General objective
The general objective of this thesis was to expand the insights in the clinical role of neuroimaging in dementia. In this thesis, we show that the clinical role of neuroimaging extends beyond diagnosis, and is important in prognosis as well. Although the main focus of the thesis is on hippocampal atrophy, we explore the clinical impact and interactions of MRI markers of atrophy and vascular damage, and compare regional measurement of hippocampal atrophy with measurement of whole brain atrophy. In the following chapter, the main findings of the thesis are summarized, followed by a discussion of the methodology and implications of these findings. Finally, recommendations for future research are given.

Summary of findings
Although there is considerable knowledge about the applicability of MRI markers in the diagnostic process of dementia, the value of these markers in prognosis is not clear. In chapter 2, we visually assessed MRI scans of patients that had visited our memory clinic between 1993 and 2006 and obtained information from general practitioners and clinical files about whether or not patients were alive. We found that vascular markers of small-vessel disease (white matter hyperintensities and especially microbleeds) predicted the risk of mortality. Where previous research shows that within a dementia population, markers of atrophy, such as medial temporal lobe atrophy and global cortical atrophy, are more strongly associated with cognitive impairment, we show that markers of small-vessel disease are clinically important because they predict mortality.

In chapter 3, we used the screening data from a large placebo controlled trial in patients with probable AD to assess the clinical significance of MRI findings that are ‘atypical’ for AD. These findings were defined as either the absence of medial temporal lobe atrophy, or the presence of extensive cerebro-vascular disease. We show that AD patients without atrophy of the medial temporal lobe perform better on almost all cognitive domains, whereas AD patients with
severe cerebro-vascular disease did not differ on any of the neuropsychological tests from AD patients without these findings. Moreover, we confirm that in AD patients, markers of atrophy are more strongly correlated with cognition than markers of small-vessel disease. Our data support the idea that AD-related pathology and vascular damage form a clinical continuum.

Chapter 4 consists of a study in which we compare the diagnostic use of 64-multi-detector row computed tomography with MRI. From 30 patients that visited our memory clinic, both a MRI and a CT scan were acquired. The scans were assessed using visual rating scales for medial temporal lobe atrophy, global cortical atrophy and white matter hyperintensities, and intra-observer agreement between MRI and CT was calculated. Results show that there was good to excellent agreement for all three scales. Although MRI probably remains superior to CT for research purposes, and has the advantage of other possible sequences that are useful in specific diagnostic questions, our results imply that for the basic diagnostic work-up of dementia, CT can be a suitable alternative to MRI.

Both hippocampal atrophy and whole brain atrophy correlate with clinical progression in AD. Nevertheless, it is not clear whether one of these markers is superior to the other, and how these two markers relate to each other. Furthermore, most studies use only cross-sectional or longitudinal measures. In chapter 5, we compare hippocampal atrophy and whole brain atrophy in their ability to distinguish between controls, MCI and AD, and their ability to predict the progression to AD within the controls and patients with MCI. For both hippocampus and whole brain, we compare the value of cross-sectional volume measurement and longitudinal volume change. We show that hippocampal measures are better able to distinguish MCI patients from controls, and whole brain measures are able to distinguish between MCI and AD. Moreover, hippocampal measures are stronger predictors of progression to AD within the non-demented patients at baseline than whole brain measures. For both hippocampal and whole brain measures, the longitudinal measurements are more sensitive than cross-sectional measurements. These findings imply that there are differences in the applicability of hippocampal atrophy and whole brain
atrophy as markers of disease progression. Hippocampal atrophy measures are more sensitive to changes occurring at early stages of the disease, and at later stages, there is an advantage in using measures of whole brain atrophy. Subsequently, in chapter 6 we investigated which baseline modalities predicted disease progression, represented by hippocampal atrophy rate. In patients with AD, MCI and controls, we evaluated associations of baseline neuropsychological data, CSF biomarkers, APOE genotype and baseline MRI measures with subsequent hippocampal atrophy rate. We found that baseline data from neuropsychology, CSF and MRI are independently associated with hippocampal atrophy rate. We conclude that predicting disease progression might best be accomplished by combining the information obtained from different modalities. Chapter 7 comprises a pilot study, in which we show the feasibility of constructing a collaborative European database of clinical and MRI data of patients with AD and its preceding clinical stages. Advances in automated MRI analyses enable the processing of large datasets, and a lot of recent research aims require large sample sizes. Efforts to construct an international cooperative dataset that is accessible for different research centres are an important response to these demands.

**Methodological considerations and implications**

**Improving diagnostic methods**

Hippocampal and whole brain atrophy are two important neuroimaging markers that monitor disease progression in dementia. It is well-established that both hippocampal atrophy and whole brain atrophy are associated with cognitive decline and clinical progression to dementia. Pathological studies show that changes in AD start in medial temporal regions, and only in later stages are found more widespread throughout the brain. We show that these progressive regional changes lead to differences in the optimal applicability of hippocampal atrophy and whole brain atrophy as markers of disease progression in AD and its preceding clinical stages. Our findings improve the methods to monitor progression, because they might influence the choice of
a neuroimaging marker, for example in clinical trials. In addition, we show that for both whole brain and hippocampus, longitudinal measurements are more sensitive markers of disease progression than cross-sectional ones. The only finding that contradicted this was that in patients with MCI, hippocampal baseline volume was a better predictor of progression than atrophy rate. We think that this reflects considerable hippocampal atrophy to have occurred in MCI, which has also been suggested by others.\textsuperscript{11,12} This implies that the advantage of longitudinal over cross-sectional measures is especially present in a situation in which not much atrophy has yet. However, longitudinal and cross-sectional measures could best be used in combination because they seem to give complementary information, shown by the additive predictive effect of hippocampal baseline volume and hippocampal atrophy rate.

