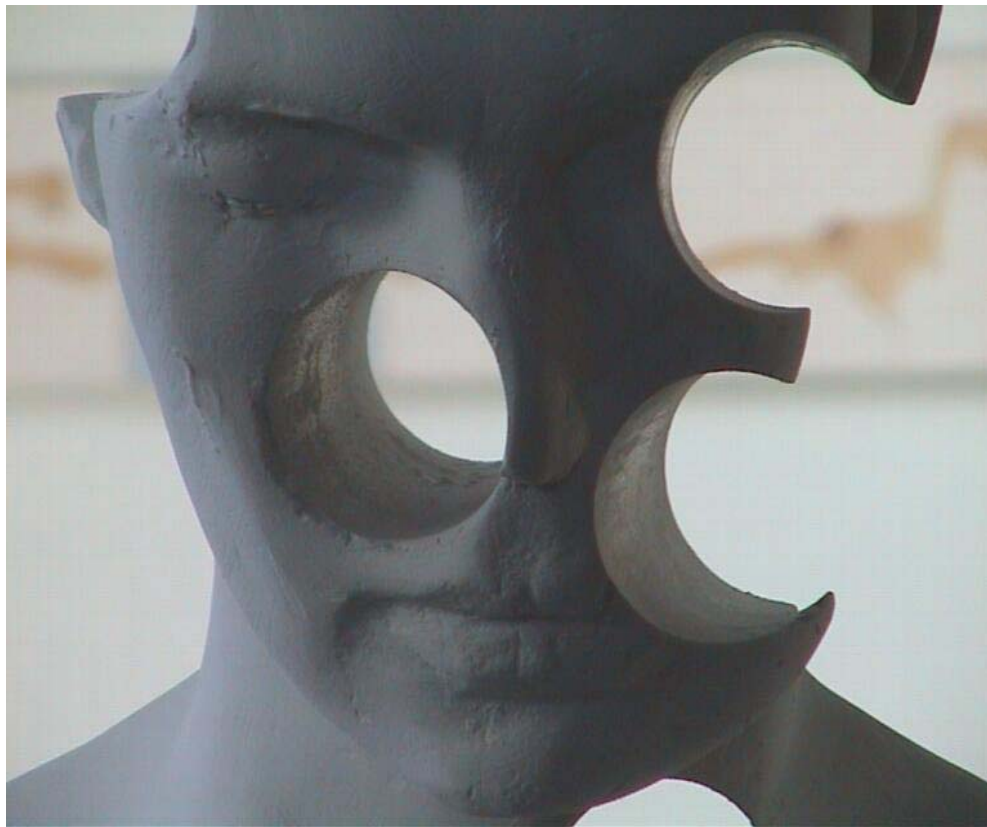**Thesis for the Cand. psych. degree**

COGNITIVE IMPAIRMENTS IN SIBLINGS OF ALZHEIMER'S DISEASE PATIENTS:

POSSIBLE PRECLINICAL SIGNS OF THE DISEASE

A neuropsychological study

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FOREWORD

Genetic research on disease has for the past years gained more and more interest and today there are great numbers of researchers all over the world trying to identify hereditary traits of many different diseases. Some researchers have claimed that medical genetic research on the Icelandic population has the advantage of a relatively homogeneous population, a high-quality health care system, and extensive genealogical records. Regarding the homogenous population, immigration to this isolated island in the North Atlantic has been limited since the first settlers arrived in the AD 870. According to the old Sagas the settlers were mostly Norwegian vikings and their Irish slaves. Although the population has increased rapidly since then, there have been some catastrophic reductions in the population. Twice nearly half of the population was eliminated thus reducing the genetic diversity present in the original settlers (Ingvarsson, 2000). Records from church books and the old Sagas have provided detailed family histories for the Icelandic population since the time of settlement. This information has recently been collected in an Icelandic nation-wide computerized genealogical database. It spans 11 centuries and includes over 600.000 individuals. That is all 282.800 living Icelanders and most of their ancestors since the 9th century. This genealogical database was gathered by the company deCODE genetics, which is a population-based genomic company conducting research into the inherited causes of common diseases (http://decode.is).

DeCODE genetics and the Swiss-based pharmaceutical firm F. Hoffman-La Roche have a research collaboration agreement regarding funding genetic research in the hope of coming up with new methods of diagnosis, more effective drug treatment and development of new drugs. The research is aimed at identifying the genetic factors involved in some 40 common diseases. The genetic study on Alzheimer's disease (AD) is among these studies and is considered to be one of their chief projects (http://decode.is).

The current study is a part of this AD research project where the purpose is to locate the gene or the genes that are responsible for the disease. It is conducted in collaboration with the geriatric division of Landspitali University Hospital and deCODE genetics. The study was carried out at the Genetic Research Service Center, deCODE genetics, and geriatric division at Landspitali University Hospital, Landakot, in Iceland from 1998 to 2001.

In January 1998, when the AD genetic study was in the beginning state, I was offered to take a part in the project and to use a part of it for my thesis work for the candidate degree in psychology at the Copenhagen University. In the project a neuropsychological assessment was performed on mild to moderate AD patients, their siblings and offspring between the ages of 40 and 85 years, and a group of normal controls. The following study is mainly focused on the cognitive performance of siblings of AD patients in order to better understand the cognitive processes during the preclinical stage of AD. These siblings had not been referred to a clinician because of memory complaints. They were matched for age, gender, and education to a control group without first-degree relatives with known dementia, to see if there is some difference on the neuropsychological measures. The siblings of AD patients were also compared to a group of age-matched patients with mild AD to see if there was some resemblance between these groups on any of the cognitive measures.

- **The main structure of the thesis**

This thesis starts with a discussion of normal cognitive changes in the elderly and how these cognitive changes can deviate from being normal and develop into dementia. This will be followed by a short discussion of the various forms of dementia. The main focus of the study is, however, on AD, the most common form of dementia. First, diagnostic criteria for AD are described, as well as the epidemiology of the disease, pathology, etiology and some risk factors. Lastly some neuropsychological studies of the earliest signs of AD will be described. After the theoretical introduction comes the empirical study where the method and the results of the current study are described. In the end, the results of the study are discussed together with a discussion of how they correspond with recent findings.

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ABSTRACT

Previous studies have shown that first-degree relatives of Alzheimer's Disease (AD) patients have an increased risk of developing dementia, and subtle cognitive impairment can be detected through neuropsychological tests before overt clinical signs appear. The purpose of this study was to examine if there is subtle cognitive impairment in siblings of AD patients (Sibs) in Icelandic pedigrees selected for genetic research. The subjects were 95 Sibs with a family history of AD and 68 normal controls (NC) without known first-degree demented relatives. Age range in both groups was 60 to 80 years. Cognitive abilities were assessed by neuropsychological tests of orientation, verbal and non-verbal memory, abstract reasoning, language, concentration, mental speed, and visuo-spatial and constructional abilities. Health information was obtained from participants by a questionnaire. Participants with known central or peripheral nervous system disorders were excluded from the study. The results showed that Sibs scored significantly lower than NC on: Orientation; Immediate and Delayed recall of Rey Complex Figure; Immediate and Delayed recall of Logical Memory (LM) of the Wechsler Memory Scale (WMS); Hard Pairs in Associate Learning of the WMS; and Trails A time measure. There were also significantly fewer Sibs that could complete the Trails B test compared to NC. The Sibs showed no impairment on the other neuropsychological measures. These findings indicate that undiagnosed AD siblings, who are about 70 years old, tend to have impaired verbal and non-verbal memory, orientation and attention, compared to age and education matched NC without known first-degree AD relatives. Furthermore, the Sib group was compared to a group of 87 mild or moderate AD patients participating in the study. This comparison revealed that about 12 percent of the Sibs had a stronger resemblance to the AD group than to the rest of the Sib group on the neuropsychological measures. Concordant with other studies the cognitive impairments, manifested by the Sib group, might be indicators of AD in the preclinical stage.

LIST OF PRESENTATIONS

Preliminary communications of this study:

Posters

5th Congress of Nordic Society for Research in Brain Ageing (NORAGE),
Umeå, Sweden, 14. – 16. October 1999.
Memory impairment in siblings of Alzheimer's disease patients
Smari Palsson[1], Haukur Palmason[1], Thuridur J. Jonsdottir[2], Jon Snaedal[3],
and Thorlakur Jonsson[4].
[1]Genetic Research Service Center, [2]National Hospital of Iceland, [3]Reykjavik Hospital, and [4]deCODE
genetics INC, Reykjavik, Iceland.

