Neuroimaging in subjective cognitive decline

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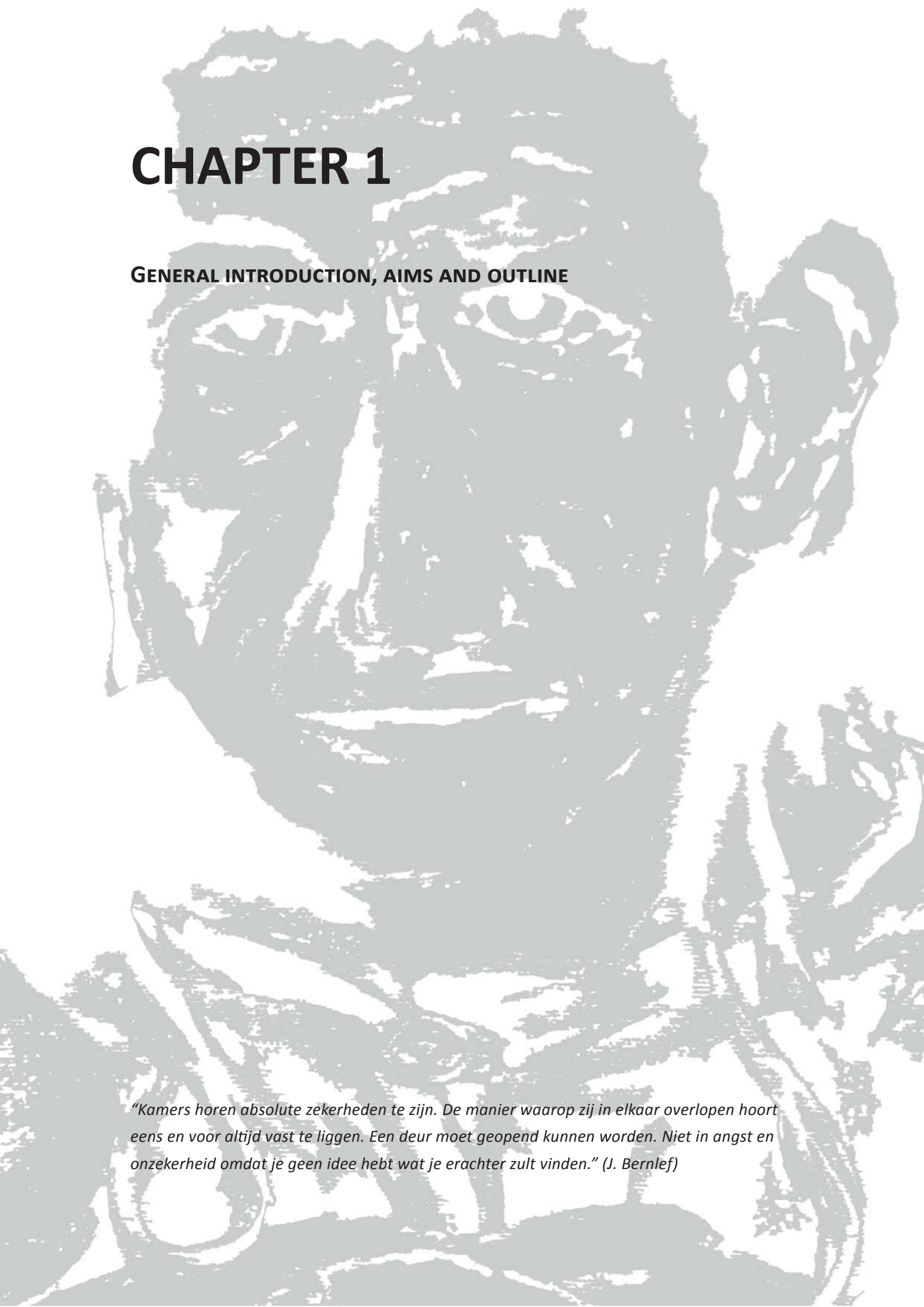
CHAPTER 1

General introduction, aims and outline



"Kamers horen absolute zekerheden te zijn. De manier waarop zij in elkaar overlopen hoort eens en voor altijd vast te liggen. Een deur moet geopend kunnen worden. Niet in angst en onzekerheid omdat je geen idee hebt wat je erachter zult vinden." (J. Bernlef)

INTRODUCTION

Dementia is the clinical manifestation of a neurodegenerative disease, which is preceded by 10-20 years of slowly progressive structural and functional brain changes.[1,2] Each of the different types of dementia is characterized by a gradual decline of cognitive function and impairment in daily functioning.

