MRI of Hippocampus in Incipient Alzheimer's Disease

By
Mikko Laakso
1996

KUOPION YLIOPISTO
UNIVERSITY OF KUOPIO
Neurologian klinikann julkaisusarja, No 37, 1996
Series of Reports, Department of Neurology

MIKKO LAAKSO
MRI OF HIPPOCAMPUS IN INCIPIENT ALZHEIMER'S DISEASE

Academic Dissertation

To be presented with the assent of the Faculty of Medicine of the University of Kuopio for public examination in Auditorium L1 of the Canthia Building of the University of Kuopio, on Saturday May 4, 1996, at noon.

Departments of Neurology and Radiology
University of Kuopio

Kuopio 1996

Author's address and distribution:

Department of Neurology
University of Kuopio
P.O.Box 1627
70211 Kuopio
FINLAND
Tel. +358 - 17 - 261 69 68 (Home)
Fax +358 - 17 - 17 30 19
E-mail: mikko.laakso@uku.fi
URL of the thesis: http://www.uku.fi/laitokset/neuro/37the.htm
URL of the UKU Neuroscience main page: http://www.uku.fi/laitokset/neuro/

Supervisors:

Professor Hilkka Soininen M.D., Ph.D.
Department of Neurology
University of Kuopio
ABSTRACT

Alzheimer's disease (AD) is the most common cause of dementia, yet impossible to diagnose precisely without invasive techniques, particularly at the onset of the disease. Therefore, a reliable diagnostic method is needed. The hippocampus is a part of the mesial temporal lobe memory system, and known to be affected early in the course of AD. Recent development of imaging techniques, particularly magnetic resonance imaging (MRI), has made the evaluation of diminutive brain structures, such as the hippocampus, conceivable. The purpose of this study was to focus on the sensitivity and specificity of different approaches of hippocampal imaging by MRI, and their applications for the diagnosis of incipient AD. Hippocampal pathology was evaluated by means of linear (interuncal distance, IUD), planimetric (hippocampal area) and volumetric measurements, complete with T2 relaxometry using an 1.5 T imager. The accuracy of hippocampal measurements was compared to that of the amygdala and the frontal lobes. Various procedures for normalization of the data to the head and brain size were compared.

A total of 193 subjects were examined: 59 patients with probable AD according to NINCDS-ADRDA criteria; 43 patients with age-associated memory impairment (AAMI) according to National Institute of Mental Health criteria; nine patients with vascular dementia (VaD) according to DSM-III-R criteria; 20 patients with Parkinson's disease, eight of whom were demented, and 62 cognitively normal control subjects of whom 42 were older and 20 younger than 50 years of age.

Bilateral volumetric hippocampal atrophy was a highly sensitive indicator of early AD. The best discriminant function analysis resulted in correct classification of 95% of AD patients versus non-demented age-matched controls. The volume of the
hippocampus also correlated with AD severity as assessed by Mini-Mental Status Examination and with tests assessing delayed recall. In contrast, the volume of the hippocampus was not significantly affected either by aging or AAMI. The specificity of hippocampal atrophy in comparison to other dementias, however, may be limited, since the hippocampus seem to display various patterns of atrophy in VaD and Parkinson's disease with and without dementia as well.

The AD group also invariably showed smaller volumes of the amygdala and frontal lobes, smaller hippocampal areas, longer IUDs and prolonged T2. Yet, evaluation of these measurements did not produce as good an accuracy in correct grouping as did hippocampal volumetry, but was compromised by age-dependence of the variables resulting in substantial overlap between the study groups.

In conclusion: volumetric hippocampal atrophy is a highly sensitive indicator in early AD. On the other hand, the specificity compared to other dementias with temporal lobe pathology may be limited. Volume of the hippocampus is not significantly affected by age or AAMI, which makes its assessment useful in detecting, or rather excluding AD and differentiating it from benign memory impairment.

National Library of Medicine Classification: WM 220, WT 155

Medical Subject Headings: aging; memory disorders; Alzheimer's disease/diagnosis, Alzheimer's disease/radiography; amygdala; dementia, vascular; frontal lobe; hippocampus; Parkinson's disease

Although history has long forgotten them, Lambini & Sons are generally credited with the Sistine Chapel floor.
-Gary Larson, Unnatural Selections

ACKNOWLEDGEMENTS

This study was carried out at the departments of Neurology and the MRI unit of the Dept. Clinical Radiology of the University and University Hospital of Kuopio, Finland in 1993 -1995. The study is a part of a larger research project aimed at investigating characteristics and treatment of memory impairment and dementia. As for me, I like to tell people that I got into the project by an accident. I thought that I was supposed to beep X-rated films day in, day out, instead of X-ray films. The (boring) truth, however, is that I drifted into the project by a mere change. I was first asked to do "a small job" by Kaarina. Eventually, more and more job got done, and the recruitment was confirmed by Hilkka. I got carried away by a subject that turned out to be most interesting. The making of this thesis has really been most rewarding (educationally, that is). And now, here we are.

Interest towards the subject made the process smooth, but still there are people who made the process even smoother. I thank my true guardian angels, Hilkka Soininen and Kaarina Partanen, who somehow managed to get the best out of me. No bosses better are likely to come up. Thank You Big Time. This book was officially reviewed by docents Jaakko Kinunnen and Juha Rinne, whom I also thank. Further, I'm grateful to my coworkers Merja Hallikainen, Päivi Hartikainen, Eeva-Liisa Helkala, Tuomo Hänninen, Mervi Kööönen, Maarit Lehtovirta, Paavo Riekkinen Jr., and Pauli Vainio for a job well done. Besides me, the blame for poor language is on Bill Gates III (Thesaurus and proof-reader of Microsoft Word) and Jan Six. So it is pretty much unpossible that any linguistic mistakes would eventually be included. Furthermore I would like to thank professors Paavo Riekkinen Sr. and Seppo Soimakallio for providing the facilities and the opportunity. Finally, I thank the people volunteering for the study, particularly the patients, without whom none of this would ever have
been possible.

This study was supported by the Medical Research Council of the Academy of Finland, the Finnish Medicine Foundation, the North Savo Fund of the Finnish Cultural Foundation, the Finnish Neurology Foundation, and the Instrumentarium Science Foundation. The original articles are reprinted with a permission from the publishers.

This book is dedicated to my mother.

Paris de Savonia, after hours, April 1996.

(For those of you who didn't get this, Kuopio has been sometimes referred to as PdS. But not very often).

MPL

---

**ABBREVIATIONS**

AAMI Age-associated memory impairment  
Aβ Amyloid-β-protein  
AD Alzheimer's disease  
ADCC Alzheimer's disease correctly classified  
ADTC State of California Alzheimer's Disease Diagnostic and Treatment Centers  
ADMC Alzheimer's disease misclassified  
ANCOVA Analysis of covariance  
ANOVA Analysis of variance  
ApoE Apolipoprotein E  
BA Brain area  
CA Cornu ammonis  
CCC Controls correctly classified  
CERAD Consortium to Establish Registry for Alzheimer's Disease  
CDR Clinical Dementia Rating Scale  
CMC Controls misclassified  
CNS Central nervous system  
CSF Cerebrospinal fluid  
CT Computed tomography  
DS Down's syndrome  
DSM-III-R Diagnostic and Statistic Manual of Mental Disorders, 3rd edition, revised  
DSM-IV Diagnostic and Statistic Manual of Mental Disorders, 4th edition  
EEG Electroencephalography  
HB Body of hippocampus  
HH Head of hippocampus  
HSF High signal foci  
HT Tail of hippocampus  
ICA Intracranial area  
ICA1 Coronal intracranial area  
ICA2 Sagittal intracranial area  
ICD International Classification of Diseases  
ICW Intracranial width  
IUD Interuncal distance  
MID Multi-infarct dementia  
MMSE Mini-Mental Status Examination  
MRI Magnetic resonance imaging  
NFT Neurofibrillary tangle  
NIMH National Institute of Mental Health  
NINCDS-ADRDA The National Institute of Neurological and Communicative
LIST OF ORIGINAL PUBLICATIONS

This thesis is based on following publications that in the text are referred by their Roman numerals I- VI

The original publications are not published here due to copyright reasons, but You might get them free of charge at Internet pages of Dept. Neuroscience and Neurology; University of Kuopio, Finland


CONTENTS:

ABSTRACT

ABBREVIATIONS

LIST OF ORIGINAL PUBLICATIONS

1. INTRODUCTION

2. REVIEW OF THE LITERATURE

2.1 DEFINITIONS OF THE STUDY CONCEPTS

2.1.1. Alzheimer's disease
2.1.2. Normal aging
2.1.3. Age-associated memory impairment
2.1.4. Vascular dementia
2.1.5. Parkinson's disease

2.2. ALZHEIMER'S DISEASE

2.2.1. Epidemiology of Alzheimer's disease
2.2.2. Clinical Alzheimer's disease
2.2.3. Pathogenesis of Alzheimer's disease
2.2.4. Neuropsychology of interest
2.2.5. Imaging of Alzheimer's disease

2.3. AGE-ASSOCIATED MEMORY IMPAIRMENT

2.3.1. Concept and controversies
2.3.2. Epidemiology of age-associated memory impairment
2.3.3. Imaging of age-associated memory impairment

2.4. NORMAL AGING

2.4.1. Imaging of the aging brain

2.5. VASCULAR DEMENTIAS

2.5.1. Concepts of vascular dementias
2.5.2. Imaging of the vascular dementias

2.6. PARKINSON'S DISEASE AND DEMENTIA

2.6.1. Imaging of Parkinson's disease

3. AIMS OF THE STUDY

4. MATERIALS AND METHODS

4.1. THE SUBJECTS

4.2. EXAMINATION OF THE STUDY SUBJECTS

4.2.1. The Alzheimer patients
4.2.2. The age-associated memory impairment subjects and the elderly controls
4.2.3. The vascular dementia and the Parkinson groups
4.2.4. The young controls
4.2.5. Neuropsychological tests

4.3. MAGNETIC RESONANCE IMAGING

4.3.1. MRI technique for volumetric studies
4.3.2. Determination of volumes
4.3.3. Measurement of the hippocampal area
4.3.4. Measurement of the interuncal distance
4.3.5. MRI Technique for T2 relaxometry
4.3.5. Normalization procedures

4.4. VALIDATION STUDIES
4.4.1. The volume measurements
4.4.2. The linear measurements
4.4.3. The relaxometry

4.5. STATISTICAL METHODOLOGY

4.6. ANALYSIS OF THE INCORRECTLY CLASSIFIED

4.7. DETERMINATION OF APOLIPOPROTEIN E GENOTYPE

5. RESULTS

5.1. DEMOGRAPHIC AND COGNITIVE DATA

5.2. VOLUMETRIC STUDIES
5.2.1. The hippocampus
5.2.2. The amygdala
5.2.3. The frontal lobes

5.3. HIPPOCAMPAL AREA

5.4. INTERUNICAL DISTANCE

5.5. RELAXOMETRY

5.6. ANALYSIS OF THE INCORRECTLY CLASSIFIED

6. DISCUSSION

6.1. SENSITIVITY AND SPECIFICITY OF HIPPOCAMPAL MEASUREMENTS IN ALZHEIMER'S DISEASE vs. NONDEMENTED SUBJECTS

6.2. ANALYSIS OF THE INCORRECTLY CLASSIFIED

6.3. THE AMYGDALA

6.4. THE FRONTAL LOBES

6.5. T2 RELAXOMETRY

6.6. HIPPOCAMPAL ATROPHY AMONG NON-ALZHEIMER CONDITIONS AND DEMENTIAS
6.6.1. Mapping the age-associated memory impairment
6.6.2. Vascular dementias
6.3.3. Parkinson's disease and dementia

CONCLUSIONS

7. REFERENCES

1. INTRODUCTION
Alzheimer's disease (AD), first described by Alois Alzheimer in 1907, is the leading cause of dementia, accounting for more than half of all dementias in old age. The path to accurate diagnosis of AD, however, is paved with difficulties, particularly at the very onset of clinical symptoms of the disease. The clinical diagnosis of AD is complicated by heterogeneity and inspecificity of the cognitive and other symptoms. Various clinical, biochemical, pharmacological, and genetic factors have consistently failed to be valid diagnostic instruments, and no early, or even ante mortem, marker for AD has yet been identified. Thus, the diagnosis of definite AD can be made only by invasive methods, either by biopsy, or more commonly, in autopsy. Current clinical diagnostic criteria refer to AD only as "probable" or "possible" (table 1; McKhann et al. 1984).

Even though no cure for AD exists either, the achievement of an early diagnosis of AD, as well as that of any other dementia, is a matter of crucial importance for several reasons. First of all, several conditions that may present as dementia are curable or at least treatable to some extent. This category includes numerous diseases such as tumors, chronic subdural haematoma, normal pressure hydrocephalus, hypothyreosis, Parkinson's disease, multiple sclerosis, even temporal arteritis (Friedland 1989; Caselli 1990; Mayeux et al. 1992; Dippel and Habbema 1993; Fontaine et al. 1994). Second, dementias are also associated with several additional symptoms other than cognitive. These include mainly neuropsychiatric and motor symptoms, such as extrapyramidal features. Many of these symptoms can be treated, and when treated properly, the patient may be able to lead normal life in a domestic environment. Often, it is plainly the untreated symptoms that lead to institutionalizing, and thereby to major costs. There are also ethical matters to be considered. Several dementias, such as AD, are extremely incapacitating, if not lethal, diseases, and thus a cause of major distress both to the patients and the people akin. Moreover, in the light of developing medical treatment for AD, it is necessary to obtain an early diagnosis to select patients who might benefit from medical intervention. Furthermore, the matter is also of interest in a fundamental scientific sense.

In short, a reliable method for early diagnosis is needed.

The diagnostic process of cognitive dysfunction, however, can be facilitated by imaging methods, particularly by magnetic resonance imaging (MRI), which enables an accurate and detailed insight of even diminutive brain structures. One such structure is the hippocampus. The hippocampus is a part of the mesial temporal lobe memory system, responsible particularly for modulation and storage of newly acquired data (Squire and Zola-Morgan 1991). The hippocampus is also known to be affected by AD in the earliest stages of the disease, and in the terminal stages, it is among the most affected structures both in terms of the number of hallmarks of AD pathology, and synaptic and neuronal loss (Hyman et al. 1984). Several imaging, particularly MRI, studies have since tried to evaluate this involvement with various methods, and consequently, have ended up in varying results.

In this study, some approaches to MRI of the hippocampus are evaluated. First, the whole volume of the hippocampus is measured. In order to obtain data as precise and reliable as possible, the volumes are measured using thin, contiguous, optimally oriented image slices in a substantial number of well-controlled study subjects. A 1.5 T imager, which makes highly accurate imaging possible, is used in the study. To assess the accuracy of less elaborate measurements, the area of the hippocampus at the level of the anterior commissure is measured. Further, use of a linear variable, the interuncal distance (IUD), is also evaluated. MR T2 relaxation time is measured in the head, body and tail of the hippocampus, in the temporal and parietal white matter at the corresponding levels, as well as in the amygdala and the thalamus. The accuracy of hippocampal volume measurements is compared to that of the adjacent amygdala. To assess the magnitude of more widespread involvement, the frontal lobe volumes are measured. The usefulness of these measurements as a tool to differentiate AD patients from controls is tested using discriminant function analyses. To exclude individual size variation, some methods for normalization are compared.

In order to examine the effect of cognitively normal aging, two control groups of young and age-matched elderly cognitively intact individuals are examined. To
assess the specificity of these measurements in different conditions, a group of non-demented subjects with age associated memory impairment (AAMI) is included in the study, as well as a group of patients with vascular dementia (VaD), and two groups of patients with idiopathic Parkinson's disease. The first of these groups is cognitively intact (PD), and the other demented (PDD).

Moreover, because of the limited accuracy of current clinical criteria, and in order to portray possible characteristics of correctly versus inaccurately classified study groups, an analysis of the incorrectly classified is performed. In the analysis, basic demographic data, some clinical features, apolipoprotein E (ApoE) genotype, and the profile of cognitive impairment in these groups are compared. Previous studies concerning imaging of AD and the hippocampus are reviewed.

2. REVIEW OF THE LITERATURE

2.1 DEFINITIONS OF THE STUDY CONCEPTS

2.1.1. ALZHEIMER'S DISEASE

AD in this study refers, unless otherwise stated, to probable AD diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS -ADRDA) criteria (McKhann et al. 1984), without further classification to subtypes. The criteria are presented in table 1.

2.1.2. NORMAL AGING

Aging does not necessarily affect memory and cognition (Rowe and Kahn 1987; Rapp and Amaral 1992), but, nonetheless, it often does. Normal aging in this study refers rather to usual aging, permitting some cognitive decline possibly to take place, than to "successful" aging, in which one is competent to lead a creative life throughout the age span. Denial of any cognitive deterioration would also prejudicially denote AAMI as a pathological phenomenon.

