta-VCI-Map/LSM/blob/main/univariate_vlsm.ipynb., SciPy software version 1.4.1). For interpretation of the VLSM results, the results are shown at the level of both individual voxels and at the level of ROIs (i.e., by summing up the number of voxels that were significant across the whole cohort in each ROI).

In the ROI-based analyses, WMH volumes within 20 white matter tracts[19] were entered as independent variables in 20 different linear mixed models with cognitive domain z-scores as the dependent variable, correcting for study site (as random effects) and total WMH volume (as a fixed effect). Correction for multiple testing was performed using a Bonferroni correction for 20 tested tracts, meaning a P-value $< .0025$ was considered statistically significant. To determine whether the results were affected by clinical diagnosis (i.e., subjective cognitive impairment, mild cognitive impairment, or dementia), the significant results from the ROI-based analysis were stratified accordingly.

As a final step, we created a strategic WMH score based on the significant (i.e., strategic) tracts that were identified in the previous steps. For each tract, we determined the distribution of WMH volumes in quartiles across the whole cohort. For each patient the WMH volume in strategic tracts was rated as: 0 = lowest quartile, 1 = second quartile, 2 = third quartile, 3 = highest quartile. Then the tract scores were added up. A lasso regression model (using 100-fold cross-validations) was used to relate total WMH volume, the strategic WMH score, age, sex, education, and brain parenchymal fraction (BPF) to each of the four cognitive domains. Lasso regression accounts for multicollinearity between independent variables, in this case, total WMH volume and the strategic WMH score, and shrinks the regression coefficients down to zero if the variable is redundant. The independent continuous variables were standardized and the model was corrected for the study site. Next, the strategic WMH score was also related to each of the cognitive domains in a multivariable linear mixed model, together with age, sex, education, and BPF. All ROI-based analyses were performed using glmnet (v4.1.3) and lme4 (v1.1.26) in R (v4.1.2).

3 | RESULTS

3.1 | Participants

A flowchart of patient selection is provided in Figure S1. The combined study sample consisted of 3525 patients (49.9% female) from 11 memory clinic cohorts, with a mean age of 71.6 years (SD 9.0). A total of 777 patients (22.0%) had subjective cognitive impairment, 1389 patients (39.4%) had mild cognitive impairment, and 1359 patients (38.6%) had dementia. The baseline characteristics and cognitive scores of the individual cohorts and combined study sample are shown in Table 1 and Table S5.

