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IMPACT OF WHITE MATTER HYPERINTENSITY LOCATION ON DEPRESSIVE SYMPTOMS IN MEMORY CLINIC PATIENTS: A LESION-SYMPTOM MAPPING STUDY

Running title: White matter hyperintensities and depressive symptoms

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ABSTRACT

Background: We investigated the association between white matter hyperintensity (WMH) location and depressive symptoms in a memory-clinic population using lesion-symptom mapping.

Methods: We included 680 patients with vascular brain injury from the TRACE-VCI cohort (age 67±8;52%F): 168 patients with subjective cognitive decline (SCD), 164 with mild cognitive impairment (MCI), and 348 with dementia. Depressive symptoms were assessed using the Geriatric Depression Scale (GDS;0-15). We applied assumption-free voxel-based lesion-symptom mapping (VLSM), adjusted for age, sex, total WMH volume and multiple testing. Next, we applied exploratory region of interest (ROI)-based linear regression analyses of major white matter tracts with additional adjustment for diagnosis.

Results: VLSM identified voxel clusters in relation to GDS in the left corticospinal tract (CST). ROI-based analyses showed no relation between WMH volume and GDS, but revealed an interaction with diagnosis in the forceps minor where larger regional WMH volume was associated with more depressive symptoms in SCD (stß=0.26, $p<0.05$), but not in MCI or dementia.

Limitations: Lack of convergence of findings between VLSM and ROI analyses, which may be due to small effect sizes and limited lesion coverage despite the large sample size. This warrants replication of our findings and further investigation in other cohorts.

Conclusions: This lesion-symptom mapping study on depressive symptoms indicates the CST and forceps minor as strategic white matter tracts in which WMH are associated with depressive symptoms in memory-clinic patients with vascular brain injury. The impact of WMH on depressive symptoms is modest, yet appears to be dependent on location of WMH and disease severity.

1. Introduction

Late-life depression is highly prevalent in older people and in patients with cognitive impairment or dementia (1). Late-life depression has been associated with vascular dementia, stroke and white matter hyperintensities (WMH) (2–4). This link between vascular disease and late-life depression has led to the 'vascular depression hypothesis' (5–7). The clinical profile of vascular depression includes loss of interest and motivation, executive dysfunctioning and psychomotor retardation (8).

The vascular depression hypothesis has been investigated intensively in population-based studies. Late-life depression is consistently associated with severity of WMH (i.e. visual rating scores; Fazekas or Scheltens scale) and larger total WMH volumes in healthy elderly (2,9). Meanwhile, studies in memory clinic populations are scarce, while this could be a clinically important population considering their generally higher vascular lesion burden and the frequent occurrence of depressive symptoms in this group. We recently showed that in memory clinic patients with Alzheimer's disease (AD) severity of WMH (measured with the Fazekas scale) was not related to depressive symptoms (10). However, we found a borderline significantly increased propensity of depressive symptoms in patients with subjective cognitive decline (SCD) with WMH. Apart from severity of WMH, recent studies suggest that specific WMH locations could predispose for the occurrence of depressive symptoms. The LADIS study found that deep WMH specifically located in the frontal and temporal locations were associated with depressive symptoms in non-disabled older subjects (11). Frontal WMH have been associated with higher depression scores on a questionnaire in patients with dementia (12). Furthermore, prefrontal and temporal WMH and WMH in specific white matter tracts as the cingulum bundle, uncinate fasciculus, and superior longitudinal fasciculus have been associated with severity of depression in patients with major depression (13,14). These results suggest disruption of in particular prefrontal-subcortical pathways as an underlying mechanism of late-life depressive

symptoms in elderly (5). Identifying specific white matter tracts in which WMH have most impact on depressive symptoms would improve our understanding of the consequences of cerebral vascular injury.

Lesion-symptom mapping is frequently used to investigate the relation between lesion location and specific clinical symptoms in patients with vascular brain injury such as WMH, infarcts and lacunes. Most lesion-symptom mapping studies on WMH have focused on the association between WMH location and cognitive functioning (15–17), while psychological symptoms of subcortical vascular lesions, such as depression and anxiety have not been addressed. In this first-ever lesion-symptom mapping study on depressive symptoms, we aimed to determine to what extent specific WMH locations contribute to depressive symptoms in memory clinic patients with vascular brain injury on MRI, and identify strategic white matter tracts in which WMH have impact on depressive symptoms.