In 2015, there were an estimated 46 million people with dementia worldwide, which is almost three times the entire Dutch population.[3] The worldwide prevalence is estimated to increase to 131.5 million by 2050, with new cases of dementia every 3 seconds.[3] Dementia also has a devastating economic impact with a worldwide cost of $(US) 818 billion in 2015.[3] These numbers represent an enormous personal and public burden. In the Netherlands, in 2011, dementia is the second most expensive illness, encompassing approximately 5.3% of the total healthcare costs. These costs are for a large part attributable to the costs of long-term care, for example in nursing homes (Rijksinstituut voor Volksgezondheid www.kostenvanziekten.nl).

In the Netherlands approximately 260.000 individuals are currently diagnosed with dementia. Alzheimer's disease (AD) is the most common cause of dementia, accounting for 60-80% of individuals with dementia.[4,5] AD pathology is characterized by brain atrophy, cortical intraneuronal Tau tangles and extracellular amyloid plaques.[6] According to the amyloid hypothesis, pathological alterations of tau are considered to be downstream effects of Aβ pathology.[7,8] The last few years clinical trials have focused on anti-amyloid approaches (active and passive immunization, γ- and β-secretase inhibitors) and anti-aggregation drugs. So far, trials of anti-amyloid approaches in mild- to moderate AD dementia have been unsuccessful,[9–11] and possible reasons for these results include treating too late (at the stage of dementia) and poor screening or diagnostic regimens (absence of amyloid biomarkers).[2] When individuals reach the stage of AD dementia brain damage likely becomes irreversible, for this reason treatment may be effective early in the disease stage.

There are a number of established risk factors associated with AD. Age is major risk factor for AD dementia, with a prevalence ranging from 1.6% in 60-64 years old to 34.4% in individuals who are older than 90 in Western Europe.[3] Among common genetic factors, the apolipoprotein E ϵ4 (APOE ϵ4) allele is a risk factor for sporadic early- and late-onset AD.[12,13] In addition, self-perceived cognitive decline is a risk factor for AD, which has been associated with a three- to six-fold increased risk of progression to dementia in cognitively normal individuals. Lifestyle related factors, including depression, physical and mental inactivity, smoking, low educational attainment, diabetes, obesity and diet are likely to play a role in the etiopathogenesis of AD, and these modifiable factors have the potential for primary prevention.[14]

Observational and pathological studies have provided evidence for the multicausality of dementia, showing that much of the variation in cognitive decline remains unexplained,[15,16] and the mechanisms that link amyloid-β to neurodegeneration are still poorly understood.[17,18] In sum, there are still many current unresolved intertwined scientific and healthcare issues, which can be summarized as follows;

1) The absence of disease-modifying drugs and/or preventive strategies
2) Incomplete understanding of etiopathogenesis, and predictive value of neuroimaging biomarkers in preclinical AD stages.

In order to get a better understanding of AD etiopathogenesis, it is of utmost importance to identify and to understand disease-related changes as early as possible, preferably in preclinical stages. Preclinical AD is characterized by AD pathology, but normal cognition.[19,20] It remains a challenge to find biomarkers associated with increased risk to clinical progression to AD in cognitively normal individuals. These challenges form the background of research presented in this thesis.

Research in this thesis focused on individuals with subjective cognitive decline (SCD). The following paragraphs will introduce the conceptual framework of SCD and neuroimaging biomarkers which can be used to study AD pathophysiology.

