In shape: a novel approach to white matter hyperintensity analysis

Kuhn, J.A.

CHAPTER 7

STUDY PROTOCOL OF THE WHIMAS: IDENTIFICATION OF NOVEL 7T MRI WHITE MATTER HYPERINTENSITY SHAPE AND BRAIN CLEARANCE MARKERS FOR CEREBRAL SMALL VESSEL DISEASE

Jasmin Annica Kuhn-Keller, Ingmar Eiling, Lydiane Hirschler, Lena Václavů, Marie-Noëlle Witjes-Ané, Marjolein Wijngaarden, Martijn Nagtegaal, Ece Ercan, Nathaly Rius Ottenheim, Marjan van der Elst, Evelien Sohl, Mark A. van Buchem, Simon Mooijaart, Matthias J.P. van Osch, Jeroen de Bresser.

Under review.

7.1 ABSTRACT

Sporadic cerebral small vessel disease (SVD) has heterogeneous underlying pathology and current SVD MRI markers do not accurately capture this heterogeneity. Novel ultra-high field (7T) brain MRI markers provide a window of opportunity to study early changes and potential determinants of SVD. White matter hyperintensity (WMH) shape is a relatively novel MRI marker of SVD and has shown prognostic potential. However, the exact microstructural changes within or surrounding WMHs or potential causes related to WMH shape variations are unknown. Furthermore, impaired brain clearance via the recently discovered brain glymphatic system may be another early change or potential cause of SVD. In the WHIMAS (white matter hyperintensity shape and glymphatics study) we aim to study the link between WMH and especially their shape with brain clearance and other MRI markers on ultra-high field (7T) brain MRI and show if these markers are associated with cognitive functioning in older adults with memory complaints.

The WHIMAS is a cross-sectional study that will be conducted at the Leiden University Medical Center (LUMC). Fifty outpatients from the memory/geriatric clinic, aged 65 years or older will be recruited for a 3T and a 7T MRI scan, as well as a standardised neuropsychological test battery (domains: memory, executive function, visuoconstruction, and processing speed). We will assess WMH shape markers (solidity, convexity, concavity index, fractal dimension, and eccentricity) and brain clearance markers (CSF-BOLD-coupling, CSF-mobility) and study their relation to other MRI markers and cognitive functioning.

We aim to understand variations in WMH shape and find their relation to cerebral SVD and markers of brain clearance and cognitive functioning. These markers early in the disease process of SVD are extremely important as they may represent a basis for future patient selection for lifestyle interventions or for treatment trials aimed at prevention of dementia.

7.2 STRENGTHS AND LIMITATIONS OF THIS STUDY

- In depth study of the link between white matter hyperintensities and especially their shape with brain clearance and other MRI markers on ultra-high field (7T) brain MRI in a memory clinic population.
- Advanced and novel imaging techniques will be used both at 3T and ultra-high field (7T) MRI combined with novel advanced image processing techniques.
- In depth study of the relation between white matter hyperintensity shape and glymphatics markers and cognitive functioning.
- This observational study serves to steer future investigations and could be extended into a longitudinal study.
- The studied markers early in the disease process of cerebral small vessel disease are extremely important as they may represent a basis for future patient selection for lifestyle interventions or for treatment trials aimed at prevention of dementia.

7.3 INTRODUCTION

Dementia is often characterized by a combination of neurovascular and neurodegenerative disease processes and mixed pathologies are common.[1] The most common mixed pathology is Alzheimer's dementia (AD) and cerebral small vessel disease (SVD).[2,3] SVD contributes to the clinical phenotype of dementia in around 45% of dementia cases.[2–4] There are two main types SVD in an ageing population. One is SVD due to arteriolosclerosis, often related to hypertension.[5] The other one is cerebral amyloid angiopathy, characterized by progressive amyloid accumulation in the vessel walls.[5] Current SVD markers, such as white matter hyperintensities of presumed vascular origin (WMH), are unspecific and they fail to accurately capture the heterogeneity of SVD pathology. Therefore, novel brain MRI markers are needed to identify early changes and potential determinants of SVD. These markers are extremely important early in the disease process of SVD as they may represent a basis for future patient selection for lifestyle interventions or as outcome markers for treatment trials (such as currently being developed for cerebral amyloid angiopathy[6] aimed at prevention of dementia.

WMH are the key brain MRI manifestation of cerebral SVD.[7] Around 92% of all individuals over 60 years of age have WMHs[8–10] and a higher WMH burden is a risk factor for occurrence of stroke and dementia.[10] Especially the volume of WMH has been extensively studied, but this is a generic and non-specific marker that only has modest prognostic value.[11] Although there is considerable variation in the shape of WMH, this marker has received only little attention.[12] Recent studies have shown that normal appearing white matter around WMH that will progress on follow-up