2. Methods and materials

TRACE-VCI (Utrecht-Amsterdam clinical features and prognosis in VCI) is a prospective observational follow-up study of 860 consecutive memory clinic patients from Dutch outpatient clinics at two university hospitals (VU University Medical Centre [VUMC] and University Medical Centre Utrecht [UMCU]) (18). All patients visited the memory clinic between September 2009 and December 2013 and underwent a 1-day standardized dementia screening that included medical history, physical and neurological examinations, screening laboratory tests, MRI scan of the brain and neuropsychological assessment. Patients with cognitive complaints and any burden of vascular brain injury on MRI were prospectively included. Further in- and exclusion criteria are described in detail elsewhere (18). Patients were divided in three categories related to the extent of cognitive impairment: dementia, mild cognitive impairment (MCI) and SCD. Patients with evidence of co-occurring neurodegenerative disease or depression were accepted as these are

common comorbid etiologies in patients with vascular cognitive impairment (VCI). We did exclude patients with nonvascular or nondegenerative primary cause of cognitive impairment, such as brain tumour, extensive traumatic head injury, substance or alcohol abuse or multiple sclerosis. Patients with primary psychiatric disease, other than depression, were excluded. The study was approved by the medical ethics committee of VUMC and UMCU. We obtained written informed consent (or from their responsible guardians if the participants were incapable of consenting) prior to research-related procedures.

2.1 Participants

A flow chart of patient selection for the present study is presented in Figure 1. Of the total of 860 patients in TRACE-VCI, 38 patients were excluded during the vascular lesion segmentation process, mostly because of insufficient quality of availability of MRI data or technical errors during data processing. Next, 100 of the remaining patients were excluded based on presence of nonlacunar infarcts or hemorrhages other than microbleeds on MRI, because such large lesions can result in the complete obliteration of white matter tracts and could thereby interfere with our analysis in which WMH volume with specific tracts is related to depressive symptoms at a group level. One additional patient was excluded due to failed lesion registration. Finally, 42 patients were excluded because of no available Geriatric Depression Scale (GDS). This resulted in a study sample of 680 patients (168 SCD, 164 MCI, 348 dementia).

For all patients, history of depression and the use of antidepressant medication (e.g. selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MOAIs)) were determined based on self-reported medical history and medication use. Presence of hypertension was determined based on self-reported medical history, medication use or a newly diagnosed hypertension defined as a

blood pressure of 140/90 mmHg or more, measured by means of sphygmomanometer. Hypercholesterolemia was determined based on self-reported medical history or medication use. Diabetes mellitus was determined based on self-reported medical history, medication use or a newly diagnosed diabetes mellitus defined as nonfasting glucose of ≥11.1 mmol/l or an HbA1c ≥48 mmol/mol (or ≥6.5%). Obesity was defined as body mass index (BMI) ≥30.

2.2 Evaluation of depressive symptoms

Depressive symptoms were assessed using the 15-item self-reported GDS, which has a maximum score of 15 (19) and higher scores indicate the presence of depressive symptoms. The GDS-15 is frequently used in clinical practice and research and is a valid and reliable screening instrument for depressive symptoms in older people (19). In our study, the GDS was verbally administered to patients by a neuropsychologist. We classified patients as having depressive symptoms if their score on the GDS was 5 or higher. In our analyses we used the continuous GDS score, because this offers the highest power to detect associations.

2.3 AD biomarkers

Cerebrospinal fluid (CSF) markers amyloid-beta$_{1-42}$ (Abeta$_{1-42}$) and total tau (tau) were available for 446 patients. CSF biomarkers were assessed using Sandwich ELISAs (Fujirebio, Gent, Belgium) (20). CSF biomarkers were considered positive for AD when tau / Abeta$_{1-42}$ ratio was > 0.52 (21). In the patients selected for this study, CSF biomarkers were only measured in patients included at VUMC as standard procedure of the memory clinic.

