CHAPTER 1

Introduction
**Purpose and motivation**

To improve patient care, and to target the socio-economical burden of dementia that is to be expected due to an increase in mean age of the population, several important goals in present clinical neuroimaging studies can be identified. These goals become even more relevant with the prospect of possible future development of disease-modifying therapies. The first of these goals is to develop and evaluate the applicability of clinical tools that enable an early diagnosis. Secondly, prediction of disease progression and improvement of prognosis are necessary to optimize patient management. Finally, especially with the prospect of future therapies that target disease-specific mechanisms, it becomes important to predict the presence of underlying neuropathological mechanisms that lead to dementia, to be able to select patients that might benefit from these treatments. This thesis explores the clinical value of hippocampal atrophy, measured on MRI, in the cognitive continuum of normal aging, mild cognitive impairment (MCI) and Alzheimer’s disease (AD). Expanding insights in the clinical value of this MRI marker might lead to earlier recognition and increased specificity in the diagnosis of AD, and thus increase the effectiveness of a patient’s management.

**General introduction**

Classically, the role of neuroimaging in the clinical work-up of dementia has been to exclude other causes of dementia, such as possible ‘treatable’ causes (tumours, hemorrhage) and vascular lesions. This role has shifted towards the recognition of findings on MRI that increase the specificity of a diagnosis of AD. Neuroimaging allows in vivo measurement of the brain tissue loss that occurs in AD. There are different approaches to measure this volume loss. Although MRI has been the modality of choice because of its high resolution and possibility to obtain three-dimensional volume scans, advances in computed tomography (CT) scanners have increased the resolution of this modality, potentially making CT a suitable alternative for MRI. Furthermore, volume measurements using MRI can be divided into cross-sectional (using a
scan from one time point per patient) and longitudinal measures (comparing scans from different time points of one patient), and can focus on different brain structures that are important in AD.

Figure 1. Coronal T1-weighted images. (a) control, no atrophy (b) patient with AD, showing widening of the gyri and ventricles, with pronounced atrophy of the hippocampus on both sides (arrows)

There are different cross-sectional methods to estimate the volume of brain structures on MRI, ranging from simple (but clinically very efficient) visual rating scales, to manual segmentation and semi-automated segmentation techniques. An advantage of MRI over many other biomarkers in AD, is its ability to monitor changes over time within a patient. Longitudinal studies use one or more scans from different time points to calculate change in volume over time within a patient. Methods to calculate longitudinal volume changes include the subtraction of volumes, derived by manual segmentation of brain structures at different time points, as well as more sophisticated, automated registration methods.
In AD, two important neuroimaging markers are whole brain atrophy and regional atrophy of the hippocampus. Hippocampal atrophy on MRI correlates with pathologically assessed volumes and number of neurons,\textsuperscript{12,13} and with neurofibrillary changes in the medial temporal lobes.\textsuperscript{14} Furthermore, hippocampal volume loss, measured on MRI, is associated with cognitive decline\textsuperscript{15,16} and with a clinical diagnosis of AD, and predicts progression from mild cognitive impairment (MCI) to AD.\textsuperscript{17,18} Although studied less extensively, more or less the same results have been found for whole brain volume and especially whole brain volume change. Longitudinal studies showed that whole brain atrophy rates are higher in AD patients than in controls,\textsuperscript{18-20} and predict progression from MCI to AD.\textsuperscript{21,22} Whole brain atrophy rate also seems to correlate with pathological neuro-fibrillary changes.\textsuperscript{23} It is not clear whether one of the two markers, whole brain atrophy or regional hippocampal atrophy, is superior to the other, and how these two markers relate to each other.
MRI findings that often occur in older age in general and in dementia in particular, are findings related to cerebrovascular disease. These findings can be divided into large vessel disease (infarcts) and small vessel disease. MRI findings of the latter are white matter hyperintensities, lacunar infarcts and microbleeds. The presence of extensive vascular neuroimaging findings is a requirement in the clinical diagnostic criteria of VaD, and MRI therefore plays an important role in distinguishing AD from VaD. Nevertheless, neuropathological studies show that in the majority of subjects with dementia, both AD-related pathology and vascular pathological changes are found, and these studies even suggest that these two types of pathology might have a synergistic effect on clinical disease severity. These findings are supported by neuroimaging studies that show that vascular findings occur more often in patients with AD than in controls, and that presence of medial temporal lobe atrophy is often found in VaD. The clinical relevance of the presence of vascular neuroimaging findings in AD is not clear.