MRI scans, already showed changes in structural integrity and hemodynamics at baseline.[13,14] Furthermore, WMH typically localize at vascular endzones and progress along more proximal parts of the perforating arteries.[15] How the perforating arteries are affected depends on the underlying pathological changes, such as large vessel atheromas at the origin of perforating arteries, small vessel atheromas or micro-embolisms.[16,17] These pathological changes may lead to hypoperfusion, defective cerebrovascular reactivity, and blood-brain barrier dysfunction,[11] which in turn may be related to increase of WMH and thus also changes in their shape.[12,17] Previous studies have also indicated that WMH shape may provide a better indication of underlying pathophysiological mechanisms than WMH volume alone and may harbor strong prognostically relevant information.[12,18–20]

SVD is a heterogeneous disease with many possible underlying causes. An important factor leading to brain changes in SVD might be impaired clearance of waste products, which has been linked to aging and dementia pathology.[7] The process of brain clearance is postulated to be partly driven by the glymphatic system, where cerebrospinal fluid (CSF) and interstitial fluid 'flush' brain tissue and transport waste products out of the brain via perivascular spaces. Some first studies have shown that in cerebral amyloid angiopathy and Alzheimer's dementia glymphatic function might be impaired.[21] Currently, brain clearance related processes can only be studied invasively in humans, for example by contrast-enhanced MRI following intrathecal injection.[22] This limitation made it difficult to implement research related to glymphatic dysfunction into clinical study protocols. However, recently developed novel ultra-high field (7T) brain MRI markers provide a window of opportunity to study the human glymphatic system in a non-invasive way.

In the WHIMAS (white matter hyperintensity shape and glymphatics study) we aim to study the link between WMH, and especially their shape, with brain clearance and other MRI markers on high field (3T) and ultra-high field (7T) brain MRI. Furthermore, we aim to study the relation between WMH shape and glymphatics markers and cognitive functioning. Studying these imaging markers in SVD is important because at an early stage cerebral SVD is a target for preventive treatment that may postpone or even prevent the occurrence of dementia and stroke. Our study contributes to the first steps in this research into early detection of dementia. We specifically strive for early detection of the potentially treatable/modifiable part of the dementia pathology, namely SVD. Previous studies have already shown that early lifestyle interventions in populations at risk can slow the pathophysiological processes of cerebral SVD.[23–25] However, it is currently impossible to non-invasively identify individuals who have an increased risk of dementia at an early stage of the disease and who may benefit most

from available lifestyle interventions or from future preventive treatment. We aim to pave the way for personalized medicine approaches by finding brain MRI biomarkers that can identify these individuals at risk.

7.4 METHODS

7.4.1 Study design

This study is an observational cross-sectional study that will be conducted at the Leiden University Medical Center (LUMC). The study (NL78641.058.21) was approved by the Medical Ethics Committee Leiden Den Haag Delft (reg. P21.114) and is registered on ClinicalTrials.gov (ID-number: NCT06010511). The patient and funding organization Alzheimer Nederland has funded part of this research and is involved in the conduct and in the dissemination plans of our study. The study involves a whole-day visit at the LUMC for each participant and includes the following procedures: a 3T brain MRI scan of 60 minutes, a 7T brain MRI scan of 60 minutes, a neuropsychological assessment, and questionnaires on demographics and vascular risk factors. An overview of the study procedures can be found in figure 7.1. Objectives of the study include the following: 1) To study the association of a more complex WMH shape with anatomical, hemodynamic, and white matter integrity abnormalities on MRI; 2) To study the association between WMH shape and cognition/other cerebral SVD markers; 3) To study the association of novel MRI markers of brain clearance with cerebral SVD markers and cognition.

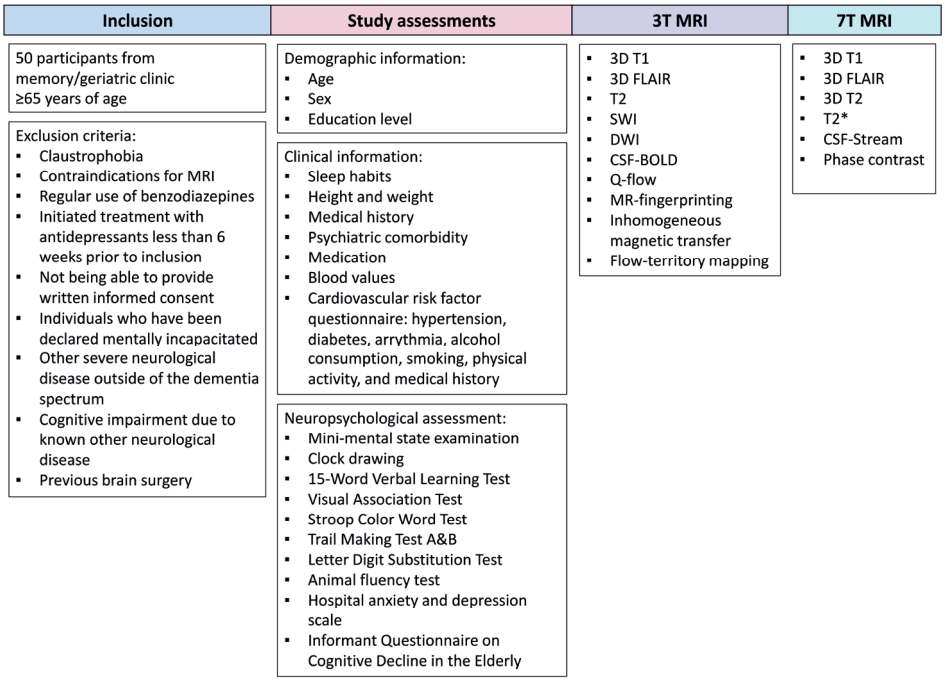

Figure 7.1. Overview of the study procedures.
3D T1: T1-weighted MRI scan; 3D FLAIR: 3D fluid-attenuated inversion recovery SWI: susceptibility-weighted scan; DWI: diffusion weighted scan; CSF: cerebrospinal fluid selective-T2prep-REadout with Acceleration and Mobility encoding