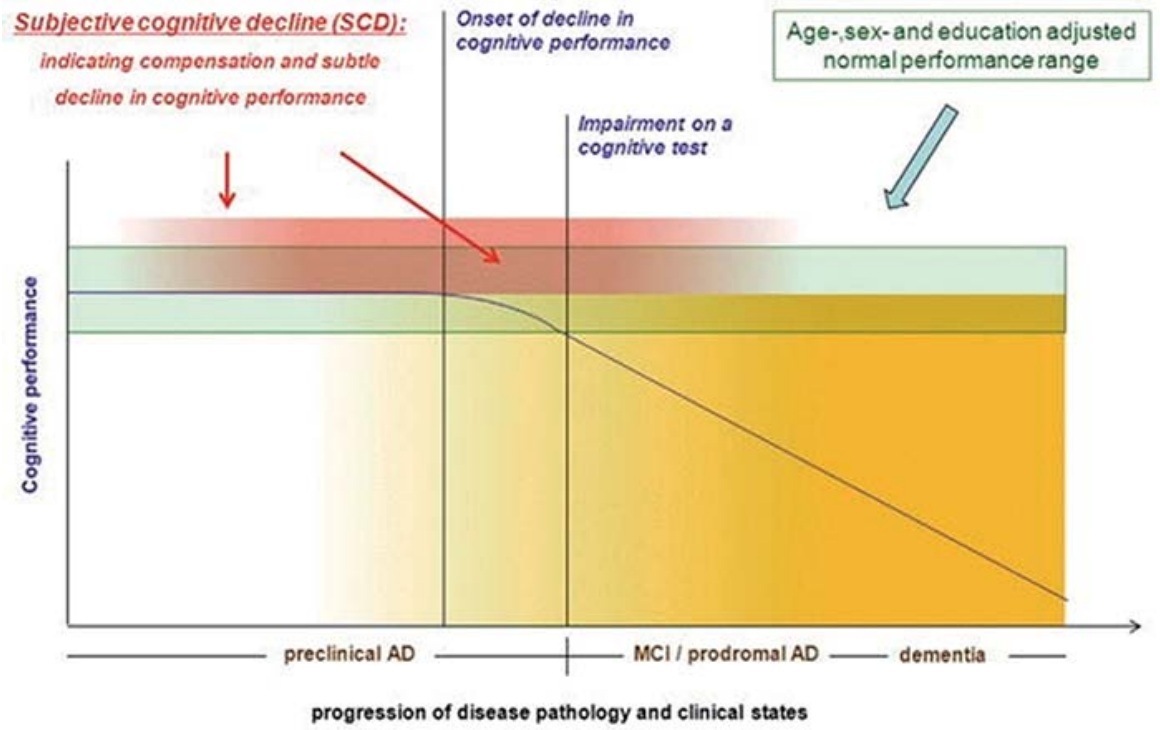


Figure 1. Conceptual framework for research on subjective cognitive decline.[24]

Subjective cognitive decline. Self-perceived cognitive decline could be one of the earliest signs of AD, and portends risk of progression to dementia.[21–23] In an effort to explore these

potentially early symptoms, a framework has been proposed that provides a common concept and terminology for studying subjective experience of cognitive decline.[24] Research presented in this thesis is in large part based on individuals with SCD who have visited our memory clinic and participate in the Subjective Cognitive ImpairmENt Cohort (SCIENCe). By definition individuals with SCD experience cognitive complaints, but results of neuropsychological assessment are within normal range. Cross-sectional memory clinic studies have shown that compared to individuals without SCD, individuals with SCD have decreased gray matter volumes,[25,26] cortical thinning in medial temporal regions,[27] altered default-mode connectivity,[28–30] and hypometabolism in the precuneus.[31] So far, studies investigating amyloid and SCD have provided inconsistent results,[32] which may depend on factors such as recruitment setting, age of onset of SCD and psychological features. In addition, SCD can be caused by a myriad of factors, one of which is preclinical AD. A vital question remains which individuals with SCD are at increased risk of cognitive decline and dementia. More specifically, which neuroimaging biomarkers could be used to predict progression to AD dementia.

Alzheimer's disease neuroimaging biomarkers

The following paragraphs will outline well-established and novel neuroimaging biomarkers which can be used to study AD pathophysiology, and postulate how each biomarker could contribute to unresolved issues.

Amyloid pathology. It has been shown that amyloid plaques and neurofibrillary tangles start to aggregate years before the onset of AD dementia, with subsequent abnormalities on structural and functional magnetic resonance imaging (MRI), cognitive impairment and clinical symptoms.[1,33] Amyloid imaging agents and cerebrospinal fluid (CSF) can both be used to verify amyloid pathology. There are several amyloid imaging agents available to visualize Aβ, some widely used radiotracers are: [^{11}C]PiB, [^{18}F]florbetapir, [^{18}F]florbetaben, [^{18}F]NAV4694 and [^{18}F]flutemetamol. In the current thesis [^{18}F]florbetapir was used to measure amyloid pathology. Accurate quantification of Aβ is important for patient management, prognostic value, monitoring progression of disease and response to disease-modifying therapies.[34–36] The first study using [^{18}F]florbetapir in humans demonstrated increased uptake in the cortex, particularly in precuneus and fronto-temporal regions, of patients with AD compared with healthy controls, presumably reflecting elevated accumulation of amyloid.[37]

To date, however, most studies have used the standardized uptake value ratio (SUVr) as semi-quantitative measure of [^{18}F]florbetapir uptake. SUVr may be too biased to identify near normal levels of amyloid deposition. More importantly, tracer kinetics and distribution are likely to be affected by underlying pathophysiological mechanisms, such as decreased perfusion known to occur in AD.[34] It is clear that a validated tracer kinetic model is important, not only for identification of early subtle and longitudinal amyloid

accumulation, but also for assessing subtle cognitive changes and cognitive complaints related to AD in individuals with SCD.