23rd Annual Mid-Year Meeting of the International Neuropsychological Society,
Brussels, Belgium, 12. – 15. July 2000.
Memory impairment in siblings of Alzheimer's disease patients
S. Palsson[1], H. Palmason[1], Th. J. Jonsdottir[2], J. Snaedal[3], and Th. Jonsson[4].
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(At this conference the International Neuropsychological Society awarded me the Phillip M. Rennick
Award as recognition of this work).

Oral presentations

15th Nordic Gerontological Congress,
Reykjavik, Iceland, 4. – 7. June 2000.
Having a sibling with Alzheimer's disease – does it increase the risk of memory impairment?
S. Palsson[1], H. Palmason[1], Th. J. Jonsdottir[2], H. Grondal[1], M. Muller[1], B. Gylfason[1], H. Palsdottir[1], B.
Freymodsdottir[1], Th. Jonsson[3], S. Bjornsson[4], P. V. Jonsson[4], J. Gulcher[3], J. Snaedal[4], and K.
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7th Nordic Meeting in Neuropsychology,
Oslo, Norway, 23. – 26. August 2001.
Prodromal cognitive impairment in siblings of Alzheimer's disease patients
S. Palsson, H. Palmason, J. Snaedal, Th. Jonsson, S. Bjornsson, P. V. Jonsson, H. Grondal, M. Muller,
J. Gulcher, & K. Stefansson.

Journal

Pálsson, S. and Pálmason, H. (2001). Er systkinum Alzheimerssjúklinga hættara við minnistruflunum
en öðrum? *Öldrun, 1*, 5-8.

ABBREVIATIONS

AACD	Aging-associated cognitive decline
AAMI	Age-associated memory impairment
AD	Alzheimer's disease
ANOVA	Analysis of variance
APA	American Psychiatric Association
ApoE	Apolipoprotein E
APP	Amyloid precursor protein
Aβ	Amyloid β protein
Canadian Study of HAWG	Canadian Study of Health and Aging Working Group
CBF	Cerebral Blood Flow
CERAD	The Consortium to Establish a Registry for Alzheimer's Disease
CT	Computed tomography
CVLT	California Verbal Learning Test
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
EEG	Electroencephalograph
ERP	Event-related potential
ICD-10	International Classification of Diseases, 10th revision
ImpSibs	Siblings of AD patient in the study who score similar to AD patient group on seven selected neuropsychological measures
IntSibs	Siblings of AD patients that scores dissimilar to the AD patient group on seven selected neuropsychological measures
LM	Logical memory subtest from the WMS
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
NC	Normal Control
NewImpSibs	Siblings of AD patient in the study who score similar to AD patient group on one selected neuropsychological test
NewIntSibs	Siblings of AD patients that scores dissimilar to the AD patient group on one selected neuropsychological measures
NFT	Neurofibrillary tangle
NIA	National Institute on Aging
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
PET	Positron emission tomography
Rey Complex Figure	Rey Osterrieth Complex Figure
SD	Standard deviation
Sibs	Siblings of AD patients that have another AD relative within six meiotic
SPECT	Single photon emission computed tomography
SPSS	Statistical package for social sciences
Trails A	Trail Making Test, Part A
Trails B	Trail Making Test, Part B
WAIS	Wechsler Adult Intelligence Scale
WHO	World Health Organization
WMS	Wechsler Memory Scale

CONTENTS

PART I: REVIEW OF THE LITTERATURE

1. INTRODUCTION

Over the past century the population of persons over 60 years has doubled in the developed countries and is beginning to increase dramatically in the developing countries as well. The consequence of an aging population has increased the incidence of dementia considerably with concomitant economic burdens (Michel, Zekry, Mulligan, Giacobini & Gold, 2001). The prevalence of dementia rises with age, being around 2-4% for individuals aged 65 years and doubling roughly every 5 years after that. The most common and perhaps the most devastating of all degenerative disorders is Alzheimer's disease (AD), accounting for 65-75% of dementia cases (McDowell, 2001). AD is an insidious, irreversible and in the end a totally dehumanizing disease. Mortality rates rise with increased levels of cognitive deficits with median survival estimated to range from 5 to 9.3 years after the onset of disease (Bianchetti & Trabucchi, 2001).

The search for an understanding of AD has been a long one. It started in 1907 when Alois Alzheimer described the first case of the illness that bears his name, a 51-year-old woman with progressive cognitive decline and behavioral changes associated with distinctive neuropathological features. For a long time there was a widespread nihilism in the clinical approach to AD, and physicians thought it was a waste of time to study or diagnose the disease because there were no known risk factors, preventive measures or treatments. During the last decades, however, much has been achieved through efforts of many multidisciplinary teams. Such teams of epidemiologists, geneticists, clinicians, pathologists, and neuropsychologists have transformed the AD research field and lead to a better understanding of risk factors, pathogenesis, clinical presentation and treatment of the disease (Bianchetti & Trabucchi, 2001). Despite years of hard work the cause of this complex disease is still not understood, and there are many risk factors that remain speculative.

In order to diagnose AD, documentation of cognitive decline as well as functional impairments in either the social or occupational domain is required. The cognitive disturbance of AD includes memory impairment, aphasia, apraxia, agnosia, and a disturbance of executive

functioning (Gil & Josman, 2001). In addition there are behavioral and personality disturbances that have drastic consequences for the patients' and the caregivers' quality of life.

The use of neuropsychological tests is the keystone of *in vivo* screening and diagnostic tools for AD (Boller & Barba, 2001). There is no biological or biochemical threshold beyond which AD can be said to begin. Several reports have documented cognitive deficits in persons who later develop AD, prior to diagnostically significant cognitive, behavioral, and social changes. It is known that AD patients show some cognitive impairment around 2-3 years prior to clinical diagnosis. This phase has often been called the preclinical phase of AD and the most pronounced and consistent cognitive deficit in this phase is in episodic memory (e.g. Almkvist, 1996).

There are no definitive preclinical diagnostic markers for AD and the diagnosis of AD in the preclinical phase is complicated by the need to differentiate common age-related cognitive decline from pathological deficits. Studies on the preclinical phase of the disease are therefore vital to characterize the insidious transition from normal ageing to AD. The main information has come from longitudinal studies of aging and studies of individuals who are genetically susceptible to AD. The best strategy is to study persons at high risk for conversion to AD (Howieson et al., 1997). Furthermore, the best future opportunities for treatment may exist in the preclinical stage, before further, irreversible brain damage has occurred. The recent developments of symptomatic pharmacological treatments for AD make the diagnosis of dementia at its preclinical stage a great scientific and public health challenge.

2. MEMORY AND AGING

2.1. Types of memory changes in the elderly

The brain and its functioning change throughout the life span, with most of the changes taking place in the very young and the elderly. As people grow older it is often difficult to define which changes are normal and which are not. Knowledge of the histology and cognitive functional changes in the normal aging brain is essential before interpreting a finding as abnormal.

Age-related changes in memory or cognition can be divided into three categories:

1. Memory changes which are age-appropriate and can be regarded as a usual consequence of normal aging

2. Memory impairments which are more severe than appropriate for a given age but not severe enough to be a sign of a disease

3. Cognitive impairments that are severe enough to be clinically diagnosed as a progressive dementia.

It is, however, often difficult to differentiate dementia from memory deficits that are considered normal at the time they are diagnosed. The concepts and terminology used for these varieties of mild memory changes in elderly are vague and inconsistent and not clearly distinguished in the literature.

2.2   Normal aging

Normal effects of aging are not identical in all cognitive areas. Some decline, but others remain mostly unaffected (e.g. Morris, 1999). Memory abilities, executive skills, and processing speed are particularly vulnerable to aging (Small, 2001). Regarding memory abilities it seems that age-related decline is restricted to specific aspects of memory such as acquisition and retrieval of new information and not to memory retention (Small, Stern, Tang, & Mayeux, 1999). In an effort to define age related cognitive changes in normal elderly, terms like *fluid intelligence* and *crystallized intelligence* have been used. In normal aging there is some loss of fluid intelligence, that is loss of skills associated with problem solving, novel tasks, new learning, speed of processing or inductive reasoning. Crystallized intelligence on the other hand tends to be preserved into old age and some intellectual aspects may even increase. Crystallized intelligence operates with previously acquired information and skills, general knowledge, comprehension and vocabulary (e.g. Koltai & Wels-Bohmer, 2000).

When referring to normal aging, researchers usually permit some memory or cognitive decline to take place.

