In shape: a novel approach to white matter hyperintensity analysis

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CHAPTER 1

GENERAL INTRODUCTION

1.1 AGEING AND DEMENTIA

With an ageing population age-related diseases such as dementia will continue to increase in the coming years.[1] This will create an increasing burden for society and health care systems.[1] There are several types of dementia, the most common ones being Alzheimer's disease, vascular dementia, frontotemporal dementia and Lewy body dementia.[2] Multiple co-existing diseases contribute to the dementia phenotype and cardiovascular risk factors are an important contributor. Cerebrovascular disease is an umbrella term for a range of conditions that result in pathological changes in or surrounding the cerebral blood vessels.[3] Large vessel disease, a type of cerebrovascular disease, is caused by atherosclerosis in the upstream arteries leading to the brain and is a major cause of ischemic stroke.[4,5] Cerebral small vessel disease (SVD) refers to a group of pathological changes affecting the cerebral small arteries, arterioles, capillaries and venules of the brain.[3] SVD is a major contributor to ischemic stroke, cognitive decline, and dementia.[6] SVD cannot be referred to as a single disease, but should be considered a combination of radiological features that can be caused by different genetic and non-genetic diseases.[3] Examples of genetic SVD forms are Dutch-type cerebral amyloid angiopathy (D-CAA) and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Genetic forms of SVD typically have a more early time of onset compared to the sporadic forms. The main types of cerebral SVD that occur in older adults are ischemic SVD (including e.g. arteriolosclerosis)[4] and sporadic cerebral amyloid angiopathy (CAA), where amyloid is deposited in the walls of the cerebral blood vessels increasing the risk for hemorrhage.[3] SVD often starts with asymptomatic changes in the vasculature and parenchyma, which can be captured best in population-based studies or in targeted studies in genetic cases. To date, treatment options are limited for vascular dementia. There are some preventive life-style changes and several new pharmaceutical options that make it important to select patients at an early stage. For example, a new pharmaceutical trial on CAA will start in 2024, also including patients with Dutch-type cerebral amyloid angiopathy[7] For patient selection and especially when aiming for the earlier disease stages, specific markers are currently lacking. This thesis aims to identify and characterize novel specific SVD markers.

1.2 NEUROIMAGING IN CEREBRAL SVD

Magnetic resonance imaging (MRI) has developed a lot since its introduction in the early 1980s. Today, MRI is a versatile technique that allows the investigation of brain changes in humans in a non-invasive manner both in clinical as well as in research settings. Changes in blood vessel properties caused by SVD, such as arteriolosclerosis, lipohyalinosis, and fibrinoid necrosis are difficult to image directly

with MRI, but they will eventually also lead to pathology of the brain parenchyma that can be made visible by MRI.[3,6] The most common SVD related brain changes are white matter hyperintensities (WMH), lacunes, microbleeds, enlarged perivascular spaces and also atrophy.[6] WMH appear as hyperintense lesions on fluid-attenuated inversion recovery (FLAIR) MRI.[6,8] WMH can be categorized into three types based on their location and extent: periventricular, confluent and deep WMH. Periventricular and confluent WMH surround the margins of the lateral ventricles, while deep WMH are punctual lesions located in the deep white matter. In clinical practice assessments of brain MRI scans are usually based on visual inspection and scoring. However, automated segmentation techniques can provide more objective results and are especially useful for research and even more when working with larger datasets. For example, WMH volumes or brain atrophy can be calculated based on automated segmentations.[9–12] Different MRI markers of parenchymal changes and their distribution over the brain can be used to discriminate different SVD types.[6,13]

SVD is a heterogeneous disease including many possible underlying pathologies. Some brain changes in SVD might be the result of impaired clearance of waste products, which has been associated with aging and dementia.[14] It is postulated that the brain clearance process is partly driven by the glymphatic system, where cerebrospinal fluid and interstitial fluid 'flush' brain tissue and transport metabolic waste out of the parenchyma via perivascular spaces. In cerebral amyloid angiopathy[15] and Alzheimer's dementia, glymphatic function might be impaired.[16] Currently, brain clearance related processes are mainly studied invasively in humans, for example by contrast-enhanced MRI following intrathecal injection.[17] In this thesis a study including non-invasive MR imaging techniques of the glymphatic system is proposed.