7.4.2 Population

We will prospectively include 50 outpatients over 65 years of age with memory complaints from the memory/geriatric clinic at one of their first visits, at the Leiden University Medical Center or the Alrijne hospital in Leiden. All participants give written informed consent prior to any study procedures. The current study involves 3T and 7T MRI and newly developed sequences and markers, especially for brain clearance, which have not been applied in patient populations before. Therefore, we performed the sample size calculation based on the WMH shape analysis. To provide a frame of reference we performed a sample size calculation using data from a previous manuscript.[26] The linear regression performed on hypertension and convexity, corrected for age and sex, was performed with data of 71 non-demented older adults. The same WMH shape analysis pipeline was used in the previous study as we aim to use in the current study. Using the data from this significant results, the sample size calculation performed in G*Power[27] showed a result of 79 participants. As the data used in the calculation was obtained from community-dwelling individuals, we expect higher effect sizes in our study consisting of a memory clinic population.

In this population, the prevalence and severity of SVD and thus WMH will be higher, justifying our assumption of increased power. At the same time we do not want to risk an underpowered study. For example, in a case-control study comparing type 2 diabetes patients with healthy controls an average effect size of 0.37 for a more complex WMH shape was found.[12] To illustrate this we have calculated the sample size with two different effect sizes that are higher than the one used in the initial calculation (0.2 and 0.3), but still lower than 0.37 (as found by De Bresser et al., 2018). These calculations resulted in a sample size of 42 or 29 participants. Therefore, a number of 50 participants should give the necessary statistical power to overcome biological and clinical variation.

In order to be eligible to participate in the current study, a participant must meet all of the following criteria; participants receive care in the outpatient memory clinic or the geriatric clinic of the LUMC or the memory clinic of the Alrijne hospital in Leiden. Inclusion can be done if the participant is over 65 years of age and eligible for MRI. Moreover, the participant has to be native-level in the Dutch language.

A potential participant who meets any of the following criteria will be excluded from participation in this study:

- Claustrophobia
- Contraindications for MRI such as metal implants and pacemaker
- Regular use of benzodiazepines
- Initiated treatment with antidepressants less than 6 weeks prior to inclusion
- Not being able to provide written informed consent (assessed by the treating physician)
- Individuals who have been declared mentally incapacitated
- Other severe neurological disease outside of the dementia spectrum
- Cognitive impairment due to known other neurological disease
- Previous brain surgery

7.4.3 Clinical data

We will collect basic demographic information including age, sex and education level. Information about medical history, psychiatric comorbidity, medication, and current blood values are extracted from the clinical file of the participant. Furthermore, a cardiovascular risk factor questionnaire is used to gather information about hypertension, diabetes, arrythmia, alcohol consumption, smoking, physical activity, and medical history. Another questionnaire includes questions about sleep

habits, using an adapted version of the Pittsburg Sleep Quality Index.[28] The sleep questionnaire is included, because of the influence of sleep on the glymphatic system.

The following tests are included in the neuropsychiatric assessment:

- Mini-mental state examination[29]
- Clock drawing[30]
- 15-Word Verbal Learning Test (immediate and delayed)[31]
- Visual Association Test[32]
- Stroop Color Word Test, 40 item version[33]
- Trail Making Test A&B[34,35]
- Letter Digit Substitution Test[36]
- Animal fluency test[37]
- Hospital anxiety and depression scale[38]
- Informant Questionnaire on Cognitive Decline in the Elderly[39]

7.4.4 MRI scans

All MRI scans are performed at the LUMC using a 3T Philips Ingenia Elition and a 7T Philips Achieva MRI scanner (Philips Healthcare). The MRI scan protocols are shown in table 7.1.

Conventional (3T) brain MRI scans will be used to determine global and functional markers of cerebral SVD, like WMH volume and presence of lacunes, microbleeds and superficial siderosis (on a 3D T1-weighted (3D T1), 3D fluid-attenuated inversion recovery (3D FLAIR), susceptibility-weighted imaging (SWI), and a diffusion weighted imaging (DWI) scan), hemodynamics (flow territory mapping;[40]). Furthermore, white matter structural integrity will be measured with a MR fingerprinting sequence[41] and an inhomogeneous magnetization transfer (ihMT) scan[42]. An fMRI scan technique will be used to measure CSF fluctuations in the 4th ventricle as a measure of brain clearance[43].