2.4 MRI protocol

Brain MRI scans were performed on 1.5 (*n* = 39) or 3.0 (*n* = 641) Tesla MRI scanners. The Scans were acquired on GE (*n* = 527, 77.5%) or Philips (*n* = 153 (22.5%) MRI scanners using a standardized protocol. MRI protocol included 3D T1-weighted, T2-weighted, T2*-weighted/susceptibility-weighted imaging (SWI) and T2 fluid-attenuated inversion recovery (FLAIR) sequences. For some patients, 3D T1 and/or FLAIR sequences were not available, therefore 2D T1 or 2D FLAIR sequences were used instead. Slice thickness, voxel size and other details for each scanner type are described in detail in Supplementary Table 1.

2.*5 Lesion segmentation*

Vascular brain injury was rated in accordance with the internationally established STRIVE criteria, which provide neuroimaging standards for classification of cerebral SVD (22). Ratings were performed by or under supervision of a neuroradiologist. Lesion segmentation was performed on T2 FLAIR images, using the T1 modality as a reference for proper lesion classification. Automated WMH segmentation was performed using the k nearest neighbour classification with tissue type priors (kNN-TTPs) method (23). This method showed no systematic errors across different MRI scanners. The resulting WMH lesion maps underwent a visual check for accuracy by two independent raters. Subsequent manual corrections were required in 6 subjects (0.9%) because of segmentation inaccuracies (i.e. missed WMH or incorrect or incomplete WMH segmentation). These corrections were performed by a single rater. In addition, presence of other lesion types was determined: lacunes were defined as sharply demarcated deep lesions with CSF-like signal on all sequences, microbleeds were defined as small dot-like hypointense lesions on T2*-weighted or SWI images. Next, manual segmentation of these

lesions was performed using in-house developed software based in MeVisLab (MeVis Medical Solutions AG, Bremen, Germany) (24,25).

2.6 Generation of lesion maps

All lesion maps were transformed to the T1 1-mm MNI-152 (Montreal Neurological Institute) brain template (26), using an in-house developed image registration pipeline that applies the elastix toolbox (27). This standardized pipeline has been recently developed and will soon be made publicly available at http://www.metavcimap.org. The registration procedure consisted of linear registration followed by nonlinear registration. As an intermediate step, registration to an age-specific MRI template was performed (28), which has previously shown to result in more successful registration of brains from patients with severe atrophy. These registration steps were combined into a single step through which the original lesion maps were registered directly to the MNI-152 space, in order to prevent intermediate interpolations and thereby improve registration accuracy. Quality checks of all registration results were performed by one rater (NAW), who compared the lesion location in MNI space with the original scans. One patient (0.14%) had to be excluded because of unsuccessful lesion registration.

2.7 Statistical analysis

PASW Statistics 25.0 for Mac (SPSS Inc., Chicago IL, USA) was used for statistical analyses. Analyses of variance (ANOVA) and Pearson χ^2 tests were performed to compare groups when appropriate.

Two independent hypothesis-free analysis methods were applied to identify WMH locations associations with depressive symptoms: 1) voxel-based lesion-symptom mapping (VLSM), which analyses the relation between presence of WMH and depressive symptoms for every individual voxel in the brain (29); and 2) exploratory region of interest

(ROI)-based analyses, which analysed the impact of lesion volume in predefined white matter tracts on depressive symptoms.

2.7.1 Voxel-based lesion-symptom mapping

VLSM was performed using Non-parametric Mapping software (NPM, version May 2016; settings: univariate analysis, Brunner-Munzel test) (29), which is suitable for non-normally distributed data. To ensure that our analyses were not biased by voxels that are only rarely affected, we set a minimum number of patients with a lesion in a particular voxel and only included voxels in our analysis that were affected by WMH in at least 14 subjects (2%) (30). VLSM analyses were performed using a *z*-score of the GDS as measure for depressive symptoms, after individualized correction for age and sex using linear regression. The analyses were repeated after additional correction for normalized total WMH volume (i.e. calculated from lesion maps after transformation to MNI-152 space). False discovery rate control ($q<0.05$) was applied to correct for multiple testing. We performed VLSM in the whole group and subsequently stratified for syndrome diagnosis.