2.3   Radiological and physiological brain investigations

Before describing brain changes following increased age it is necessary to describe briefly the non-invasive techniques that are used to detect and measure these changes.

Structural techniques such as *X-ray computed tomography scans* (CT scans) and, with greater accuracy, *magnetic resonance imaging* (MRI) are used to examine brain anatomy. Functional or physiologic imaging techniques, on the other hand, can reveal information about blood flow or metabolism in various brain regions. *Single photon emission computed tomography* (SPECT) measures *regional cerebral blood flow* (CBF). *Positron emission tomography* (PET) can measure either CBF or glucose metabolism, allowing more accurate quantification of perfusion or metabolic processes (Mazziotta, 2000). PET is much more expensive than SPECT, and therefore less used in clinical application, although being a better tool for research purposes (Richards & Hendrie, 1999). Studies indicate that PET may reveal metabolic abnormalities that precede morphologic changes demonstrable on anatomic imaging studies such as CT or MRI (Giacometti, Davis, Alazraki, & Malko, 1994). *Functional MRI* (fMRI) is a combination of structural and functional scans with potential for more precise mapping of cortical activation and anatomic detail than the techniques mentioned above.

One of the most widely used investigative techniques in neurology is the *electroencephalo-graphy* (EEG) This is the technique of recording the electrical activity of the brain through the skull by means of electrodes placed on the scalp. Similar to EEG is the *event-related potential* (ERP).

2.4   The normal aging brain

It seems that after the age of 50 years there may be some loss of brain volume or neurons in normal elderly people without neurological deficits. Focal white matter abnormalities are seen in 30-80% of cognitively normal elderly subjects. The decrease of volume in the cerebral hemisphere is generally thought to be greatest in the frontal and temporal lobes (Cabeza & Nyberg, 2000; Giacometti et al., 1994). The lateral and third ventricular volumes also increase

by aging (Giacometti et al., 1994). By contrast, the volume of the hippocampus[1] seems to remain remarkably unaffected by normal aging (Morrison & Hof, 1997). Studies revealed a gradual decrease in CBF and metabolism with advancing age, possible due to decreased brain volume and atrophy (Giacometti et al., 1994). Several studies have shown that lateralized patterns of brain activity tend to be less pronounced in aging. This phenomenon has been described as *hemispheric asymmetry reduction in old adults* (HAROLD; in Cabeza & Nyberg, 2000). However, there are some post-mortem studies which have indicated that healthy brain aging up to age of 89 is possible, showing no or very little neocortical pathology in subjects carefully determined to be non-demented during life (Morris, 1999).

Medial temporal lobe structures, including the hippocampal formation, the perirhinal and entorhinal cortex play a critical role in explicit memory, specifically in the encoding of new memories (Díaz-Olavarrieta, Ostrosky-Solis, de la Cadena, Rodriquez, & Aloson, 1997; Grady et al., 1995). The name "entorhinal" refers to its location inside the rhinal sulcus, in the olfactory area. The entorhinal cortex is located on the medial surface of the temporal lobe (Brodmann's area 28), rostrally beneath the amygdaloid complex and caudally beneath the hippocampus. It extends from subicular cortex to the upper lip of the rhinal fissure and is a part of the hippocampal formation[2], the other areas of which are the hippocampus proper, dentate gyrus, and subicular complex. Much of the communication between the hippocampal formation and the neocortex[3] passes through the entorhinal cortex, which has reciprocal connections with the hippocampus and various other cortical structures. These connections of the entorhinal cortex with cortical and subcortical systems form an integral component of the medial temporal lobe memory system (Carlson, 1991; Gómez-Isla et al., 1996; Kolb & Whishaw, 1996). Nyberg, McIntosh, Houle, Nilsson, & Tulving (1996) showed a strong positive correlation between verbal episodic retrieval and blood flow in left medial temporal structures in normal

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[1] Deep to the parahippocampal gyrus, within the temporal lobe, lies the hippocampus. As a part of the limbic system the principal function is in relation to memory. Hippocampus is divided into four areas based of differences in the architecture of the pyramidal cell layers. That is CA_1, CA_2, CA_3, and CA_4 that are numbered in sequence from the subiculum to the edge of the cortex (Nolte, 1993).

[2] The hippocampal formation is made up of the hippocampus, dentate gyrus, and parahippocampal gyrus of the temporal lobe (Nolte, 1993).

[3] The vast majority of the cortical surface is neocortex, or almost all the cortex that can be seen from the outside of the brain. Also referred to as isocortex consisting of six layers (Nolte, 1993).

individuals. This strong positive correlation was related to retrieval success rather than retrieval attempt. In a PET study, Grady et al. (1995) showed a lack of cortical and hippocampal activation among old people during encoding compared to young people. Old people did however show a normal right prefrontal activation during recognition. They suggest that this lack of activation during encoding could explain the age-related memory impairments that are found in several studies.

2.5   Terminology of mild memory problems

Many terms have been used by researchers to describe mild memory problems in people that are growing old. The terms *benign senescent forgetfulness* and *age associated memory impairment* (**AAMI**) have been used for mild memory problems which are beyond what is considered typical for healthy aging, although not sufficient to meet criteria for dementia (Koss, 1994; Small et al., 1994). The AAMI criteria were proposed by the National Institute of Mental Health (NIMH) work group in 1986 and refer to persons aged 50 years and older who are experiencing a decline or loss in memory function and perform at least one standard deviation below the mean of younger people on memory tests. Furthermore, the person ought to be otherwise healthy and without depression and dementia (Shah, Tangalos, & Petersen, 2000). Studies show that patients with AAMI have an increased risk of developing dementia (Tierney, Szalai, Snow, Fisher, Nores et al., 1996). It is therefore unclear whether AAMI is, as some have stated, dementia in the beginning of the clinical course, (Johansson & Zarit, 1997), or in fact a phenomenon of normal aging (Koivisto et al., 1995). Some researchers state that almost all older persons could be diagnosed with AAMI (up to 90%) and that the concept therefore has little practical utility (Shah et al., 2000).

Aging-associated cognitive decline (**AACD**) is research criteria which refer to impairment relative to a normal age matched group instead of young normals as in the AAMI criteria (Richards, Touchon, Ledesert, & Richie, 1999).

Mild cognitive impairment (**MCI**) is a rather new concept originating from the Mayo Clinic group. It is used in clinical research on age-related cognitive disorders and refers to complaints of memory loss in elderly which are considered to have a high probability of evolving towards AD (Petersen et al., 1999). Studies suggest that MCI and AD have similar anatomical loci,

with the main difference being functional rather than structural changes, and the degree of the impairment (Friedrich, 1999; Morris et al., 2001). It is therefore likely that MCI is in fact, in most cases, AD in the earliest clinical phase, before it progresses into dementia (Milwain, 2000). As there is, however, no formal consensus on the conceptual basis of MCI or its diagnostic algorithms, there is some confusion to its relation to other similar concepts (Ritchie & Jacques, 2000). To eliminate the confusion of diagnosing MCI, Petersen et al. (1999) have formulated the following clinical criteria:

1. A self reported memory complaint, preferably corroborated by a family member.
2. A detectable memory deficit abnormal for age (about 1.5 standard deviation below the norm).
3. Normal general cognitive functioning aside from memory.
4. Ability to carry out such activities of daily living as driving a car and balancing a checkbook.
5. Absence of dementia.
   (Petersen et al., 1999; 2001)

Individuals who develop MCI are at a higher risk of developing AD although not all progress to AD (Flicker, Ferris, & Reisberg, 1993; Shah et al., 2000). Longitudinal studies indicate that persons with MCI progress to dementia at a rate of approximately 10 to 15% per year, compared with a rate of 1 to 2% per year in control subjects (Petersen et al., 1999).

The period from onset of mild cognitive symptoms to the time of diagnosis of AD has often been termed *prodromal* AD (e.g. Dubois, 2000; Johnson & Albert, 2000) and more frequently *preclinical* AD (e.g. Almkvist, 1996; Bondi, Monch, Galaso, & Butters, 1994; Jacobs et al., 1995; Linn et al., 1995; Reiman et al., 1996). Goldman et al. (2001) stated that: "the term preclinical AD should refer to a condition of histopathologic AD that is unaccompanied by any cognitive symptoms or impairment" (pp. 361-362). They found pathological signs of AD in the brain samples of people who did not show any signs of dementia or cognitive impairments. Others, however, use the term when referring to condition of cognitive impairments that later

develops into clinically diagnosed AD. As the term preclinical phase of AD is more widely used it will be used in this study.