TABLE 1 Baseline characteristics of individual cohorts and merged dataset

Characteristics	ADNI-1/2/3/GO (n = 994)	ACE (n = 52)	Alzheimer UC Davis (n = 641)	Brain IMPACT (n = 53)	FAVR (n = 47)	Harmonization (n = 207)	PRODEM (n = 367)	TRACE-VCI (n = 821)	UMCC (n = 227)	VASCAMY (n = 76)	YOAD (n = 40)	Total (n = 3525)
Female, n (%)	483 (48.6)	21 (40.4)	363 (56.6)	26 (49.1)	19 (40.4)	106 (51.2)	207 (56.4)	382 (46.5)	88 (38.8)	42 (55.3)	22 (55.0)	1759 (49.9)
Age in years, mean (SD)	71.7 (7.4)	68.2 (8.2)	76.0 (7.5)	73.8 (7.1)	70.8 (7.5)	73.0 (8.9)	74.7 (8.8)	67.5 (8.5)	66.0 (13.0)	74.1 (6.1)	60.6 (5.0)	71.6 (9.0)
Education in years, mean (SD)	16.2 (2.6)	11.3 (3.5)	12.8 (4.8)	13.2 (2.9)	15.3 (3.0)	6.2 (4.8)	11.2 (2.6)	11.7 (3.5)	11.5 (4.0)	12.7 (4.4)	15.0 (2.9)	12.9 (4.4)
Patient ethnicity, n (%)	Asian, 17 (1.7), Afro-caribbean 44 (4.4), White 905 (91.0), Other 22 (2.2)[a]	Asian 1 (1.9), Afro-caribbean 2 (3.8), Caucasian 41 (78.8), Other 6 (11.5)[b]	Asian 29 (4.5), Afro-caribbean 152 (23.7), Hispanic 146 (22.8), White 307 (47.9), Other 7 (1.1)	N/A	N/A	Asian 190, (91.8), Other 17 (8.2)	European 367 (100)	>90% European[d]	>90% European[d]	N/A	Caucasian 38 (95.0), Afro-caribbean 2 (5.0)	Asian 237 (6.7), Afro-caribbean 200 (5.7), Caucasian/ European/ White 2601 (73.8), Hispanic 146 (4.1), Other 52 (1.5)[c]
Diagnosis, n (%)												
SCI	240 (24.1)	2 (3.8)	197 (30.7)	12 (22.6)	0	19 (9.2)	0	193 (23.5)	81 (35.7)	33 (43.4)	0	777 (22.0)
MCI	572 (57.5)	18 (34.6)	314 (49.0)	40 (75.5)	29 (61.7)	84 (40.6)	0	207 (25.2)	88 (38.8)	37 (48.7)	0	1389 (39.4)
Dementia	182 (18.3)	32 (61.5)	130 (20.3)	1 (1.9)	18 (38.3)	104 (50.2)	367 (100)	421 (51.3)	58 (25.6)	6 (7.9)	40 (100)	1359 (38.6)
Dementia – etiology, n (%)												
Alzheimer's dementia	N/A	30 (57.7)	N/A	1 (1.9)	18 (38.3)	85 (41.1)	319 (86.9)	283 (34.5)	28 (12.3)	N/A	40 (100)	804 (22.8)
Vascular dementia	N/A	0	N/A	0	0	19 (9.2)	15 (4.1)	34 (4.1)	17 (7.5)	N/A	0	85 (2.4)
Frontotemporal dementia	N/A	0	N/A	0	0	0	19 (5.2)	25 (3.0)	0	N/A	0	44 (1.2)
Lewy body dementia	N/A	0	N/A	0	0	0	6 (1.6)	18 (2.2)	0	N/A	0	24 (0.7)
Dementia with other etiology	N/A	2 (3.8)	N/A	0	0	0	8 (2.2)	36 (4.4)	13 (5.7)	N/A	0	59 (1.7)
CDR median (IQR)	1.0 (1.0)[c]	N/A	0.5 (0.5)[b]	N/A	N/A	1.0 (0.5)[c]	0.5 (0.5)[b]	0.5 (0.5)	0.5 (0.5)[c]	0.5 (0.5)[c]	N/A	0.5 (0.5)[c]

(Continues)

TABLE 1 (Continued)