Ultra-high field (7T) brain MRI scans will be used to determine WMH shape (solidity, convexity, concavity index, fractal dimension, and eccentricity) and other markers of cerebral SVD in or surrounding the WMH, like enlarged perivascular spaces, (cortical) microinfarcts and microbleeds (on a T1-, T2-, FLAIR, and a T2*-weighted scan). Examples of WMH segmentations and the shape markers are shown in figures 7.2 and 7.3. Moreover, a recently implemented MRI technique called CSF-STREAM (CSF-selective-T2prepared REadout with Acceleration and Mobility encoding) will be used to measure CSF-mobility in perivascular spaces, as a proxy of glymphatic activity[44]. An example of measurements obtained with this technique can be seen in figure 7.4.

Heart rate and respiratory signal will be measured during the scans (3T and 7T MRI) with standard vendor-supplied equipment, namely a respiratory belt and pulse oximeter.

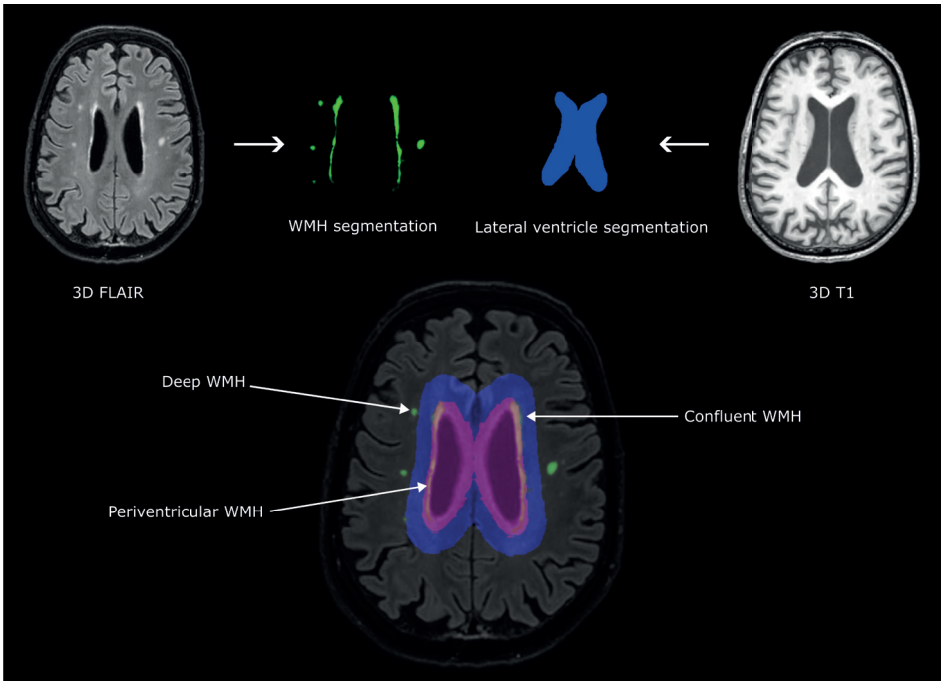

Figure 7.2. Overview of the MRI image processing pipeline for WMH shape. WMHs are automatically segmented from FLAIR MRI scans. T1-weighted scans are used to segment the lateral ventricles. The lateral ventricle masks are inflated and used to delineate between periventricular/confluent WMH. Then, the WMH shape markers are calculated on individual lesions.

Table 7.1 MRI scan protocols on the 3T and 7T MRI scanner.

	Purpose	Contrast parameters	Resolution (acquisition)	Resolution (reconstruction)	Field of View	Acquisition time (min)	Additional information
3T MRI							
3D T1	Anatomical information	TR/TE = 9.9/4.6 ms	1 mm isotropic	1 mm isotropic	256 mm	4:20	Flip angle = 8°
3D FLAIR	WMH, lacunes	TR/TI = 4800/1650 ms TE = 346 ms	0.98 x 0.98 x 1.00 mm^3	0.92 x 0.92 x 0.5 mm^3	220 mm	4:48	Refocusing angle = 40°
T2	Perivascular spaces	TR = 4490 ms; TE = 80 ms	0.40 x 0.50 x 3.00 mm^3	0.22 x 0.22 x 3.00 mm^3	230 mm	2:15	Flip angle = 90°
SWI	Iron, microbleeds, superficial siderosis	TR = 31 ms; TE = 7.20 ms	0.60 x 0.60 x 2.00 mm^3	0.23 x 0.23 x 1.00 mm^3	220 mm	2:35	Flip angle = 17°
DWI	Acute or recent ischemic lesions	TR = 3206 ms; TE = 67 ms;	1.96 x 2.44 x 5.00 mm^3	0.86 x 0.86 x 5.00 mm^3	220 mm	0:38	b-value = 1000
CSF_BOLD	CSF-BOLD coupling	TR = 370 ms; TE = 25 ms	2.88 x 2.88 x 5.00 mm^3	2.40 x 2.40 x 5.00 mm^3	230 mm	5:07	Flip angle = 40°
Q-flow	Large vessel flow	TR/TE = 15/7.2 ms;	0.45 x 0.45 x 4.00 mm^3	0.45 x 0.45 x 4.00 mm^3	230 mm	1.02	Venc =80 cm/s
MR-fingerprinting	White matter structural integrity; Myelin-water imaging	TR/TE = 15/3.0 ms	1.00 x 1.00 x 4.00 mm^3	1.00 x 1.00 x 4.00 mm^3	240 mm	5:00	Flip angle range: 10.0° - 60.0°
Inhomogeneous magnetic transfer	White matter structural integrity	TR/TE = 90/1.31 ms	2.29 x 2.29 x 5.00 mm^3	1.72 x 1.72 x 5.00 mm^3	220 mm	7:17	Flip angle = 7°
Flow territory mapping	Perfusion scan	TR/TE = 4550/16 ms	2.50 x 2.56 x 5.00 mm^3	1.88 x 1.88 x 5.00 mm^3	240 mm	4:56	