2.1.3. AGE-ASSOCIATED MEMORY IMPAIRMENT

AAMI in this study refers to subjects strictly meeting both the inclusion and exclusion criteria for AAMI proposed by National Institute of Mental Health (NIMH): they are 50 years of age or older, have a subjective sense of cognitive decline, perform at least 1 standard deviation (SD) below the mean for young adults on standard measures of memory function, are not demented, and have no other medical or psychiatric condition that may account for the memory decline (Crook et al. 1986). In this context, AAMI is not primarily located on the "cognitive continuum" from normal cognition to dementia. On the other hand, the possibility of deterioration is not completely excluded. The complete AAMI criteria are listed in table 2.

2.1.4. VASCULAR DEMENTIA

All the VaD patients present with multi-infarct dementia (MID) and are diagnosed according to revised Diagnostic and Statistic Manual of Mental Disorders (DSM -III-R) criteria (American Psychiatric Association 1987).

2.1.5. PARKINSON'S DISEASE
All the PD patients represent typical idiopathic PD. The dementia in PD is diagnosed in agreement with DSM-III-R criteria.

**Table 1. CRITERIA FOR CLINICAL DIAGNOSIS OF ALZHEIMER'S DISEASE - NINCDS-ADRDA WORK GROUP**

I. The criteria for the clinical diagnosis of PROBABLE Alzheimer's disease include:
- dementia established by clinical examination and documented by the Mini-Mental test, Blessed Dementia Scale, or some similar examination, and confirmed by neuropsychological tests;
- deficits in two or more areas of cognition;
- progressive worsening of memory and other cognitive functions;
- no disturbance of consciousness;
- onset between ages 40 and 90, most often after age 65; and
- absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

II. The diagnosis of PROBABLE Alzheimer's disease is supported by:
- progressive deterioration of specific cognitive function such as language (aphasia), motor skills (apraxia), and perception (agnosia);
- impaired activities of daily living and altered patterns of behavior;
- family history of similar disorder, particularly if confirmed neuropathologically; and
- laboratory result of:
  - normal lumbar puncture as evaluated by standard techniques,
  - normal pattern or nonspecific changes in EEG, such as increased slow-wave activity, and evidence of cerebral atrophy on CT with progression documented by serial observation.

III. Other clinical features consistent with the diagnosis of PROBABLE Alzheimer's disease, after exclusion of causes of dementia other than Alzheimer's disease, include:
- plateaus in the course of progression of the illness;
- catastrophic verbal, emotional, or physiological outbursts, sexual disorders, and weight loss;
- other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder;
- seizures in advanced disease; and
- CT normal for age.

IV. Features that make the diagnosis of PROBABLE Alzheimer's disease uncertain or unlikely include:
- sudden, apoleptic onset;
- focal neurological findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and
- seizures or gait disturbances at the onset or very early in the course of the illness.

V. Clinical diagnosis of POSSIBLE Alzheimer's disease:
- may be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course;
- may be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of dementia; and
- should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

VI. Criteria for diagnosis of DEFINITE Alzheimer's disease are:
- the clinical criteria for probable Alzheimer's disease and
- histopathologic evidence obtained by biopsy or autopsy.

VII. Classification of Alzheimer's disease for research purposes should specify features that may differentiate subtypes of the disorder, such as:
- familial occurrence;
- onset before age of 65;
- presence of trisomy-21; and
- coexistence of other relevant conditions, such as Parkinson's disease.

**Table 2. PROPOSED CRITERIA FOR THE DIAGNOSIS OF AGE-ASSOCIATED MEMORY IMPAIRMENT - NATIONAL INSTITUTE OF MENTAL HEALTH WORK GROUP**

1. INCLUSION CRITERIA
   a. Men and women at least age 50 years
   b. Complaints of memory loss reflected in such everyday problems as difficulty remembering names of individuals following introduction, misplacing objects, difficulty remembering multiple items to be purchased or multiple tasks to be performed, difficulty remembering telephone numbers or zip codes, and difficulty recalling information quickly or following distraction. Onset of memory loss must be described as gradual, without sudden worsening in recent months.
   c. Memory test performance that is at least 1 SD below the mean established for young adults on a
MRIs of Hippocampus in Incipient Alzheimer's Disease

standardized test of secondary memory (recent memory) with adequate normative data. Examples of specific tests and appropriate cutoff scores are listed below, although other measures with adequate normative data are equally appropriate.

Test Cutoff score

- Benton Visual Retention Rest (number correct, Adm.) 6 or less
- Logical Memory subtest of the Wechsler Memory Scale (WMS) 6 or less
- Associate Learning subtest of the WMS 13 or less

d. Evidence of adequate intellectual function as determined by a scaled score of at least 9 (raw score of at least 32) on the Vocabulary subtest of the Wechsler Adult Intelligence Scale.

e. Absence of dementia as determined by a score of 24 or higher on the Mini Mental State Examination.

2. EXCLUSION CRITERIA

a. Evidence of delirium, confusion, or other disturbances of consciousness
b. Any neurologic disorder that could produce cognitive deterioration as determined by history, clinical neurologic examination, and, if indicated, neuroradiologic examinations. Such disorders include AD, Parkinson's disease, stroke, intracranial hemorrhage, local brain lesions including tumors, and normal pressure hydrocephalus.
c. History of any infective or inflammatory brain disease including those of viral, fungal, or syphilitic etiologies.
d. Evidence of significant vascular pathology as determined by a Hachinski Ischemic Scale score of 4 or more or by neuroradiologic examination.
e. History of repeated minor head injury (eg, in boxing) or a single injury resulting in a period of unconsciousness for 1 hour or more.
f. Current psychiatric diagnosis according to DSM -III criteria of depression, mania or any major psychiatric disorder.
g. Current diagnosis or history of alcoholism or drug dependence.
h. Evidence of depression as determined by a Hamilton Depression Rating Scale score of 13 or more.
i. Any medical disorder that could produce cognitive deterioration including renal, respiratory, cardiac, and hepatic disease; diabetes mellitus unless well controlled by diet or oral hypoglycemics; endocrine, metabolic, or hematologic disturbances; and malignancy not in remission for more than 2 years.

Determination should be based on complete medical history, clinical examination (including electrocardiogram), and appropriate laboratory tests.
j. Use of any psychotropic drug or any other drug that may significantly affect cognitive function during the month prior to psychometric testing.

2.2. ALZHEIMER'S DISEASE

2.2.1. EPIDEMIOLOGY OF ALZHEIMER'S DISEASE

Several figures on the prevalence of dementias and AD have been published, but direct comparison of these figures is difficult due to methodological differences. Some conclusions can be drawn though: AD is the leading cause of dementia, being responsible for more than half of all dementias in old age. The prevalence and incidence of AD are age-dependent, and the number of AD patients is expected to grow due to increasing proportion of elderly people (Sulkava et al. 1985; 1986; Fratiglioni et al. 1991; Rocca et al. 1991 a; Juva et al. 1993; Skoog et al. 1993; Wernicke and Reischies 1994). It has been even proposed that dementia might be an inevitable phenomenon in each and every life, should one live long enough (Drachman 1994). Yet, recent studies have proposed dementia as not being inevitable, but rather "age-related" than "aging-related" (Hyman et al. 1995; Ritchie and Kilden 1995; Sobel et al. 1995).

In Helsinki, the prevalence of dementia at ages 75, 80, and 85 has been reported to reach 4.6 %, 13.1 % and 23.3 %, respectively (Juva et al. 1993). In Finland, the number of demented patients altogether is expected to reach about 68 000 by the year 2000, and about 95 000 by the year 2030. The cost for institutionalization of these patients alone is expected to reach FIM 5.9 billion in the year 2000, and 8.6 billion in 2030 (Sulkava et al. 1986). The cost of dementia in the USA by 2040 is estimated to be as high as USD 150 billion (Schneider and Guralnik 1990).

Given that, a cure for AD and other dementias, not to mention accurate diagnostic
methods, are urgently needed.

2.2.2. CLINICAL ALZHEIMER'S DISEASE

The NINCDS -ADRDA criteria define dementia as "a condition in which there is decline of memory and other cognitive functions in comparison with patient's previous level of function as determined by a history of decline in performance and by abnormalities noted from clinical examination and neuropsychological tests", and continue: "confirmation of dementia syndrome by neuropsychological tests should be based on measurable abnormalities in two or more aspects of cognition" (McKhann et al. 1984).

No definite early test or marker for AD exists. Various clinical, neuropsychological, biochemical, pharmacological, and genetic factors have been evaluated as tools for early diagnosis, but none of them has turned out to be unabridged. So far the diagnosis of definite AD can be confirmed only by pathological examination of brain tissue obtained by biopsy or at autopsy. Thus, in clinical practice, the diagnosis is based on typical features of the disease (gradual progression of intellectual and functional decline without other distinguishing features), and exclusion of other conditions causing dementia or cognitive dysfunction. Usually an AD diagnosis requires a follow-up of at least six months.

Memory loss is typically the earliest sign of AD. Besides memory loss, AD may present other neuropsychologic symptoms, such as impairment of judgment, language, learning, abstract thinking, visuo-spatial skills, and praxis. AD may further present changes in personality, disorientation, sleep disturbances and hallucinations. At the onset of disease some motor symptoms may be present, including rigidity or myoclonus, snout reflex or increased jaw jerk (McKhann et al. 1984; Friedland et al. 1988; Friedland 1993). Rare cases considered as AD with focal onset, such as hemiparesis or visual disturbances, have also been reported (Jagust et al. 1990; Levine et al. 1993). On the other hand, all of these symptoms may be encountered in nondemented elderly people and in various non -AD dementias as well (McKhann et al. 1984; Gibb et al. 1985; Mayeux et al. 1985; Neary et al. 1988; Friedland 1993; Kritchevsky and Squire 1993; Mendez et al. 1993; Duffy and O'Carrol 1994). Based on clinical heterogeneity, some subgroups of AD, such as typical, early - and late-onset (presenile/senile), benign (slow progression), rapid progression, behavioral, myoclonic, extrapyramidal, sporadic, familial, and AD in trisomy 21, have been proposed (McKhann et al. 1984; Mayeux et al. 1985; Friedland et al. 1988). The existence of these subtypes is somewhat unclear and controversial with most acclaimed evidence on behalf of true subtypes being genetic. Yet, identification of a true AD subtype might have an impact on the evaluation of the patients' prognosis (Mayeux et al. 1985; Friedland et al. 1988) and response to various treatment strategies (Blass 1993; Byrne and Arie 1994).

2.2.3. PATHOGENESIS OF ALZHEIMER'S DISEASE

The background, pathophysiology and pathology of AD do not constitute a single universally accepted concept either. The clinical heterogeneity of AD described above is a result of variation in the distribution, quality and severity of pathological changes in the brain. This diversity has even led to the assumption that AD might be considered as a convergent syndrome rather than a single disease (Blass 1993). In brief, currently AD is considered to be a multifactorial disease, with a combination of aging, genetic aberrations and/or environmental factors triggering the pathological cascade: accumulation of hallmarks of AD pathology, preceding, followed or accompanied by cytoskeletal and mitochondrial abnormalities, loss of neurons and synaptic connections, impaired cellular homeostasis, inflammatory reaction, and gliosis, which eventually lead to the clinical presentation of the disease to take place. The classic pathological changes considered as hallmarks of AD, in a yet unknown order of importance, are amyloid deposits and neurofibrillar changes.

Amyloid is a generic term used to describe a group of biochemically heterogenous proteins found in a number of diseases and tissues, which share the common properties of Congo red staining and resistance to proteolysis. An amyloid protein, Aβ, is a major component of senile plaques (SP). The neuritic or classical SP consist of a fibrillar amyloid core surrounded by dystrophic neurites and reactive microglia.
In diffuse plaques, the Aβ is not fibrillar nor compacted in the core, and does not associate with dystrophic neurites or glia. Further, amyloid may be found in neocortical blood vessels (Glenner and Wong 1984).

The neurofibrillary changes may present as neurofibrillary tangles (NFT), and neuropil threads (Braak and Braak 1991). The NFTs develop within the soma of the neuron, and after degeneration of the parent cell convert into extraneuronal structures, and are finally engulfed and degraded by astrocytes (Braak and Braak 1991). The NFTs are composed of paired helical filaments, which have a microtubule associated protein tau as their major subunit (Goedert et al. 1991). The neuropil threads are abnormal neurites and are closely correlated with the distribution of NFTs (Perry et al. 1991).

Recently, ApoE polymorphism and its connection to AD has been intensively studied. ApoE is a plasma protein that binds to low-density lipoprotein receptor and is involved in the transport of cholesterol and other lipids in various cells of the body (Mahley 1988). ApoE is involved in the growth and regeneration of both peripheral and central nervous tissues during development and following an injury. In the central nervous system (CNS) ApoE is synthesized by astrocytes, in which injury provokes a considerable increase of ApoE mRNA. This has been also shown to take place in rat hippocampus (Poirier et al. 1991; 1993). The gene for ApoE is located on the proximal arm of chromosome 19, in fact, in the very same region where a gene for late-onset familial AD is located (Pericak-Vance et al. 1991).

ApoE phenotype is determined by three different alleles, epsilon 2, 3, and 4. These alleles determine ApoE polymorphism, resulting in six possible phenotypes epsilon 2/2, 2/3, 2/4, 3/3, 3/4, and 4/4. ApoE epsilon 4 allele is recognized as a risk factor for late-onset familial (Strittmatter et al. 1993) and sporadic (Saunders et al. 1993; Koller et al. 1995) AD in a dose-dependent manner, that is, the risk increases with an increasing number of epsilon 4 alleles (Corder et al. 1993; Frisoni et al. 1995). In contrast, epsilon 2 allele appears to have a protective effect for AD (Benjamin et al. 1994; Corder et al. 1994; Royston et al. 1995). The risk associated with epsilon 4 may lose its significance after a certain age and may no longer be a risk among the oldest old (Hyman et al. 1995; Sobel et al. 1995).

The exact role of ApoE in the pathogenesis of AD is unknown, but isoform-specific differences have been identified in the binding of ApoE to β-protein, and to Aβ. It is supposed that ApoE epsilon 2 and 3 stabilize the structures, whereas epsilon 4 is a susceptibility factor leading to increased vulnerability or a cause of pathologic alterations (Strittmatter and Roses 1995). Besides AD, subjects carrying the epsilon 4 allele also have higher levels of total and low-density-lipoprotein cholesterol (Utermann et al. 1984), a higher risk for myocardial infarct and coronary heart disease (Menzel et al. 1983; Stengård et al. 1995) and VaD (Frisoni et al. 1994 a.), but not for PD or PDD (Hardy et al. 1994; Marder et al. 1994; Koller et al. 1995).

Neuropathological diagnosis of Alzheimer's disease

Apart from the typical clinical picture, a histopathological confirmation is required for the diagnosis of definite AD. Two histopathological criteria, based on semiquantitative assessment of SPs, have been commonly in use, the earlier National Institute of Aging (or Khachaturian) criteria (Khachaturian 1985), and the later criteria proposed by the Neuropathology Task Force of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (Mirra et al. 1991). The "definitiveness of the definition", however, is highly questionable: First of all, the central event or events of AD are unknown. The primary dispute in this area mainly concerns the importance and role of amyloid versus neurofibrillary changes in the pathogenetic process (Roses 1994; Selkoe 1994).

Second, the criteria are based on the assessment of number and quality of SPs and do not include assessment of NFTs. Of all AD hallmarks, however, NFTs seem to display most characteristic, hierarchical distribution pattern and to best correlate with pathological staging (Braak and Braak 1991; Jellinger et al. 1991; Price et al. 1991; Hyman et al. 1995) and clinical severity in AD (Chrsytal et al. 1988; Braak and Braak 1991; Arriagada et al. 1992 a.; Berg et al. 1993; Bierer et al. 1995; Hyman et
In the initial stages of AD, the NFTs are first observed to appear in medial temporal lobe, or more specifically, in the entorhinal cortex (transentorhinal pre-alpha/layer II) and/or in the hippocampus (CA1/subiculum). At the end-stage, these regions are most severely affected (Hyman et al. 1984; 1990; 1995; Ball et al. 1985; Braak and Braak 1991). The adjacent amygdala appears to be affected later (Braak and Braak 1991) and the pattern of pathological hallmarks in it seems less characteristic (Hyman et al. 1990). These structures are strongly interrelated by multiple reciprocal connections (Hyman et al. 1990). The pathology of AD is thought to disconnect input, output and intrinsic connections of these structures (Hyman et al. 1984; 1990). At later stages, these hallmarks are more widespread and can be detected in all cortical areas, leading to gradual worsening of memory impairment along the progression of the disease. The pattern of amyloid deposits is different from that of the NFTs, with the deposition beginning from the basal isocortex rather than the temporal pole (Braak and Braak 1991).