Characteristics	ADNI-1/2/3/GO (n = 994)	ACE (n = 52)	Alzheimer UC Davis (n = 641)	Brain IMPACT (n = 53)	FAVR (n = 47)	Harmonization (n = 207)	PRODEM (n = 367)	TRACE-VCI (n = 821)	UMCC (n = 227)	VASCAMY (n = 76)	YOAD (n = 40)	Total (n = 3525)
Vascular risk factors, n (%)												
Current smoking	290 (29.2)[c]	N/A	N/A	4 (7.5)[a]	1 (2.1)[a]	16 (7.7)[a]	20 (5.4)[c]	164 (20.0)[a]	N/A	4 (5.3)[a]	4 (10)[a]	503 (14.3)[c]
Previous smoking	N/A	N/A	N/A	27 (50.9)[a]	20 (42.6)[a]	N/A	72 (19.6)[c]	317 (38.6)[a]	N/A	23 (30.3)[a]	11 (27.5)[a]	470 (13.3)[c]
Hypertension	475 (47.8)[a]	N/A	417 (65.0)[b]	N/A	19 (40.4)[a]	158 (76.3)[a]	223 (60.8)[c]	304 (37.0)[a]	79 (34.8)[b]	39 (51.3)[a]	6 (15.0)[a]	1720 (48.8)[b]
Hypercholesterolemia	N/A	N/A	358 (55.9)[c]	17 (32.1)[a]	13 (27.7)[a]	149 (71.9)[a]	166 (45.2)[c]	367 (44.7)[a]	0 (0)[c]	28 (36.8)[a]	8 (20.0)[a]	1106 (31.4)[c]
Diabetes Mellitus	N/A	N/A	172 (28.8)[b]	6 (11.3)[a]	8 (17.0)[a]	85 (41.0)[a]	47 (12.8)[c]	137 (16.7)[a]	37 (16.3)[a]	0 (0)[a]	2 (5.0)[a]	494 (14.0)[c]
Atrial fibrillation	N/A	N/A	30 (4.7)[c]	N/A	3 (6.4)[a]	22 (10.6)[a]	38 (10.4)[c]	N/A	N/A	5 (6.6)[a]	N/A	98 (2.8)[c]
History of prior stroke	9 (0.9)[a]	N/A	60 (9.3)[b]	0 (0)[a]	2 (4.3)[a]	75 (36.2)[a]	17 (4.6)[c]	71 (8.6)[a]	16 (7.0)[c]	3 (3.9)[a]	1 (2.5)[a]	254 (7.3)[b]
History of prior TIA	N/A	N/A	31 (4.8)[b]	4 (7.5)[a]	N/A	16 (7.7)[a]	11 (3.0)[c]	N/A	N/A	N/A	N/A	62 (1.8)[c]
History of prior other vascular events	476 (47.9)[c]	N/A	N/A	13 (24.5)[a]	9 (19.1)[a]	14 (6.8)[a]	8 (2.2)[c]	81 (9.9)[a]	109 (48.0)[c]	5 (6.6)[a]	N/A	715 (20.3)[c]
BMI, mean (SD)	N/A	N/A	N/A	N/A	N/A	24.4 (3.8)[c]	24.9 (3.9)[c]	N/A	26.0 (6.2)[b]	25.3 (3.4)[a]	25.3 (4.0)[b]	25.3 (4.7)[c]
Imaging characteristics												
WMH volume (mL), median (IQR)	2.6 (5.6)	5.0 (16.6)	7.3 (13.9)	3.1 (7.5)	8.0 (8.4)	13.5 (20.4)	11.4 (20.5)	8.0 (18.2)	11.5 (26.1)	4.3 (10.1)	1.9 (1.6)	6.1 (14.1)
BPF, median (IQR)	0.7 (0.1)[c]	0.7 (0.1)[b]	0.7 (0.0)	0.7 (0.1)	0.7 (0.1)[b]	0.6 (0.1)[c]	0.7 (0.0)	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)	0.7 (0.0)	0.7 (0.1)[c]
Strategic WMH score, mean (SD)	3.9 (0.1)	6.5 (0.5)	6.5 (0.1)	5.4 (0.4)	7.5 (0.4)	8.0 (0.2)	8.5 (0.2)	6.0 (0.1)	7.8 (0.3)	5.4 (0.4)	2.9 (0.4)	6.0 (3.9)
Global cognitive outcome, mean (SD)												
MoCA	22.9 (5.1)[c]	N/A	N/A	N/A	N/A	15.9 (6.9)	N/A	N/A	N/A	N/A	N/A	21.5 (6.2)[c]
MMSE	27.4 (2.7)[b]	22.6 (4.8)[b]	26.0 (4.0)[c]	27.8 (2.2)	25.6 (3.6)	20.5 (6.1)	21.9 (4.4)[a]	24.3 (4.8)[a]	25.8 (4.9)[a]	27.3 (2.7)	23.3 (5.7)	25.0 (4.7)[b]

Abbreviations: SCI, subjective cognitive impairment; MCI, mild cognitive impairment; CDR, Clinical Dementia Rating; BPF, brain parenchymal fraction; MoCA, Montreal Cognitive Assessment; MMSE, Mini-Mental State Examination; N/A, not available.

[a]Missing in < 1%.

[b]Missing in 1-10%.

[c]Missing in > 10%.

[d]Not standard registered in study protocol.