Another advance in methodology is the availability of high-resolution CT. We showed that there is a good agreement in visual rating of medial temporal lobe atrophy, global cortical atrophy and white matter hyperintensities between MRI and multi-detector CT, making the latter a good alternative for MRI in the basic clinical work-up of dementia. Nevertheless, the availability of different sequences with specific contrasts remains an advantage of MRI, and will remain important for certain specific observations, such as the presence of microbleeds. Furthermore, MRI will remain the preferred method for research purposes because of its ability to obtain 3-dimensional datasets with high resolution and contrast between gray and white matter.

**Disease progression**

Currently, the diagnosis of AD is made using clinical criteria,\textsuperscript{13} based on the presence of dementia, with specific clinical characteristics. We know that neuropathological changes occur long before this clinical threshold has been reached.\textsuperscript{10,14} Advances in research into possible disease-modifying therapies lead to the imperative to identify AD before irreversible damage occurs.\textsuperscript{15} Since the introduction of the clinical diagnostic criteria, research has identified many different biomarkers that are related to AD. In chapter 6, we abandoned the clinical diagnosis of AD as an outcome, and instead used hippocampal atrophy
rate as a marker of disease progression in the cognitive continuum of AD. We show that different modalities give independent and additional information about disease progression, expressed by hippocampal atrophy rate. This implies that combining information from different modalities might be a good approach to pursue the objective of an earlier and more specific diagnosis.

In a previous study, using an overlapping sample, we showed that there is no association between CSF biomarkers and whole brain atrophy rate. Comparing these results with the findings in this thesis, where we show that CSF levels of p-Tau are independently associated with hippocampal atrophy rate, indicates another difference between regional hippocampal atrophy and whole brain atrophy as neuroimaging markers in AD. It has been suggested that p-Tau reflects the formation of neurofibrillary tangles, and atrophy of medial temporal lobe structures has also been related to neurofibrillary changes. In addition, it has been shown that, although whole brain atrophy rate is associated with cognitive decline, it is not very specific, and occurs in other neurodegenerative disorders than AD. We therefore hypothesize that hippocampal atrophy (rate) is a more specific marker for progression of AD-related pathology than whole brain atrophy (rate).

Apart from their role in increasing diagnostic specificity, MRI findings provide prognostic information, as we showed that they predict mortality in a memory clinic population. Although markers of atrophy are more strongly associated with cognition, in chapter 2 we show that markers associated with small-vessel disease, and especially the presence of microbleeds, have more impact on mortality. Although the clinical significance of microbleeds is not yet completely clear, we show that they are important because they are associated with poorer survival. The high prevalence of microbleeds, even further elevated in a dementia population, underlines the importance of future studies addressing their aetiology, clinical impact, and the implications for treatment and management. An urgent dilemma that should be addressed is the association of microbleeds with future development of intracranial hemorrhages and the consequences of the presence of microbleeds for anti-coagulant treatment.
Contribution of vascular pathology

The co-existence of AD pathology and vascular pathology, and their combined contribution to the development of dementia, is subject to many recent studies. Neuropathological studies have shown that in the majority of patients with dementia, both pathologies co-exist. MRI studies have shown that vascular findings occur more often in AD, and MTA is often found in VaD. It has been suggested that vascular pathology might have important impact on the development of symptoms in the presence of AD-related neuropathological changes. We show that in patients with a clinical diagnosis of AD, the presence of additional, severe, cerebro-vascular MRI findings does not lead to differences in clinical profile (chapter 3). The findings of this study support the hypothesis that markers of atrophy are more strongly associated with cognition than markers related to small vessel disease. Interestingly, this has also been shown by others in patients with a clinical diagnosis of VaD. From these findings, we hypothesize that the presence of AD-related pathology and vascular pathology lead to a clinical continuum. It may be difficult, if not impossible, to distinguish between the two, based on their clinical profile. MRI might play an important role in the recognition of the presence of one or both of these pathological mechanisms. Future research needs to address whether these findings might have consequences for treatment strategy, be it treatment targeting AD-pathology, vascular risk prevention or a combination of both.

Recommendations for future research

Important goals in future neuroimaging research in AD consist of the improvement of methods that could detect AD at an early stage, and are more specific to the underlying neuropathological changes. To address the goal of early detection, studies should focus on patients with subjective complaints. In this population, information from different modalities should actually be combined to explore their individual and combined contribution to the prediction of future clinical course. Because these studies need large sample sizes and long
follow-up duration, cooperative efforts to construct large datasets becomes very important. The Alzheimer’s disease neuroimaging initiative (ADNI)27 in the United States is a good example of such efforts, which should be followed by other initiatives. These large datasets enable different centers with their own specific expertise to access the data, resulting in more efficient use of the available data. With the current prospect of possible disease-modifying therapies, the ability of neuroimaging to help predict the presence of specific neuropathological findings becomes important. In addition to the continued need for studies with neuropathological confirmation, pharmaceutical studies can produce valuable information. Data from pharmaceutical studies should be used to investigate whether neuroimaging and other methods can contribute in the selection between patients who will and patients who will not benefit from a treatment.

In conclusion, this thesis advances the knowledge of the clinical applicability of neuroimaging markers in dementia, with a focus on hippocampal atrophy. We show that neuroimaging is a useful tool to monitor disease progression, even at early stages, and has prognostic value, in addition to its diagnostic use. Furthermore, we expand the insights in the contribution of vascular and AD-related neuroimaging findings. Amongst other biomarkers in AD, neuroimaging will be an important tool in the future, when an earlier and more specific diagnosis and evaluation of disease progression become very important clinical goals.
Reference List


