Neurovascular imaging markers of brain aging

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General Introduction

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INTRODUCTION

Most countries in the world are experiencing growth in the number and proportion of older persons in their population. With the world facing an aging demographic, strategies to preserve health in the elderly and to prevent age-related diseases are a priority for governments worldwide.[1] Among age-related diseases, those affecting the brain are of particular importance since they impose a high psychological, social and financial burden to societies. The term "brain aging" refers to the neuroanatomical and neurophysiological changes that occur with increasing age and eventually impair cognitive, motor and social abilities.[2, 3] Increasing age is associated with structural and functional changes in the brain resulting in varying degrees of neuropsychological decline, comprising cognitive deterioration.[4] Conditions affecting the brain vasculature are a common denominator for age-related brain changes. The resulting vascular changes impair the physiological response of increase in cerebral blood flow triggered by neural activation, which is a critical mechanism that matches oxygen and nutrient delivery with the increased demands in active brain regions.[5, 6] Apart from these age-related changes, increasing age is also associated with the occurrence of diseases that have a deleterious effect on the brain (i.e. hypertension and diabetes) and specific neurodegenerative disorders directly affecting brain tissue. Consequently, determining what changes are based on the aging process ('normal aging') and which are due to concurrent diseases directly or indirectly affecting the brain ('pathological aging') is challenging at least.[7]

The extent of structural and functional changes in the aging brain as well as age-related cognitive changes vary extensively between individuals.[8] These changes seem to have a long subclinical period before they become symptomatic. Early detection of subclinical disease is important to increase our understanding of the underlying processes and to be able to install treatment before irreversible changes have occurred.[9] Population-based studies are of great value to study disease in the asymptomatic phase. As opposed to hospital-based referral samples, population-based epidemiological studies examine community-dwelling or random samples from the general population. Participants are not selected based on a given disease, but rather to represent the general population of the areas sampled, so that observations from such a sample are generalizable to the underlying source population.[10] In this type of study, extensive phenotyping is typically done that offers the assessment of multiple potential disease determinants at baseline.[9] Some population-based studies are longitudinal studies that involve repeated observations of the same participants over time. This type of study is particularly useful for evaluating the relationship between risk factors and the development of disease since individuals may be free of the disease of interest in the beginning of the study but might develop it over the course of the study.[11] However, the identification of the intermedi-

ate processes or the exact changes that occur in the tissue at risk can be difficult and remains a challenge.

One way of capturing the trajectories of tissue changes is to use radiologic imaging. Imaging can be used to demonstrate changes that occur in the human body that may reflect early disease, intermediate factors or risk indicators of disease. The neuroimaging technique of choice to study the brain in epidemiological studies is Magnetic Resonance Imaging (MRI).[7] Using MRI to study brain aging in population-based studies gives us the ability to monitor structural and functional change over time and to express changes in a quantitative way, yielding more power to detect small changes.[9, 12] Furthermore, the absence of ionizing radiation is an additional feature of MRI that makes it an attractive method to apply for population-based studies.

Large population based longitudinal studies on aging using radiological imaging are scarce. One of the few studies of this type is the Age, Gene/Environment Susceptibility–Reykjavik Study (The AGES–Reykjavik Study). The AGES–Reykjavik Study was designed to examine risk factors, including genetic susceptibility and gene/environment interaction, in relation to disease and disability in old age. The study is multidisciplinary, providing detailed phenotypes related to the cardiovascular, neurocognitive, and musculoskeletal systems, and to body composition and metabolic regulation. Relevant quantitative traits, subclinical indicators of disease, and medical diagnoses are identified by using biomarkers including radiological imaging.[13]

The general aim of this thesis was to study the frequency, causes and consequences of pathologic brain aging specifically focusing on sub-clinical and clinical MRI manifestations of vascular (small vessel disease) and neurodegenerative (brain atrophy) disease. A second aim was to improve the accuracy of the tools to quantify brain tissue so to better reflect the imaging characteristics of older people. All data presented in this thesis are from the AGES-Reykjavik Study including 5764 elderly men and women. The data is based on cross-sectional and longitudinal assessments of the brain with MRI measures.