2.7.2 Region of interest-based analysis

ROIs were created using the John Hopkins University (JHU) diffusion tensor imaging (DTI)-based white matter atlas (31) with a probability threshold of 10%. Regional WMH volumes were calculated in millilitres for each patient for 20 white matter tracts. Next, bilateral white matter tracts were merged to create a single ROI by combining the volumes. The GDS was standardized into a *z*-score. WMH volumes within the resulting 11 ROIs were added as independent variables to linear regression models, which included age, sex and memory clinic center of inclusion as covariates (Model 1). When we found a significant association, we repeated the analysis with additional adjustment for normalized total WMH volume (Model 2). In addition, we performed extra analyses with adjustment for

antidepressant medication and MRI field strength and vendor (Model 3). To investigate if associations with the ROIs differed according to diagnostic group (SCD, MCI or dementia), interaction terms (dummy-diagnosis*ROI) were included in the model. When we found an interaction between syndrome diagnosis and the ROI (p<0.10), results were subsequently stratified for syndrome diagnosis, and the standardized betas (stß) were displayed for each diagnostic group separately. When no significant interaction was found, the interaction term was removed from the model and the overall stß was reported.
Finally, we performed an additional linear regression analyses in a subgroup of patients with CSF biomarkers (n = 446) to determine whether the impact of WMH location was influenced by co-occurring AD pathology. To investigate if associations differed among the patients with positive versus negative CSF biomarkers, we used interaction terms (amyloid status*ROI).

3. Results

Demographic data and MRI measures are summarized in Table 1. No differences were noted between the original TRACE-VCI cohort and the present study sample (data not shown). Patients with SCD were younger compared to patients with MCI or dementia. Patients with dementia had lower scores on the GDS than patients with SCD (dementia: 3.2±2.7 vs. SCD: 4.6±3.5; p<0.001). Patients with MCI or dementia less often used antidepressant medication compared to SCD (dementia: 12%; MCI: 11% vs. SCD: 20%; p<0.05). Total WMH volume was highest in patients with dementia and MCI, compared to SCD (dementia: [median (IQR)] 11.5 (22.8); MCI: 11.6 (18.7) vs. SCD: 5.0 (10.7), p<0.001).

3.1 Voxel-based lesion-symptom mapping

VLSM was used as an assumption-free method to investigate whether presence of WMH

in specific voxels in the brain was significantly associated with depressive symptoms on the GDS, independent of total WMH volume. The distribution of WMH is illustrated by the lesion prevalence map in Figure 2A. WMH showed a symmetrical distribution and were most prevalent in periventricular and fronto-parietal regions.

The results of the VLSM analysis are shown in Figure 2B. We found voxels with a significant association between the presence of WMHs and depressive symptoms, after correction for age, sex, total WMH volume and multiple testing. These significant voxels were almost exclusively located within the corticospinal tract (CST), near the superior longitudinal fasciculus (SLF) and the temporal part of the SLF. The exact number of significant voxels within each white matter tract is provided in Table 2.

Subsequently stratification for syndrome diagnosis showed no significant voxels for any subgroup.

3.2 Region of interest-based analyses

We used ROI-based analyses to determine whether WMH volumes within predefined white matter tracts were associated with depressive symptoms. Table 3 shows the association between total and regional WMH volume and depressive symptoms.

Both total WMH volume as regional WMH volume in specific tracts were not related to depressive symptoms. We found interactions between syndrome diagnosis and regional WMH volume in the forceps minor, anterior thalamic radiation, inferior fronto-occipital fasciculus and the inferior longitudinal fasciculus, suggesting that the association between depressive symptoms and regional WMH volume in these regions is different for SCD, MCI and dementia. Subsequent stratification for syndrome diagnosis showed that in patients with SCD regional WMH in the forceps minor was associated with more depressive symptoms (standardized beta [stß] = 0.16, $p<0.05$). Additional adjustment for normalized total WMH volume resulted in a slightly stronger association (stß = 0.26,

p<0.05). There were no significant associations for MCI and dementia. Finally, we performed analyses with additional adjustment for antidepressant medication and MRI field strength and vendor, and the results were unchanged (data not shown).