3.   DEMENTIA

Dementia is an acquired syndrome of decline in memory and other cognitive functions due to disease of the brain, sufficient to interfere with daily function and affect daily life in people with unclouded consciousness (American Psychiatric Association [APA], 1994; World Health Organization [WHO], 1994). In dementia there are disturbances of

> multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language and judgement. Consciousness is not clouded. The impairments of cognitive function are commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behaviour, or motivation
>
> (WHO, 1994, F00-F03).

In order to make a specific diagnosis of one of the dementia syndromes the first stage is to confirm that dementia is actually present, because a deficit in memory or cognition is not equivalent to early dementia. Several possible factors other than dementia may contribute to a decline in memory function. It can be difficult to distinguish dementia from delirium or depression especially as it can coexist with dementia (APA, 1994; WHO, 1994).

The *American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders version 4* (DSM-IV; APA, 1994) and *the World Health Organization 10th International Classification of Diseases* (ICD-10; WHO, 1994) provide concise definitions of dementia. Dementia according to DSM-IV criteria is "the development of multiple cognitive deficits that include memory impairment and at least one of the following cognitive disturbances: aphasia, apraxia, agnosia, or a disturbance in executive functions" (APA, 1994, p. 134). The most significant causes of dementia are mentioned in the following.

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1. **Alzheimer's disease.**

   Alzheimer's disease is the most common dementia and will be illustrated thoroughly below.

2. **Vascular dementia**

   Vascular dementia is frequently associated with hypertension and can have abrupt onset (stroke) or insidious onset with stepwise deterioration of dementia (Wetterling, Kanitz, & Borgis, 1994). *Ischemic* disease often results in vascular dementia, and *cerebral hypoxia* and *haemorrhage* may also do so (Morris, 1994). Vascular dementia also includes what Hachinski popularised as *multi-infarct dementia* in which multiple completed strokes involve cortical and subcortical areas (Geldmacher & Whitehouse, 1997). The typical cognitive pattern in vascular dementia includes prominent frontal/executive dysfunction, usually with less language impairment than is seen in AD (Geldmacher & Whitehouse, 1997). Vascular dementia is considered to be second to AD as the most common cause of dementia, and is responsible for up to 15% of all pathologically diagnosed cases of dementia (Morris, 1994). *Binswanger's* disease is among the dementing syndromes attributed to cerebrovascular origins that are associated with diffuse subcortical white matter disease (Geldmacher & Whitehouse, 1997).

3. **Frontotemporal dementia.**

   Frontotemporal dementia is associated with frontotemporal cerebral atrophy with prominent personal and behavioral changes. It is characterized by disinhibition or apathy, gross impairments in judgment, inappropriate behavior, diminished insight, loss of social and personal awareness, and psychiatric symptoms (The Lund & Manchester Groups, 1994; Neary et al., 1998). It overlaps with other diseases such as *Pick's disease* and *motor neuron disease* or *amyotrophic lateral sclerosis* (Lishman, 1998; Morris, 1994).

4. **Diffuse Lewy body disease**

   The neuropathological hallmark of dementia with Lewy bodies is the findings of numerous *eosinophilic* inclusions (Lewy bodies) in cortical neurons of patients with dementia. In diffuse Lewy body disease the memory deficits are typically gradual but they may have a fluctuating course and are accompanied by visual

hallucinations early in the course of dementia. Extrapyramidal dysfunction is often mild and may not respond to levodopa (Morris, 1994; Serby & Samuels, 2001).

5. **Other dementias**

   Among other diseases which can also cause dementia are for example *Parkinson's disease, Huntington's diseas*e, *multiple sclerosis* (MS), *progressive supranuclear palsy*, *Creutzfeldt-Jakob disease*, and *AIDS*.

   Some dementias are potentially reversible, including drug or alcohol related dementias, dementias due to metabolic causes e.g. *Thyroid* and *Vitamin B$_{12}$* deficiency, and dementia due to depression (Morris, 1994).

4. ALZHEIMER'S DISEASE (AD)

4.1 Brief history of AD

In 1906, Alois Alzheimer gave a lecture where he described the first case of the illness that, thanks to Emil Kraepelin, bears his name (Maurer, Volk, & Gerbaldo, 1997). Alzheimer published a detailed report of this patient a year later. The patient was a 51-year-old woman with progressive cognitive decline and behavioral change. Most interesting is Alzheimer's description of the association between cognitive decline and distinctive neuropathologic features of senile plaques and neurofibrillary tangles (Alzheimer, 1907).

4.2 Diagnosis of AD

AD is a progressive neurodegenerative disorder that frequently starts with memory impairment, but is invariably followed by a progressive global cognitive impairment which impacts behavior and performance. These characteristics make AD a severely debilitating disease, not only for the patient, but for caregivers as well. The diagnosis of AD relies on cognitive and behavioral indicators that overlap with changes seen in normal cerebral aging. Early diagnosis is thus difficult, and medical care is frequently delayed as subclinical impairments are generally not considered worthy of treatment. Treatment starts after clinical diagnosis of AD and by then the impairment has often reach a level of incapacity that is intolerable for the family or dangerous for the individual.

AD has often been divided into *familial*[4] AD, which sometimes follows a certain inheritance pattern, and *sporadic* AD, where no other cases in the family is known. The age of onset of AD varies between individuals and can vary with more than 50 years. Because of this difference in age at onset, some have divided AD into *early-onset* (occurring in people younger than 65) or the more common *late-onset* (occurring in those 65 and older; WHO, 1994). Early-onset AD is rare, comprising about 10 percent of all AD cases, with around 1-2% running in families (Swartz, Black, & George-Hyslop, 1999). Early-onset AD also often progresses faster than the late-onset form, and is characterized by more rapid cognitive deterioration, greater frequency of language disturbance, more severe and widespread neurochemical abnormalities, and a greater density of neurohistologic lesions (Villareal & Morris, 1998).

AD is a diagnosis of inclusion based on patient history, physical examination, neuropsychological testing, and laboratory studies. In recent years, standardized diagnostic criteria for AD have been developed and greatly improved the reliability of clinical diagnosis. Three main sets of diagnostic criteria for AD have become widely accepted:

1. The Diagnostic and Statistical Manual of Mental Disorders 4th edition (*DSM-IV*; APA, 1994).
2. International Classification of Mental and Behavioural Disorders, 10th edition (*ICD-10*; WHO, 1994).
3. The National Institute of Neurological, Communication Disorders and Stroke/Alzheimer's Disease and Associated Disorders Association (*NINCDS-ADRDA*) research diagnostic criteria for AD (McKhann et al., 1984).

The NINCDS-ADRDA criteria permit levels of certainty to be assigned to the diagnosis. A probable or possible diagnosis of AD requires that dementia is established clinically with the cognitive impairment documented using a test such as Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) or some similar examination, and confirmed using formal neuropsychological testing. The criteria offer little guidance as to which

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[4] Familial requires that more than one case of a disorder has occurred among within first-degree relatives (Bird, 2000).

neuropsychological tests to use in diagnosing AD. The NINCDS-ADRDA criteria propose deficits in two or more areas of cognition with progressive worsening of memory and other cognitive functions. It requires an onset of the disease between the ages of 40 and 90 years (McKhann et al., 1984; see table 1).

The diagnostic sensitivity and specificity of the NINCDS-ADRDA criteria of AD have been reported to be as high as 85-98% (Klatka, Schiffer, Powers, & Kazee, 1996; Lopez et al., 2000). However, there are some who think AD that is frequently misdiagnosed, even in as much as 10-30% of those given the AD diagnosis (Cacabelos, 1996). When using the NINCDS-ADRDA criteria there is some risk of labelling frontotemporal dementia as AD, but appropriate neuropsychological tests can differentiate them (Varma et al., 1999). Some claim that the disease which is called AD is in fact a mosaic of diseases that have different causes but similar clinicopathologic features (e.g. Tabaton, 1994).

Table 1.

Criteria for clinical diagnosis of AD – NINCDS-ADRDA Work Group (McKhann et al., 1984, p. 940).