	Purpose	Contrast parameters	Resolution (acquisition)	Resolution (reconstruction)	Field of View	Acquisition time (min)	Additional information
7T MRI							
3DT1	Anatomical information	TR/TE = 4.2/1.9 ms	0.90 x 0.90 x0.90 mm^3	0.85 x 0.85 x 0.90 mm^3	246x 246x174 mm	2:22	Flip angle: 7°
3D FLAIR	WMH, lacunes	TR/TI = 8000/2200 ms TE = 252 ms	0.70 x 0.70 x 1.40 mm^3	0.68 x 0.68 x 0.70 mm^3	240x209x180 mm	5:12	Flip angle:90°
3D TSE (T2)	Perivascular spaces, arteries	TR = 3000 ms TE = 283 ms	0.75 x 0.75 x 0.75 mm^3	0.65 x 0.65 x 0.75 mm^3	250x250x190 mm	4:06	Flip angle=100°
T2* Duyn	Iron, microbleeds, superficial siderosis, veins	TR/TE = 1830/25 ms	0.24 x 0.24 x 1.00 mm^3	0.23 x 0.23 x 1.00 mm^3	240x180x101 mm	10:32	Flip angle 60°
CSF-STREAM	CSF mobility in the perivascular spaces	TR = 3430 ms TE = 497 ms	0.45 x 0.45 x 0.45 mm^3	0.45 x 0.45 x 0.45 mm^3	250x250x190 mm	21:57	Flip angle 90° degrees
2x Phase contrast	CSF flow in/out of the cranium	TR/TE = 6.7/3.6 ms	1.72 x 1.72 x 10.0 mm^3	0.63 x 0.63 x 10.0 mm^3	110x110	2x2:08	Venc 10 cm/s and venc 80 cm/s Flip angle 4°