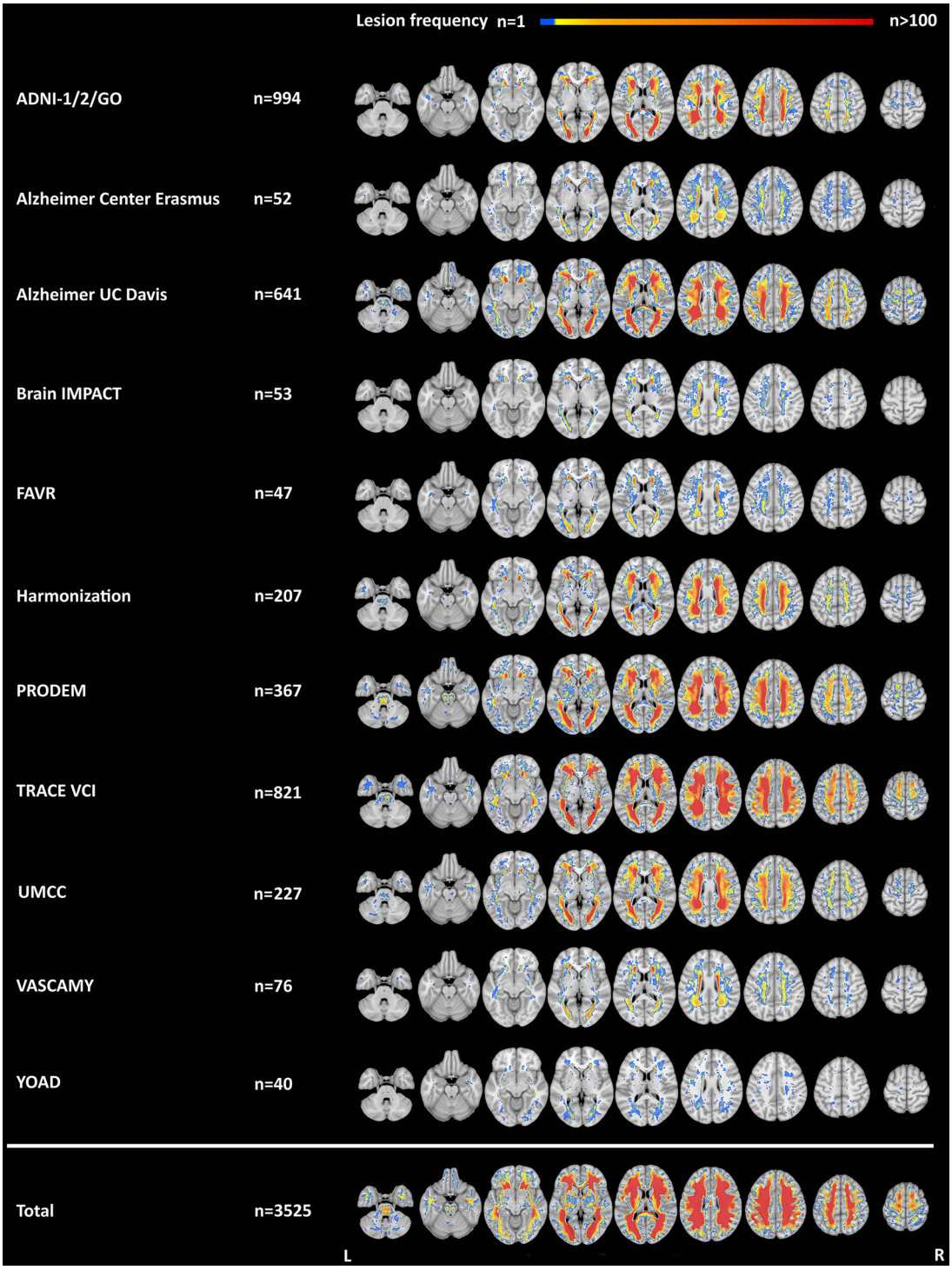

FIGURE 1 WMH prevalence map of individual cohorts and merged cohort. This figure shows how often each location in the brain was affected by WMH in individual cohorts and the collective dataset. Blue voxels are damaged in less than five subjects, and would be excluded from the VLSM analysis if each cohort would be analyzed separately. As shown in the bottom row, merging of datasets allows many more voxels to pass the threshold for inclusion (yellow: n = 5; red: n ≥ 100). L = left, R = Right (by convention for lesion symptom mapping analysis).

3.2 | Voxel-based lesion symptom mapping analysis

Lesion prevalence maps of the individual cohorts and combined study sample are shown in Figure 1.

For each of the four cognitive domains, VLSM identified significant voxels, after correction for total WMH volume and multiple testing. These voxels were mostly located in the periventricular region and were part of the anterior thalamic radiation and forceps major for all

TABLE 2 ROI-based results: Significant results from the mixed linear model analysis

		Attention & executive functioning			Information processing speed			Language			Verbal memory		
Model	Independent variables	Coefficient	SE	*P*-value	Coefficient	SE	*P*-value	Coefficient	SE	*P*-value	Coefficient	SE	*P*-value
1	WMH volume	−0.007	0.001	<.001*	−0.007	0.002	<.001*	−0.006	0.002	.009	−0.006	0.001	<.001*
2	Model 1 + Anterior thalamic radiation L	−0.216	0.044	<.001*				−0.328	0.089	<.001*	−0.341	0.053	<.001*
3	Model 1 + Anterior thalamic radiation R	−0.170	0.046	<.001*							−0.303	0.055	<.001*
4	Model 1 + Forceps major	−0.143	0.018	<.001*	−0.190	0.035	<.001*	−0.151	0.037	<.001*	−0.191	0.022	<.001*
5	Model 1 + Inferior fronto-occipital fasciculus L	−0.192	0.057	<.001*				−0.385	0.118	.001*			