I. The criteria for the clinical diagnosis of PROBABLE Alzheimer's disease include:
a) Dementia established by clinical examination and documented by the Mini-Mental test, Blessed Dementia Scale, or some similar examination, and confirmed by neuropsychological tests.
b) Deficits in two or more areas of cognition.
c) Progressive worsening of memory and other cognitive functions.
d) No disturbance of consciousness.
e) Onset between ages 40 and 90 years, most often after age 65.
f) 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:
a) Progressive deterioration of specific cognitive function such as language (aphasia), motor skills (apraxia), and perception (agnosia);
b) Impaired activities of daily living and altered patterns of behavior;
c) Family history of similar disorder, particularly if confirmed neuropathologically;
d) Laboratory result of:
i. Normal lumbar puncture as evaluated by standard techniques.
ii. Normal pattern or nonspecific changes in EEG, such as increased slow-wave activity.
iii. 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:
a) Plateaus in the course of progression of the illness.
b) Associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physiological outbursts, sexual disorders, and weight loss.
c) Other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder.
d) Seizures in advanced disease.
e) CT normal for age.

IV. Features that make the diagnosis of PROBABLE Alzheimer's disease uncertain or unlikely include:
a) Sudden, apoleptic onset.
b) Focal neurological findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness.
c) Seizures or gait disturbances at the onset or very early in the course of the illness.

V. Clinical diagnosis of POSSIBLE Alzheimer's disease:
a) May be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or system disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course.
b) 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
c) 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:
a) The clinical criteria for probable Alzheimer's disease.
b) 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:
a) Familial occurrence.
b) Onset before age of 65.
c) Presence of trisomy-21.
d) Coexistence of other relevant conditions, such as Parkinson's disease.

The most reliable way to diagnose AD is by neuropathology and is, according to NINCDS-ADRDA, necessary in diagnosing definite AD. There are three sets of post mortem criteria which are most widely used:

1. The classical criteria of *Khachaturian* from 1985, consisting mostly of number of senile plaques in multiple brain areas. Neurofibrillary tangles were not necessary for this diagnosis[5].

2. Second is a modification of Khachaturian criteria, proposed by the *Consortium to Establish a Registry for Alzheimer's Disease* (CERAD), where the main difference is that the senile plaques must be of the neuritic plaques diffuse type. The CERAD criteria depend on a semiquantitation score in 3 neocortical brains areas rather than an absolute cut-off (Mirra et al., 1991).

3. Finally, the most restrictive guidelines for the neuropathological diagnosis of AD are the criteria proposed by *The National Institute on Aging-Reagan Institute* (NIA-RI; Hyman & Trojanowski, 1997). There are some changes regarding the number of neuritic plaques required and more focus is on neurofibrillary tangles than in the previous criteria (see more about the difference of these criteria in e.g. Hyman, 1998). According to the study by Schmitt et al. (2000) the NIA-RI guideline is more sensitive in detecting subtle early changes than the other criteria because of the emphasis on the neurofibrillary tangles.

4.3   Clinical course of AD

The clinical course of AD typically involves a gradual onset and slow but continuous progression. Usually the first clinical sign of AD is an episodic memory problem and it is the cardinal feature of the disease. It is manifested by impaired acquisition and retrieval of information, for example, failure to recall conversations and details of recent events, or frequent misplacement of items (e.g. in Morris, 1994; Villareal & Morris, 1998). In the incipient period of the disease the patient is usually independent in activities of daily living.

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[5] Senile plaques and neurofibrillary tangles are described later.

That is social skills and basic self-care abilities are usually unaffected, although perhaps somewhat impaired relative to past performance.

In this early stage, the patient often appears normal to casual observation. Additionally, the patient often minimizes or denies any cognitive problems, mostly because of reduced insight which is one of the characteristics of the disease and often very difficult both for the patient and for his relatives (e.g. Morris, 1994; Villareal & Morris, 1998). Early in the disease, problems in executive function are displayed as impaired judgement and problem solving, e.g. difficulties in balancing the chequebook or operating appliances (Villareal & Morris, 1998). Later or in the middle stage of the disease the patient may have some difficulties in finding even familiar locations due to geographical disorientation. Language disturbances usually develop later than visuo-spatial dysfunction and may include word-finding difficulty, hesitancy of speech, and diminished verbal output. Personality changes also occur, and AD patients may become passive, disinterested, and withdrawn (Villareal & Morris, 1998; NIA, 1999). Emotional outbursts and disturbing behavior, such as wandering and agitation, are also common and become more frequent in the later stages of the disease. Eventually, the AD patient becomes bedridden, incontinent, totally helpless, and unresponsive to the outside world (NIA, 1999). The average patient may expect to live about nine years after symptom onset, ranging from 3 to 20 years (Small, Peter, et al., 1997).

4.4   Epidemiology of AD

People tend to live longer and the total global population is growing older. About 605 million people were 60 years old or older in the year 2000, and it is estimated that there will be around 1,200 millions by the year 2025 (Kalache, 1999). In Iceland, the number of people 70 years old or older was about 8.2% of the total population in the year 2000 (the total population being around 282.800 in January 2001) and is estimated to be as high as 11.5% in the year 2025 (Jonsdottir, 2001). In USA the population of those 85 years old and older were around 4.9 million (1.8% of the population) in the year 2000, and estimated to be 6.6 million by the year 2010 (2.3% of the population; Albert & Drachman, 2000).

The longer one lives, the more likely one is to develop dementia of the AD type (Albert & Drachman, 2000). Some have even postulated that dementia might be an inevitable phenomenon of senescence, should one live long enough (Drachman, 1994).

Around 1.7-1.9 millions people were thought to have suffered AD in the year 2000 in USA. Inclusion of mild AD individuals raised the estimation as high as 4 million cases (reviewed in Hy & Keller, 2000).

It is difficult to compare the incidence or prevalence of dementia and AD between studies because of differences in methodology used. In some studies, people with mild dementia are included but in others not (Andersen, Launer, et al., 1999; Hy & Keller, 2000).

The incidence of dementia per 1,000 person-years varies between studies from 2-12 in 65-69 year olds; 6-27 in 70-74; 17-52 in 75-79; and 32-82 in 80-84 years old (Andresen, Launer, et al., 1999; Canadian Study of Health and Aging Working Group [Canadian Study of HAWG], 2000; Paykel et al., 1994). Pathological studies indicate that these numbers are somewhat overestimated, at least in those who are 85 years old or older (Crystal et al., 2000).

AD is the most common cause of dementia and accounts for about 65-75% of demented cases (Launer et al., 1999; Kawas, Gray, Brookmeyer, Fozard, & Zonderman, 2000; Ott et al., 1995). The incidence of AD increases drastically with age but decreases according to the level of severity used to define a case (e.g. Hy & Keller, 2000). In most studies the overall incidence rate of AD doubles approximately every 5 years after the age of 65, except in the oldest age groups where there is some slowing of incidence rate (Canadian Study of HAWG, 2000; Kawas et al., 2000).

Incidence rate per 1,000 person-years of AD is 1-2 in 65-69 year old; 3-4 in 70-74; 9-11 in 75-79; 19-22 in 80-84; 56-65 in 85-89; and around 88 in 90 years old and older (Andersen, Nielsen, et al., 1999; Kawas et al, 2000; Letenneur et al. 1999; Ott et al., 1995).

Incidence for AD seems to differ between races, being substantially higher among Hispanics and African Americans compared to Caucasians (Albert & Drachman, 2000; Tang et al., 2001). According to Tang et al. (2001) the incidence rate for whites is 0.4% in 65-74; 2.6% in 75-84; 4.2% in 85 year old and older per person-year. But for all races 1.3% in 65-74; 4.0% in 75-84; 7.9% in 85 and older per person-year. Another study showed differences in incidence of AD according to populations, where age-standardised annual incidence rates were significantly

lower among those residing in Nigeria compared to African Americans, or 1.15% and 2.52%, respectively (Hendrie et al., 2001). What is interesting with this longitudinal study of Hendrie et al. is that they used identical methods and groups of investigators in the comparison between two different populations of developed and developing countries.

4.5   The impact of AD

AD has not only a dramatic personal impact on patients and their family, but also an economic impact. The economic burden of AD varies according to the stage of the illness. The patient's dependency on others increases as the disease progresses. When caregivers are no longer capable of caring for the patient at home, the patient is hospitalized or placed in a nursing home.

AD puts a heavy economic burden on society. According to a Danish study the annual cost of medical care, domestic care, home help, nursing home and special equipment for non-demented patients adds up to $ 2.800 per person. The cost for very mildly to severely demented patients increased with greater severity of the illness from $ 6,200 to $ 26,000 (Andersen, Søgaard, et al., 1999). The annual cost of caring for one AD patient in USA is estimated to be from $ 18,000 to $ 36,000 depending on the severity of the illness (NIA, 1999). The annual cost for caring for AD patients living in the community in the United Kingdom was, as in other studies, directly related to the severity of the patient's illness or around $ 9,800 for mild AD to $20,100 for severe AD (Soutre, Thwaiter, & Yeardley, 1999). Although there is some variance of the annual cost of caring for AD patients between cultures it is clear that the cost is staggering. Some studies include in the calculation of economic cost not only direct cost as in medical and long-term care and lost productivity, but also indirect costs such as resource loss and family care. The annual national cost of caring for AD patients in USA is estimated to be approaching 100 billion dollars (Morris, 1999).

