General Introduction and outline

GENERAL INTRODUCTION

Worldwide, populations are aging. As a result, this will lead to an increase in prevalence of common age-related brain diseases such as cognitive decline, dementia and neurovascular diseases. These diseases pose a high burden on our society, both in terms of suffering as well as financially. From a perspective of disease prevention, the search for potentially modifiable etiologic factors and a better understanding of the pathophysiological pathways of age-related brain diseases is of major importance. One approach in this is to study brain disease in its earliest stage, before clinical symptoms arise. Subclinical brain changes are thought to occur years, if not decades, prior to onset of clinical symptoms of many age-related diseases[1], and with advanced, non-invasive imaging methods we are able to study these subclinical brain changes directly. In the past, research has mainly focused on cerebral grey matter in age-related diseases. Nowadays, also an important role of cerebral white matter in age-related diseases has been established. White matter constructs approximately 50% of the brain volume and consumes 43.8% of brain's total energy.[2] White matter is important for the connection of, and the communication between different cortical regions and consists of different white matter tracts, which play a different role in different brain functions. Macrostructural white matter damage such as white matter atrophy and white matter hyperintensity load, is visible on a conventional MRI. However these macrostructural changes constitute only the tip of the iceberg of the white matter pathology that have occurred.[3] To improve understanding of the pathophysiology and pathways of age-related brain diseases it is important to identify white matter pathology in an early and preclinical phase. More recently, microstructural white matter changes, not visible for the naked eye has therefore gained interest and is thought of as an earlier and potentially more sensitive marker of white matter damage.[3]

Diffusion tensor imaging (DTI) is a non-invasive magnetic resonance imaging suitable to quantitatively assessing white matter microstructural changes.[4] DTI is sensitive to the random movement of water molecules, which is dependent on the underlying tissue properties or microstructure. DTI can not only be used to characterize the underlying white matter microstructure, but also to reveal the anatomical paths of white matter tracts by connecting voxels with analogous directional diffusion-profiles, the so called tractography.[5]

Imaging data of white matter microstructural changes from the general population might help to disambiguate between normal and abnormal, help to understand underlying mechanisms of pathology and may help to identify persons at risk for a certain disease. However, population data on determinants of white matter microstructural changes globally but in particular in specific white matter tracts in the middle-aged and elderly are scarce.

AIM OF THIS THESIS

The objectives of this thesis were two-fold: Firstly, to study determinants of white matter microstructural changes. The brain is not an organ on itself but is connected with all other organs in our body and therefore we are in particular interested in the systemic influences on the brain of different organs. Secondly, to investigate the link between white matter microstructural and age-related brain diseases. In both aims, I focused both on the white matter microstructural changes across the whole brain, but also across different white matter tracts. My research was embedded within the Rotterdam Study, which is a population-based cohort study since 1990, investigating causes and consequences of diseases in the elderly.[6] From 2005 onwards, MRI scanning including DTI was added to the core study protocol.[7] The entire Rotterdam Study population undergoes regular cognitive assessments and is continuously monitored for major events, including dementia and vascular brain disease.

OUTLINE OF THIS THESIS

Chapter 2 discusses determinants of white matter microstructural damage. In **chapter 2.1** I describe the change in DTI-measures in aging. In **chapter 2.2 and 2.3** I focus on the association between kidney function and white matter microstructural integrity and retinal microvasculature and white matter microstructural changes respectively. **Chapter 2.4** is dedicated to the relation between lung function and white matter microstructure. In **chapter 2.5** I examined the association between thyroid function and white matter microstructural changes.

In **chapter 3** I present the association of global white matter microstructural changes but also in specific tracts with different age-related brain diseases. In **chapter 3.1** I focus on a transitional stage between normal aging and dementia, namely mild cognitive impairment and studied the determinants, MRI markers and prognosis of mild cognitive impairment. **Chapter 3.2** describes the link between tract-specific white matter microstructural integrity and cognitive functioning. In **chapter 3.3** I examined the relation between white matter microstructural integrity and risk of dementia in a longitudinal study. **Chapter 3.4** describes the association of white matter tract microstructural integrity and hearing impairment in the elderly. **Chapter 3.5** addresses the relation between white matter microstructural integrity and risk of mortality. **Chapter 3.6** focuses on the genetic variation underlying cognition and the relation with clinical outcomes and imaging markers. In **chapter 3.7** I applied a previously proposed prediction tool, namely the Disease State Index, to evaluate the prediction of cognitive decline using several features including DTI-measures.

Finally, in **chapter 4** the main findings of this thesis are summarized. Additionally, I discuss in more detail possible underlying pathways and methodological considerations of the performed studies and of diffusion tensor imaging in general. Furthermore, I will consider implications of the findings with respect to clinical practice, after which I will discuss future perspectives.

CHAPTER REFERENCES

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