The hippocampus

The hippocampus is a brain structure, located at the infero-medial temporal lobe, and is part of the limbic system. It plays a crucial role in learning and memory, and is also involved in systems controlling emotional behaviour and motor control. The hippocampus has been identified to be a primary location of AD pathology, eventually leading to loss of neurons. This volume loss can be detected in vivo by MRI. Different methods exist to assess hippocampal atrophy. Visual rating scales have been developed that allow semi-quantitative assessment of atrophy according to predefined criteria. The scale we use in this thesis (range 0-4), is based on characteristics of the hippocampus and features of surrounding structures of the medial temporal lobe. Interrater agreement of this method is moderate to good. A second method consists of segmentation of the hippocampus on MRI. Although (semi) automated segmentation methods have been described, the gold standard still consists of manual delineation of a region of interest (ROI) around the hippocampus on coronal slices, and calculation of the volume by multiplying the total surface on these slices by slice thickness. Calculation of longitudinal change in volume within the hippocampus can be performed by comparing segmented hippocampal volumes. However, more sophisticated, semi-automated registration methods have been developed. After a registration algorithm matches a serial scan onto the reference scan, the registration matrix can be used to describe the difference in volume between these two scans. In this thesis, we use a regionally optimized non-linear registration method of serial scans onto corresponding baseline scans, which we quantify within manually constructed ROIs of the hippocampus on the baseline scan to measure hippocampal atrophy rate. Because the deformations applied by the registration algorithm are constrained by general laws of fluid dynamics, this registration method is called ‘fluid’ registration.
Aims and outline
The general objective of this thesis was to extend the insights in the clinical applicability of MRI markers in AD and its preceding clinical stages, with an emphasis on the measurement of hippocampal atrophy. We evaluate the use of different methods, comparing CT with MRI and comparing the measurement of regional hippocampal atrophy with the measurement of whole brain atrophy. Furthermore, we focus on the use of hippocampal atrophy as a marker of disease progression, and try to identify the prognostic value of MRI markers. Thirdly, we investigate the relevance of vascular MRI findings in dementia in relation to markers of atrophy.

Outline per chapter
The presence of dementia is associated with increased mortality, and within a dementia population, several clinical and demographic risk factors have been identified that are associated with an increased risk of mortality. However, the role of neuroimaging in predicting mortality is not clear. In chapter 2, we investigate the predictive value of MRI variables on mortality in patients that had visited our memory clinic. Baseline MRI findings of atrophy and vascular damage were assessed by visual rating scales and information about whether patients were still alive was attained.

In chapter 3, we use the screening data from a clinical trial to investigate the significance of vascular findings in AD by comparing demographic, clinical and neuropsychological characteristics of AD patients with and without these findings. In addition, we investigate associations between vascular MRI findings and MRI markers of atrophy with cognitive performance in AD.

Because of its higher resolution, MRI has been the neuroimaging modality of choice in dementia, over CT. However, advances in technology have improved the resolution of CT scanning. In chapter 4, we investigate whether high-reso-
olution CT can be used in the diagnostic process of dementia, by calculating the agreement of MRI and CT for visual rating scales of global and regional atrophy and small vessel disease.

In chapter 5, we compare the applicability of measurements of regional hippocampal volume and whole brain volume by comparing their ability to distinguish between subjective complaints, MCI and AD, and their ability to predict progression to AD within patients with subjective complaints and MCI. We compare cross-sectional and longitudinal measurement of the hippocampus and whole brain.

In chapter 6, we use the rate of hippocampal atrophy over time, calculated using a regional, non-linear registration algorithm, as a proxy for disease progression in a population of patients with AD, MCI and subjective complaints. We assessed which baseline data from neuropsychological examination, APOE genotyping, cerebrospinal fluid biomarkers and baseline MRI parameters were associated with subsequent hippocampal atrophy rates.

Chapter 7 comprises a pilot study in the feasibility of setting up a collaborative database with clinical, biochemical and neuroimaging data of AD patients in Europe. These data were gathered from patients with AD, MCI and subjective complaints, from seven European centres. Results from basic visual rating of the scans were compared with results from a large database in the United States as validation.

In chapter 8, the main findings are discussed in the light of recent literature and recommendations for future research are given.
Reference List