The magnitude of AD as a worldwide health problem is steadily increasing, with growing economic burdens on society for the care of AD patients. This has placed AD as a research priority. Interventions that could hinder or at least delay the onset of AD will have an enormous positive public health impact (Albert & Drachman, 2000). If the onset of AD could be delayed on an average of only by half to one year it would result in annual savings of

Billions of dollars worldwide (NIA, 1999).

4.6   Etiology of AD

4.6.1   Age and gender

As described earlier in the epidemiology chapter, the risk of developing AD increases
exponentially with growing age. There are many other factors that are thought to increase the
risk of an individual to develop AD. A number of studies have reported that females have
higher risk of developing AD (e.g. Canadian Study of HAWG, 2000; Hy & Keller, 2000;
Launer et al., 1999; Munoz & Feldman, 2000). Then there are others who fail to show this
higher risk of dementia for women than for men (Kawas et al., 2000 [trend not significant];
Small, Fratiglioni, Viitanen, Winblad, & Backman, 2000; Zubenko et al., 1999). In the
EURODEM studies no gender differences were found in the incidence of AD until after the
age of 85 years, where women had a higher risk of developing AD (Andersen, Launer, et al.,
1999). Similar results were found in the PAQUID project of Letenneur et al. (1999), where
women had higher risk of developing AD after the age of 80 years. This gender difference was
once thought to reflect the greater number of females in the older age group due to higher
mortality in males, higher risk of dementia at very old age, and increased likelihood of vascular
or mixed dementia in males. Even when these variables are corrected for, the rates are still
elevated for females (Lapane et al., 2001; Swartz et al., 1999). Increased risk for women to
develop AD could therefore be due to biological differences, survival differences, or cohort
differences in behavior and exposure (Launer et al., 1999).

4.6.2   Education

Many studies have found a negative relationship between length of education and risk of
developing AD (Letenneur et al., 1999; Munoz & Feldman, 2000; Ott et al., 1995; Räihä,
Kaprio, Koskenvuo, Rajala, & Sourander, 1998; Touchon & Ritchie, 1999). There are also
others who fail to show such a correlation (Del Ser, Hachinski, Merskey, & Munoz, 1999;
Kawas et al., 2000 [trend – not significant]; Launer et al., 1999; Moceri, Kukull, Emanuel, van
Belle, & Larson, 2000; Zubenko et al., 1999). There are many factors that can influence the
correlation between education and AD. For example it is likely that individuals with higher
education have had more practice and opportunities to develop problem solving strategies than

those with shorter education. This could be reflected in a better neuropsychological test performance masking AD impairment for some time. Neuropsychological tests are highly sensitive to educational variables, and illiteracy correlates with an extremely low performance on most neuropsychological tests (Lopera et al., 1997). Controlling for the length of education is therefore necessary when using neuropsychological measures in assessing AD, and this control may in practice be insufficient, resulting in an overestimation of AD of the poorly educated and underestimation of AD in the highly educated. It is also necessary to take into account that in many societies high education mean better economy, better medical attention, better life standard, and therefore possibly less exposure to risk factors (Launer et al., 1994; Munoz & Feldman, 2000; Touchon & Richie, 1999). Researchers have also referred to some non-biological explanations, such as education, that may increase the synaptic density or efficiency and thereby have some protective effects against dementia (in Del Ser et al., 1999).

4.6.3   Head injury

Whether head injury increases the risk of developing AD remains controversial. Many studies indicate that people who have a history of severe or moderate head injury are at increased risk of developing AD (Plassman et al., 2000). According to Plassman et al. the risk of developing AD increases with increased severity of the brain injury, even if it was in early adult life. However, there are some studies who fail to show a correlation between head trauma and dementia (e.g. Launer et al., 1999; Mehta et al., 1999). Some state that head trauma is only a risk factor when accompanied the presence of the ApoE 4 allele (Mayeux et al., 1995). Others have however failed to confirm this finding (Mehta et al., 1999).

The discrepancies among studies addressing head injury and increased risk of AD could partly be due to the method of collecting of the information regarding the head injury. For individuals with cognitive impairment, the history of head injury comes from a proxy informant, who often is not very reliable. More reliable information is medical records (Plassman et al., 2000).

4.6.4   Aluminium toxicity

Exposure to toxins is thought to be a risk factor for AD. Some state that contact with *aluminium* increases the risk of developing AD. Aluminium has been found to accumulate in neurons with neurofibrillary tangles (Khachaturian, 1985), but the results have been conflicting

regarding the association between exposure to aluminium and the increased risk of developing AD (e.g. in van Duijn, 1996). Aluminium is neurotoxic if it reaches the brain, but studies show that neither the clinical syndrome nor the pathology resemble AD (Munoz & Feldman, 2000).

4.6.5 Other potential factors on AD development

Early-life risk factors for AD such as mother's age at patient's birth, number of siblings, birth order, and weight at birth have been studied. Some studies have found a correlation between these variables and the increased risk of developing AD, but others have failed to show this correlation (e.g. in Moceri et al., 2000). Some studies have shown that regular physical activity can lower the risk of AD (Laurin, Verrault, Lindsay, MacPherson, & Rockwood, 2001). There are furthermore researchers who state that regular consumption of red wine can lower the risk of AD, but this has not been carefully studied. Red wine, on the other hand, has been shown to have beneficial effects on cardiovascular health (summarised in Breitner, 1999).

4.6.6 Genes and chromosomes

AD has a heterogeneous etiology and over the past 20 years has been associated with a large number of putative environmental causative factors as described above. Another risk factors is a positive family history of AD, a hypothesis which has more recently led to studies on genetic mutations and vulnerability genes. AD is inherited as an autosomal dominant trait only in few families, but many researchers have studied concordance rate for twins. Concordance rate for monozygotic twins has been reported to be 50-83% and for dizygotic pairs 30-42% (Gatz et al., 1997; Kumar et al., 1991; Rocca and Amaducci, 1988; Small, et al., 1994). The concordance rate in monozygotic twin pairs is however much lower than expected from an autosomal dominant disease thus suggesting that environmental or other non-genetic factors also contribute to AD (Kumar et al., 1991; Nee et al., 1987; Rocca & Amaducci, 1988). The risk of developing AD, if there is one case of AD in the family, increases three times for others in the family. If there is more than one affected family member the risk increases seven fold (van Duijn et al., 1991). This is somewhat lower in the study by Launer et al. (1999) who found an increased risk for AD of 1.6, if there is a history of dementia in two or more first-

degree family members. Individuals with no family history of AD and without an ApoE 4[6] allele have a lifetime actuarial risk of approximately 9% of developing AD, whereas an individual with both features has a risk of approximately 40% (van Duijn et al., 1991). Some studies, on the other hand, have not shown any difference in subjects with a family history of AD compared to those without such a history on any of the baseline demographic, neuropsychological, or metabolic measures. According to the study of Small, La Rue, Komo, Kaplan, & Mandelkern (1995) having just one first-degree relative with AD was found not to increase the risk of subsequent cognitive decline unless the presence of the ApoE 4 allele was evident.

As stated earlier some familial AD cases have an early onset, and about half of them are known to be caused by three different gene mutations on the following three chromosomes.

1. Mutation in the APP gene on *chromosome 21*. The mutation occurs near the beginning and end of the beta-amyloid (Aβ) peptide and increases the production of Aβ, particularly the form with 42 amino acids, which has the greatest association with neurotoxicity (Munoz & Feldman, 2000)

2. Mutation in a gene on *chromosome 14*, called *presenilin 1*. This mutation also increases the production of Aβ 42 and appears to account for a majority of cases of familial early-onset AD (Greenfield, Gouras, & Huaxi Xu, 1998).

3. Mutation in a gene on *chromosome 1*, called *presenilin 2*. It appears in people migrated from Germany to Volga River area of Russia (Cummings, Vinters, Cole, & Khachaturian, 1998).

Mutations account for only a small number of AD cases or less than 2%. Scientists are now trying to reveal how mutations of these genes cause the onset of AD, but it is known that they increase the production of Aβ peptide (Cummings et al., 1998).