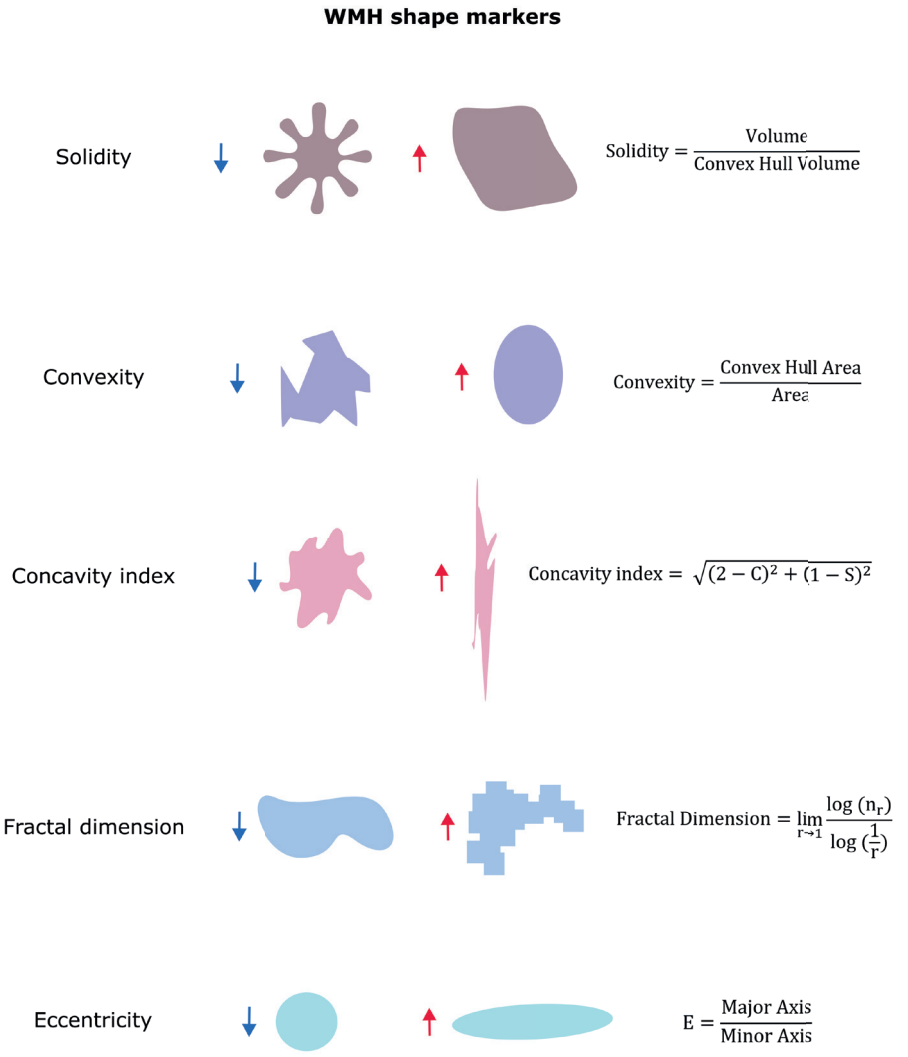

Figure 7.3. Examples of shapes with high or low values of different shape markers. Solidity, convexity, concavity index, and fractal dimension are calculated for periventricular/confluent WMH. Eccentricity and fractal dimension are the shape markers that are calculated for deep WMH.

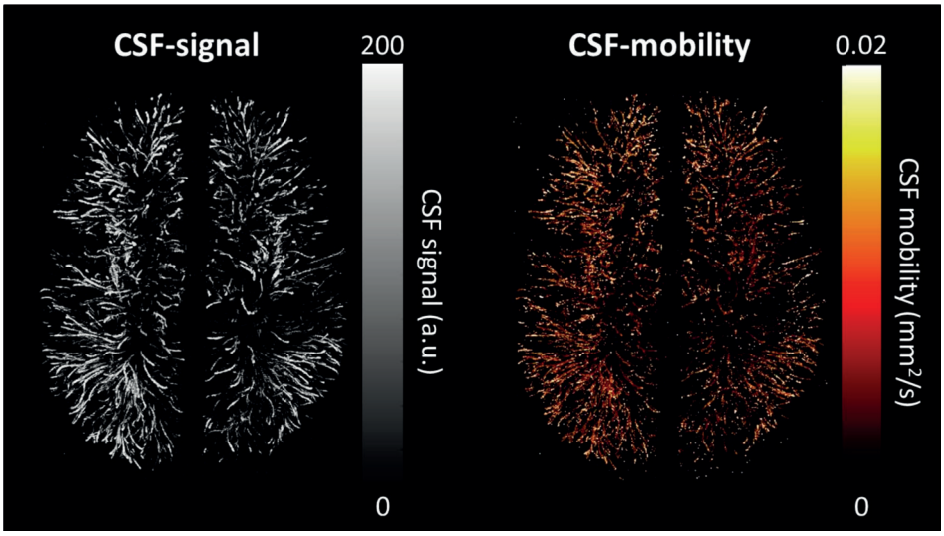

Figure 7.4. Examples of images obtained with the CSF-STREAM sequence as a measure of glymphatic activity. An image of the CSF-signal is shown on the left, and on the right is an example of a CSF-mobility map.

7.4.5 Statistics

Linear and logistic regression analyses will be performed to investigate the association between WMH shape and brain clearance/other MRI markers/cognitive functioning. Potentially confounding demographic variables, such as age, sex, level of education and vascular risk factors will be included as covariates for subsequent analyses. The distributions of the variables will be tested for normality. If applicable, appropriate nonparametric test will be used of variables will be log transformed. For the main analyses the significance will be set at $p < 0.05$.

7.5 DISCUSSION

SVD in an ageing population has heterogeneous underlying pathology which current MRI markers do not accurately capture. Novel 7T brain MRI markers provide a window of opportunity to study early structural changes and potential determinants of SVD. WMH shape is a relatively novel MRI marker and earlier studies have shown prognostic potential.[18,19] However, the exact microstructural changes within or surrounding WMHs or potential determinants related to WMH shape variations remain unknown. Furthermore, impaired brain clearance via the recently discovered brain glymphatic system may be another early change or potential cause of SVD.[45] In the WHIMAS study we aim to study the link between WMH and especially their shape with brain clearance and other MRI markers on high field (3T) and ultra-high

field (7T) brain MRI. Furthermore, we aim to study the relation between WMH shape and glymphatics markers and cognitive functioning.

The WHIMAS study will generate data that can be used to postulate underlying mechanisms related to WMH shape variations as we will study the association between a more complex WMH shape and advanced structural and functional markers of cerebral SVD. We expect to gain a better understanding of the structural correlates of WMH shape variation using and combining the advanced measurements at 7T MRI. WMH shape has previously been related to an increased long-term dementia risk[18] and increased long-term stroke- and mortality risk.[19] In our study we expect that a more irregular shape of WMH will be related to disease severity (captured by other SVD markers) and cognition (memory, executive function, visuoconstruction, and processing speed). Moreover, we expect to capture WMH shape and other structures that may influence shape (such as veins) better at 7T MRI due to an increased spatial resolution. This will allow a more precise investigation of WMH shape in relation to other SVD markers and structural changes.