3.3 Exploratory region of interest-based analyses in a subgroup of patients with CSF biomarkers

Subsequently, we performed exploratory analyses in a subgroup of patients with CSF biomarkers (*n* = 446; Supplementary Table 1). We did not find significant interactions between amyloid status and WMH volume in relation to depressive symptoms in any region.

4. Discussion

This lesion-symptom mapping study on depressive symptoms indicates the CST and forceps minor as strategic white matter tracts in which WMH are associated with depressive symptoms in a memory clinic cohort of patients with vascular brain injury. The overall impact of WMH on these symptoms was modest, but WMH location appeared to be particularly important in patients with SCD.

The analyses (VLSM and ROI-based linear regression) used in this study resulted in different strategic WMH locations. We detected an association between regional WMH in the CST and depressive symptoms only at the voxel-level and the number of significant voxels was limited (only 15 out of 5975 voxels). At the regional level, with the ROI-based analyses, we found no congruent correlation with the CST but identified a modest association between the forceps minor and GDS only in the subgroup with SCD. The statistical power (due to more rigorous correction for multiple testing) for the VLSM analyses might have been insufficient. However, a main advantage of VLSM is the very high spatial resolution. Meanwhile, our results regarding the forceps minor are consistent

with previous findings on the role of WMH in frontal and temporal locations in depression (5,11). The lack of convergence of findings from the VLSM and ROI analyses may reflect that effect sizes are quite small. Moreover, the exploratory nature of the ROI analysis warrant replication of our findings and further investigation in other large memory-clinic cohorts with optimal lesion coverage.

The vascular depression hypothesis proposes that WMH caused by cerebrovascular disease disrupt the frontostriatal-subcortical circuits and thereby predispose for late-life depression (32). Previous studies on white matter pathways and depressive symptoms have primarily employed diffusion tensor imaging (DTI). Most studies examined patients with major depressive disorder (MDD) or patients with late-life depression. A recent review on white matter alterations in emotional disorders (ranging from MDD to anxiety disorders and obsessive compulsive disorders) found reduced fractional anisotropy (FA) as marker for white matter integrity) in fronto-temporal and fronto-parietal white matter tracts compared to healthy controls (33). The largest clusters of reduced FA incorporated several white matter tracts, including the left forceps minor, the anterior thalamic radiation, the inferior fronto-occipital fasciculus and the uncinate fasciculus. A study in non-demented patients with small vessel disease (SVD) found lower white matter integrity in patients with depressive symptoms, in particular in the prefrontal white matter tracts (34). In contrast, a previous study in a small group of patients with MDD found *increased* white matter integrity in the CST compared to controls using tractography clustering methods (35). Previous research suggests that DTI underestimates fractional anisotropy in regions where fasciculi cross. As the CST is located in an area with crossing fasciculi (i.e. the superior longitudinal fasciculus), these results measured with DTI may be interpreted with caution (36). However, our lesion-symptom mapping analyses in a large cohort of memory clinic patients including an adjustment for multiple comparisons using a FDR correction also

showed an association between the CST and depressive symptoms. Our results provide further evidence for a potential role for the CST in depressive symptoms. The CST is a descending tract of the central nervous system, starting in the cortex terminating in the spinal cord and is known to be involved in controlling movements of the limbs and trunks. It is possible that our findings with the CST are related to psychomotor symptoms in depression. It is known that depression comprises many combinations of clinical symptoms. Population-based and clinical (in patients with major depression disorder) studies have investigated the presence of these depressive 'subtypes' and suggest the reflection of specific neurobiological biomarkers in particular brain regions between the subtypes (37,38). In the present study, we only had access to the total GDS score. Future research with different measures for depressive symptoms is needed to identify the potential presence of depressive subtypes in a memory clinic population.