There is no evidence that these known mutations play a major role in the more common sporadic or late-onset AD (Cummings et al., 1998). Studies have shown one genetic risk factor

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[6] ApoE 4 stands for epsilon 4 allele of the *apolipoprotein E gene* on chromosome 19 and has been shown to be associated with an increased risk for late onset AD – see further discussion of ApoE status below.

to be associated with an increased risk of developing late non-familiar AD and that is the ApoE 4 allele, on *chromosome 19* (e.g. Sabbagh, Galanski, & Thal, 1998).

There are studies that have linked late-onset familial AD with *chromosome 12* with sporadic susceptibility gene polymorphisms (Roses, 1997). Furthermore, according to three related studies published recently investigators have identified one or more genes on *chromosome 10* that are associated with AD (Myers et al., 2000; Ertekin-Taner et al., 2000; Bertram et al., 2000).

Down syndrome has consistently been shown to be a genetic risk factor for AD. It seems that all those with Down syndrome over the age of 35 develop the characteristic neuropathological features of AD. Down syndrome is due to the inheritance of an extra copy of *chromosome 21*, as mentioned earlier mutation in the APP gene on this chromosome is linked to early onset AD (reviewed in Holland & Oliver, 1995).

4.6.7   ApoE

ApoE polymorphism and its connection to AD have been intensively studied. ApoE is a polymorphic plasma protein that binds to a low-density lipoprotein receptor and is involved in the transport of cholesterol and phospholipid between cells (Tabaton, 1994). ApoE is involved in the growth and regeneration of both peripheral and central nervous tissues during development and following an injury (Munoz & Feldman, 2000; Swartz et al., 1999). The exact role of ApoE in the pathogenesis of AD is unknown but studies indicate that ApoE is important regarding synapse, neurite and cell loss in AD, both directly and indirectly by affecting amyloid and tau metabolism (Strittmatter et al., 1994; reviewed in Swartz et al., 1999).

Three different alleles exist for the ApoE gene, epsilon 2, 3, and 4. These alleles determine ApoE polymorphism, resulting in six possible phenotypes epsilon (ε) 2/2, 2/3, 2/4, 3/3, 3/4, and 4/4. ApoE 3 is the most common version found in the general population and may play a neutral role in AD. Studies indicate that ApoE 4 inhibits axon outgrowth whereas ApoE 3 may be a factor in extending it (Swartz et al., 1999).

In contrast to ApoE 4 the relatively rare ApoE 2 allele appears to have a protective role in AD both by decreasing the risk of developing AD and by increasing the age of onset if AD does develop (reviewed in Swartz et al., 1999).

Researchers have found that ApoE 4 is associated with severe memory loss in AD. The inheritance of one or two copies of the ApoE 4 allele increases the risk for late-onset familial AD and for sporadic AD. This is somewhat different between studies, ranging from a 3- to 15-fold increased risk of developing AD depending on the number of the ApoE 4 allele copies (see in Munoz & Feldman, 2000). ApoE 4/3 allele increases the risk of developing AD three times and ApoE 4/4 about 10 times (Frikke-Schmitt et al., 2001; Kuusisto et al., 1994).

Presence of the ApoE 4 allele correlates with an earlier age of onset and an increased density of neuritic plaques (Cummings et al., 1998; Reiman et al., 1996). Some have suggested that the ApoE 4 allele affects age of onset rather than alter the rate of progression of AD (Swartz et al., 1999). It is interesting to note that the risk associated with ApoE 4 loses its significance after a certain age. It seems to exert its maximal effect before age 70 and have no influence on development of cognitive decline or mortality in the very elderly (Juva et al., 2000). Resent genetic studies on late-onset AD have indicated that the *cystatin C* gene is a susceptibility allele to the disease after age 75 or 80, that is at an age when ApoE is no longer a major risk factor (Crawford et al., 2000; Finckh et al., 2000). It is therefore possible that different genes may influence AD at different times of life.

Studies have shown that there are ethnic and racial differences in the risk of AD and the contribution of ApoE. Some recent studies indicate that carrying an ApoE 4 allele is a greater determinant of risk of AD in Caucasians than in Hispanic Americans or in African Americans. However, Hispanic Americans and African Americans may have a higher overall risk of AD than Caucasians (Hendrie et al., 2001; Tang et al., 1998; Farrer, 2000). Icelandic studies indicate that the ApoE association in AD is similar to what is found in the other Nordic countries and the British nation. The odd ratios for ApoE 4 homozygotes generally range from 7-19 and for ApoE 3/4 heterozygotes range from 2.8-4.4 (Jonsson et al., unpublished).

In spite of the important role of ApoE, the use of ApoE genotyping as a presymptomatic predictive test or as a stand-alone diagnostic test for AD is not supported by professionals (Swartz et al., 1999; Tierney, Szalai, Snow, Fisher, Tsuda et al., 1996). The mere inheritance of one or two ApoE 4 alleles does not predict AD with certainty. Some may have one or two ApoE 4 alleles and not get AD whereas others with AD have none (Munoz & Feldman, 2000; Swartz et al., 1999). The genetic counselling regarding the ApoE 4 is therefore very complex and the general consensus has been that it should not be offered as a routine presymptomatic test (American College of Medical Genetics/American Society of Human Genetics Working Group on ApoE and Alzheimer's Disease, 1995). The ApoE genotype is only a reliable prognostic indicator of who will develop AD when memory test performance is also included (Small, Mazziotta et al., 1995; Tierney, Szalai, Snow, Fisher, Tsuda et al., 1996). Furthermore, the ApoE 4 allele has been reported to correlate to memory impairments (episodic) in non-demented elderly people (Swan, et al., 1999; Swartz et al., 1999).

4.6.8 Further AD genes research

The exciting gene search for additional candidates for risk factors of late-onset AD continues in the hope of improving the understanding of the disease and to help with diagnosing, treating or even preventing the disease. There is a promising study on the Arab population that due to high family size and inbreeding is considered ideal for genetic study. Studies on this population indicate that a recessive gene is involved in AD (Bowirrat, Friedland, Chapman & Korezyn, 2000). The Icelandic population is another population that is well suited for genetic research, as it is relatively homogeneous, has good medical records, and most importantly extensive genealogical records. The Icelandic company deCODE genetics and the Swiss-based pharmaceuticals firm F. Hoffmann-La Roche announced August the year 2000 that their scientists had successfully mapped a novel gene that possibly contributes to the occurrence of the common form of AD (Th. Jonsson, personal communication, 2002; http://decode.is).

4.7 Neuropathology of AD

4.7.1 Amyloid Precursor Protein

Amyloid is a generic term used to describe a group of biochemically heterogeneous proteins found in a number of diseases and tissues. *Amyloid precursor protein* (APP) is one of these

proteins and it is embedded in the nerve cell's membrane. It appears to play an important role in the growth and survival of neurons. It may protect neurons against damage and, furthermore, helps damaged neurons to repair themselves and to grow after brain injury (Saitoh & Mook-Jung, 1996). There are two kinds of proteases (kind of enzymes) that cleave the APP into protein fragments. One is β/γ secretase (1-42 fragment), which helps cleave APP to form *beta-amyloid* (Aβ). The other is α secretase (between residues 16 and 17) that cleaves the APP in the middle (forms APPs) so that Aβ cannot be formed (Munoz & Feldman, 2000). The Aβ is of two different lengths. The shorter one is more soluble and aggregates slowly (Aβ-40 amino acid peptide). The longer and the "sticky" one (Aβ- 42) rapidly aggregates into long filaments outside the cell and forms the amyloid plaques that are characteristic of AD in brain tissue (Satoh & Mook-Jung, 1996; Greenfield, et al., 1998). A G-protein-coupled neurotransmitter receptor controls the process of the two secretases that cleave APP. It increases the α-secretase process and inhibits the process of β-secretase. Stimulated cells increase secretion of APPs and reduce secretion of β-amyloid compared to unstimulated cell (Holmes & Wilkinson, 2000).

Evidence indicates that Aβ deposition is an early and necessary first process in AD pathology and it could precede other brain changes and clinical symptoms, perhaps by decades (see in Swartz et al., 1999). Aβ toxicity could play a major role in explaining neuronal destruction following AD. Aβ disrupts connections between cells in the immediate area around the plaque and reduces the ability of some blood vessels in the brain to dilate. This makes neurons more susceptible to different kinds of damage such as ischemia. Aβ could also cause damage by increasing intracellular calcium[7], but too much calcium inside cells leads to cell death. Possible mechanisms of Aβ toxicity also include anomalies in the potassium channel, kinase activation or enhancement of glutamate toxicity. Another possible harmful effect of Aβ neuronal toxicity is causing inflammation in the brain or by generating free radicals (Saitoh & Mook-Jung, 1996). But generation of free radicals is a popular subject today and will be described later.