Animal studies suggest that dysfunction of the glymphatic system plays a major role in the initiation and progression of not only neurodegenerative pathologies, but also SVD.[45] Novel non-invasive markers of brain clearance that we will use in our study will allow us to study brain clearance in vivo in a non-invasive way. In our study we expect to find an association between CSF mobility and disease severity. Moreover, the BOLD-CSF coupling has been found to be reduced in patients with Alzheimer's disease[46] and cerebral amyloid angiopathy.[47] Therefore, in our study we expect that the CSF-BOLD coupling will be reduced in our patient population, and will show an association with disease severity.

Biomarkers early in the disease process of cerebral SVD are extremely important as they may represent a basis for future patient selection for lifestyle interventions and as outcome markers of treatment trials aimed at prevention or treatment of dementia. The results of our study will contribute as a body of evidence for novel brain MRI markers that could hopefully serve as early biomarkers for SVD.

Strengths of our study include the specific patient population and the use of advanced ultra-high field 7T MRI state of the art imaging techniques in combination with advanced image processing techniques largely developed within our research group. The current study serves to steer future investigations and could be extended into a longitudinal study.

In conclusion, in the WHIMAS study we aim to find brain MRI changes that represent early determinants or changes of cerebral SVD. These markers early in the disease process of SVD are extremely important as they may represent a basis for future patient selection for lifestyle interventions or for treatment trials aimed at prevention of dementia.

7.6 ACKNOWLEDGEMENTS

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7.7 REFERENCES

1. Jellinger KA, Attems J. Challenges of multimorbidity of the aging brain: a critical update. J Neural Transm. 2015;122:505–21.
2. Kovacs GG, Milenkovic I, Wöhrer A, et al. Non-Alzheimer neurodegenerative pathologies and their combinations are more frequent than commonly believed in the elderly brain: A community-based autopsy series. Acta Neuropathol. 2013;126:365–84.
3. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: A statement for healthcare professionals from the American Heart Association/ American Stroke Association. Stroke. 2011;42:2672–713.
4. Brundel M, Heringa SM, De Bresser J, et al. High Prevalence of Cerebral Microbleeds at 7Tesla MRI in Patients with Early Alzheimer's Disease. Journal of Alzheimer's Disease. 2012;31:259–63.
5. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol. 2010;9:689–701.
6. Voigt S, Koemans EA, Rasing I, et al. Minocycline for sporadic and hereditary cerebral amyloid angiopathy (BATMAN): study protocol for a placebo-controlled randomized double-blind trial. Trials. 2023;24:1–6.
7. Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: Insights from neuroimaging. Lancet Neurol. 2013;12:483–97.
8. Bos D, Wolters FJ, Darweesh SKL, et al. Cerebral small vessel disease and the risk of dementia: A systematic review and meta-analysis of population-based evidence. Alzheimer's and Dementia. 2018;14:1482–92.
9. de Leeuw F -E., de Groot JC, Oudkerk M, et al. Hypertension and cerebral white matter lesions in a prospective cohort study. Brain. 2002;125:765–72.
10. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ. 2010;341:288.
11. Alber J, Alladi S, Bae H, et al. White matter hyperintensities in vascular contributions to cognitive impairment and dementia (VCID): Knowledge gaps and opportunities. Alzheimer's & Dementia: Translational Research & Clinical Interventions. 2019;5:107–17.
12. De Bresser J, Kuijf HJ, Zaanen K, et al. White matter hyperintensity shape and location feature analysis on brain MRI; Proof of principle study in patients with diabetes. Sci Rep. 2018;8:1–10.
13. Promjunyakul NO, Dodge HH, Lahna D, et al. Baseline NAWM structural integrity and CBF predict periventricular WMH expansion over time. Neurology. 2018;90:e2107–18.
14. Maillard P, Fletcher E, Lockhart SN, et al. White matter hyperintensities and their penumbra lie along a continuum of injury in the aging brain. Stroke. 2014;45:1721–6.
15. Duering M, Csanadi E, Gesierich B, et al. Incident lacunes preferentially localize to the edge of white matter hyperintensities: insights into the pathophysiology of cerebral small vessel disease. Brain. 2013;136:2717–26.
16. Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. Lancet Neurol. 2019;18:684–96.
17. Gouw AA, Seewann A, Van Der Flier WM, et al. Heterogeneity of small vessel disease: A systematic review of MRI and histopathology correlations. J Neurol Neurosurg Psychiatry. 2011;82:126–35.
18. Keller JA, Sigurdsson S, Klaassen K, et al. White matter hyperintensity shape is associated with long-term dementia risk. Alzheimer's and Dementia. 2023;19:5632–5641.
19. Ghaznawi R, Geerlings MI, Jaarsma-Coes M, et al. Association of White Matter Hyperintensity Markers on MRI and Long-term Risk of Mortality and Ischemic Stroke. Neurology. 2021;96:e2172–83.