Third, the pathological hallmarks of AD may be observed in nondemented individuals as well (Khachaturian 1985; Ulrich 1985; Crystal et al. 1988; Mirra et al. 1991; Arriagada et al. 1992 b.; Bouras et al. 1993; Langui et al. 1995). The pattern of these changes seems to resemble that of AD and may thus represent preclinical AD. It might also suggest that the distinction between AD and aging is merely quantitative. Recent studies have, however, contradicted this theory of accelerated aging by suggesting different patterns of hippocampal neuronal loss in aging and in AD (West et al. 1994; Bobinski et al. 1995).

Fourth, the interrater agreement for neuropathological findings required for the diagnosis of definite AD has been reported to reach only moderate to substantial agreement (Paulus et al. 1992).

2.2.4. NEUROPSYCHOLOGY OF INTEREST

The NINCDS-ADRDA criteria propose decline in several areas of cognition in AD, and at least two are required for a diagnosis of dementia. The criteria do not take any further stand on behalf of any particular test that would best measure cognitive function, or be the most sensitive or specific to AD or even to dementia (McKhann et al. 1984).

It is clear that memory functioning is not merely based on the integrity of the hippocampus. However, in this context memory function considered to be mediated by or related to the hippocampus is of special interest and focused on. Also, of interest are those subtypes of cognition that are considered to remain particularly unaffected by aging, and conversely, are considered to be affected early in dementia, or more specifically in AD.

Selective lesions or isolation of the hippocampus are known to produce memory storage deficits, while preserving immediate and remote recall as well as general intelligence. By contrast, an isolated lesion of the amygdala (Squire and Zola-Morgan 1991) or entorhinal cortex (Hodges and Patterson 1995) alone is not considered sufficient enough to impair memory. Recent concept of the amygdala and memory suggests that the amygdala has a role in understanding, and perhaps storage of the emotional significance of events, as well as arousal and attention, but the amygdala is not considered directly to mediate nonemotional memory (Gallagher and Holland 1994; Clark 1995).

For the purpose of this study, it does seem that of all the neuropsychological tests those assessing (visual or verbal) delayed recall emerge above all. First, they remain particularly intact in cognitively normal aging. Second, impaired performance in these tests is a sensitive and early feature of dementia, or lesions of the hippocampus and the adjacent cortical areas (Hélkala et al. 1988; Morris et al. 1989; Petersen et al. 1992; 1994; Welsh et al. 1992; Howieson et al. 1993 a.; Golomb et al. 1994 a.; Hodges and Patterson 1995). It would therefore be tempting to assume that poor performance in tests assessing delayed recall would in fact reflect a memory storage deficit, and therefore hippocampal damage. In addition, in some MRI studies hippocampal volume has also been shown to correlate with delayed recall performance (Scheltens et al. 1992; Golomb et al. 1994 a.; Deweer et al. 1995) as well as with clinical severity as assessed by MMSE (Kesslak et al. 1991, Scheltens et
al. 1992; Golomb et al. 1994 b.; Leh éricy et al. 1994; Deweer et al. 1995). The right hippocampus has been considered particularly important for visual, and the left for verbal memory (Miller et al. 1993). Some impaired performance in delayed recall has also been reported in PD (Levin et al. 1989; Mahler and Cummings 1990), though with the performance exceeding that of AD patients (Helkala et al. 1988).

2.2.5. IMAGING OF ALZHEIMER'S DISEASE

Despite the diagnostic predicament described above, the diagnosis of cognitive dysfunction can be facilitated by imaging methods that today are an integral part of the diagnostic work-up of patients with suspected dementia. Recent development of MRI has offered new insights and possibilities in the field of neuroimaging. In this field, MRI shows superior anatomic accuracy compared to computed tomography (CT) or perfusion imaging methods (positron emission tomography, PET; single photon emission computed tomography; SPECT). MRI non-invasively provides both quantitative and qualitative data of in vivo tissue. Properties of MRI also enable multiplanar evaluation of diminutive, irregularly shaped brain structures, such as the hippocampus.

The dawn of Alzheimer imaging

In the beginning, approaches to AD imaging were faced with major obstacles in all the essentials of creditable study: sensitivity, specificity, and reproducibility. These earliest studies on AD imaging that based on pneumoencephalography, and even later studies with CT or MRI, focused mainly on two different approaches. One was to evaluate conventional brain atrophy, the other to evaluate changes in the white matter.

Computed tomography and evaluation of brain atrophy

Previous CT studies, and even some more recent MR studies, have focused on the evaluation of gross brain atrophy in AD. These studies are foremost based on assessing the dilatation of various ventricular and subarachnoidal spaces, and the enlargement of sulci, using linear measurements and indices, planimetry, or volumetry (LeMay et al. 1986; Nagata et al. 1987; Drayer 1988 a; b; DeCarli et al. 1990; 1992; Shear et al. 1995). In fact, few studies applying CT have been able to classify up to 90 % of AD patients and control subjects correctly. In these studies, the best results have been obtained by longitudinal follow-up, demonstrating an accelerated rate of volumetric atrophy (DeCarli et al. 1990; 1992; Shear et al. 1995).

The face value of these measurements, however, must be criticized as somewhat questionable, because gross brain atrophy may occur in normal elderly without any neurological or other deficits whatsoever, and may therefore be regarded as "physiological atrophy" (Nagata et al. 1987; Drayer 1988 a; DeCarli et al. 1990; 1992). Physiological differences in ventricular volumes, for example, may reach 200 % or more (DeCarli et al. 1990). Therefore, in early AD most CTs appear normal, or close to normal, and do not differentiate AD from normal aging or other neurodegenerative or neuropsychiatric disorders that might clinically resemble AD (DeCarli et al. 1990; 1992). Also, the qualitative interpretation of these findings has often lacked reproducibility (DeCarli et al. 1990; Davis et al. 1992). Moreover, detailed imaging of the temporal lobes in conventional axial CT images is virtually impossible due to beam hardening artifacts (DeCarli et al. 1990).

These findings gathered strongly restrict the use of CT as a true and reliable diagnostic tool for AD. Until the use of MRI becomes a standard procedure in dementia examination protocol, the value of CT should, however, not be underestimated, since it nonetheless is relatively inexpensive and useful in detecting vascular and some treatable causes of dementia.

Imaging of white matter pathology

There is also a myriad of studies that have focused on imaging of white matter pathology. Changes in the white matter have for example been referred to as leukoaraiosis in CT studies (Hachinski et al. 1987), and high signal foci (HSF) or "unidentified bright objects" (UBO) in MRI studies. These HSF have generally been
classified as either periventricular or deep white matter HSF, and they refer to nonspecific changes.

Imaging of white matter pathology has confronted similar obstacles as studies of common atrophy - studies have reported these changes to be a normal phenomenon throughout life span (Autti et al. 1994) and appear in normal (at least nonsymptomatic) aging in 30-80 % of elderly individuals. Numerous well -controlled studies have also failed to find differences in HSF between normal subjects and AD patients (Fazekas et al. 1987; Drayer 1988 a.; b.; Kozachuk et al. 1990; Leys et al. 1990; Harrel et al. 1991; Kumar et al. 1992; Yetkin et al. 1992; Erkinjuntti et al. 1994; Wahlund et al. 1994). Their interpretation has been reported to suffer from poor intra- and interrater agreement, and they can be mixed with normal structures, such as Virchow -Robin spaces or deep gyri (Drayer 1988 a; Leys et al. 1990; Davis et al. 1992; Yetkin et al. 1992).

HSF have been associated with a spectrum of histological changes, but their origin is thought to be most likely vascular (Drayer 1988 a; Englund et al. 1988; Bowen et al. 1990; Fazekas et al. 1993; Erkinjuntti et al. 1994). Yet a recent study with 1H -MR spectroscopy failed to find in vivo evidence for ischemic process underlying HSF (Rosenberg 1995). Another recent study could not link these findings to arteriolopathy but instead linked these changes to loss of myelinated axons (Scheltens et al. 1995).

Briefly, atrophic changes and incidental HSF may be found in the elderly, whether symptomatic or not. Gross atrophy or large, confluent HSF may represent a more profound pathologic process but no reliable linkage of these incidental findings to support the diagnosis of AD, or any particular disease for that matter, have been confirmed. In 1992, CERAD published a report according to which, in spite of immense effort, no consensus has been achieved in finding uniformity or interrater agreement for methodology and interpretation of the MRI findings in AD (Davis et al. 1992).

**AD imaging - focusing on the temporal lobe**

With the ascent of MRI era, many recent studies on AD have focused on various approaches to imaging of the temporal lobe structures. Considering imaging in AD, the hippocampus is the logical region of interest (ROI) for several reasons. It is a part of the mesial temporal lobe memory system (Squire and Zola -Morgan 1991) and known to be affected early in the course of AD, if not being the primary site (Hyman et al. 1984; Ball et al. 1985; Braak and Braak, 1991; Hyman et al. 1995). Histopathological studies have demonstrated that the amygdala is also severely damaged in AD, with pathological changes occurring in the nuclei that receive or give raise to hippocampal or entorhinal projections (Kromer -Vogt et al. 1990; Scott et al. 1991; Mann 1992), but the AD pathology in amygdala seems to appear in later stages of the disease (Braak and Braak 1991).

**Imaging of the AD hippocampus revisited**

Several studies have tried to evaluate both normal anatomy and pathology of the hippocampus and its possible use for diagnostic purposes, with results varying vastly depending upon the study setting. The use of imaging planes oriented perpendicular to the long axis of the hippocampus, combined with optimal imaging parameters (heavily T1 -weighted) that maximize gray/white matter contrast, have made measurements of the entire hippocampus, including the anterior part, not only feasible, but also reliable and reproducible (Naidich et al. 1987; Press et al. 1989; Squire et al. 1990; Bronen and Cheung 1991 a; b; c; Jack et al. 1992 a; b; Tien et al. 1992; Watson et al. 1992; Bartzokis et al. 1993; Mark et al. 1993). In normal subjects, several studies have reported the hippocampus to be larger on the right than on the left (Jack et al. 1989; 1992 b; Press et al. 1989; Starkman et al. 1992; Watson et al. 1992; Soininen et al. 1994; Zipursky et al. 1994, Sullivan et al. 1995). No difference has been noted in some other studies (Cook et al. 1992; Bhatia et al. 1993), and one study reported the left side being larger (Ashtari et al. 1991). Common variations of the hippocampus include notching of the uncus (Bronen and Cheung 1991 c.) and presence of a developmental hippocampal sulcus remnant (Sasaki et al. 1993). True anomalies are rare, but may be associated with agenesis corporis callosi,
lissencephaly or holoprosencephaly (Baker and Barkovich 1992).

Among the first MRI studies on AD hippocampus in 1988 Seab and coworkers detected hippocampal area to be reduced by 49 %, with no overlap between ten AD patients and seven control subjects. In 1991, Kesslak et al. found a similar reduction of 48.8 % in hippocampal volume in eight AD patients compared to seven age matched controls. In the same year, Dahlbeck et al. introduced a variable called interuncal distance (IUD). The IUD was presented as a simple diagnostic method for AD, obtainable from a single slice on a MR scan. Widening of IUD was considered to reflect hippocampal atrophy, and it was proposed that an IUD of 30 mm or more would suggest the presence of AD. Later, normative data for IUD supported the hypothesis that in normal control subjects the IUD is not likely to exceed 30 mm (Doraiswamy et al. 1993). Yet recent studies have strongly questioned the value of IUD measurement due to inaccuracy and considerable overlap between AD patients and controls (Early et al. 1993; Howieson et al. 1993 b; Ishii 1994). Comparable linear measurements have also been reported with no better success (LeMay et al. 1986; Scheltens 1992; Erkinjuntti et al. 1993).

In the study of Jack et al. (1992 a), 85 % of the hippocampal volumes in early AD patients fell below those of controls. Pearlson et al. (1992) found the area of the AD hippocampus being approximately 60 % of the area in controls. Scheltens et al. (1992) reported a discriminating sensitivity of 81 % by visual assessment of the hippocampus and temporal lobe. Later this result was reported to correlate significantly with volumetric atrophy (Vermersch et al. 1994).

In 1993, Killiany et al. were able to correctly identify 100 % of the controls and the early AD group in a discriminant function analysis including a combination of volumes of the hippocampus and temporal horn of the lateral ventricle. Conversely, in a study by Cuénod et al. (1993), the hippocampus measured from a single slice did not differ significantly in size between the early AD group and controls. In agreement with this, Erkinjuntti and coworkers (1993) found only 41 % sensitivity in differentiating the early AD group from the controls by a single slice.

Lehéricy et al. (1994) accomplished 100 % accuracy by combining volumes of the hippocampus with volumes of the amygdala. Using the volume of the hippocampus alone they reached an accuracy of 89 % in the correct classification of 26 study subjects. The study of Frisoni et al. (1994 b) also displayed hippocampal atrophy in AD patients, but overlap between patients and controls compromised the findings. In the study of Ikeda et al. (1994) hippocampal area in AD patients was about 70 % of that of controls. A recent study reported the volume of hippocampus to be smallest in a subgroup of AD patients with the ApoE epsilon 4 allele (Lehtovirta et al. 1995 b). Hippocampal imaging may also have found application other than being of mere diagnostic aid: assessment of the volume of the hippocampus might also be of use in pinpointing those AD patients who might benefit from drug treatment (Riekkinen et al. 1995).

Kirsch et al. (1992) reported a prolonged hippocampal magnetic resonance T2 relaxation time in AD, and a correlation between T2 and the clinical severity of the disease. The average hippocampal T2 was reported to be up to 30 ms longer in the AD group than in controls. An ultra low field imager (0.04 T) was used for relaxometry in the study. Similar findings are associated with temporal lobe epilepsy (TLE), in which T2 relaxometry has been shown to be a relatively sensitive method for detecting an epileptogenic focus in the hippocampus (Jackson et al. 1993). When measured at 7 T in vitro, however, T2 did not indicate the presence or severity of AD or vary between hippocampal subfields (Huesgen et al. 1993). Similarly, in the study of Christie et al. (1988), T1 values measured at 0.08 T were similar for AD patients and controls.

**Imaging of the AD amygdala revisited**

MRI studies focusing on the amygdala have resulted in various results as well. Whereas some authors have found atrophy of the amygdala to be a sensitive indicator of AD (Pearlson et al. 1992; Cuénod et al. 1993; Lehéricy et al. 1994), others in turn have failed to confirm this (Killiany et al. 1993; Lehtovirta et al. 1995 b).
In a previous study, Pearlson et al. (1992) were able to identify correctly 67% of 15 patients with moderately severe AD and 100% of 16 controls using the combined volumes of left amygdala and left entorhinal cortex. The amygdala was diminished approximately 35% compared to controls. Only two slices were measured. Cuénod et al. (1993) measured volumes of the amygdala in 11 patients with early AD and 6 controls and found a 43.5% decrease in amygdala volume with only single overlap between AD and control groups. No correlation between the size of the amygdala and age was found. In 1994, Lehéricy et al. achieved a 94% correct classification of 18 AD patients and 8 controls using volumes of the amygdala (100% when using the combined volumes of amygdala and hippocampus). The atrophy increased with the severity of the disease.

On the other hand, Killiany et al. (1993) did not detect significant differences in volume of the amygdala in eight early AD patients and seven controls. There was, however, a trend towards atrophy. Another study also found no significant atrophy of the amygdala between controls and patients with early AD, with the exception of a subgroup of AD patients carrying two ApoE epsilon 4 alleles (Lehtovirta et al. 1995).

2.3. AGE-ASSOCIATED MEMORY IMPAIRMENT

2.3.1. CONCEPT AND CONTROVERSIES

AAMI can easily be regarded as a highly controversial concept. The history of AAMI, and comparable conditions, goes back to 1958, when Kral first introduced the term "benign senescent forgetfulness" to describe a mild memory disorder in the elderly. Since then this state of memory impairment has gone under several titles or subtitles, such as Very Mild Cognitive Decline (Reisberg et al. 1982), Mild Forgetfulness (Reisberg et al. 1986), Questionable dementia (Hughes et al. 1982; Chertkow et al. 1995), Limited Cognitive Disturbance (Gurland et al. 1982), Mild Neurocognitive Disorder (Gutierrez et al. 1993), Mild Cognitive Impairment (American Psychiatric Association 1987; WHO 1992; Ebly et al. 1995; Petersen et al. 1995), Cognitively Impaired Not Demented (Ebly et al. 1995), Age -Associated Cognitive Decline (WHO 1992; Caine 1993). It has also been suggested that AAMI should be divided into Age -Consistent Memory Impairment and Late -Life Forgetfulness (Blackford and LaRue 1989; Smith et al. 1991; Caine 1993). Recently, DSM-IV has introduced a modified diagnostic category of Age -Related Cognitive Decline, as well as the concept of Mild Neurocognitive Disorder (American Psychiatric Association 1994).

