1

General introduction
**Dementia**

Dementia is defined as an acquired impairment of cognitive function in at least two domains, including memory, which interferes with normal social or occupational performance and is not attributable to delirium or psychiatric disorders. The most commonly used criteria for the diagnosis of dementia are those defined in the DSM-IV.

**Epidemiology**

Dementia is a chronic disorder that is particularly common in the elderly. Worldwide, 24.3 million people have dementia, with 4.6 million new cases of dementia every year. In Europe, the prevalence of dementia in subjects aged over 65 years has been estimated to be 6.4% of the population in a meta-analysis pooling data of 11 European population-based studies. Age is a major risk factor for dementia, with the prevalence nearly doubling every five years of age-increase between ages 60 and 85. It is estimated that within the next 50 years the number of patients with dementia in Europe will rise to over 16 million, due to the increasing life-expectancy in Western society. Besides the physical, social and psychological burden on carers of patients with dementia, the financial burden on society will grow exponentially too.

**Types of dementia**

Dementia can be caused by various underlying diseases. The most common type of dementia is Alzheimer’s disease (AD), which accounts for about 70% of cases in the elderly. The second most common cause of dementia is vascular dementia (VaD). Other, less common, causes include dementia with Lewy bodies (DLB) and fronto-temporal lobar degeneration (FTLD). Below the age of 65 years dementia is far less common, and the distribution of underlying causes differs from that observed in the elderly; thus in this age-category, whilst AD remains the most common cause, the prevalence of AD is reduced to one third of patients, with VaD accounting for approximately 18%. Other types of dementia, such as FTLD are relatively more prevalent, accounting for 12% of dementia cases in these younger patients. Due to overlap in clinical presentation, differentiating between the various types of dementia can be difficult in clinical practice.

**Alzheimer’s disease**

**Clinical features**

AD is characterized by an insidious onset of cognitive decline, typically starting with deficits in episodic memory. Patients and their family complain for example of forget-
ting recent personal and family events, losing items around the house, and repetitive questioning. As the disease progresses, deficits in other cognitive domains, such as aphasia, apraxia, agnosia, visuo-spatial difficulties and executive dysfunction, arise gradually. Psychological and behavioral problems such as mood disorders, psychosis, agitation and sleep disorders, occur more frequently as the disease becomes more severe. The patient becomes increasingly dependent on others and often has to be cared for in a nursing home. The average survival in AD is typically about 6 years from the onset of symptoms to death, depending on age at onset, ranging from about 8 years in those with an onset before the age of 75 to 4 years in those with an onset after the age of 85 years.6

Diagnosis and neuropathology
In everyday practice the diagnosis of AD is made using clinical criteria, the most frequently used of which are those proposed by the National Institute of Neurological and Communicating Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) Work Group (table 1).7

A definitive diagnosis of AD can only be made by pathological examination of the brain at autopsy or after brain biopsy. Alzheimer-type pathology is characterized by extracellular neuritic plaques, consisting of beta amyloid, and intracellular neurofibrillary tangles consisting of hyperphosphorylated tau-protein. This pathology, which in AD starts to accumulate years before the first cognitive symptoms arise,9 is present, to a much lesser extent, in normal aging too. The staging system developed