Consistent with our previous study we did not find an association between WMH and depressive symptoms in patients with dementia (10). However, our previous results of a higher propensity of depressive symptoms in patients with SCD and WMH is consistent with the present study, as we found an association between regional WMH in the forceps minor and depressive symptoms in patients with SCD. The forceps minor is a commissural fibre that connects the medial and lateral surfaces of both frontal lobes. It has previously been associated with executive dysfunctioning and reduced psychomotor speed in patients with vascular brain injury (15), which are core cognitive deficits in patients with late-life depression and VCI. Studies in patients with SCD found subthreshold symptoms of depression and anxiety (39). Most of the patients with SCD do not necessarily meet the diagnostic criteria for a psychiatric disorder such as MDD. Affective symptoms in SCD show increased risk of progression to mild cognitive impairment and dementia suggesting the subthreshold symptoms of depression as possible manifestation of preclinical AD in

these individuals (40,41). Conversely, our subsequent analyses in a subgroup with CSF biomarkers showed that the association between WMH and depressive symptoms is not influenced by Alzheimer pathology. To investigate whether factors other than WMH and Alzheimer pathology could explain these results, research in other cohorts is needed to provide more evidence. In addition, more complex multivariate models (e.g. Bayesian network analysis or multivariate lesion-symptom mapping) might be of value.

Among the limitations of the study is that we used the GDS-15 as measure of depressive symptoms. Cognitive impairment in MCI and dementia may affect diagnostic accuracy of the GDS (42). However, the design of the GDS with questions structured in a yes/no format makes it easy to use, even for patients with cognitive impairment. The level and severity of depressive symptoms in this study, in particular in patients with dementia, was relatively low, but were consistent with previous studies in memory clinic populations (10,43). Yet, this may have reduced the effect sizes and sensitivity to detect associations, despite the large sample size. Second, a relatively high number of patients with SCD used antidepressant medication (20%) compared to patients with MCI (11%) or dementia (12%). The antidepressant medication may have decreased the severity of depressive symptoms and led to lower scores on the GDS and thus an underestimation of the association between WMH location and depressive symptoms. However, the use of antidepressant medication will be more common in those with higher scores on the GDS, but additional analyses with adjustment for antidepressant medication showed similar results. Finally, inclusion of our patients at tertiary referral centers, and the exclusion of patients with cortical infarcts could limit the generalizability of our findings. On the other hand, the TRACE-VCI cohort is a large memory clinic cohort of patients with a large spectrum of vascular brain injury and different levels of cognitive impairment not limited to specific clinical diagnoses such as vascular dementia or Alzheimer’s disease. In addition, the use of data from different MRI scanners could have influenced the quality of the WMH

segmentations and subsequent analyses. However, we have assessed performance of our segmentation method and the method we used showed no systematic errors across MRI scanners.

Nevertheless, additional adjustment for field strength and vendor did not change our results. The use of different MRI scanners could also be seen as a strong point of our study as this highlights the robustness of our approach and increases the generalizability of our results. Moreover, the large lesion coverage, in particular in the fronto-parietal regions, allowed us to include a large number of white matter tracts leading to greater accuracy and statistical power. Second, we performed two independent hypothesis-free statistical analyses (VLSM and ROI-based linear regression models).

The present study provides further insight into the relationship between WMH location and depressive symptoms by performing a large scaled lesion-symptom mapping study on depressive symptoms.

In conclusion, we showed that the impact of WMH on depressive symptoms is modest, but appears to be dependent on location of WMH particularly in patients with SCD. Our results suggest different etiologies of depressive symptoms within a memory clinic population with vascular brain injury. Changes in white matter tracts might underlie the occurrence of depressive symptoms in memory clinic patients with vascular brain injury.

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Figure 1. Flowing chart of patient selection

NOTE: MRI: magnetic resonance imaging; GDS: Geriatric depression scale.