By a glance at this multitude of criteria, one can easily imagine that one of the main controversies of AAMI and related conditions is the use and accuracy of current criteria. It is not known whether all these criteria refer to the same state, and if not, which of them would best define an individual or a group that meets the concept of AAMI at the abstract level. Such an individual would have a memory impairment, but not be demented, nor necessarily going to get demented. The position of AAMI on the "cognitive map" is another controversy: is AAMI a variation in normal aging, an independent phenomenon, or a transitional state in a continuum between cognitively healthy aging and dementia? The continuum was first suggested by Brayne and Calloway (1988). However, such a continuum was not insinuated by the NIMH Work Group criteria. They do state the term is nonspecific with regard to etiology, and does not necessarily imply that the disorder is nonprogressive. Major deterioration, however, would cause the diagnosis to be excluded. In any case, the use of different criteria make direct comparison with previous studies impossible. In this study the concept of "benign senescent forgetfulness" refers to the strict research criteria for AAMI as proposed by the NIMH work group in 1986 (Crook et al.) as presented in table 2.

All of the essential components of AAMI criteria; subjective memory complaints, objective memory tests, intellectual capacity testing and exclusion criteria, have been criticized. The criteria for AAMI have been criticized as too broad and overinclusive (Bamford and Caine 1988; Smith et al. 1991; O'Brien and Levy 1992; Caine 1993). Smith et al. even state that a plain memory complaint itself might guarantee the diagnosis of AAMI. Vice versa, subjective denial of memory impairment would automatically cause the diagnosis to be excluded (Ebly et al. 1995). Also, the medical
exclusion criteria may be too restrictive (Smith et al. 1991; Koivisto et al. 1995). Further, the prevalence of AAMI may vary depending upon the memory tests and cut-off points used (Smith et al. 1991) and is affected by intellectual capacity (Koivisto et al. 1995). According to Ebly et al. (1995) an optimal diagnosis would require longitudinal follow-up, making a comparison to previous mental function possible. In the absence of this possibility, the norms should be adjusted for age, education and other relevant variables.

The proportion of memory impairment patients that finally get demented has varied between the studies. Reisberg et al. (1986) did not find any clinical change over a 3.6 year follow up in subjects who were in the "forgetfulness phase". In the follow-up study of Hämminen et al. (1995), after an average follow-up of, similarly, 3.6 years, 59% of the study subjects still met AAMI criteria; only 9% were classified as demented. In a study of Petersen et al. (1995) 55% of subjects with mild cognitive impairment (score 0.5 on Clinical Dementia Rating scale) became demented during the 54 month follow-up.

Pathology of AAMI and related disorders, if they do not represent early AD, is complicated as well. Aging and cognitive impairment in the elderly are associated with multiple changes in various transmitter systems (McEntee and Crook 1990; 1991; 1992; 1993). It is likely that such changes would result in different pictures of memory impairment depending on the transmitter system affected.

A study has suggested that the ApoE epsilon 4 allele is not a risk factor for AAMI, proposing that AAMI might be a phenomenon closer to normal aging than to AD (Koivisto et al. 1994). On the other hand, two recent studies have reported a lower cognitive performance in nondemented subjects carrying ApoE epsilon 4 allele suggesting accelerated cognitive aging (Feskens et al. 1994; Reed et al. 1994). As normal individuals, memory impaired persons carrying an epsilon 4 allele are more likely to become demented (Petersen et al. 1995).

No matter what the status of AAMI finally turns out to be - a variation, an independent disorder, or an early clinical manifestation of AD - due to it's high prevalence, achieving a correct diagnosis of AAMI is as important as that of AD.

2.3.2. EPIDEMIOLOGY OF AGE-ASSOCIATED MEMORY IMPAIRMENT

In Kuopio, the prevalence of AAMI has been reported to be 38.4% in a randomly selected population of 1049 subjects aged 60-78 years. The prevalence of AAMI was opposite to that of AD: it was more common in men (42.5%) than in women (35.7%), and its prevalence decreased with advancing age (Koivisto et al. 1995). Using strict AAMI criteria, the prevalence of AAMI was expectedly lower (19%) in subjects starting from the age of 50 in the study of Barker et al (1995).

As stated previously, the reported prevalence depends upon the criteria, the tests and the cut-off points used. In a Spanish study, the prevalence of AAMI was 7.1% in subjects 65 years or older (Coria et al. 1993). In a recent study of subjects 65 or older, 30% were classified as "cognitively impaired not demented". Only 25% of those "cognitively impaired not demented" met the strict criteria of AAMI (Ebly et al. 1995).

2.3.3. IMAGING OF AGE-ASSOCIATED MEMORY IMPAIRMENT

A recent MRI study reported minor changes in the hippocampus and the amygdala in AAMI subjects. Hippocampal right-left asymmetry was diminished, but otherwise hippocampal volumes did not differ statistically between AAMI subjects and age-matched controls. This strongly suggests a closer relationship of AAMI to normal aging than to AD (Soininen et al. 1994). In the study of Chertkow et al. (1995), 25% of subjects with questionable dementia/age-associated cognitive decline displayed decreased hippocampal volumes.

2.4. NORMAL AGING

As previously stated, aging does not inevitably associate with memory loss (Rowe and Kahn 1987; Rapp and Amaral 1992). Conversely, a deficit in memory or...
cognition is definitely not equivalent to early dementia. Several possible factors other than dementia may contribute to a decline in memory function, such as medication, motivation, co-operation, depression, or AAMI. Memory complaints are common findings also among nondemented elderly, and the performance of aged individuals has been reported to decline in several subtypes of cognition (Craik 1990; Petersen et al. 1992). Of special interest in this context are those subtypes of cognition that are considered to remain particularly unaffected by aging and are affected early in dementia.

Coarse epidemiological approximations of the prevalence of normal aging can be derived from studies that assess prevalence of both AAMI and dementia. After exclusion of both these conditions, the remainder gives an estimate of the proportion of cognitively normal aging. Thus determined, the prevalence of cognitively normal aging in the study area was 37.5 % in the age-group 60-78 was 37.5 % (Koivisto et al. 1995). Similarly, in the study of Eby et al. (1995), the prevalence was 32 %. Surprisingly enough, a recent study reported a prevalence of 44 % of cognitively intact elderly among Finnish centenarians (Sobel et al. 1995). In the study of Barker et al. (1995) the prevalence of normal aging was as high as 73 %. These figures may be slightly too high including subjects who suffer from cognitive deficits caused by other conditions such as depression or side-effects of medication.

2.4.1. IMAGING OF THE AGING BRAIN

Imaging of the aging brain is an important issue, because knowledge of normal changes is essential before interpreting a finding as abnormal. Briefly, the brain remains moderately constant until 50 years of age, followed by highly variable physiological atrophy with increasing age. Focal abnormalities of white matter are seen in 30-80 % of elderly subjects without neurological deficits. After 50 years of age, only 50 % of brains are free of atherosclerotic changes (Nagata et al. 1987; Drayer 1988 a.; DeCarli et al. 1990). By contrast, the volume of the hippocampus seems to remain remarkably unaffected by normal aging (Jack et al. 1989; Bhatia et al. 1993; DeCarli et al. 1994; Zipursky et al. 1994; Sullivan et al. 1995). In nondemented individuals carrying an ApoE epsilon 4 allele, a slightly diminished asymmetry of hippocampal volumes has been reported (Soininen et al. 1995).

2.5. VASCULAR DEMENTIAS

2.5.1. CONCEPTS OF VASCULAR DEMENTIAS

VaD is the second most common type of dementia after AD. Again, estimates of prevalence vary substantially (Brust 1988; O'Brien 1988; Rocca 1991 b.) but together these two types of dementia, separately or mixed, may account for as much as 90 % of all the dementias (Sulkava et al. 1985; Dippel and Habbema 1993; Skoog et al. 1993). The mixed dementia may be due to coincidental occurrence of two prevalent disorders, or mixed degenerative and vascular pathology may be associated with cerebral amyloid angiopathy (Chui et al. 1992).

The term "vascular dementia" is heterogeneous in every possible sense. There are several vascular events that may result in various conditions with different pathological and clinical expression. Also these events have been described by various nosologies and by various different criteria, such as DSM III-R or IV (American Psychiatric Association 1987; 1994), ADDTC (State of California Alzheimer's Disease Diagnostic and Treatment Centers; Chui et al. 1992), NINDS - AIREN (The National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences; Roman et al. 1993), or ICD (International Classification of Diseases; WHO 1992). The NINDS - AIREN criteria appear to cover a wide range of causes, and classify VaD into MID, strategic single -infarct dementia, small -vessel disease, dementia due to hypoperfusion, hemorrhagic dementia, and dementia by other mechanisms, which are all described in detail (Roman et al. 1993). MID can be further subtyped as cortical or subcortical, resulting in a slightly different clinical picture (Erkinjuntti 1987; Roman et al. 1993). And once more, these criteria have only succeeded in producing only moderate to substantial diagnostic interrater agreement (Lopez et al. 1994).

Mechanisms of dementia related to vascular events vary. Briefly, the essential factors
contributing to damage are quality, location, volume, and number of lesions (Tatemichi 1990; Garcia and Brown 1992; Roman et al. 1993). Thus, a lesion of the posterior cerebral artery, mainly responsible for hippocampal circulation, might cause hippocampal damage (Tien et al. 1994). Hippocampal sclerosis, leukoencephalopathy and multiple lacunae associated with VaD have been described (Crystal et al. 1993). In experimental animal studies, chronic cerebrovascular insufficiency without infarcts has been reported to mimic AD -type changes in the hippocampus, including CA1 damage, high signal intensities in the hippocampal region predominantly on the right side, MR spectroscopic changes, alterations in local cerebral blood flow and spatial memory dysfunction in aged, but not young rats (de la Torre et al. 1992).

2.5.2. IMAGING OF THE VASCULAR DEMENTIAS

Apart from imaging of stroke, VaD imaging has also focused largely on HSF, but as stated above, their role in diagnosis is, if not useless, undetermined. The NINDS - AIREN criteria require brain imaging for the diagnosis of VaD (Roman et al. 1993). They state, however, that "there are no pathognomonic brain CT or MRI images of vascular dementia". Instead, absence of cerebrovascular lesions on CT or MRI is considered strong evidence against vascular etiology and constitutes as the most important element to distinguish VaD from AD. Neuroimaging is also implied in the ADDTC criteria, according to which "two or more ischemic strokes with at least one outside the cerebellum" are required (Chui et al. 1992).

2.6. PARKINSON'S DISEASE AND DEMENTIA

PD is one of the most common burdens of aging, and a major cause of dementia as well. The prevalence of PD in Finland has been reported to be 120/100 000, with the relative frequency of dementia reaching 30 % (Marttila and Rinne 1976). Higher figures of the frequency of dementia have been reported to vary from 40 to 70 % with the percentage increasing with age (Mayeux et al. 1992).

The dementia occurring in PD is not a single entity either, but consists of a variety of dementia syndromes, in which the clinical picture depends on different pathogenetic mechanisms in different neurotransmitter systems. The typical dementia in PD has been described as a mild subcortical dementia resulting from dopaminergic insufficiency. The most severe type of PDD is the "mixed" PDD, that is PDD combined with AD, the prevalence of which has been reported to be 10 - 60 % of the patients with PD (Mahler and Cummings 1990). AD and PD do share some neurochemical abnormalities in the brain such as deficits in the cholinergic, serotonergic, noradrenergic and dopaminergic systems (Rinne et al. 1991; Kerwin et al. 1992; Lange et al. 1993). As in AD, and normal aging, NFTs have been detected in PD hippocampus and the entorhinal region (Ball 1984; Jellinger 1987; Ince et al. 1991; Jellinger et al. 1991; Bancher et al. 1993; Braak et al. 1993). In PD, the pattern of NFTs has been variously reported to correlate (Bancer et al. 1993), to have a low correlation (Ince et al. 1991) or not to correlate with the severity of dementia (Chui et al. 1986). Some deficits of performance in tests assessing delayed and cued recall have been reported in PD (Levin et al. 1989; Mahler and Cummings 1990).

2.6.1. IMAGING OF PARKINSON'S DISEASE

Routine MRI does not reveal any particular structural patterns of damage in the brains of patients suffering from PD (Drayer 1988 b; Huber 1989). Some attention has been paid to imaging of signal intensities due to abnormal accumulation of iron or other molecules that might exhibit magnetic susceptibility in various locations (Drayer 1988 b). A recent study proposed a decreased T2 in the substantia nigra, nucleus caudatus and putamen in patients with PD, with an overlap compromising the diagnostic value (Antonini et al. 1993). Later, another study confirmed a decreased T2 in substantia nigra, but reported an increased T2 in putamen (Ryvlin et al. 1995). Nevertheless, iron is known to accumulate in these regions also in normal aging (Drayer 1988 a), and in other parkinsonian (plus) syndromes, such as Shy –Drager syndrome, olivopontocerebellar atrophy, and striatoniagral degeneration (Drayer 1988 b). And again, iron has been reported to accumulate in nucleus caudatus, putamen and globus pallidus in AD brain as well (Bartzokis et al. 1994). These findings strongly decrease the usefulness of such measurements to be of any particular aid for differential diagnostics.
3. AIMS OF THE STUDY

The hippocampus is known to be damaged early in AD. Several previous MRI studies have evaluated possible hippocampal involvement in AD with varying results. In this study, different methods of evaluating hippocampal involvement are compared. It is hypothesized that the hippocampus is atrophied in AD and spared in normal aging, and possibly in non-AD dementias. The purposes of this study are:

1. To evaluate hippocampal involvement in incipient AD using volumetry, measurement of hippocampal area, interuncal distance and T2 relaxometry.
2. To compare the accuracy of these hippocampal measurements to those of the amygdala and the frontal lobes.
3. To compare findings in the AD group to those in nondemented young and elderly controls, thus evaluating the effect of aging on the normal hippocampus.
4. To compare these findings to those in subjects suffering from AAMI, and to evaluate the state of AAMI with respect to normal aging versus AD.
5. In order to assess the specificity of the findings to Alzheimer’s dementia, to compare them to those found in common dementias and degenerative disorders other than AD, that is, VaD and PD with and without dementia.

In summary, to find a method, that would improve the accuracy of diagnosis of incipient AD.

4. MATERIALS AND METHODS

4.1. THE SUBJECTS

The final study population consists of a total of 193 subjects: 59 patients fulfilling the NINCDS-ADRDA criteria for probable AD (McKhann et al. 1984), 44 subjects fulfilling the National Institute of Mental Health criteria for AAMI (Crook et al. 1986), 9 patients with vascular dementia (VaD) according to DSM-III-R criteria (American Psychiatric Association 1987), 20 patients with idiopathic Parkinson’s disease (PD), out of whom 8 demented (PDD), 42 cognitively normal age-matched elderly controls (old controls; OC), and 20 cognitively normal controls younger than 50 years of age (YC). Due to different sample sizes at different times in the study segments, and some missing data, this number may vary a little, but on those occasions this is stated separately. Brief clinical characteristics of the study groups are presented in table 3.

| Table 3. Basic clinical characteristics of the study groups |
|-----------------|---|---|---|---|---|---|
|                | AD  | VaD | PDD | PD  | AAMI | OC  | YC  |
| Nr              | 59  | 9   | 8   | 12  | 44   | 42  | 20  |
| M/F             | 30/29 | 3/6 | 5/3 | 6/7 | 11/32 | 19/23 | 10/10 |
| Age, Years      | 70 +/- 8 | 76 +/- 4 | 71 +/- 2 | 68 +/- 5 | 70 +/- | 72 +/- | 28 +/- |
AD, Alzheimer's disease; VaD, vascular dementia; PDD, Parkinson's disease with dementia; PD, Parkinson's disease; AAMI, age-associated memory impairment; OC, old controls; YC, young controls; MMSE, Mini-Mental Status Examination. Possible significant differences may be found in the results chapter.

The ethics committee of Kuopio University and University Hospital approved the study. All subjects provided their informed consent for participation in the study following an explanation of the study protocol.

4.2. EXAMINATION OF THE STUDY SUBJECTS

4.2.1. THE ALZHEIMER PATIENTS

The AD patients were recruited at diagnostic examinations or were recently diagnosed. They underwent a structured interview, a general physical and clinical neurological examination; assessment of clinical severity by Mini Mental Status Examination (MMSE) (Folstein et al. 1975), Clinical Dementia Rating scale (CDR) (Hughes et al. 1982) and Brief Cognitive Rating Scale (Reisberg et al. 1983); assessment of extrapyramidal signs using the Webster Parkinson's Disease scale (Webster 1968); assessment of depressive signs by the Hamilton scale (Hamilton 1960); an extensive battery of laboratory tests to exclude secondary causes of dementia; comprehensive neuropsychological testing listed below; EEG and event related potentials; SPECT scan; and MRI of the brain. All patients scored less than four in the modified ischemic scale (Rosen et al. 1980). Seventeen AD patients had a history of coronary heart disease and 10 had well controlled hypertension. According to the CDR scale, 5 AD patients had questionable dementia (0.5), 34 had mild (1) and 15 had moderate (2) dementia.