<table>
<thead>
<tr>
<th>Table 1 NINCDS-ADRDA criteria for the diagnosis of probable Alzheimer’s disease7</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Dementia established by clinical examination and confirmed by neuropsychological tests</td>
</tr>
<tr>
<td>2. Deficits in two or more areas of cognition, including memory impairment</td>
</tr>
<tr>
<td>3. Progressive worsening of memory and other cognitive functions</td>
</tr>
<tr>
<td>4. No disturbances of consciousness</td>
</tr>
<tr>
<td>5. Onset between ages 40 and 90</td>
</tr>
<tr>
<td>6. Absence of systemic disorders or other brain disease that in and of themselves could account for the progressive deficits in memory and cognition</td>
</tr>
</tbody>
</table>
by Braak and Braak describes the extent, location and sequence of accumulating neurofibrillary tangle pathology, which in AD progresses in a typical fashion, starting in the transentorhinal and entorhinal areas, before spreading to the hippocampus, the association cortices, and the rest of the cortex. The accumulation of beta amyloid and tau is associated with neuronal cell death, the result of which can be appreciated at a macroscopic level as atrophy, with widening of sulci and the ventricular system and thinning of the cortex. The focality of atrophy in AD reflects the typical pattern of progression of neuropathology. Medial temporal lobe structures, such as the hippocampus, are prominently affected in early stages of the disease. There is evidence that, besides Alzheimer-type pathology, cerebrovascular pathology plays a role in AD. The majority of subjects with late-onset AD show co-existing vascular pathology at post-mortem, and previous studies have suggested that the two pathologies interact.

Table 2 Criteria for amnestic Mild Cognitive Impairment by Petersen et al.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Memory complaint, preferably corroborated by an informant</td>
</tr>
<tr>
<td>2.</td>
<td>Objective memory impairment for age and education, at neuropsychological testing</td>
</tr>
<tr>
<td>3.</td>
<td>Normal general cognition</td>
</tr>
<tr>
<td>4.</td>
<td>Preserved activities of daily living</td>
</tr>
<tr>
<td>5.</td>
<td>No dementia</td>
</tr>
</tbody>
</table>

Mild Cognitive Impairment

As the transition from normal aging to dementia occurs gradually, a stage exists in which subjects who are developing dementia experience cognitive decline not yet severe enough to fulfill diagnostic criteria for dementia. Several clinical definitions for this intermediate phase exist, of which the criteria for amnestic mild cognitive impairment (MCI) developed by Petersen et al. are most frequently used (table 2).

Subjects who fulfill criteria for amnestic MCI are at an increased risk of developing clinical AD at a rate of about 12% per year, as compared to 1-2% per year in the age-matched general population. However, it is increasingly recognized that the application of current MCI criteria results in a heterogeneous group of subjects. Not all subjects with MCI will develop AD: some will develop other types of dementia,
whereas others will remain stable or even improve.\textsuperscript{15,16} The neuropathologic outcome of patients dying with dementia, who had a prior diagnosis of amnestic MCI, has been shown to be heterogeneous, often consisting of two or more distinct pathologic entities.\textsuperscript{17} On the other hand, criteria for amnestic MCI exclude subjects who present with first cognitive symptoms in a non-memory domain. Recently, clinical subtypes of MCI have been proposed, based on the presence or absence of memory impairment (amnestic versus non-amnestic), and on the number of cognitive domains affected (single versus multiple domains).\textsuperscript{18} It is presumed that subjects with single-domain amnestic MCI will mainly progress to clinical AD, but the outcome of the other subtypes remains unknown.

Pathological studies have shown that subjects with amnestic MCI have increased numbers of neurofibrillary tangles in medial temporal lobe structures compared to cognitively normal controls.\textsuperscript{19} However, many concomitant pathologic abnormalities such as argyrophilic grain disease, hippocampal sclerosis and vascular lesions were also observed.\textsuperscript{19,20} A better understanding of the pathological processes that play a role in MCI, may lead to clues for a more accurate identification of subjects with neurodegenerative diseases in the early stages. This in turn may permit accurate and early implementation of preventive and therapeutic strategies. Magnetic resonance imaging (MRI), which allows for a non-invasive, repeatable, in vivo, assessment of brain structure, is increasingly used as a diagnostic tool in these patients.

**HIPPOCAMPAL ATROPHY ON MRI**

Additional markers adding support to clinical diagnoses of AD are sought. A well-known diagnostic marker for AD is hippocampal atrophy on MRI.