Note: This table shows the results of the ROI-based analysis using a mixed linear model. The results are corrected for study site using random effects. Only significant results with a negative coefficient are shown. All remaining results (i.e., non-significant or with a positive coefficient) are shown in Table S7). A Bonferroni correction for 20 tests (i.e., 20 ROIs for major white matter tracts were included) was applied and a *P*-value < .0025 was considered statistically significant (indicated by *). The independent variables (i.e., total WMH volume and regional WMH volumes) are not standardized. The coefficient therefore corresponds to the change in cognitive functioning (decrease in z-score) associated with each 1 ml increase of the independent variables.

four domains. Additional voxels involved several additional tracts, that varied between cognitive domains (Table S6 and Figure S2).

3.3 | ROI-based analyses

In the linear mixed model for each of the 20 major white matter tracts, a significant negative correlation was found between WMH volume in the left and right anterior thalamic radiation, the forceps major, and the left inferior fronto-occipital fasciculus and cognitive functioning, independent of total WMH volume and study site, and after correction for multiple testing. The forceps major was associated with all four cognitive domains, whereas the remaining three significant tracts were specifically associated with one, two or three of the cognitive domains (significant results shown in Table 2 and results shown in Table S7). Figure S3 shows the identified strategic WMH tracts. In the stratified analysis according to clinical diagnosis, effect sizes were mostly consistent with the overall analyses for subjective cognitive impairment and mild cognitive impairment, whereas in the dementia group most associations between WMH and cognition were attenuated (Table S8).

3.4 | Strategic WMH score

The strategic WMH score was developed to capture the total burden of WMH in strategic white matter tracts into a single score. Scores per tracts ranged from 0 (lowest quartile of WMH volume) to 3 (highest quartile); cut-off values per tract are provided in Table S9. The scores of the four tracts that were identified in the previous analyses were summed up and the total score ranged from 0 to 12. Patients with the highest quartiles of WMH volume in all four strategic tracts (corresponding with a score of 12) had lower performance on all cognitive domain scores compared to the remaining patients, with a mean difference in z-score ranging from −0.28 to −0.41 across domains (Table S10).

In the multivariable Lasso regression model (including age, sex, education, total WMH volume, the strategic WMH score, BPF, and study site as independent variables), the strategic WMH score was a stronger determinant of all four cognitive domain scores than total WMH volume (Table 3); the strategic WMH score rendered total WMH volume redundant in all models except for executive functioning. In the multivariable linear mixed model, a significant correlation was found between the strategic WMH score and each of the four cognitive domains, independent of age, sex, education, BPF, and study site (Table 4). In contrast, total WMH volume was only significantly associated with one out of four cognitive domains (i.e., attention & executive functioning) after correcting for age, sex, education, BPF, and study site (Table S11).

4 | DISCUSSION

This large multicenter study provides strong evidence that the cognitive impact of WMH in memory clinic patients depends on location.

TABLE 3 Lasso regression results

Model	Independent variables	Attention and executive functioning Coefficient	Information processing speed Coefficient	Language Coefficient	Verbal memory Coefficient
1	Age	0.113	0.156	R	0.057
	Sex	0.036	R	−0.037	R
	Education	0.305	0.217	0.624	0.180
	BPF	0.341	0.507	0.324	0.401
	Total WMH volume	−0.033	R	R	0.061
	Strategic WMH score	−0.116	−0.069	−0.106	−0.166

Note: A lasso regression model was used to relate total WMH volume, the strategic WMH score, as well as age, sex (0: male, 1: female), education and BPF to each of the four cognitive domains. Lasso regression corrects for multicollinearity between independent variables, and reduces the coefficients to zero (indicated by R in the table) if the variable is redundant. The independent variables age, years of education, BPF, total WMH volume, and strategic WMH score are standardized, which means the reported coefficients correspond with the change in cognitive functioning (i.e., increase or decrease in z-score) associated with 1SD change in the independent variable. The model is also corrected for the 11 study sites by including these as dummy variables (coefficients of study sites are not shown).