4.2.2. THE AGE-ASSOCIATED MEMORY IMPAIRMENT SUBJECTS AND THE ELDERLY CONTROLS

The AAMI and the OC groups were examined alike. They were derived from a randomly selected population of 1049 individuals who participated in an epidemiological study on the prevalence of dementia and memory disorders in the Kuopio area (Koivisto et al. 1995). The AAMI subjects and the age-matched controls were randomly drawn from this population. Finally, subjects were included in the study if they were willing to complete the whole study protocol.

The criteria of Crook et al. (1986) were used to identify AAMI. The AAMI subjects were 50 years of age or older, had subjective memory problems disturbing their everyday life, showed an objective impairment in memory tasks, and got a score of seven and less on the Benton Visual Retention Test (Benton 1967) or 13 or less on the Paired Association Subtest of the Wechsler Memory Scale (WMS) (Wechsler 1945). Otherwise, the cognitive capacity of AAMI subjects was within the normal range: they scored 32 or more on the Wechsler Adult Intelligence Scale Vocabulary Subtest (Wechsler 1955) and 24 or more on the MMSE. They had no other disease or medication accounting for memory disorders. Four AAMI subjects and one elderly control had a coronary heart disease, and four AAMI subjects and four elderly controls had hypertension. The screening also included an interview concerning
medical history, registration of subjective memory complaints with a Memory Complaint Questionnaire (Crook et al. 1992), memory tests mentioned in the AAMI criteria, and short neuropsychological tests to identify potential dementia cases (Koivisto et al. 1992). The subjects also filled in the Geriatric Depression Rating Scale (Yesavage et al. 1983) to assess occurrence of depressive symptoms. Further investigation included clinical neurological examination, comprehensive neuropsychological testing, EEG, event related evoked potentials, and MRI.

4.2.3. THE VASCULAR DEMENTIA AND THE PARKINSON GROUPS

All the VaD patients suffered from multi-infarct dementia. All the PD patients had a typical idiopathic PD with the three classical symptoms of PD: tremor, hypokinesia and rigidity. The test battery for these groups basically included the same clinical and laboratory tests and comprehensive neuropsychological testing as the AD, AAMI and OC groups. Special attention was paid to excluding secondary causes of parkinsonism.

4.2.4. THE YOUNG CONTROLS

The young controls were students or staff members volunteering for the study. They were healthy and had no history of CNS or systemic diseases or medication.

4.2.5. NEUropsychological Tests

A comprehensive battery of neuropsychological tests was used to assess the cognitive performance of the study subjects. Verbal memory was examined with the list learning test using shopping items (Helkala et al. 1988). A "yes" or "no" recognition of the words in the list was asked after a 30 minute delay filled with other psychometric tests. The story recall test with the Boston approach was used as well (Millber et al. 1986). Recall of the story was tested immediately and after a 30 minute delay. Visual memory was examined with the Heaton Visual Reproduction Test (Russell 1975). Recall of the figures was tested both immediately and after a 30 minute delay.

Nelson's version of the Wisconsin Card Sorting Test (Nelson 1976), Trail Making test A and B (Reitan 1958), and Verbal Fluency test (Borkowski et al. 1967) were used to assess executive functions. The maximum time of 150 seconds for Trail Making A and 300 seconds for Trail Making B was allowed. If the test was not completed in the time allowed, the missing letters or numbers were scored as omissions. In the Verbal Fluency Test, the subject was asked to produce as many words as they could beginning with letters P, A and S in one minute for each letter. The score was the number of words correctly named.

Furthermore, verbal functions were assessed with the Boston Naming Test (Kaplan et al. 1983), visuospatial functions with cube copying test, clock setting test and the Block Design subtest of Wechsler Adult Intelligence Scale (Wechsler 1981; Goodglass and Kaplan 1972), and praxic functions of the hand using Luria's method (Helkala et al. 1988) (data not shown).

4.3. MAGNETIC RESONANCE IMAGING

4.3.1. MRI Technique for Volumetric Studies

The subjects were scanned with a 1.5 T Magnetom (Siemens, Erlangen) using a standard head coil and a tilted coronal 3D gradient echo sequence (magnetization prepared rapid gradient echo: time of repetition 10 ms, time of echo 4 ms, time of inversion 250 ms, flip angle 12°, field of view 250 mm, matrix 256x192, 1 acquisition) resulting in contiguous T1 weighted partitions with a slice thickness of 1.5-2.0 mm oriented perpendicular to the long axis of the hippocampus (figure III.1.A).
The boundaries of the ROI were outlined by a trackball driven cursor and the number of voxels within the region was calculated by using an in house developed program for standard work console. The outlining of the boundaries always proceeded from anterior to posterior in a sequential fashion. The measurements were performed by a single rater blinded to the clinical data or diagnostic category of the study subjects (I, IV-VI).

4.3.2. DETERMINATION OF VOLUMES

Data from standard anatomical atlases of the human brain (Duvernoy 1988; DeArmond et al. 1989) as well as from several previous articles (Naidich et al. 1987; Bronen and Cheung 1991 a; b; c; Amaral et al. 1992; Jack et al. 1992 a.; Tien et al. 1992; Watson et al. 1992; Bartzokis et al. 1993) were used as guidelines to determine the boundaries of the amygdala and the hippocampus in oblique coronal MRI sections.

The hippocampus

The hippocampus included the dentate gyrus, the hippocampus proper and the subicular complex. The rostral end of the hippocampus when it first appears below the amygdala, was the anatomical starting point. The caudal end of the hippocampus was taken as the section in which the crura of the fornices depart the hippocampal tail (I, IV-VI). Examples of hippocampal delineation are presented in figure 1.

Figure 1. Examples of delineation of the hippocampus of an Alzheimer patient, most posterior slice drawn presented at bottom right.

The amygdala

The amygdala is a heterogeneous structure composed of several nuclei in cortical and subcortical areas. The whole amygdala as it appears on the screen was contiguously outlined (I, VI). In detail, the amygdala is considered to include the deep nuclei (which include lateral, basal, accessory basal, and paralaminar nuclei), the superficial nuclei of the amygdala (the anterior cortical nucleus, the medial nucleus, the nucleus of the lateral olfactory tract, the periamygdaloid cortex, and the posterior cortical nucleus), as well as the remaining nuclei (the anterior amygdaloid area, the central nucleus, the amygdalohippocampal area, and the intercalated nuclei) (Amaral et al. 1992). Examples of amygdaloid delineation are presented in figure 2.

Figure 2. Examples of delineation of the amygdala. Alzheimer patient.
The frontal lobes were selected as a ROI in order to ascertain whether the atrophy rate of temporal lobe structures exceeds that of the frontal lobes. The frontal lobes were outlined on every third slice. Therefore, due to thin slices, the measurement was done at intervals of 5 mm. The number of slices measured ranged between 14 and 18. The most anterior slice was the one with clearly visible gyri. The most caudal slice included in the measurement was the first one in which the anterior commissure was first present. On the most posterior slices, a straight line was drawn from the bottom of the lateral fissure (ventral insular sulcus) to the medially located choroidal fissure in order to separate the temporal lobe from the frontal lobe. The volumes of the lateral ventricles were also measured and consequently subtracted from the volume of the slice. The volume of each slice was multiplied by three, and thereafter the slice volumes were summed up (I). Examples of frontal lobe delineation are presented in figure 3.

Figure 3. Examples on delineation of the frontal lobes.
First slice on top left, last on bottom right.
4.3.3. MEASUREMENT OF THE HIPPOCAMPAL AREA

The hippocampal area was measured from the slice in which the anterior commissure was first present when proceeding from anterior to posterior (IV).

4.3.4. MEASUREMENT OF THE INTERUNCAL DISTANCE

The IUD in the study is defined as a shortest possible distance between the hippocampal heads (pes) on a coronal slice at the level where the anterior commissure was first present (II). Measurement of the IUD is presented in figure II. 1

4.3.5. MRI TECHNIQUE FOR T2 RELAXOMETRY

The method used for T2 relaxometry was similar to that described by Jackson et al. (1993). T2 maps were calculated in each of three oblique coronal 8 mm sections from 16 images obtained at echo times of 22 to 262 using a Carr-Purcell-Meiboom-Gill sequence. The interslice gap was 2.0 mm. The tilting angle was perpendicular to the long axis of the hippocampus.

The T2 maps were generated by a computer program that fitted a single exponential to the signal intensity data of corresponding pixels from all 16 echoes after ensuring that no motion artifacts were visible in the source images. The T2 relaxation time was thus calculated for each pixel, and an image was then constructed in which pixel intensity corresponded to the calculated T2. The T2 images thus generated were magnified by a factor of 2.3-2.5.

In this study T2 was measured in the head, body and tail of the hippocampus, in the temporal and parietal white matter at the corresponding levels, as well as in the amygdala and the thalamus. These variables are identical to those of Kirsch et al. (1992) except for the hippocampus being measured at three sites instead of one.

Mean hippocampal T2 was measured within the anatomic boundaries of the hippocampus by selecting the largest possible circular ROI with minimum 8, but typically 30 -50 pixels (40-60 mm³), within the anterior, middle and posterior sections corresponding to head, body and tail of the hippocampus, respectively. Boundaries where partial volume effects might occur were carefully avoided. ROIs were placed similarly in the amygdala (100 pixels, 125 mm³, shown in the anterior section in 98 % of cases), the thalamus (100 -150 pixels, 125 -190 mm³, in the posterior section in 83 % of cases) and the temporal (50 -70 pixels, 63-88 mm³) and parietal (200 pixels, 250 mm³) white matter in each of the three sections. Since the values basically do not represent any distinct anatomic locations, the T2 of temporal...
and parietal white matter is presented as an average of the three sections (III; figures III.1.B.C.)

4.3.5. NORMALIZATION PROCEDURES

In order to exclude the effect of individual head and brain sizes, various methods for normalization were tried in the study. The normalized values were used in the statistical analyses. The methods used for normalization differ between the variables and the substudies, and are presented individually when used.

ICA refers to intracranial area. Two different ICAs were measured. ICA1 (figure 4.) refers to a coronal ICA measured at the level of the anterior commissure, and ICA2 (figure 5.) to a sagittal ICA measured in the midsagittal scout image (II, IV-VI).

Brain area (BA) (figure 6.) refers to the area of the brain measured at the level of the anterior commissure with the lateral and ventricular spaces excluded (I, VI).

Intracranial width (ICW) is a variable that was used in normalization of the IUD (figure II.1). ICW is a straight line through the inner cranium measured horizontally at the level of the head of the hippocampus. In cases where the heads were not on the same horizontal level, the intracranial line was tilted horizontally at the midpoint of the IUD (II).

Figure 4. The coronal intracranial area. A control subject.

Figure 5. The sagittal intracranial area. A control subject.
4.4. VALIDATION STUDIES

4.4.1. THE VOLUME MEASUREMENTS

The intrarater agreement in volumetry of the hippocampus and the amygdala has been reported earlier (Soininen et al. 1994). The interrater reproducibility between two raters was tested in 16 subjects. The differences between the volumes obtained by two raters compared to the mean of these two measurements were 4.1 % for the right hippocampus, 1.6 % for the left hippocampus, 8.7 % for the right amygdala and 3.7 % for the left amygdala, respectively (1).
4.4.2. THE LINEAR MEASUREMENTS

The interrater reliability for IUD was tested between two raters in 16 subjects. The mean of the measurements was 26.4 for rater 1 and 26.3 for rater 2. The intraclass correlation coefficient was 0.82, ANOVA F(1,15) = 0.014, p = 0.907. Furthermore, in 16 subjects IUD was measured 1-3 slices (max. 4.5-6.0 mm) posterior in the same patient. The correlation coefficient between these two measurements was 0.64, p<0.01 (II).

4.4.3. THE RELAXOMETRY

Intra- or interrater agreements were not evaluated for the measurement of T2. However, in order to assess the stability of T2, five repeated measurements of the same YC volunteer were performed within a 12-month period. The mean coefficient of variation in different locations of the hippocampus and the amygdala was 2.6% (range from 1.3 to 3.7%), 6.6% (6.4-6.8%) in the thalamus, 6.8% (6.3-7.2%) in the temporal and 3.4% (3.0-3.8%) in the parietal white matter.

4.5. STATISTICAL METHODOLOGY

The data were analyzed utilizing SPSS-PC+ V.4.1 software (SPSS Inc., Chicago, IL). Analysis of variance (ANOVA) was used to compare the means over the study groups. The Duncan method was applied in post hoc analysis to detect which groups differed significantly. For T2 times that were significantly different across the study groups, ANOVA adjusted for presence of hypertension and coronary heart disease was performed. In the analysis of psychometric test scores, education was included as a covariate (ANCOVA). In the study of the amygdala, multivariate analysis of variance (MANOVA) was used for repeated measures by side (right, left) x diagnostic group x gender, for raw and normalized volumes.

Correlations were calculated using a two-tailed Pearson's correlation test. The categorial data, such as gender and ApoE distribution were analyzed by a Chi-square test. To test the accuracy of the measurements in distinguishing AD patients from controls, stepwise discriminant function analysis (Wilk's method) was used. The results are expressed as mean ± SD. The level of statistical significance of differences is p<0.05.

For discrimination analyses, the IUD and the volumes of hippocampus and amygdala were multiplied times 10 or 100 to produce reasonable numbers for the statistics.

4.6. ANALYSIS OF THE INCORRECTLY CLASSIFIED

For this analysis the study group was rearranged into four groups: AD patients correctly classified (ADCC), AD incorrectly classified (misclassified; ADMC), controls correctly (CCC) and incorrectly classified (CMC). The control group includes only the AAMI and the OC groups. Thus, and due to some missing data, the size of the study group varies between 137 and 140. The size of the individual study groups varies as follows: ADCC 46-49, ADMC 6-9, CCC 76-79, CMC 6-9. The compared variables in the analysis were basic demographic data, such as age and gender; assessment of clinical severity with different rating scales; assessment of accompanying symptoms other than mnemonic, and the ApoE genotype. Finally, the clinical data of the incorrectly classified AD patients was individually reappraised (IV).
4.7. DETERMINATION OF APOLIPOPROTEIN E GENOTYPE

Samples of venous blood were collected in EDTA-tubes and ApoE genotype was determined from blood leukocytes. DNA was extracted by the standard phenol-chloroform extraction. ApoE genotypes were analyzed using polymerase chain reaction, HhaI digestion and polyacrylamide gel electrophoresis as described earlier (Hixon and Vernier 1990; Tsukamoto et al. 1993; Lehtovirta et al. 1995 b.) with slight modifications.

5. RESULTS

5.1. DEMOGRAPHIC AND COGNITIVE DATA

The AD patients and the nondemented elderly controls did not differ significantly in age. Among the demented groups ANOVA showed a significant difference in age, the VaD patients being older than AD or PD patients [F(4,107)=2.7, p<0.05]. The groups were sex-matched except for the AAMI group in which women were overrepresented. Duration of dementia did not differ between the demented patient groups. Duration of PD was slightly longer in the PDD group than in the PD group, but not significantly (IV-VI).

By definition, the MMSE scores were lower for the demented patients than for the age matched study groups (p<0.0001) (IV). The OC and PD groups performed better in the MMSE than the AD, VaD and PDD groups (p<0.05); the VaD group had lower scores than the AD and PDD groups (p<0.05) (VI).

The YC group had had a longer education than the OC, AAMI or AD groups [F(3,139)=44.5, p<0.0001]. All the groups differed from each other with a significance of p<0.05. Significance of cognitive performance did not change with education as a covariate in the analyses. Compared to the AD group, education was lower in the VaD, PD and PDD groups (p<0.05).

The ischemic scores differed significantly between the groups (p<0.0001), the VaD and PDD groups having higher scores than AD, PD and OC groups (p<0.05). However, none of the PDD patients received an ischemic score higher than 4. The Webster scores were significantly higher in PD and PDD than in AD and VaD groups (ANOVA/Duncan p<0.05). VaD patients had a history of cerebral infarcts. At the time of the neurological examination, right hemiparesis was present in one VaD patient and left hemiparesis in another. Two AD patients also had had a history of cerebral infarct. The frequency of coronary heart disease was 19/50 (38 %) in AD, 6/9 (67 %) in VaD, 3/8 (38 %) in PDD, 2/12 (17 %) in PD patients and 1/34 (3 %) in controls. The frequency of hypertension was 24 % in AD, 100 % in VaD, 0 % in PDD, 8 % in PD and 12 % in OC (VI).

5.2. VOLUMETRIC STUDIES

5.2.1. THE HIPPOCAMPUS

Mean hippocampal volumes for the study groups are presented in table 4, and their
distribution in figures 7 and 8. In general, men had larger hippocampi than women. In the OC group, hippocampal volumes correlated strongly to the coronal and sagittal intracranial areas (p<0.001). Differences in volumes by gender vanished after normalization. In the nondemented groups, age was not significantly related with the right (r= 0.19) nor the left (r= 0.19) hippocampal volume. The same was true when the analysis was done by gender. In women the r values were -0.13 and -0.20; and in men -0.12 and -0.04, respectively. Normalization did not change the pattern (IV).