1.3 WMH SHAPE

Traditionally, WMH were investigated in research settings by visual rating scales or volume measurements.[18] While WMH volume is an objective measure that can be obtained automatically, it is also a rather crude measure. When inspecting MRI scans visually, WMHs can appear very different from each other in shape and location, even if their calculated volumes may be roughly the same. However, measures to objectively quantify such differences that may easily be caught by the eye of a neuroradiologist were lacking. For example, the borders of WMH can in some cases look smooth while in other cases they are irregular and complex. To automatically quantify shape differences of WMHs, several WMH shape markers were introduced previously.[19,20] For periventricular/confluent WMH solidity, convexity, concavity index, and fractal dimension specific measures were introduced using the formulas shown

in Figure 1.1.[20] High solidity and convexity, as well as low concavity index and fractal dimension reflect a more irregular shape. For deep WMH, the shape markers that were found appropriate are fractal dimension and eccentricity. Higher eccentricity suggests a more elongated shape. Periventricular/confluent WMH and deep WMH have very different shape appearances which is why different shape markers are used for each of them to most accurately capture their shape.

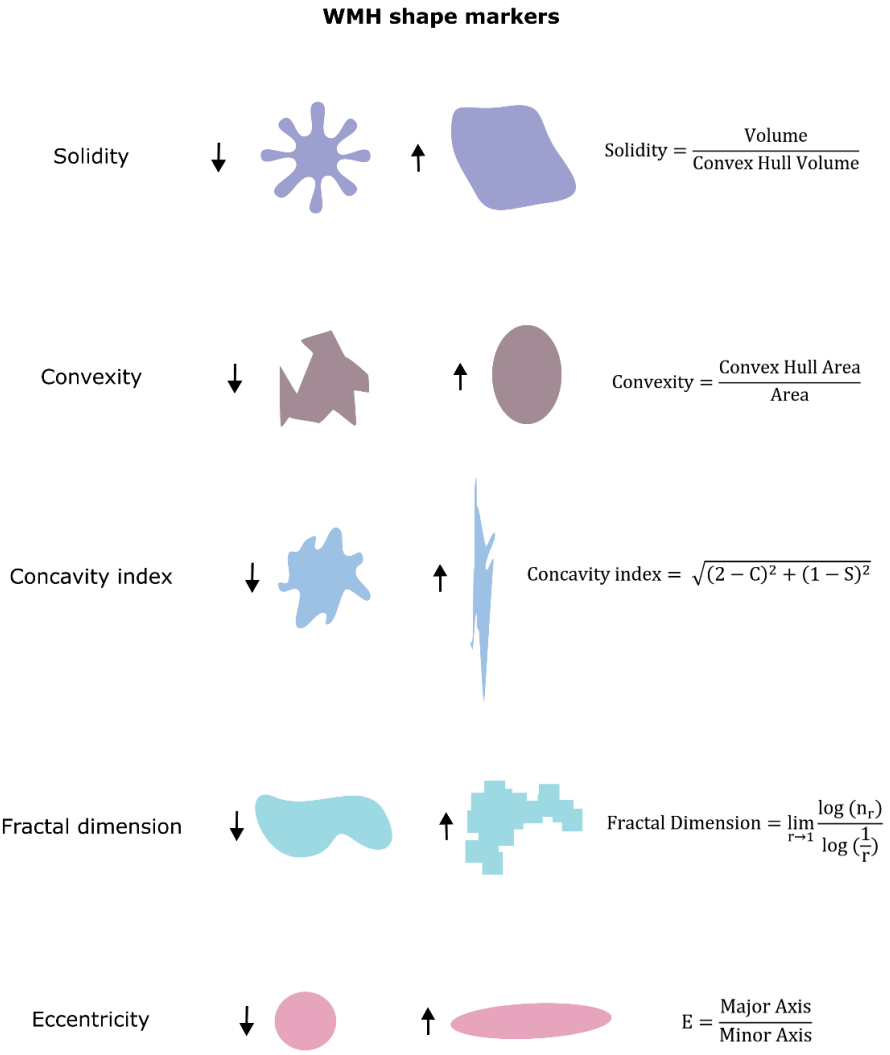

Figure 1.1. Illustration of shapes and different shape markers. Solidity, convexity, concavity index, and fractal dimension are calculated for periventricular/confluent WMH. Eccentricity and fractal dimension are calculated for deep WMH. This Figure is modified from figure 7.3 of **Chapter 7**.