Atrophy, particularly of the medial temporal lobe, is the MRI hallmark of dementia due to AD.[38,39] It has been suggested that a specific pattern of regional atrophy in the temporal, parietal, and frontal gyri, which has been coined the cortical AD-signature, shows changes very early in the disease process.[40,41] Moreover, it has been found that cortical thinning of the AD-signature region is predictive for incident dementia due to AD as early as a decade before diagnosis.[42] It is currently unknown whether thinner cortex in cognitively intact patients with self-perceived memory complaints is associated with increased risk of MCI or dementia over time. In addition, if cortical thickness in individuals with SCD is associated with cognitive functioning over time.

Grey matter brain networks. Evidence is accumulating that structural brain changes leading to cognitive decline and dementia are not restricted to specific regions such as the medial temporal lobe, but rather include widespread changes in structure, function and organization of the brain.[43,44] Structural organization of the brain can be investigated using grey matter networks by means of graph theory.[45] Grey matter networks offer a possibility to precisely study brain organization, and networks may explain more variance related to cognitive decline compared to volumetric measurements.[45] Grey matter network alterations may already manifest at early, preclinical stages of the disease.[46] It is still unclear, however, whether grey matter network alterations in cognitively normal individuals are associated with cognitive decline, and if this affects specific cognitive domains.

Functional brain connectivity. Functional brain changes may precede structural abnormalities and may therefore serve as a potential early AD biomarker.[47,48] Resting-state functional (rsf)MRI connectivity is expressed as increasing temporal covariance of metabolically active brain regions. Altered connectivity is found in AD vulnerable brain regions (e.g. posterior default-mode network (pDMN), largely comprising the posterior cingulate cortex) in cognitively normal individuals with AD risk factors, which could therefore reflect an early disease mechanism related to future cognitive decline.[29,49–53] So far, rsfMRI studies on cognitively intact individuals have found both increased,[29,47,50,51,54] decreased[55,56] and mixed[49] pDMN connectivity in relation to the presence of AD risk factors. It remains unclear, however, whether SCD is related to altered functional connectivity, and whether altered connectivity is predictive of early cognitive changes.

Rationale and aims

So far, most neuroimaging studies investigating SCD have used a cross-sectional design which restricts making causal inferences. In this thesis, well-established and novel neuroimaging biomarkers were investigated in relation to cognitive changes in cross-sectional and longitudinal studies.