20. Ghaznawi R, Geerlings MI, Jaarsma-Coes MG, et al. The association between lacunes and white matter hyperintensity features on MRI: The SMART-MR study. Journal of Cerebral Blood Flow and Metabolism. 2019;39:2486–96.
21. Peng W, Achariyar TM, Li B, et al. Suppression of glymphatic fluid transport in a mouse model of Alzheimer's disease. Neurobiol Dis. 2016;93:215–25.
22. Ringstad G, Valnes LM, Dale AM, et al. Brain-wide glymphatic enhancement and clearance in humans assessed with MRI. JCI Insight. 2018;3:e121537.
23. Bath PM, Wardlaw JM. Pharmacological treatment and prevention of cerebral small vessel disease: a review of potential interventions. Int J Stroke. 2015;10:469–78.
24. Dichgans M, Zietemann V. Prevention of vascular cognitive impairment. Stroke. 2012;43:3137–46.
25. Mok V, Kim JS. Prevention and Management of Cerebral Small Vessel Disease. J Stroke. 2015;17:111–22.
26. Keller JA, Kant IMJ, Slooter AJC, et al. Different cardiovascular risk factors are related to distinct white matter hyperintensity MRI phenotypes in older adults. Neuroimage Clin. 2022;35. doi: 10.1016/j.nicl.2022.103131
27. Faul F, Erdfelder E, Lang AG, et al. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 2007;39:175–91.
28. Buysse DJ, Reynolds CF, Monk TH, et al. The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. Psychiatry Res. 1989;28:193–213.
29. Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189–98.
30. Royall DR, Cordes JA, Polk M. CLOX: an executive clock drawing task. J Neurol Neurosurg Psychiatry. 1998;64:588–94.
31. Brand N, Jolles J. Learning and retrieval rate of words presented auditorily and visually. J Gen Psychol. 1985;112:201–10.
32. Lindeboom J, Schmand B, Tulner L, et al. Visual association test to detect early dementia of the Alzheimer type. J Neurol Neurosurg Psychiatry. 2002;73:126–33.
33. Stroop, J. R. (1935). Studies of Interference in Serial Verbal Reactions. Journal of Experimental Psychology, 18, 643-662.
34. Reitan RM. The relation of the trail making test to organic brain damage. J Consult Psychol. 1955;19:393–4.
35. Tombaugh TN. Trail Making Test A and B: normative data stratified by age and education. Arch Clin Neuropsychol. 2004;19:203–14.
36. Van Der Elst W, Van Boxtel M, Van Breukelen G, et al. The Letter Digit Substitution Test: normative data for 1,858 healthy participants aged 24-81 from the Maastricht Aging Study (MAAS): influence of age, education, and sex. J Clin Exp Neuropsychol. 2006;28:998–1009.
37. Van Der Elst W, Van Boxtel MPJ, Van Breukelen GJP, et al. Normative data for the Animal, Profession and Letter M Naming verbal fluency tests for Dutch speaking participants and the effects of age, education, and sex. J Int Neuropsychol Soc. 2006;12:80–9.
38. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand. 1983;67:361–70.
39. Jorm AF, Jacomb PA. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): socio-demographic correlates, reliability, validity and some norms. Psychol Med. 1989;19:1015–22.
40. Gevers S, Bokkers RP, Hendrikse J, et al. Robustness and Reproducibility of Flow Territories Defined by Planning-Free Vessel-Encoded Pseudocontinuous Arterial Spin-Labeling. American Journal of Neuroradiology. 2012;33:E21–5.

41. Jiang Y, Ma D, Seiberlich N, et al. MR fingerprinting using fast imaging with steady state precession (FISP) with spiral readout. Magn Reson Med. 2015;74:1621–31.

42. Ercan E, Varma G, Mädler B, et al. Microstructural correlates of 3D steady-state inhomogeneous magnetization transfer (ihMT) in the human brain white matter assessed by myelin water imaging and diffusion tensor imaging. Magn Reson Med. 2018;80:2402–14.

43. Fultz NE, Bonmassar G, Setsompop K, et al. Coupled electrophysiological, hemodynamic, and cerebrospinal fluid oscillations in human sleep. Science (1979). 2019;366:628–31.

44. Hirschler L., Aldea R., Petitclerc L., Ronen I., de Koning P.J.H., van Buchem, M. A., van Osch M.J.P. High resolution T2-prepared MRI enables non-invasive assessment of CSF flow in perivascular spaces of the human brain. In: Proceedings of the 28th Annual Meeting of ISMRM, Montréal, Canada, 2019. Abstract 0746.

45. Benvenuto H, Nedergaard M. Cerebral small vessel disease: A glymphopathy? Curr Opin Neurobiol. 2022;72:15–21.

46. Han F, Chen J, Belkin-Rosen A, et al. Reduced coupling between cerebrospinal fluid flow and global brain activity is linked to Alzheimer disease-related pathology. PLoS Biol. 2021;19:e3001233.

47. Hirschler L., Zanon Zotin, M.C., Lewis, L.D., Horn, M.J., Gurol, M.E, Viswanathan, A., Polimeni, J.R., van Osch, M.J.P., van Veluw, S.J., and Greenberg, S.M. Coupling between low-frequency hemodynamic oscillations and cerebrospinal fluid flow is altered in patients with cerebral amyloid angiopathy. ISMRM conference abstract 2023.