Different WMH types (periventricular/confluent and deep) and also different WMH shape patterns seem to be associated with different underlying pathological changes. A more irregular shape of WMH go hand-in-hand with more severe parenchymal changes.[21–23] Furthermore, a previous study has shown that a more irregular WMH shape was associated with increased stroke risk and increased mortality in patients with manifest arterial disease.[24] I hypothesize that different underlying SVD pathologies result in a different WMH shape that can be quantified by MRI-based WMH shape markers. These shape markers may provide a more detailed characterization of WMH than volume alone.

1.4 AGES-REYKJAVIK STUDY

Large longitudinal population-based studies focused on ageing are rare since they are expensive and labor-intensive to carry out. This study type is, however, extremely valuable as it allows investigations with high statistical power. At the same time, they provide high external validity, since the participants of the study come from the general population with minimal inclusion bias.

A substantial part of this thesis is focused on data from the Age-Gene/Environment Susceptibility (AGES)-Reykjavik study, a large population-based study.[25] The AGES–Reykjavik study originates from the Reykjavik Study, a cohort established in 1967 to prospectively study cardiovascular disease in the general population of Iceland. Included participants were born between 1907 and 1935 and were living in Reykjavik in 1967. For the AGES-Reykjavik study, participants that were still alive were randomly selected for a follow-up between 2002 and 2006 when they underwent amongst other measures, a baseline brain MRI scan and cognitive assessment.[26] Another visit took place between 2007 and 2011, where the same brain MRI protocol and the same cognitive assessments were repeated.[27] Furthermore, the participants were followed for dementia outcome up to 13.4 years after the first MRI scan session through vital statistics and hospital records, and by the nursing home and home-based resident assessment instrument.[28] The AGES-Reykjavik study is an extensive multidisciplinary study and includes besides neuroimaging and neurocognitive data also genetic, cardiovascular and musculoskeletal data.[25] In the related chapters of this thesis, the focus will be on neuroimaging and neurocognitive data obtained as part of the AGES study.

1.5 AIM AND OUTLINE OF THIS THESIS

The overarching aim of this thesis is to exploit the shape of WMHs to better characterize WMH and thereby to improve the clinical interpretation of WMHs and to investigate whether it could predict clinical outcome. This thesis is mostly based on non-demented and community-dwelling older individuals. Moreover, a study set up focusing on a memory-clinic population will be discussed to get more pathology-focused insights into the formation of WMH.

In **Chapter 2**, the association of different cardiovascular risk factors with WMH shape was investigated in older adults as included in the Biomarker Development for Postoperative Cognitive Impairment in the Elderly (BIOCOG) study. The study included non-demented older adults scheduled for major elective surgery. Next, in **Chapter 3**, it was examined whether WMH shape is related to long-term progression of cerebrovascular disease in the AGES Reykjavik dataset. Besides WMH, different types of infarcts, microbleeds and enlarged perivascular spaces and their relationship with WMH shape were evaluated in this chapter. In **Chapter 4**, the focus was on investigating the association between baseline WMH shape and cognitive decline measured in three different domains (memory, executive function, and processing speed) over 5.2 years in the AGES Reykjavik dataset. In **Chapter 5**, the association of baseline WMH shape and long-term dementia risk after up to 13.4 years was assessed in the AGES Reykjavik study. In **Chapter 6**, brain MRI phenotypes were obtained using a hierarchical clustering method in the AGES Reykjavik dataset. In a second step, it was investigated whether these phenotypes are related to long-term risk (10 years) for dementia. In **Chapter 7**, a novel prospective cross-sectional study is presented applying WMH shape markers and other cutting-edge MRI techniques to further understand processes involved in SVD. This WHIte MAtter hyperintensity Shape and glymphatics (WHIMAS) study is focused on brain MRI determinants of cognitive impairment in geriatric clinic outpatients. Lastly, in **Chapter 8**, the main findings of this thesis and future directions of research are discussed.

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