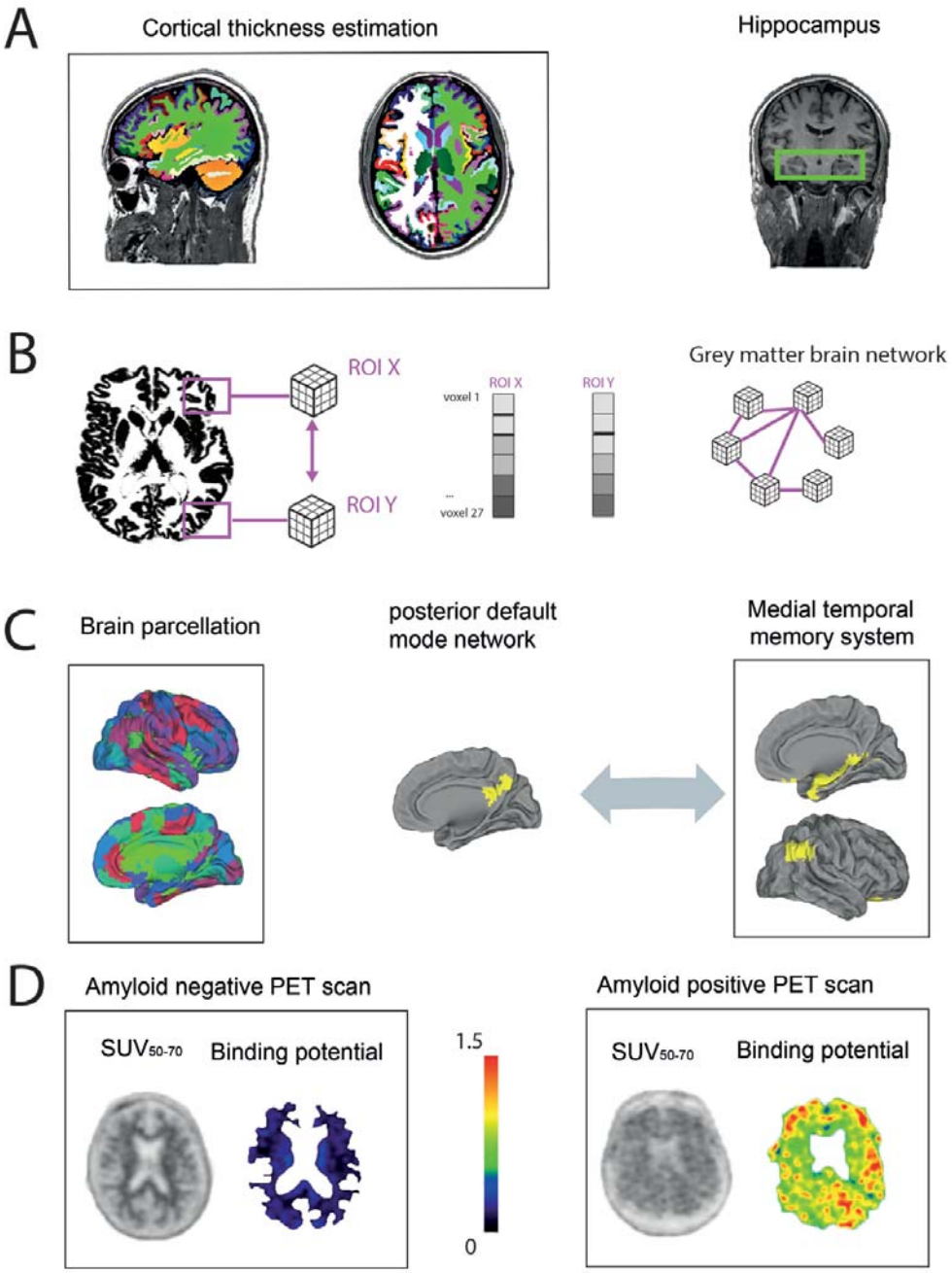


Figure 2. Examples of neuroimaging techniques which were used for this thesis. Structural (volumetric) neuroimaging measures consisted of cortical thickness and the hippocampus (A [right] in green). Cortical thickness of the AD-signature was estimated according to the Desikan-Killiany atlas (A[left] in color). Grey matter network were based on ROIs consisting of 3x3x3 voxels. Whole-brain Pearson (r) correlations were calculated between regions of interest (ROIs) based on pixel intensities, with subsequent statistical thresholding (permutations) in order to create brain networks (B). Resting-state functional MRI, based on temporal covariance of blood-oxygenated level dependent level response, was extracted in AD vulnerable regions located in the default mode network (C). Panel D depicts examples of [^{18}F]florbetapir amyloid negative (left) and positive (right) scans with SUV_{50-70} (inverted color grey scale according to the standardized visual reading of [^{18}F]florbetapir) and (quantitative) binding potential (RPM in rainbow color scale) images.

More specifically, we aimed to:

1) Investigate the predictive value of structural MRI for cognitive decline and clinical progression in individuals with SCD.
2) Investigate associations between amyloid and resting-state fMRI and patterns of cognitive complaints and cognition.

Outline of the thesis

Part 1. In the first part of this thesis we provide an overview of the Subjective Cognitive ImpairmENt Cohort (SCIENCe), design, initial cross-sectional results, and evaluation of *SCD-plus* criteria (**chapter 2)**.

Part 2 focuses on the predictive value of baseline structural MRI markers in relation to longitudinal cognitive changes and clinical progression. In **chapter 3** we evaluated whether thinner cortex of the AD-signature region is related to incident clinical progression in individuals with SCD. Subsequently, in **chapter 4,** we aimed to investigate whether thinner regional cortical thickness is associated with rate of decline over time in the cognitive domains of memory, attention, language and executive functioning. Evidence is accumulating that brain changes leading to cognitive decline and dementia are not restricted to specific regions such as the medial temporal lobe, but rather include widespread changes in structure, function and organization of the brain. In **chapter 5**, we therefore investigated whether grey matter network alterations can explain decline in specific cognitive functions. In addition, in **chapter 6,** we investigated the effects of SCD on brain connectivity and cognition in individuals with a family history of AD.

In **part 3** we investigated associations between amyloid, cognition and cognitive complaints in individuals with and without SCD. Firstly, in order to more accurately quantify amyloid-β deposition for subsequent research projects in this thesis, we provided an optimal kinetic model for [^{18}F]florbetapir binding in **chapter 7.** In **chapter 8**, myloid-β accumulation was investigated in relation to spontaneous speech derived linguistic parameters. Finally, in **chapter 9** we investigated whether amyloid-β load is associated with cognitive complaints in individuals with subjective cognitive decline.

This thesis ends with a general discussion and conclusions in **chapter 10**.

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