The AD patients showed significantly smaller raw and normalized volumes of both hippocampi (ANOVA, p<0.0001) compared to nondemented controls (I, IV). The volumes did not differ significantly when the AD patients were divided into two groups, one group having had the disease less for than and the other for 36 months (the average duration) or more. The absolute volumes were smaller in patients with a longer duration. In the duration less than 36 months group, the volumes of hippocampus were 2394 mm³ on the right and 2141 mm³ on the left. In the 36 months or more group the volumes were 2223 mm³ and 1952 mm³, p=0.38 and p=0.22, respectively. When the patients were grouped into those having had the disease for a year or less vs. the remaining patients, the hippocampal volumes displayed a nonsignificant trend of being larger in the patients with the longer duration. In the less than a year group the volume of the hippocampus on the right was 2294 mm³ and 2036 mm³ on the left. In the duration more than a year group, the corresponding volumes were 2323 mm³ and 2058 mm³, respectively, p=0.91.

Hippocampal volumes did not differ significantly between OC and AAMI groups (I, IV). These groups were therefore combined into one large control group for further analyses. The combined OC/AAMI group consists of 86 subjects matched for age and gender with the AD patients.

The value of volume measurements to differentiate AD patients from controls was tested in five discriminant function analyses (IV). The analyses included 1) the raw volumes of the hippocampus; 2) the raw volumes and gender; 3) the volumes normalized for the coronal ICA1; 4) the volumes normalized for the sagittal ICA2, and 5) the volumes normalized to brain area/ICA1. The young controls were excluded from the discrimination analyses.

The analysis including the volumes of the right and left hippocampus yielded a sensitivity of 83.6 % and a specificity of 89.4 % (Chi square 104.8, df 2, Wilks' lambda 0.46, p<0.0001). The analysis explained 54 % of the variance between groups. The volume of the left hippocampus alone accounted for 53 %. The analyses using normalized volumes resulted in similar sensitivity and specificity. The highest sensitivity (94.4 %) was achieved in the analysis in which the hippocampal volumes were normalized taking into account both the coronal intracranial area and brain area. The results of the analyses are presented in table IV 3.

When the hippocampal volumes of the OC, AD, VaD, PD, and PDD groups were compared, ANOVA showed significant differences over the study groups both on the right and on the left (p<0.0001) (IV table 2, figure 1 A and B ). The OC group showed larger volumes on both sides than the other study groups (p<0.05). The right hippocampal volumes of VaD patients were also larger than those of AD, PD and PDD patients (p<0.05). On the left side, the AD patients had significantly smaller volumes than VaD and PD patients. The raw volumes in the PDD group, were even smaller than in the AD group, though not significantly. In the VaD group, two out of the nine patients had no atrophy at all, four had bilateral atrophy and three had unilateral atrophy. These patterns of atrophy could not be explained by other findings in the MRI such as number, size or strategic location of the infarcts (V).

In the AD group, the volume of the left hippocampus significantly correlated with MMSE score (r=0.42, p=0.029), immediate story recall (r=0.39, p=0.029) and delayed story recall (r=0.50, p=0.003) (I, table 5).

Table 4. Raw hippocampal volumes (mm³) +/- standard deviation by group. The distribution of the volumes is graphically presented in figures 7 and 8.

<table>
<thead>
<tr>
<th>Group</th>
<th>AD</th>
<th>VaD</th>
<th>PDD</th>
<th>PD</th>
<th>AAMI</th>
<th>OC</th>
<th>YC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MRI of Hippocampus in Incipient Alzheimer's Disease
5.2.2. THE AMYGDALA

Amygdaloid volumes were determined for the AD, AAMI, OC and YC groups. Table VI 2 presents the mean raw and normalized amygdaloid volumes for these groups, and mean volumes separately for men and women. Figure VI 1 displays the scatterplots of the volumes per study group.

The volumes were significantly smaller for AD patients than for all other groups (p<0.05). The AAMI and the OC groups did not differ significantly from each other, and were combined into a one large OC/AAMI group. The YC group differed from AD, AAMI and OC in the left amygdaloid volumes and from AD and OC in the right amygdaloid volumes. Accordingly, the normalized volumes differed across the study groups by group [F(3,138)=21.8, p<0.0001] and side [F(1,138)=26.4, p<0.0001] but not by gender (F=0.9, p>0.05) (VI).

<table>
<thead>
<tr>
<th>Right Hippocampus</th>
<th>2337 +/- 704</th>
<th>2975 +/- 572</th>
<th>2152 +/- 391</th>
<th>2557 +/- 360</th>
<th>3319 +/- 447</th>
<th>3394 +/- 519</th>
<th>3554 +/- 607</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Hippocampus</td>
<td>2070 +/- 562</td>
<td>2406 +/- 448</td>
<td>2042 +/- 215</td>
<td>2401 +/- 380</td>
<td>3100 +/- 399</td>
<td>3435 +/- 536</td>
<td>3478 +/- 466</td>
</tr>
</tbody>
</table>

Figure 7. The distribution of the unnormalized volumes of the left hippocampus of the study groups. Both genders are included.

Figure 8. The distribution of the unnormalized volumes of the right hippocampus by the study group. Both genders are included.
In the study groups, age correlated significantly (p<0.001) with raw (Figure VI 2) 
(r=-0.31 on the right and r=-0.41 on the left) and normalized (r=-0.28 on the right and 
r=-0.37 on the left) amygdaloid volumes. When the AD group was excluded, age still 
correlated significantly with raw (r= -0.29, p=0.003 on the right and r= -0.37, 
p<0.0001 on the left) and normalized (r= -0.24, p=0.018 on the right and r= -0.30, 
p=0.002 on the left) volumes. In the AD group, only the volume of the left amygdala 
correlated with age (r= -0.28 , p<0.05). On the other hand, the normalized right 
amygdala was strongly independent of age (r= -0.04, p=0.79). Interestingly, in the 
young control group, raw (r=-0.63, p=0.003 on the right and r=-0.80, p<0.0001 on the 
left) and normalized (r=-0.63, p=0.003 on the right and r=-0.75, p<0.0001 on the left) 
volumes correlated highly significantly with age. In this group the raw and 
normalized volumes of the left amygdala also correlated with education (p<0.05) 
(VI).

MANOVA for repeated measures by side (right, left) x group x gender for raw 
volumes showed significant effects of group [F(3,139)=20.1, p<0.0001), side [F 
(1,139)=26.8, p=0.0001) and gender [F(1,139)=10.8, p<0.001], but no interactions 
(p>0.05) group x side, group x gender or gender x side. Irrespective of the diagnostic 
group, the unnormalized volumes were larger for men and on the left side (VI).

Three discrimination function analyses were performed, including 1. the raw 
volumes, 2. the normalized volumes, and 3. the normalized volumes and age. Since 
the volume of amygdala did not differ significantly between the OC and AAMI 
groups, these groups were combined again, and the YC group was excluded.

The analysis including the normalized volumes produced the best correct 
classification: 41/54 (75.9 %) of AD patients and 52/72 (72.2 %) of the combined 
AAMI and OC group, and the overall correct classification 73.8 % (Chi -square 40.2, 
df 1, Wilks' lambda 0.72, p<0.0001). In all the analyses only the volume of the left 
amygdala entered the model. Thus, adding the normalized volume of the right 
amygdala or age, or both, did not improve the diagnostic sensitivity or specificity.

In the AD patients, there was no significant correlation between clinical severity 
assessed by MMSE and raw or normalized amygdaloid volumes (r= -0.09 on the right 
and r=0.14 on the left, p>0.05). The duration of the disease did not correlate with the 
volumes of the amygdala either (VI).

5.2.3. THE FRONTAL LOBES

The volumes of the frontal lobes were determined for AD, AAMI, OC and YC 
groups. Compared to the YC group, volumes were diminished in all other groups 
(right unnormalized, F(3, 146)=13.6, p<0.0001, left unnormalized F(3, 145)=12.9, 
p=0.0001, right normalized F(3, 146)=25.0, p<0.0001, left normalized F(3,145) 
=23.2, p<0.0001). Again, volumes in the OC and AAMI groups did not differ from 
each other, but differed from the YC group (p<0.05). Compared to age -matched 
controls, the volumes of the AD group were diminished in 10.5 % on the right and 
12.8 % on the left when unnormalized, and 14.5 % on the right and 15.3 % on the left 
when normalized.

In the discriminant function analysis the frontal volumes produced the following 
overall classification accuracies: right unnormalized 68 %, left unnormalized 68 %, 
right normalized 68 %, and left normalized 71 %.

The volume of the left frontal lobe correlated significantly with the Trail -Making A 
test (r=-0.44, p=0.013): the longer time spent in the test, the smaller the volume of 
the left frontal lobe. The number of errors in the Trail -Making A test also correlated 
with the volume of the left frontal lobe (r=-0.44, p=0.014) (I).

5.3. HIPPOCAMPAL AREA

The hippocampal area measured at the level of the anterior commissure was
significantly smaller on the right and left for AD patients and AAMI subjects than for older and younger controls (p<0.05). On the left AD patients also differed significantly from AAMI subjects (p<0.05). The areas on both sides correlated to the actual volume on the right (r=0.70, N=125, p<0.0001) and on the left (r=0.71, p<0.0001). The discriminant function analysis between the AD and the OC group produced a sensitivity of 76.9 % and specificity of 72.4 %, resulting in an overall correct classification of 75.3 % (Chi square 36.1, df 2, Wilks’ lambda 0.63, p<0.0001). The hippocampal areas were unnormalized (IV).

5.4. INTERUNCAL DISTANCE

The IUD data are summarized in Table II 2. IUD was measured for AD, AAMI, OC and YC groups. ANOVA over the study groups showed a significant difference in standard IUD [F(3,137)=11.4, p<0.0001]. The YC group showed significantly shorter IUD compared to the three older groups (p<0.01), but the OC, AAMI and AD groups did not differ from each other. The scatterplots (Figure II 2 a) demonstrate the overlap of IUD values across the study groups.

IUD exceeded the proposed pathological limit of 30 mm in 21/54 (37 %) of AD patients, in 13/40 (33 %) of AAMI subjects, in 6/27 (22 %) of OC, and in 1/20 (5 %) of YC group. The cut -off point of 30 mm resulted in 37 % sensitivity and 72 % specificity to separate AD from combined AAMI and OC groups. The positive predictive value was 53 % and the negative predictive value was 59 %.

There was also a significant difference in IUD/ICW (p<0.0001). The YC group differed from all the other groups (p<0.01), whereas the values of the AD group were comparable with those of the age -matched older groups. The IUD/ICA and IUD/BA values were also significantly smaller for YC compared to the OC, AAMI and AD groups (p<0.01). In addition, the AD group differed significantly from OC and AAMI groups in IUD/ICA (p<0.05) and IUD/BA (p<0.01). Despite these significant differences, the variables overlapped across the age -matched study groups (Figure II 2 b).

In the whole study population age correlated significantly (p<0.0001) with IUD (r=0.41), IUD/ICW (r=0.41), IUD/ICA (r=0.45), IUD/BA (r=0.55) as well as with brain area (r= -0.59). Similar significant correlations (p<0.0001) with age were observed when only the nondemented subjects (young and old controls and AAMI subjects) were included in the analysis. Within the AD group standard and adjusted IUD was not related to age, but brain area was (r= -0.41, p<0.01). Brain area also correlated significantly with age for AAMI subjects ( -0.48, p<0.01) and old controls (r= -0.39, p<0.05).

In the first stepwise discriminant function analysis including IUD, IUD/ICW, IUD/ICA, IUD/BA, age and sex, 72 % of AD patients and 79 % of age -matched nondemented elderly subjects were correctly classified (Wilks' lambda 0.69, Chi -square 42.5, df 5, p<0.00001). This model explained only 31 % of the variance between groups. The best distinguishing variable, IUD/BA, explained 13 % of the variance, and the further contribution of other variables was less (IUD/ICW 8%, sex 4%, age 3% and IUD/ICA 2%). In the second analysis, including IUD/BA, age and sex, 63% of AD patients and 72% of nondemented elderly were correctly classified (Wilks' lambda 0.82, Chi-square 22.8, df 3, p<0.00001).

The mean IUD for AD patients with CDR questionable, mild and moderate dementia was 28.9 ± 1.7 mm, 28.7 ± 4.6 mm and 30.9 ±5.7 mm, respectively. The difference in standard or normalized IUD was not significant between the AD groups with differing clinical severity. Within the AD group, there was no significant correlation between MMSE test scores and IUD either (II).

5.5. RELAXOMETRY
Table III 1 presents the results of the relaxometry for AD, AAMI, OC and YC groups. ANOVA showed significant differences in T2 of the right hippocampal head ($p<0.01$) and tail ($p<0.05$) between AD and nondemented study groups; AD patients differed from OC (head) and from OC and AAMI (tail). For T2 of the right hippocampal head, which showed the most clear significant difference, the 95% confidence intervals of the means were 95.7 -101.2 ms for AD, 90.6 -96.8 ms for AAMI, 87.4 -95.9 ms for OC, and 92.9 -99.3 ms for YC groups. The T2 of the amygdala did not differ between groups.

In AD patients, T2 of the left hippocampal head correlated significantly with MMSE scores ($r=-0.44$, $p<0.01$) (Figure III. 2). Table III. 2 and Figure III. 3 show that T2 in the hippocampal head and tail differed significantly between AD patients at CDR stages 0.5, 1 and 2, as well as OC. AD patients with moderate dementia differed both from OC and AD patients with mild disease. In AD patients, T2 did not correlate with memory test scores (data not shown).

The T2 of temporal white matter on the left was significantly prolonged both in AD and OC groups ($p<0.05$) and the parietal relaxation times in all elderly groups were prolonged compared to young controls ($p<0.05$). The T2 of the thalamus on both sides was also significantly longer in the AD and AAMI groups ($p<0.05$) than in the YC group. In AAMI, the T2 of the structures studied did not differ significantly from elderly controls.

The differences in T2 remained significant in ANOVA adjusted for a history of hypertension and coronary heart disease. No significant correlations between age and hippocampal T2 were found (Figure III 4). Thus, the prolongation of T2 in the hippocampal head and tail of AD patients was not explained by either age or by the presence of vascular diseases. In contrast, T2 in temporal and parietal white matter was significantly related to age in the whole study population, including nondemented subjects (AAMI, OC, YC), with $r$ ranging from 0.27 to 0.45 ($p<0.01$) (Figure III 5). Therefore, the increased T2 in cortical white matter is explained by age rather than by the diagnostic category or by a history of hypertension or coronary heart disease (III).

In VaD, the T2 was prolonged in the left hippocampal head (106 ms, $p<0.001$) and in both the right and left tail (106 ms, $p<0.05$ compared to AD). T2 values in PD and PDD did not differ from nondemented controls.

The average T2 of cerebrospinal fluid (CSF) from fourteen measurements of the lateral ventricles was 2214 ± 544 ms.

5.6. ANALYSIS OF THE INCORRECTLY CLASSIFIED

The analysis of the incorrectly classified is based on the classification of AD patients versus nondemented subjects by hippocampal volume. The main results of the analysis are presented in Table IV 4. Correctly and incorrectly classified AD patients did not differ significantly in age, sex, age at onset, duration of disease, education, extrapyramidal signs assessed by the Webster scale, depressive symptoms evaluated by the Hamilton scale, ischemic scores, or frequency of a positive family history. As expected, hippocampal volumes were significantly larger in the ADMC than in the ADCC group ($p<0.0001$). The ADMC patients also had significantly higher MMSE scores ($p<0.05$) as well as less severe memory impairment in tests assessing delayed recall of the Heaton Visual Reproduction test ($p<0.05$) and the story ($p=0.0002$) than ADCC patients. Otherwise the profile of cognitive deficits was similar in both groups.

The incorrectly classified controls were significantly older than those correctly classified. They also showed smaller hippocampal volumes ($p<0.0001$), and more severe memory decline evident from the Buschke Selective test total ($p<0.01$) and
long term scores (p<0.001). Performance in other cognitive domains was equivalent for these two groups.

Individual evaluation of follow up data on the nine incorrectly classified AD patients showed that only two of the patients could be considered to show merely typical features of AD. Of the other seven patients, one patient had experienced a vascular insult and possibly had VaD, one patient had strong extrapyramidal signs and may therefore represent atypical PD or Lewy body disease or variant of AD, two patients had a strong family history for AD but had very mild disease, scoring 26 and 27 points in the MMSE examination and showing no deterioration during the follow-up. Three patients exhibited frontal features. No follow up data for the older controls or AAMI subjects are available yet.

### 6. DISCUSSION

This study focused on MRI of the hippocampus, and its use in the diagnosis of early AD. Hippocampal atrophy appears not to be a finding specific to AD, but a sensitive finding in dementias with temporal lobe involvement. The lack of hippocampal atrophy, however, appears to be highly accurate for exclusion of AD, and perhaps other dementing conditions. Therefore it can be concluded that this study provides strong evidence on behalf of using hippocampal volumetry in the characterization of memory impairment.