TABLE 4 Mixed linear model results—strategic WMH score

Model	Independent variables	Attention and executive functioning			Information processing speed			Language			Verbal Memory		
		Coefficient	SE	*P*-value	Coefficient	SE	*P*-value	Coefficient	SE	*P*-value	Coefficient	SE	*P*-value
1	Age	0.121	0.022	<.001*	0.193	0.042	<.001*	−0.006	0.047	.921	0.068	0.028	.015*
	Sex	0.041	0.035	.238	−0.006	0.067	.943	−0.061	0.072	.402	−0.013	0.044	.775
	Education	0.624	0.041	<.001*	0.530	0.091	<.001*	1.229	0.084	<.001*	0.376	0.052	<.001*
	BPF	0.349	0.023	<.001*	0.568	0.043	<.001*	0.327	0.047	<.001*	0.420	0.030	<.001*
	Strategic WMH score	−0.146	0.021	<.001*	−0.090	0.040	.023*	−0.124	0.042	.003*	−0.128	0.026	<.001*

Note: A multivariable mixed linear model was performed to determine the independent associations between age, sex, education, BPF and the strategic WMH score, and the four cognitive domains. The results are corrected for study site using random effects. All continuous variables (age, education, BPF, and strategic WMH score) were transformed into standardized scores. A *P*-value < .05 was considered statistically significant (indicated by *).

The combined results of the VLSM and ROI analyses identified the left and right anterior thalamic radiation, the forceps major, and the left inferior fronto-occipital fasciculus as strategic tracts, with specific tract-domain relationships. Stratification of the results according to clinical diagnosis showed that the effect sizes were attenuated in patients with dementia, compared to patients with subjective and mild cognitive impairment. A strategic WMH score, which integrates WMH volumes in four strategic tracts, outweighed total WMH volume in terms of its association with performance on each of the four cognitive domains and was significantly associated with lower performance on each of the four cognitive domains, independent of brain atrophy, age, sex, and level of education.

The results of the complementary VLSM and ROI analyses showed strong convergence in terms of strategic tracts identified. Yet, there were also some different results, (i.e., the VLSM analysis identified significant voxels in several tracts that were not reproduced in the ROI analyses; vice versa, the ROI analysis identified several tracts that contained relatively few significant voxels in the VLSM analysis) likely inherent to the fundamentally different approach underlying these two analytical methods. Despite the large sample size and the substantial lesion coverage that was achieved in the VLSM analyses, significant relationships with cognition were observed in only a relatively small subset of voxels (Table S6). This is probably due to the heterogeneous distribution of WMH that we observed: a large proportion of tested voxels proved to be affected in a relatively small number of patients despite the large sample size, impacting statistical power in these voxels. In the subset of voxels that were affected in a larger number of patients the results were fully consistent with the ROI analyses, supporting the validity of the findings. Of note, in a previous large-scale VLSM study on infarcts, we did not encounter similar challenges in achieving high lesion coverage throughout the brain.[20] This is likely due to the fact that infarcts are often larger with a more widespread lesion distribution pattern than WMH, following vascular territories. Our observations, therefore, indicate that ROI analyses may be the preferred technique to study strategic WMH locations for cognitive impairment. An additional advantage is that tract-based ROIs reflect

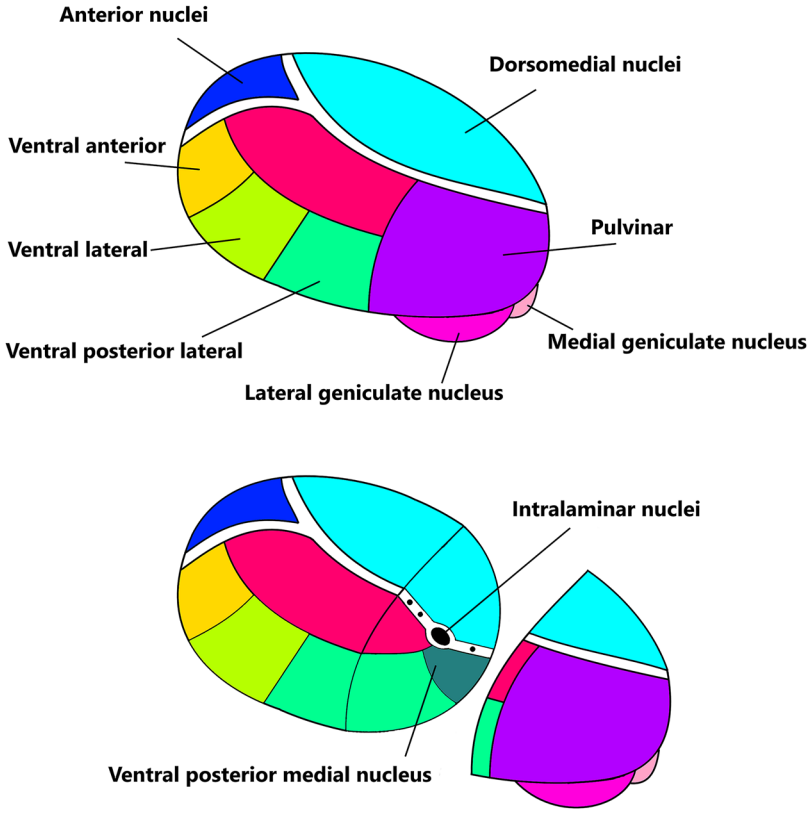

FIGURE 2 Schematic figure showing a dorsolateral view of the left thalamus. In the bottom drawing, the posterior part of the thalamus is removed to show nuclei that are otherwise obscured from view.