Figure 2. Voxel-based lesion-symptom mapping: lesion prevalence map and results

NOTE: WMH: white matter hyperintensities; FDR: false detection rate; CST: corticospinal tract.
(A) Voxel-wise lesion prevalence of white matter hyperintensities (WMH) in the study population, projected on the Montreal Neurological Institute 152 T1 template. A minimum threshold of 14 subjects with damage in a given voxel was applied. Z-coordinates: -5, 5, 15, 25, 35.
(B-D) Voxel-based lesion-symptom mapping results for the Geriatric Depression Scale score, shown in axial (B), sagittal (C) and coronal (D) planes. Significant voxels after correction for multiple comparisons, age, sex and normalized total WMH volume are shown in red (settings: Brunner Munzel test; FDR $q<0.05$). Significant voxels were located in the corticospinal tract (CST). Regions of interest were derived from the JHU DTI-based atlas with a probability threshold of 10%. The JHU-derived CST is shown in blue; the voxels included in the VLSM analysis (i.e. damaged in ≥14 subjects) are shown in yellow. Coordinates: sagittal: X= -25; coronal: Y = -32; axial: Z = 33, 38.

Table 1. Demographics of the study population

Demographics	**Study sample** (*n* = 680)		**SCD** (*n* = 168)		**MCI** (*n* = 164)		**Dementia** (*n* = 348)				**Post hoc differences**[1]
	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	F	*p*	
Age in years	67.1	8.2	62.9	7.5	68.2	8.5	68.6	7.7	31.27	<0.001	S<M=D
Education[2]	4.9	1.3	5.1	1.4	5.2	1.2	4.7	1.3	9.47	<0.001	S=M>D
MMSE	24.3	4.8	27.7	2.2	26.5	2.3	21.7	5	169.15	<0.001	S>M>D
GDS	3.7	3	4.6	3.5	3.7	2.8	3.2	2.7	12.66	<0.001	S>M=D
	N	%	N	%	N	%	N	%	χ^2	*p*	
Sex, female	320	57	83	49	72	44	165	47	1.045	0.593	n.s.
Presence of depressive symptoms[3]	200	29	72	42	51	31	77	22	23.750	<0.001	S>M>D
AD biomarkers[4]											
AD biomarkers available	446	66	112	67	100	61	234	67	2.054	0.358	n.s.
AD biomarkers positive	242	54	26	23	52	32	164	70	67.315	<0.001	S<M<D
History of depression[5]	86	12	34	20	16	9	36	10	11.673	<0.01	S>M=D
Use of antidepressant medication[5]	97	14	35	20	19	11	43	12	7.926	<0.05	S>M=D
Vascular risk factors[5]											
Hypertension	577	84	133	79	141	86	303	87	5.717	0.057	n.s.
Hypercholesterolemia	287	42	66	39	81	49	140	40	4.615	0.100	S<M>D
Diabetes mellitus	123	18	23	13	39	23	61	17	5.853	0.054	S<M>D
Obesity (BMI≥30)	144	21	43	25	34	20	67	19	3.687	0.450	n.s.
Currently smoking	132	19	36	21	32	19	64	18	1.205	0.877	n.s.
Imaging characteristics											
Patients with at least 1 lacune	124	18	22	13	44	26	58	16	11.675	<0.01	S<M>D
Patients with at least 1 microbleed[6]	296	44	62	37	76	46	158	45	4.388	0.111	n.s.
	MEDIAN	IQR	MEDIAN	IQR	MEDIAN	IQR	MEDIAN	IQR	F	*p*	
Total WMH volume in ml[7]	9.1	18.0	5.0	10.7	11.6	18.7	11.5	22.8	15.418	<0.001	S<M=D

NOTE: SCD: Subjective cognitive decline; MCI: mild cognitive impairment; MMSE: Mini-mental state examination; GDS: Geriatric depression scale; AD: Alzheimer's disease; BMI: body mass index; WMH: white matter hyperintensities; IQR: interquartile range; SD: standard deviation. One-way ANOVA or χ^2 were performed, respectively. Data are presented as mean±SD or number (percentage). [1]S=SCD; M=MCI; D=dementia. [2]Level of education was classified according to the system of Verhage ranging from 1 to 7 (low to highly educated). [3]Presence of depressive symptoms indicates a score of ≥5 on the GDS. [4]AD biomarkers are available as cerebrospinal fluid total tau/amyloid $\beta_{1\text{-}42}$ (abnormal when >0.52 (21)). [5]History of depression, antidepressant use and presence of vascular risk factors (i.e. hypertension, hypercholesterolemia and diabetes mellitus) was determined based on self-reported medical history and medication use or newly diagnosed (for hypertension and diabetes mellitus). [6]Data missing in five patients. [7]Standardized WMH volumes were calculated from lesion maps after transformation to the MNI-152 standard space.