Several approaches for the evaluation of hippocampal involvement were chosen, starting with volumetry, for which thin, contiguous, optimally oriented T1-weighted slices were used. This method is easily applicable, relatively quick to learn and use (approximately 10 minutes to obtain the volumes bilaterally), and provides substantial intra- and interrater accuracy. The importance of using thin slices cannot be overemphasized, since even with slices as thin as 3 mm, partial volume effect may cause a 30% error in the volume of the hippocampus when coronal slices are used (Cook et al. 1992). Furthermore, various methods for normalization were tried. All measurements were performed blindly by a single rater and in a similar manner. The study subjects were well documented and their number is representative - by far the largest in a study of this method. Second, the sensitivity of volumetry was compared to that of a single measurement of hippocampal area, and a linear measurement, the IUD. Third, MR T2-relaxation times for head, body and tail of the hippocampus were measured. Moreover, sensitivity and specificity of hippocampal imaging were compared to those of the adjacent amygdala and frontal lobes.

The hippocampus was chosen as a ROI since it is known to be important in memory functioning (Squire and Zola Morgan 1991) and known to be affected and atrophied early in the course of AD (Hyman et al. 1984; 1990; 1995; Ball et al. 1985). By contrast, the volume of the hippocampus seems to remain practically unaffected by normal aging (Bhatia et al. 1993; DeCarli et al. 1994). Imaging of the hippocampus has been found to be reliable (Squire et al. 1990; Jack et al. 1992 a; b). Nevertheless, MRI studies of the hippocampus have produced mixed results in diagnosing AD.

All previous major findings were supported by this study: the hippocampus is atrophied early in AD; performance in several memory functions that are considered to be mediated by the hippocampus declined and correlated with hippocampal volume, whereas no correlations between hippocampal volume and tests assessing non-mnemonic performance were found. In nondemented subjects there was no
significant correlation between hippocampal volume and age. This was the case despite the fact that the VC group can easily be referred to as "supernormal" control group; they were students of medicine and staff members, some having a Ph.D in medicine. It was also found that a short-cut in methodology, such as measurement of the hippocampal area or IUD on a single slice, is likely to produce an inaccurate result.

6.1. SENSITIVITY AND SPECIFICITY OF HIPPOCAMPAL MEASUREMENTS IN ALZHEIMER'S DISEASE vs. NONDEMENTED SUBJECTS

The hippocampus is atrophied already at an incipient clinical AD. The best discriminative value of the volumetric hippocampal atrophy found in this study, the overall accuracy of 87.1\% 92.0 \%, demonstrates that MRI of the hippocampus provides entirely additional data to support the clinical diagnosis of AD versus nondemented subjects. Particularly, the specificity was high, 92.9 \% at best. The sensitivity for the AD group, probably bargaining at the expense of specificity, could be raised up to 94.4 \% by taking into account the overall brain atrophy. This analysis also yielded the best overall accuracy of 92.0 \%. It is important to notice that the hippocampal volumes did not correlate to duration of AD but were atrophied in the AD group having the disease last less than a year.

The measurement of the hippocampal area produced a correct overall classification of only 75 \%. The IUD, using a cut-off point of 30 mm suggested in the literature, produced only a sensitivity of 37 \% and a specificity of 72 \%. The T2 was significantly prolonged in the right hippocampal head and tail and the prolongation was not explained by high age or presence of vascular disorders. The actual diagnostic value, however, was compromised by substantial overlap between the study groups.

It does seem that the use of volumetry is the one and only common denominator found in the studies that have ended up in a good discriminating accuracy (Kesslak et al. 1991; Jack et al. 1992 a; Killiany et al. 1993; Lehéricy et al. 1994). No contradictory findings have been reported. Instead many simpler linear and planimetric measurements have not been as successful (LeMay et al. 1986; Cuénod et al. 1993; Early et al. 1993; Erkinjuntti et al. 1993; Howieson et al. 1993 b.). This trend is also supported by the experience of the CT studies (LeMay et al. 1986; DeCarli et al. 1990). Occasional studies, such as that of Seab et al. (1988), have provided better accuracy. Still, the average accuracy of linear measurements in distinguishing AD patients from controls seems to range from 65 to 75 \%, as presented in this study as well.

It is presumable that simple measurements are far too much subject to individual variability, to variability caused by rotation of the head in every possible dimension, and are also more easily affected by various aberrations, such as artifacts or volume averaging. These sources of error are avoided only by measuring the whole ROI, preferably by using thin slices.

Normalization methods used in this study did not notably improve the accuracy. This is not completely unexpected, because the study subjects were well matched and their number was large enough to allow much of individual variance to vanish. The significane of proper normalization must, however, not be underestimated, but be considered as an important procedure for exclusion of normal variation and particularly differences due to gender. In the OC group, the volume of the hippocampus correlated to cranial area, and men do tend to have larger head size.

Normalization variables have varied a plenty in the literature. An often proclaimed normalization variable is intracranial volume, which logically seems most authoritative. Still, the demarcation of the intracranial volume is often merely stated and seldom defined in detail. Also, delineation of a bony structure is manditorially somewhat arbitrary, since compact bone is not properly visualized by MRI. This is
true in this study as well, since at least the coronal intracranial area is drawn along the most clear signal, which is caused by subcutaneous adipose tissue. Therefore, the method includes calvarium, and the proper name for the variable might be the cranial area. However, the normalization is performed similarly for each and every study subject using not too simple, and therefore vulnerable, a variable. The sagittal ICA (ICA 2) has been previously considered as a valid method for normalization (Free et al. 1995). Judging by this study, the coronal ICA (ICA 1) is a valid method as well. The intracranial width emerges to be too vulnerable a method for accurate normalization. Normalization to BA deserves further attention. This method can not be regarded as a reliable variable for normalization of atrophic changes, since it is vulnerable to physiological, and neurodegenerative, atrophy in itself. Therefore an index between two atrophying, or preferably diminishing, structures might end up as a normal result or at least worse accuracy. Oppositely, normalization of atrophic changes in which there occurs dilatation, or growth, by BA might improve the accuracy. Still, normalization to BA might provide some information of the nature or amount of the atrophy of a certain structure compared to more generalized overall atrophy. As for the future, in order to obtain a vastly accepted imaging protocol for pooling comparable data from multicenter studies, and to define normal and pathological ranges for the hippocampal volumes, a commonly accepted imaging protocol, including proper normalization, is needed.

6.2. ANALYSIS OF THE INCORRECTLY CLASSIFIED

Analysis of the incorrectly classified is based on evaluation of study subjects who were incorrectly classified by hippocampal volumetry. Curiosity about the analysis of the incorrectly classified arose from the fact, that any current clinical criteria can not be regarded as water-proof either in separating AD from normal impairment along aging, not to mention non-AD dementias (Erkinjuntti et al. 1986; Tierney et al. 1988; Kukull et al. 1990; Risse et al. 1990; Welsh et al. 1992; Almkvist and Bäckman 1993; Blacker et al. 1994). The sensitivity and specificity of the NINCDS ADRA criteria have been reported to vary between kappa 0.83 0.92 and 0.65 0.84, respectively (Kukull et al. 1990; Blacker et al. 1994). Thus, it is probable that despite careful clinical diagnosis by the same raters, the study sample includes patients grouped as AD but who are not demented, or then suffer from a non AD dementia. Vice versa, it is also possible that the control group includes subjects with subclinical dementia, or subjects who are later bound to develop dementia. It is also possible that some patients would represent heterogeneity of AD, in which the hippocampus remains relatively unaffected by the disease.

To reexamine the presence of dementia, results of basic cognitive tests and tests assessing delayed recall were compared. As stated previously, the tests assessing delayed recall have been documented to be sensitive to dementia and spared by aging (Petersen et al. 1992; Welsh et al. 1992; Howieson et al. 1993 a.). In addition, the hippocampal volume has shown to correlate with performance in tests assessing delayed recall (Scheltens et al. 1992; Golomb et al. 1994 b.; Deweer et al. 1995). To examine the presence of possible subtypes of AD or non AD dementia, such as Pick's disease, frontal lobe dementia, Lewy body disease, or a dementia syndrome, some symptoms that may appear with AD but more typically are associated with other forms of dementia were compared (Gibb et al. 1985; Mayeux et al. 1985; Friedland et al. 1988; Neary et al. 1988; Reichman and Cummings 1990; Friedland 1993; Mendez et al. 1993; McKee et al. 1994). All the AD patients that were incorrectly classified using volumetry were individually reappraised from follow up data. Of course, this analysis does not reveal or exclude mistakes in volumetry possibly made by "rater asleep at the console".

The ADMC group performed significantly better in the MMSE and tests assessing delayed recall, but their deficits in other cognitive domains were similar to those of ADCC. Individual reevaluation showed that seven out of nine AD patients to have features that relate to other forms of dementia or to have very mild AD. Thus, the true discriminative accuracy may be even higher than reported. This is particularly true in regard to false positives. All the epsilon 4 homozygote AD patients were
correctly classified. Among the nondemented elderly there were seven epsilon 4 homozygotes, and they all were correctly classified as well. Follow-up data on controls and AAMI subjects was not available.

6.3. THE AMYGDALA

The raw and the normalized volumes of the right and the left amygdala in AD patients compared to the combined OC/AAMI group were diminished 18.9/21.9 % and 21.0/23.6 %, respectively. Using these volumes a correct overall classification of 74 % of these study subjects was achieved. No significant correlation between the clinical severity assessed by MMSE and amygdaloid volumes was found.

The MRI of the amygdala has also been a matter of controversy. The discrepancy in the magnitude of volume loss of the amygdala in this and previous studies may be explained by the less severe dementia with a relatively short duration, and narrowness of the clinical severity of the study group as well as probably by methodological differences in outlining the amygdala. Since the amygdala is a heterogeneous structure composed of numerous nuclei in both cortical and subcortical areas, its strict anatomic boundaries in MRIs have been found difficult to determine, and the demarcation of these borders has been somewhat arbitrary, often resulting in compromises (Pearlson et al. 1992; Bartzokis et al. 1993; Cunod et al. 1993; Killiany et al. 1993; Lehéricy et al. 1994). This, in turn, may result in exclusion of nuclei responsible for changes in the volume. An exact delineation of the amygdala was considered difficult in this study as well: the reproducibility of the volume of hippocampus was found to be more reliable than that of the amygdala. Demarcation of the amygdala was considered particularly difficult in its anterior parts.

Histopathologic studies have indeniably demonstrated that the amygdala is damaged in AD, with pathological changes occurring mostly in the nuclei that receive or give rise to hippocampal or entorhinal projections (Kromer-Vogt et al. 1990; Scott et al. 1991; Mann 1992; Vereecken et al. 1994). The results of these post-mortem studies are not readily comparable with current findings. It is likely that the trend towards atrophy reflects the course of the disease process, proceeding from more affected regions, such as the entorhinal cortex and the hippocampus, towards the amygdala. Thus, judging by volumetric atrophy, the amygdala is not one of the primary sites of AD. Correlations between the amygdala and severity of the disease or memory functions were not found, supporting the current concept according to which the amygdala is not directly involved in memory functioning.

6.4. THE FRONTAL LOBES

The volumes of the frontal lobes compared to nondemented controls were diminished. Aging also contributed to the size. The decrease of the volumes in percentage was a little less than that of amygdala, but the discriminating accuracy was about similar. Thus, volumes of frontal lobes apparently reflect merely enhanced and unspecific overall atrophy of AD brain. Also, the factor contributing to the widespread volume loss appears to be present already at the early stage of the disease, and the AD, at the level of the novel symptoms, has already proceeded beyond the temporal pole. On the other hand, aging itself does affect the volume of the frontal lobes more than it does the temporal lobe (Cowell et al. 1994; DeCarli et al. 1994).

6.5. T2 RELAXOMETRY
A significant prolongation of T2 in the right hippocampal head and tail was found which could not be explained by either age or presence of vascular disorders. In AD, the global clinical severity, but not the memory test scores, correlated with the T2 of the left hippocampal head. The T2 was prolonged in AD patients with moderate disease, whereas values for those in the mild stage were comparable to those of controls. The T2 of amygdala did not differ between the groups. In the neocortical white matter, significant differences of the T2 were not related to AD, but were explained by high age.

Even though differences in the T2 were found, the diagnostic value was compromised by major overlap in the study groups. No significant side-to-side differences were discovered, nor was there any segmental pattern of T2 values in the three anatomical regions of the hippocampus. The considered pathological limit of about 110 ms was exceeded in only 3 patients of the AD group and none of the controls. Those few could by statistics represent a rare dementia with hippocampal sclerosis as a primary pathologic finding (Zweig et al. 1989; Jellinger 1994). The mean T2 of all the regions of the hippocampus in normal controls groups was comparable to those reported by Kirsch et al. (1992) and Jackson et al. (1993).

In addition to the prolongation of T2 in the hippocampus reported by Kirsch et al., a visually increased hippocampal T2 signal in AD has been reported (Fazekas et al. 1987). The visually detectable high signal, however, is probably due to hippocampal sulcus remnant present in 39 % of people without temporal lobe pathology (Sasaki et al. 1993), or due to dilatation of choroidal and hippocampal fissures (George et al. 1990). When measured at 7 T in vitro, the T2 did not indicate the presence or severity of AD or vary between hippocampal subfields (Huesgen et al. 1993). T1 values measured at 0.08 T were reported to be similar for presenile AD patients and controls in the study of Christie et al. (1988).

The T2 (spin-spin or transverse relaxation) is dependent on numerous factors, such as observation frequency, temperature, mobility of observed spin, and presence of large molecules, paramagnetic ions and molecules, or other outside interference. In most tissues one component, usually water (or CSF), dominates the relaxation behavior. In the presence of two components with different relaxation properties, the quantitative interpretation is even more complicated (Rinck 1993 a.). Many pathologic conditions are known to produce alterations in factors that account for the observed relaxation behavior of tissues. The most important of these is the increased presence of water, in the region. There are many possible reasons for this such as hippocampal fissure and/or uncual sulcus, developmental cyst (Bronen and Cheung 1991 b,c; Sasaki et al. 1993), increased CSF in atrophying region, lacunae, and oedema.

Another common cause of prolonged T2 is considered to be gliosis or glioma (Bronen et al. 1991). In AD, the chronic inflammation resulting from the accumulation of amyloid is known to produce microgliosis and astrocystosis (McGeer et al. 1989; Delacourte 1990; Mandbyur and Chuirazzi 1990; Ohgami et al. 1991). The T2 arising from both microgliosis and astrocystosis might be difficult to interpret: the signal of astrocystosis might increase the overall signal whereas T2 might be shortened due to iron in microglia, NFTs or SPs in the hippocampus (Leveugle et al. 1994; Antonini et al. 1993; Drayer 1988 a, b).

Further possibilities are normal variations between subjects and within one individual, and variations caused by anatomical position or machine drift (Harvey et al. 1991), pharmaceuticals (Karlik et al. 1986), hamartoma, vascular malformations, nonspecific calcification, scarring (Bronen et al. 1991), flow artifacts, volume averaging, observer variation, poor image quality, or differences in imaging parameters. It is also noteworthy that T2 of the hippocampal body did not show differences between the groups. This might be due to the fact that, when using proper tilting, the body does not curve. It may be possible, that when measuring more irregularly shaped atrophied head or tail, partial volume averaging of CSF might occur. However, since the underlying sources of the T2 are not yet determined, it is also possible that the T2 signal arises from factors that are entirely independent of those producing the atrophic changes.

The T2 (spin-spin or transverse relaxation) is dependent on numerous factors, such as observation frequency, temperature, mobility of observed spin, and presence of large molecules, paramagnetic ions and molecules, or other outside interference. In most tissues one component, usually water (or CSF), dominates the relaxation behavior. In the presence of two components with different relaxation properties, the quantitative interpretation is even more complicated (Rinck 1993 a.). Many pathologic conditions are known to produce alterations in factors that account for the observed relaxation behavior of tissues. The most important of these is the increased presence of water, in the region. There are many possible reasons for this such as hippocampal fissure and/or uncual sulcus, developmental cyst (Bronen and Cheung 1991 b,c; Sasaki et al. 1993), increased CSF in atrophying region, lacunae, and oedema.
The contradictory results of this study compared to the study of Kirsch et al. might be partly explained by larger sample size and the fact that most of the patients in the present study had mild dementia. Prolongation of the hippocampal T2 was not seen until in moderate dementia showing that the measurement of the hippocampal T2 does not help in diagnosing mild AD. Also, in the present study a 1.5 T imager was used compared to a 0.04 T imager used in the study by Kirsch et al. A 1.5 T imager has a better signal-to-noise ratio. Thus, it is possible that a low signal-to-noise ratio would result in noisy T2 maps. Consequently, it might be easier to avoid CSF in the measured ROI at high field. The field strength should not affect the interpretation of T2 as much as it would affect that of T1 (Rinck 1993 a.). Methodologically, the Carr-Purcell-Meiboom-Gill sequence used in the study is adequate (Rinck 1993 b.).