the functional organization in the white matter. Moreover, as we show here, the results of ROI-based WMH pattern analyses can be translated to a strategic WMH score with the potential for application in individual patients.

Prior studies on strategic WMH locations (including patients with cognitive symptoms due to vascular and/or Alzheimer's disease,[7,21–25] patients with CADASIL,[26,27] and asymptomatic community-dwelling individuals[28–34]) already generated evidence that the cognitive impact of WMH depends on location, while one study did not find a relationship between WMH location and cognitive impairment.[35] The anterior thalamic radiation and regions within the corpus callosum have been most consistently identified as strategic white matter tracts across these studies,[6,24] which is consistent with our findings. The anterior thalamic radiation connects anterior and dorsomedial thalamic nuclei with the frontal and cingulate cortices[36] (see also Box 1 and Figure 2), and the corpus callosum forms the main connection between the cerebral hemispheres, which adds plausibility to our finding that lesions in these tracts have a major effect on cognitive performance in multiple domains. Several other tracts have been suggested as strategic by prior studies (e.g., the superior longitudinal fasciculus, inferior longitudinal fasciculus, uncinate fasciculus, cingulum of the hippocampus, cingulum of cingulate gyrus), but not reproduced by others. Even though we found significant voxels in several of these tracts in the VLSM analysis, this was not confirmed in the ROI analyses, indicating that these tracts may not be strategic in the setting of a memory clinic.

The strengths of the current study are the large sample size and unprecedented white matter coverage in our VLSM analysis. Including data from 3525 memory clinic patients, we achieved 63% lesion coverage in the voxel-based analysis. By including cohorts from multiple continents, we achieved geographical diversity, benefitting the generalizability of the results. Another strength is the availability of detailed neuropsychological assessment and normative cognitive data, which allowed us to calculate and pool norm-referenced z-scores for four different cognitive domains. Furthermore, we used previously published imaging processing pipelines that create uniform output in terms of WMH maps in standardized MNI space, which allows for the pooling of imaging data created with diverse MRI scanners and sequences and performed rigorous quality checks.

Several potential limitations should be noted. First, post-hoc pooling of data from multiple cohorts resulted in a heterogeneous population, and several cohorts included a highly selected sample of patients, which may affect generalizability to the general memory clinic population. Given that the majority of patients were of Caucasian ethnicity and/or European ancestry, generalizability to other ethnicities needs to be addressed in future studies. We have corrected for cohort-specific effects by including study site as a covariate in the regression models. Nevertheless, external validation is needed to assess generalizability. Second, the relationship between strategic WMH locations and cognition may be confounded by etiology. It is possible that the relation between WMH in the forceps major (in part) and cognition is driven by an association with Alzheimer's pathology, given that a high amyloid burden is associated with posterior WMH.[37] The relation between WMH in the ATR and cognition matches previous observations in patients with isolated vascular disease (e.g., CADASIL[26,27]) and community-dwelling individuals,[28–34] suggesting that this association reflects vascular pathology. Third, Table S6 shows that WMH

BOX 1 The thalamus—a central player in cognition

The thalamus is positioned at the center of the brain, both anatomically and functionally, given that the thalamic nuclei have projections to nearly the entire neocortex, subcortical nuclei, brain stem nuclei and cerebellum. The function of the thalamus in relaying primary sensory information (i.e., the lateral and medial geniculate nucleus for visual and auditory input respectively, and the ventral posterior nuclei for somatosensation and gustation) and motor function (ventral anterior and ventral lateral nucleus) is generally well known among clinicians. In contrast, the critical role of the thalamus in cognition may be more easily overlooked. The observation in the current study that WMH in the anterior thalamic radiation, which relays input from the anterior and medial thalamic nuclei to frontal and cingulate cortices, have a disproportionally large impact on multiple cognitive domains highlights the central role of the thalamus in many cognitive functions. This brief primer puts these findings in context by summarizing several major thalamic nuclei in terms of connectivity and cognitive aspects, and may serve as a brief introduction to cognitive thalamic anatomy (see also Figure 2). For further reading and additional anatomical detail see.[40,41]

Anterior thalamic nuclei

These nuclei have bidirectional connections to the fornix and frontal and cingulate cortices, and form part of the Papez circuit for episodic memory. Lesions in these nuclei or their projections can cause pronounced deficits in *episodic memory, executive functioning and language* (particularly naming and fluency[36,42]).