*Anatomy and function of the hippocampus*

The hippocampus is a small, arched structure in the medial temporal lobe, bulging in the temporal horn of the lateral ventricle (figure 1). Three segments can be distinguished, a head, body and tail. Anteriorly, the hippocampal head is bordered by the amygdala, and posteriorly, the hippocampal tail disappears under the splenium of the corpus callosum. Medially, the hippocampus is bordered by the entorhinal cortex, to which it is connected via the subiculum. The hippocampus is a bilaminar structure, consisting of the cornu Ammonis (hippocampus proper) and the gyrus dentatus, with one lamina rolled up inside the other.\textsuperscript{21}

The role of the hippocampus and adjacent structures in memory function has been firmly established since the effects of bilateral medial temporal lobe resection were
described in patient H.M. in the 1950’s. This patient had a severe amnesia after a bilateral medial temporal lobe resection because of epilepsy. Since then animal and human studies have shown that the hippocampus is involved in all modalities of declarative memory: episodic, semantic and spatial memory. Furthermore, the hippocampus is involved in emotional behavior, motor control and regulation of hypothalamic function.

**Hippocampal atrophy on MRI in AD**

Focal atrophy in the hippocampal region on MRI has been the focus of extensive study as a marker for AD, as it reflects the typical pattern of progression of Alzheimer-type neuropathology (figure 2). Neuropathological studies have shown that hippocampal volumes, as measured using MRI, correlate well with the neuropathological burden at post-mortem. Furthermore, hippocampal atrophy has been shown to be associated with cognitive performance and especially memory function in healthy controls and patients with AD. Many studies initially using CT and later MRI,
have assessed the diagnostic value of hippocampal atrophy for AD, using various visual, linear and volumetric measurements (for overview see:29,30). In a meta-analysis of studies using visual and linear measurements of medial temporal lobe atrophy (MTA) on MRI, the overall sensitivity and specificity for detection of AD compared with controls was estimated to be 85% and 88% respectively.30 It has been suggested that the medial temporal lobe structures may be less involved in AD with a presenile onset (<65 years);31 on the other hand, it has been speculated that hippocampal atrophy might loose its sensitivity as a marker for AD in the oldest old,32 as hippocampal atrophy occurs, to a lesser extent, in normal aging as well.33

Besides Alzheimer-type pathology, other types of pathology, such as vascular pathology, mesiotemporal sclerosis, argyrophyllic grain disease and other neurodegenerative diseases can affect the hippocampus too.17,34,35 Hippocampal atrophy on MRI has also been described in subjects with non-Alzheimer types of dementia.36-40 This may potentially limit the diagnostic value of hippocampal atrophy as a marker for AD in the differential diagnosis with other types of dementia.

Studies in MCI have shown that hippocampal atrophy is detectable before subjects are clinically demented, in parallel with the accumulation of Alzheimer-type pathology which may start decades before cognitive deficits become apparent.8 Hippocampal volumes in MCI have been shown to be intermediate between those in normal aging and AD, and the presence of hippocampal atrophy in subjects with amnestic MCI is associated with a diagnosis of dementia at follow-up.42,43
Longitudinal studies of hippocampal atrophy

Cross-sectional studies using hippocampal volumes to differentiate between diagnostic groups have limited value, due to large inter-individual variability in brain volumes. Analysis of hippocampal volume change using serial MRI reduces this problem, as each subject is used as its own control. Rates of hippocampal atrophy in controls increase with age, and are estimated to be about 1-2% above age 70. However, longitudinal studies have shown that in AD hippocampal atrophy rates are markedly increased to about 4-8%/year. In MCI, rates of hippocampal atrophy are intermediate to those observed in controls and patients with AD, with accelerated rates in amnestic MCI predicting progression to AD. Rate of hippocampal atrophy could be a useful tool to identify subjects at risk of developing AD. Furthermore, rates of hippocampal atrophy are promising markers of disease progression, as they have been shown to correlate with change in cognitive measures, such as the Mini-Mental State Examination (MMSE) and memory tests. However, apart from AD itself, risk factors associated with accelerated rates of hippocampal atrophy are not yet clear.