In this study, the overlap between the groups was considerable and it is concluded that the T2 relaxometry of the hippocampus or other structures studied here are of no use in diagnosing AD at its early stage.

6.6. HIPPOCAMPAL ATROPHY AMONG NON-ALZHEIMER CONDITIONS AND DEMENTIAS

Hippocampal atrophy is not a phenomenon completely specific for AD. There are some conditions that must be considered when judging the atrophy.

Patients with Down's syndrome (DS) constantly develop dementia after 40 years of age. As in AD, CT studies have revealed overall brain atrophy with affection of the temporal lobe (Lai and Williams 1989; Schapiro et al. 1989). Also, MRI study has reported hippocampal atrophy in DS, with the atrophy being more profound in demented patients. The same studies also reported an unexplained enlargement of the parahippocampal gyrus in DS (Kesslak et al. 1994; Raz et al. 1995). Even though differentiation of dementia from a possible mental retardation is the cause of uncertainty, the dementia overrepresented in DS, and hippocampal atrophy, bears no dilemma for differential diagnosis, since it has been considered to be AD, and has even been mentioned in subtypes of AD in the NINCDS-ADRDA research criteria (McKhan et al. 1984). Patients with DS show similar clinical symptoms as do patients with AD (Brugge et al. 1994); in both diseases there are similar neuropathological (NTs, SPs, loss of hippocampal area) (Mann et al. 1990) and neurochemical findings (Godridge et al. 1987). Further, DS is due to trisomy of chromosome 21, which also harbors genes for Aβ precursor and familial AD, and may therefore lead to increased Aβ burden (Tanzi et al. 1987; St. George-Hyslop et al. 1987). Therefore, the hippocampal atrophy in DS can in fact be weighed as data that mostly supports the findings of the AD studies.

Recent study has also proposed the hippocampus being diminished in another genetic disorder, Turner's syndrome (Reiss et al. 1993). By contrast, in fragile X syndrome the hippocampus has been reported to be enlarged (Reiss et al. 1994). In that study the control group, however, consisted of subjects suffering from other developmental disorders, such as DS patients, and the average hippocampal volume was smaller than what is proposed in this study.

Hippocampal atrophy has also been reported in amnestic conditions due to temporal lobe pathology (Press et al. 1989; Kritchevsky and Squire 1993). On the other hand, the volume of the hippocampus has been reported to remain unaffected in non temporal amnesias, for example in Wernicke Korsakoff syndrome (Valenstein et al. 1987; Squire et al. 1990), and even in traumatic amnesia with anterior temporal lobe pathology (Kapur et al. 1992). Infections or inflammations, such as Herpes simplex encephalitis and paraneoplastic limbic encephalitis, that may cause amnesia or dementia by affecting the temporal lobe may also influence the hippocampal volume (Lacomis et al. 1990; Kapur et al. 1994; Yoneda et al. 1994). This in turn might have an effect on the hippocampal volumes in HIV dementia. Amnesias must be regarded as a differentially important category, since amnesia may initially be misdiagnosed as AD, or the first symptom for AD may be amnesia (Katzman 1986; Kritchevsky and Squire 1993).
The symptomology of schizophrenia may also include memory dysfunction, resembling that of classic amnestic syndrome, that is unattributable to motivation, cooperation or side effects of the medication (Duffy and O’Carrol 1994). Also the volume of hippocampus may be affected by the pathology of schizophrenia. In the twin study of Suddath et al. (1990) 14 out of 15 monozygotic twins affected by schizophrenia had bilaterally diminished volumes of the hippocampus. Bogerts et al. (1993) found correlation between diminished volume of the hippocampus amygdala complex and positive psychotic symptoms. Despite significant atrophy of the complex, the study groups presented overlap in 75% of the cases. Zipursky et al. (1994), on the other hand, found no differences in the hippocampal volumes between schizophrenics and controls. Even schizophrenia may be associated with entorhinal pathology (Arnold et al. 1991). The volume of hippocampus has been reported to be spared in another differentially important neuropsychiatric concept, pseudo dementia caused by depression (Coffey et al. 1993; O’Brien et al. 1994). In dementia associated with multiple sclerosis, hippocampal plaques and demyelinization visible in MRI has been reported (Fontaine et al 1994; Tsolaki et al. 1994).

Apart from memory disorders, the best known condition in which hippocampal atrophy occurs, is temporal lobe epilepsy (TLE). In TLE, MRI volumetry has already found a place both in research and clinical decision making, in which detection of atrophy and signal abnormalities of the hippocampus have been found to be useful tools in the lateralization of the epileptogenic focus. In TLE the hippocampus is mostly atrophied unilaterally, and often accompanied with changes in morphological appearance (Cook et al. 1992; Jackson et al. 1993).

Further review for MRI of the hippocampus in cognitive dysfunction is restricted, since no data appears to be available. But, what about the other functions of the hippocampus? Does pathology in the olfactory system or of adequate response to stimuli affect the hippocampal volume? In Kallman’s syndrome (hypogonadotrophic hypogonadism with congenital anosmia) hippocampal–amygdaloid volume has been reported to remain the same as with controls (Yousen et al. 1993). The stress, and the stress response, modulated by corticosteroids is a matter of controversy. Corticoid excess is known to cause cytotoxic hippocampal damage (Stein-Behrens et al. 1994). That excess has been reported to cause modest hippocampal atrophy detected by MRI (Starkman et al. 1992; Bremner et al. 1995), but an another study could not replicate the finding (Axelson et al. 1993).

6.6.1. MAPPING THE AGE-ASSOCIATED MEMORY IMPAIRMENT

On the basis of this study, AAMI can be separated from dementia by the hippocampal volumetry. In a previous study the volume of hippocampus in AAMI was spared, but the normal right-left asymmetry was diminished (Soininen et al. 1994). The diminished asymmetry may imply that in some of the study subjects, the pathologic process of AD has begun. This sparing of the volume of the hippocampus in general, however, strongly supports the assumption that AAMI, by NIMH criteria, is related rather to normal aging than to dementia and cannot be located into the cognitive continuum. Besides the volume of the hippocampus, the OC and the AAMI groups did not significantly differ from each other in the volumes of the amygdala or the frontal lobes, in the length of the IUD or the hippocampal or amygdaloid T2.

These findings gathered it is concluded that non-dementia memory impairment can be diagnosed and reliably differentiated from dementia by MRI methods, particularly by hippocampal volumetry. Given the high prevalence of AAMI (Barker et al. 1995; Koivistö et al. 1995) and substantial validity of the criteria (Hänninen et al. 1995), AAMI in terms of prognosis and differential diagnosis, in relation to AD, is more important than VaD.

6.6.2. VASCULAR DEMENTIAS

This study indicates that hippocampal atrophy appears not to be a specific finding to AD, but it also occurs in VaD and PDD as well as, to a lesser degree, in PD without dementia.

The patterns of atrophy in the VaD group are most interesting, but more difficult to
explain. Four patients had bilateral hippocampal atrophy, two had no atrophy at all, and three had unilateral atrophy. In three out of the four patients with unilateral atrophy, the right hippocampus was larger. Other findings in T2-weighted axial MR images could not clarify the nature of these findings. No large or strategic infarcts or other lesions were found in the temporal lobes or in the area of the posterior cerebral artery, responsible for the circulation to the hippocampus. However, it is likely that these patterns of atrophy represent the results of different vascular lesions or etiologies. One might assume, that in those two VaD patients without atrophy the lesions causing the dementia do not affect the size of hippocampus at all. Likewise, in cases with unilateral atrophy, the lesions affect the hippocampus on only one side. The cases with bilateral atrophy have vascular lesions affecting the hippocampus bilaterally, or alternatively they may well represent mixed dementia, that is, the combination of AD and VaD. In a previous autopsy study, the presence of mixed dementia was surprisingly high: three out of four patients considered to have VaD had also AD, and 5/16 patients considered to have mixed dementia had AD alone (Wade et al. 1987).

These findings need definitely to be further surveyed, and the background of this asymmetry explained by a pathologic confirmation, since VaD is the differentially most important type of dementia for AD, in terms of both numbers and because there is potential for prevention and intervention for VaD.

6.3.3. PARKINSON'S DISEASE AND DEMENTIA

Major atrophy of the hippocampus in PDD and even PD is a bit of a surprise, and difficult to explain as well. Temporal lobe pathology plays apparently more important role in PD than previously emphasized. No temporal atrophy in MRI of the PD brain has been previously reported. Even though markers of AD pathology are known to be found in PD brains, hippocampus and entorhinal cortex (Jellinger 1987; Braak et al. 1993), the hippocampal atrophy was not primarily supposed to reach, and exceed, the atrophy observed in AD. This is because AD changes may be observed in nondemented aging as well (Bouras et al. 1993; Langui et al. 1995), but the MRI of hippocampus reveals practically no atrophy, not even sporadically, in nondemented elderly, several out of whom by statistics would be harboring landmarks of AD pathology under the microscope. This raises a question whether the volumetric atrophy is caused by factors other than the classical AD landmarks. The T2 of the hippocampus did not differ between the PD groups and the nondemented controls.

The number of PD subjects in this study is restricted, and a possible coexistence of AD cannot be excluded in PDD patients, but still, the trend towards atrophy in PD patients indicates profound pathologic process to take place in the temporal lobe. The pattern of the hallmarks of AD in the PD hippocampus might be different from that in AD. The amygdala is known to be affected in PD as well, but the pattern of affection and atrophy is not similar to that observed in AD (Braak et al. 1994). More sophisticated MRI techniques than plain volumetry would be probably required to reveal a possibly distinct pattern of atrophy.

CONCLUSIONS

1. Hippocampal atrophy is a highly sensitive indicator of incipient AD. It's evaluation by MRI volumetry provides entirely additional data to support the diagnosis. In contrast, simpler measurements or T2 relaxometry provided only little diagnostic aid. The volume of the hippocampus
correlated significantly with clinical severity assessed by MMSE, and with tests assessing delayed recall, which is considered to be affected early in dementia and may reflect hippocampal dysfunction.

2. The volume of the hippocampus is not significantly affected by normal aging.

3. AAMI can be differentiated from dementia by hippocampal volumetry. Judging by hippocampal volumes AAMI is a phenomenon of normal aging rather than an intermediate in the continuum from normal cognition to dementia.

4. Hippocampal atrophy may not be a phenomenon specific to dementia in AD, but a common feature of dementias with temporal lobe pathology. Hippocampal atrophy was also found in VaD and PD as well. In PD, temporal lobe pathology appears to be present more often and more severe than usually described. The hippocampus was atrophied bilaterally in some, but not all, VaD cases, and displayed unilateral pattern in some. Since VaD is most important type of dementia to be differentiated from AD, this phenomenon will need some further attention in future studies.

5. Volumetry of the amygdala or frontal lobes provide little substantial data to help with MRI diagnosis.

All and all, hippocampal volumetry is useful in excluding AD and separating it from benign, (non-parkinsonian) age-associated memory impairment.

7. REFERENCES


Arnold SE, Hyman BT, Van Hoesen GW, Damasio AR. Some cytoarchitectural abnormalities of the entorhinal cortex in schizophrenia. Arch Gen Psychiatry 1991;48:625-632


Axelson DA, Doraiswamy PM, McDonald WM, Boyko OB, Tupler LA, Patterson LJ, Nemeroff CB, Ellinwood EH Jr, Krishnan KR. Hypercortisolemia and hippocampal changes in depression. Psychiatry Res 1993;47:163 173


Benton AL. The visual retention test as a constructional praxis task. Conf Neurol 1967;29:1 16


Borkowski JG, Benton AL, Spreen O. Word fluency and brain damage. Neuropsychologia


Brust JCM. Vascular dementia is overdiagnosed. Arch Neurol 1988;45:799-801

Byrne EJ, Arie T. Tetrahydroaminoacridine and Alzheimer's disease. For the few, but we don't know which few. BMJ 1994;308:868-869


Clark GA. Fear and loathing in the amygdala. Current Biology 1995;5:246-248


Cook MJ, Fish DR, Shorvon SD, Straughan K, Stevens JM. Hippocampal volumetric and


Doraiswamy PM, McDonald WM, Patterson L, Husain MM, Figiel GS, Boyko OB, Krishnan KR. Interuncal distance as a measure of hippocampal atrophy: normative data on axial MR imaging. AJNR 1993;14:141-143

Drachman DA. If we live long enough, will we all be demented? Neurology 1994;44:1563-1565


Duffy L, O'Carroll R. Memory impairment in schizophrenia - a comparison with that observed in the Alcoholic Korsakoff Syndrome. Psychol Med 1994;24:155-165


Early B, Escalona PR, Boyko OB, Doraiswamy PM, Axelson DA, Patterson L, McDonald WM, Krishnan KRR. Interuncal distance measurements in healthy volunteers and in patients with Alzheimer disease. AJNR 1993;14:907-910


Friedland RP. 'Normal'-pressure hydrocephalus and the saga of the treatable dementias. JAMA 1989;262:2577-2581


Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56-62


Howieson DB, Holma LA, Kaye JA, Oken BS, Howieson J. Neurologic function in the optimally


Jackson GD, Connelly A, Duncan JS, Gadian DG. Detection of hippocampal pathology in intractable partial epilepsy: Increased sensitivity with quantitative magnetic resonance T2 relaxometry. Neurology 1993;43:1793-1799


Lai F, Williams RS. A prospective study of Alzheimer disease in Down syndrome. Arch Neurol...


Mark LP, Daniels DL, Naidich TP, Williams AL. Hippocampal anatomy and pathologic alterations on conventional MR images. AJNR 1993;14:1237-1240


Press GA, Amaral DG, Squire LR. Hippocampal abnormalities in amnesic patients revealed by high resolution magnetic resonance imaging. Nature 1989;341:54-57


Reed T, Caramelli D, Swan GE, Breitner JCS, Walsh KA, Jarvik GP, Deeb S, Auwerx J. Lower cognitive performance in normal older adult male twins carrying the apolipoprotein E 4 allele. Arch Neurol 1994;51:1189-1192


Reitan RM. Validity of the Trail Making test as an indicator of organic brain damage. Perc Mot Skills 1958;8:271-276


Ritchie K, Kildea D. Is senile dementia "age -related" or "ageing -related"? - evidence from meta -analysis of dementia prevalence in the oldest old. Lancet 1995;346:931-934


Rosenberg GA. Significance of white matter hyperintensities on MRI in the elderly (a syllabus). American Academy of Neurology annual meeting 1995, Seattle WA.


Schneider EL, Guralnik JM. The aging in America. JAMA 1990;263:2335-2340


Stein-Behrens B, Mattson MP, Chang I, Yeh M, Sapolsky R. Stress exacerbates neuron loss and cytосkетal pathology in the hippocampus. J Neurosci 1994;14:5373-5380


dementia in Finland. Neurology 1985;35:1025-1029


Sullivan EV, Marsh L, Mathalon DH, Lim KO, Pfefferbaum A. Age-related decline in MRI volumes of temporal lobe gray matter but not hippocampus. Neurobiol Aging 1995;16:591-606


Tien RD, Felsberg GJ, Crain B. Normal anatomy of the hippocampus and adjacent temporal lobe: high resolution fast spin echo MR images in volunteers correlated with cadaveric histologic sections. AJR 1992;159:1309-1313


Webster DD. Clinical analysis of the disability on Parkinson's disease. Mod Treat 1968;5:257-262

Wechsler D. A standardized memory scale for clinical use. J Psychol 1945;19:87-95


Yetkin FZ, Haughton VM, Fischer ME, Papke RA, Daniels DL, Mark LP, Hendrix LE, Asleson RJ, Johansen J. High signal foci on MR images of the brain: observer variability in their quantification. AJR 1992;159:185-188


---

PUBLICATIONS
SERIES OF REPORTS,
DEPARTMENT OF NEUROSCIENCE
AND NEUROLOGY AT UKU


No. 4 Rolf Danner: Adverse effects of anticonvulsive treatment on peripheral nerve conduction and posterior dominant EEG rhythm. 1982. 55 p. + appendix.


No. 8 Esa Mervaala: Evoked potential in human epilepsy. A neurophysiological


No. 16 -


No. 22 Antti Valjakka: The subcortical afferentation of the hippocampus and noradrenergic lesions as experimental models of dementia. 1992. 89 p. + appendix.


No. 25 Maria Mazurkiewicz: The effects of enhanced GABAergic transmission on cognitive functions: An experimental study.


No. 31 Outi Heinonen: Neuropathological and peripheral markers of Alzheimer's disease with special emphasis on ß-amyloid accumulation. 1994. 89 p. + appendix.

No. 32 Minna Riekkinen: The interaction between cholinergic and serotoninergic systems in the modulation of spatial navigation and passive avoidance behavior. 1994. 125 p.


No. 35 Mervi Pitkänen: The role and pharmacological modulation of the NMDA receptor/channel on hippocampal synaptic transmission and behavior. 1995. 98 p. + appendix.


(URL: http://www.uku.fi/laitokset/neuro/39the.htm)