Dorsomedial nucleus

This nucleus receives input from basal ganglia, amygdala and hypothalamus and projects to the prefrontal cortex. Lesions/disconnections can cause emotional instability (disinhibition, mood disturbances, apathy), and deficits in *memory and executive functioning*.[36]

Pulvinar

This group of nuclei is located in the dorsal thalamus and is best known for its critical role in sensory integration. It receives visual and auditory input from the lateral and medial geniculate nuclei respectively, as well as input on eye and head movements and position from the superior colliculi, and relays information to visual and semantic association areas in posterior cortical regions. Consequently, lesions can cause *spatial neglect, many types of agnosia, sensory aphasia, optic ataxia* and disrupt other aspects of *visuomotor function*. A more complete summary is provided elsewhere.[43]

Reticular and intralaminar nuclei

Input from the ascending reticular activating system (ARAS) is relayed in the intralaminar nuclei of the thalamus. Together with the reticular nucleus of the thalamus, these nuclei play a critical role in arousal and attention, which explains why bithalamic infarcts can cause *coma and severe deficits in attention*.[36,44]

were highly prevalent in certain tracts, and rare in other tracts (e.g., the cingulum of the hippocampus), which may have resulted in detection bias. Fourth, we were unable to correct for the presence of brain infarcts and lacunes because these variables were not available for most cohorts. Fifth, it should be noted that WMH as a marker of white matter injury is less sensitive compared to for example diffusion tensor imaging (DTI).[38] Nevertheless, our study shows that the information regarding the cognitive impact that can be extracted from visible WMH can be improved by taking location into account, which is relevant given the more widespread availability of routine structural MRI compared to DTI. Finally, total WMH volume, regional WMH volumes, and the strategic WMH score are highly correlated (i.e., a higher WMH volume corresponded with higher strategic WMH scores in each of the cohorts, see Table 1), which may induce collinearity and reduce the precision of their coefficients in multivariable linear regression models. We therefore used lasso regression to compare the relative importance of regional and total WMH in our dataset (Table 3).

Currently, in clinical practice, attribution of cognitive impairment in individual patients to WMH is primarily based on total WMH burden. Our findings suggest that WMH location may be a more accurate diagnostic biomarker to support the diagnosis of SVD-related cognitive impairment. Implementing WMH location-based tools may aid clinical diagnosis by allowing clinicians to discriminate WMH that are impairing cognition from age-related WMH with lesser clinical effects. Yet, such implementation requires further work. The score needs to be externally validated to establish generalizability, also considering ethnicity. Moreover, validation in datasets with biologically defined Alzheimer's disease (AD) or pure vascular pathology is recommended. Normative data for the strategic score should be obtained from community-based cohorts, ideally stratified for relevant demographics including age, sex, and ethnicity. Furthermore, calculation of the score needs to become automated. The brain image processing procedure that was used in the current study is suitable for a research setting, but additional programming is required for use in clinical settings. Implementation in clinical practice requires a tool that automatically performs WMH segmentation, registration and calculation of the strategic WMH score, using raw MR images as input, and allow for a visual quality check of the results. When estimating the relevance of WMH in explaining cognitive impairment in individual patients, information on other types of pathology, both vascular and otherwise, should also be taken into account, given our

observation that even though brain atrophy and the strategic WMH score both significantly contributed to the linear mixed model (Table 4), the effect size (i.e., the coefficient) of brain atrophy was much larger than the effect size of the strategic WMH score. Ideally, other lesion types and brain atrophy should therefore also be assessed quantitatively and weighted according to age, together with the strategic WMH score.[39]

In summary, we found that the impact of WMH on cognition depends on location. We identified four significant white matter tracts that were associated with cognitive impairment in memory clinic patients. Based on these tracts, a strategic WMH score was developed that was an independent determinant of performance on four cognitive domains. These results suggest that, with further refinement, WMH location might become a useful diagnostic biomarker for SVD-related cognitive impairment.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

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