OUTLINE OF THIS THESIS

The aim of **chapter two** was to create a multi-purpose brain template and atlases generated from MR images of elderly individuals in a common non-linear space. Here the problem of using brain template and atlases based on MR images of young individuals in aging research is addressed. The objective of **chapter three** is to evaluate the feasibility of using pseudo-continuous arterial spin labeling (pCASL) to measure brain perfusion in

very old individuals with a commercial 1.5-Tesla MRI system. In the **fourth chapter** of the thesis the brain tissue volumes in the AGES-Reykjavik Study cohort are presented. In this study both cross-sectional and longitudinal estimates of brain atrophy and white matter lesion (WML) load were quantified based on automatic tissue segmentation of brain tissues on MR images. In **chapter five** it is investigated whether baseline CMBs by number and location are associated with the rate of cognitive decline and incident dementia over a 5-year period. **Chapters six and seven** are dedicated to brain infarcts detected on MR images in the general population. The objectives are to investigate the prevalence and incidence of brain infarcts and cerebrovascular risk factors of incident infarcts in cortical, subcortical, cerebellar, and overall brain regions. Further, to investigate cognitive change and the risk of incident overall dementia in relation to prevalent and incident infarcts in those brain regions. In **chapter eight** the incidence and location of cerebral microbleeds (CMBs) is examined, and whether a spectrum of modifiable lifestyle and lipid factors predict new CMBs in relation to their location. **Chapter nine** aims to measure and compare total cerebral blood flow and brain perfusion estimates with MRI in individuals with and without atrial fibrillation. **Chapter ten** summarizes key findings of this thesis.

1. World population ageing, department of economic and social affairs population division, united nations. 2018
2. Howieson DB. Cognitive skills and the aging brain: What to expect. *Cerebrum: the Dana Forum on Brain Science*. 2015;2015:cer-14-15
3. Janacsek K, Fiser J, Nemeth D. The best time to acquire new skills: Age-related differences in implicit sequence learning across human life span. *Developmental Science*. 2012;15:496-505
4. Mak E, Su L, Williams GB, Watson R, Firbank M, Blamire AM, O'Brien JT. Longitudinal assessment of global and regional atrophy rates in alzheimer's disease and dementia with lewy bodies. *NeuroImage : Clinical*. 2015;7:456-462
5. Boltze J, Kleinschnitz C, Reymann KG, Reiser G, Wagner D-C, Kranz A, Michalski D. Neurovascular pathophysiology in cerebral ischemia, dementia and the ageing brain – current trends in basic, translational and clinical research. *Experimental & Translational Stroke Medicine*. 2012;4:14
6. Tarantini S, Tran CHT, Gordon GR, Ungvari Z, Csiszar A. Impaired neurovascular coupling in aging and alzheimer's disease: Contribution of astrocyte dysfunction and endothelial impairment to cognitive decline. *Experimental Gerontology*. 2017;94:52-58
7. Lockhart SN, DeCarli C. Structural imaging measures of brain aging. *Neuropsychology review*. 2014;24:271-289
8. Bartrés-Faz D, Arenaza-Urquijo EM. Structural and functional imaging correlates of cognitive and brain reserve hypotheses in healthy and pathological aging. *Brain Topography*. 2011;24:340
9. Vernooij MW, de Groot M, Bos D. Chapter 5 - population imaging in neuroepidemiology. In: Aminoff MJ, Boller F, Swaab DF, eds. *Handbook of clinical neurology*. Elsevier; 2016:69-90.
10. Lieb W, Vasan RS. Scientific contributions of population-based studies to cardiovascular epidemiology in the gwas era. *Front Cardiovasc Med*. 2018;5:57-57
11. Caruana EJ, Roman M, Hernández-Sánchez J, Solli P. Longitudinal studies. *J Thorac Dis*. 2015;7:E537-E540
12. Wang X, Huang W, Su L, Xing Y, Jessen F, Sun Y, Shu N, Han Y. Neuroimaging advances regarding subjective cognitive decline in preclinical alzheimer's disease. *Mol Neurodegener*. 2020;15:55-55
13. Harris TB, Launer LJ, Eiriksdottir G, Kjartansson O, Jonsson PV, Sigurdsson G, Thorgeirsson G, Aspelund T, Garcia ME, Cotch MF, et al. Age, gene/environment susceptibility-reykjavik study: Multidisciplinary applied phenomics. *Am J Epidemiol*. 2007;165:1076-1087