Table 2. Voxel-based lesion-symptom mapping results: significant voxels per anatomical region of interest, after correction for age, sex, total WMH volume and multiple testing.

Anatomical regions (JHU atlas)	Region size in voxels (n)	Tested voxels (n)	Significant voxels (n)
Forceps major	22285	9537	0
Forceps minor	35840	5063	0
Anterior thalamic radiation	43203	13661	0
Corticospinal tract	27767	5975	15
Cingulum	13829	1309	0
Parahippocampal white matter	5234	0	0
Inferior fronto-occipital fasciculus	49378	24187	0
Inferior longitudinal fasciculus	37450	9955	0
Superior longitudinal fasciculus (SLF)	59703	29336	1
Temporal part of SLF	22910	12710	1
Uncinate fasciculus	15662	4371	0

NOTE: JHU: John Hopkins University (JHU) diffusion tensor imaging (DTI)-based white matter atlas; SLF: Superior longitudinal fasciculus. Tested and significant voxels for each anatomical region, after correction for age, sex, total WMH volume and multiple testing by applying a false discovery rate (FDR).

Table 3. Region of interest-based analyses

Anatomical regions (JHU atlas)		**All** (*n* = 680)		**SCD** (*n* = 168)		**MCI** (*n* = 164)		**Dementia** (*n* = 348)	
		stß	*p*	stß	*p*	stß	*p*	stß	*p*
Total WMH volume	Model 1	-0.03	0.47						
Forceps major	Model 1	-0.06	0.16						
Forceps minor	Model 1¥	0.05	0.20	0.16	0.04	0.04	0.63	0.03	0.66
	Model 2¥	-		0.26	0.02	-		-	
Anterior thalamic radiation	Model 1¥	-0.01	0.85	0.05	0.55	0.07	0.45	-0.07	0.24
Corticospinal tract	Model 1	0.03	0.46						
Cingulum	Model 1	-0.02	0.70						
Inferior fronto-occipital fasciculus	Model 1¥	-0.05	0.23	0.05	0.53	-0.02	0.78	-0.10	0.06
Inferior longitudinal fasciculus	Model 1¥	-0.04	0.30	0.11	0.17	-0.05	0.58	-0.10	0.07
Superior longitudinal fasciculus	Model 1	-0.03	0.42						
SLF, temporal part	Model 1	-0.03	0.46						
Uncinate fasciculus	Model 1	-0.01	0.78						

NOTE: SCD: subjective cognitive decline; MCI: mild cognitive impairment; JHU: John Hopkins University; SLF: Superior longitudinal fasciculus.

¥: Significant interaction term; subsequently stratification for syndrome diagnosis.

Results are presented as standardized beta (stß). This assumption-free region of interest-based analysis served to identify strategic white matter tracts in which WMH volume is correlated with depressive symptoms, independent of total WMH burden. The GDS, as measure of depressive symptoms, was standardized into a *z*-score. We excluded the tract parahippocampal white matter (JHU atlas) from our analyses due to the limited WMH in this tract. Age, sex, center and syndrome diagnosis were first entered into a linear regression model (Model 1). If regional volumes showed a statistically significant ($p<0.05$) association in model 1, normalized total WMH volume was added to the model (Model 2). To check if associations between depressive symptoms and the anatomical region differed according to diagnostic group, interaction terms (dummy diagnosis*anatomical region) were included in the model. When we found an interaction between syndrome diagnosis and anatomical region ($p<0.10$), the results were subsequently stratified for syndrome diagnosis and the stß is displayed for each diagnostic group separately. When no significant interaction was found, the interaction term was removed from the model and the overall stß is reported.