Small vessel disease

White matter hyperintensities (WMH) and lacunar infarcts (lacunes) are generally viewed as evidence of microvascular pathology. Both are commonly observed on MRI throughout the cognitive spectrum (figure 3). The clinical significance of WMH remains unclear. In both AD and normal aging, WMH have been associated with subtle cognitive deficits, especially in executive function and psychomotor speed. In MCI with concomitant WMH, an increased risk of dementia has been reported. The neuropsychological correlates of lacunes remain unclear as well.
Chapter 1

MRI methodology

Previous studies have assessed atrophy of the hippocampal region using a variety of different methods, ranging from relatively simple visual rating scales and linear measurements using either CT or MRI to more complicated volumetric and semi-automated measurements using MRI. The methods used in this thesis are reviewed below in more detail.

Medial temporal lobe atrophy scale

The MTA-scale developed by Scheltens et al., provides a measure for global atrophy of the medial temporal lobe, and is based on visually scoring the height of the hippocampus and the width of the surrounding CSF. The severity of MTA is scored from 0 (no atrophy) to 4 (most severe atrophy), on each side of the brain on a coronal T1-weighted MRI sequence (table 3 and figure 4).

This simple scale is easy to learn and has been proven to have fair to good inter-rater reliability and good intra-rater reliability, and has a reasonably good correlation with hippocampal volumes measurements. Clinical studies have shown that this measure can differentiate between AD and controls, and is predictive of dementia in subjects with MCI.

Hippocampal volumetry

Compared to visual rating scales, volumetric analysis is a more detailed method to assess accurately regional volumes of a number of brain structures, including the hippocampus. This method involves manual delineation of a region of interest on

<table>
<thead>
<tr>
<th>Score</th>
<th>Width of choroid fissure</th>
<th>Width of temporal horn</th>
<th>Height of the hippocampus</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>↑</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>↑↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>3</td>
<td>↑↑↑</td>
<td>↑↑</td>
<td>↓↓</td>
</tr>
<tr>
<td>4</td>
<td>↑↑↑↑</td>
<td>↑↑↑</td>
<td>↓↓↓</td>
</tr>
</tbody>
</table>

A score of 0 to 4 is given separately for the left and right side. (↑) = increase; (↓) = decrease.
sequential slices of a volumetrically acquired scan (figure 5). Different anatomical protocols can be used to outline the hippocampus, one of which is that designed by Jack et al. The dentate gyrus, subiculum, fimbria and alveus are measured, and referred to as hippocampus. Hippocampal volume can then be computed by summing the delineated area of the region of interest on each slice, and multiplying by the slice thickness.

Measuring hippocampal volumes from serially acquired scans from the same individual, provided the scans are accurately spatially matched (registered), provides a measure of change over time. This hippocampal volume loss can then be divided by the inter-scan interval to provide the rate of hippocampal atrophy, usually described as a percentage per year.

Various new techniques are being developed to allow automated rather than manual assessment of hippocampal atrophy rates, with the aim of reducing operator...
time and variability. However, most of these techniques still require some manual intervention and have not been tested in a clinical setting to date. Thus, manual segmentation is currently considered the gold standard for hippocampal volume analysis. Unfortunately, this is a time-consuming method that requires well-trained operators and is subject to human errors in delineation. Especially, in longitudinal analysis of volume change, uncorrelated errors on serial scans may decrease reliability of measurements. More time-efficient and reliable techniques to measure hippocampal volume change on MRI are needed.

Figure 5 Hippocampal volumetry

Example of manually delineated hippocampal regions of interest on coronal T1-weighted MRI scan.
REFERENCES

5. Harvey RJ, Skelton-Robinson M, Rossor MN. The prevalence and causes of dementia in people under the age of 60 years. J Neurol Neurosurg Psychiatry 2003;74:1206-1209.
Chapter 1