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[7] Calcium is an element that helps cells in many ways, e.g. carrying nerve signals (Carlson, 1991).

4.7.2 Amyloid plaques

Three types of amyloid-related plaques[8] are recognized in the brain of AD patients:

1. **Diffuse plaques** that contain no amyloid core and do not associate with dystrophic neurites or glia. Diffuse plaques are not symptomatic in the course of AD (Sabbagh et al., 1997).

2. **Neuritic plaques** are the classical amyloid plaques that consist of a dense, largely insoluble fibrillar amyloid core intermingled with fragments of dead and dying neurons and non-nerve cells such as microglia and astocytes (Pirozzolo, Inbody, Sims, Strittmatter, & Baskin, 1989). The irregular neuritic plaque masses range from 50 to 200 μm in diameter. Neuritic plaques not only include amyloids, but also among other components tau protein α_1-antichymotrypsin, ApoE, glycosaminoglycans, neurotransmitters, and transmitter-related enzymes (Cummings et al., 1998).

3. **Burnt out plaques** that consist of an isolated dense amyloid core (Cummings et al., 1998).

Neuritic plaques in AD are primarily concentrated in the cerebral cortex and hippocampus and also to a lesser degree the corpus striatum[9], amygdala[10], and thalamus (Pirozzolo et al., 1989). Already in the earliest stage of AD large neocortical plaque density and dramatic entorhinal neuronal loss have been identified (Haroutunian et al., 1998; Morris, 1999).

4.7.3 Neurofibrillary Tangles/Tau

Neurofibrillary tangles are the second hallmark of AD and consist of abnormal collections of twisted fibres that build up inside neurons (Braak & Braak, 1991).

In healthy neurons *tau* binds to microtubules and helps stabilize them so they form a structure like train tracks. These microtubule tracks guide nutrients and molecules from the bodies of the cells down to the ends of the axon. In cells affected by AD the tau is changed chemically

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[8] The amyloid plaques are also known as senile plaques, but after they were recognized to contain the Aß protein as the major pathologic constituent, scientist have more commonly referred to them as amyloid plaques.
[9] Caudate nucleus and putamen are anatomically and functionally closely related to each other and are sometimes referred to as corpus striatum (Nolte, 1993).
[10] The amygdala lies near the temporal pole, between the inferior horn of the lateral ventricle and the lentiform nucleus (putamen and globus pallidus) and is a part of the limbic system (Nolte, 1993).

causing the microtubules to fall apart and the structures to collapse. The chemically altered tau twists into paired helical filaments that are wound around each other. This collapse of the transport system may first result in malfunctions in communication between nerve cells and later may lead to neuronal death (Johnson & Jenkins, 1996; Swartz et al., 1999). These filaments are the major substances found in neurofibrillary tangles. Abnormal processing of tau appears to increase more than 20-fold in AD patients compared with healthy age matched controls, and increases dramatically as the disease progresses (Lishman, 1989). Studies show that the formation of tangles and the loss of neurons progress together over the course of AD (in Swartz et al., 1999).

Neurofibrillary tangles usually show a highly characteristic pattern of distribution with only minor inter-individual variations. Braak and Braak (1991) described three neuropathologic stages of AD based upon qualitative evaluation of changes in the distribution pattern of neurofibrillary tangles. In the first stage (*transentorhinal stage*) there is mild to severe pathology in the transentorhinal regions located between the entorhinal region proper and the adjoining temporal cortex. Some mild neuronal changes may also be seen in the CA_1 cells of the hippocampal region. In the next stage (*limbic stage*) there is severe damage in the entorhinal and hippocampal regions, and some limited damage in the isocortex. That are some scattered tangles in the basal regions of the frontal, temporal, and parietal lobes. In the last stage (*isocortex stage*) the isocortex is severely affected and the extrapyramidal system is also affected, besides more severe lesions in regions affected during previous stages (Braak & Braak, 1991).

There is a correlation between the number of cortical neurofibrillary tangles and the degree of cognitive impairment (Giannakopoulos et al., 1998; 1999; 2000; Iraizoz et al., 1999). Neurofibrillary tangles are important in detecting incipient or presymptomatic stage of AD in histopathological diagnosis (Johnson and Jenkins, 1996; Schmitt et al., 2000). The transentorhinal stage is a preclinical period when the disease is not clinically recognized. Limbic stage is a clinically incipient period when the disease is first diagnosed. Finally, in the isocortical stage AD is fully developed (Brakk & Braak, 1991, Schmitt et al., 2000).

4.7.4 Summary on plaques and tangles

Scientists have known about amyloid plaques and neurofibrillary tangles since Alois Alzheimer reported them in his article in 1907 (Alzheimer, 1907). Although recent researches have revealed much about plaques and tangles, their function in AD is still not fully understood. An interesting study by Morsch, Simon, & Coleman (1999) showed that neurofibrillary tangles do not necessarily lead to death of CA_1 hippocampal neurons in AD. They stated that these neurons could survive with neurofibrillary tangles for about 20 years.

Plaques and tangles are the classical pathological hallmarks of AD, seen at postmortem. The Braaks described neuropil threads as a third AD marker. Neuropil threads are abnormal neurites and closely correlated with the distribution of neurofibrillary tangles (Braak & Braak, 1991).

According to many studies (e.g. Giannakopoulos et al. 1998, 1999, 2000) neurofibrillary tangle densities in AD correlate with the severity of various cognitive impairments measured with neuropsychological tests such as apraxia, visual agnosia, temporal and spatial disorientation and semantic memory. Whereas senile plaques correlate neither to clinical severity or neuropsychological deficits in AD.

Plaques and tangles are also found in non-demented elderly subjects, although in a much lesser extent, and are morphologically identical to those seen in AD. They are, however, not found in normal young and middle-aged people (see in Swartz et al., 1999; Munoz & Feldman, 2000; Pirozzolo et al., 1989). In the normal elderly and mildly demented tangles can be found in the limbic[11] regions, particularly in the CA_1 region of the hippocampus and the entorhinal cortex, but virtually none are found outside of the temporal lobe (Haroutunian et al., 1999; Morris, 1999; Schmitt et al., 2000). The opposite pattern was found for plaques in the normal elderly, they were more prevalent in neocortical and allocortical[12] regions than in medial temporal lobe structures (Schmitt et al., 2000). In a study on non-demented elderly individuals, the pathology confirmed a preclinical AD before cognitive impairment or decline was detected on

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[11] The limbic system consists of a number of structures (e.g. cingulate gyrus, hippocampal formation, amygdala, septum) with complex and often looped connections that all ultimately project into the hypothalamus, (e.g. fornix, stria terminalis, ventral amygdalofugal pathway, and medial forebrain bundle; Nolte, 1993).

[12] Allocortex is made of some restricted parts of the base of the telencephalon (paleocortex) and the hippocampal fomation (archicortex; Nolte, 1993).

neuropsychological measures sensitive to very mild AD (Goldman et al., 2001). The preclinical AD cases showed similar neuronal number and brain volume as healthy brain cases, whereas the mild AD had significant decreases in cell number. Goldman et al. therefore suggest that AD lesions must be present sufficiently long to produce neuronal or synaptic loss before cognitive symptoms appear.

There are no established biochemical markers to identify AD used in clinical routine. This could however change in the future. According to recent study by Andreasen et al. (2001) screening for tau and Aβ-protein in the cerebrospinal fluid can have a role in differentiating early AD from normal aging and psychiatric disorders. The predictive value for AD was greater than 90% when using this screening method, but to be useful clinically it needs to be detectable in easily collected fluids such as blood and urine (Andreasen et al., 2001). It seems that DNA oxidation in the cerebrospinal fluid mirrors the brain degeneration, having the potential to be used as an index of disease progression in the future (Lovell & Markesbery, 2001).

4.7.5   Atrophy in AD

One of characteristic pathologies of AD is nerve cell and synapse loss leading to selective brain atrophy (Swartz et al., 1999). It particularly affects larger neurons of the cortex. The atrophy leads to disruption of nerve cell communication, metabolism, and repair processes. Neuronal loss is more severe in younger than in older patients (Cummings et al., 1998).

The hallmark of neuronal death in AD is in the hippocampus and the anterior and medial temporal lobes, followed by parietal, occipital and frontal cortex degeneration (Cummings et al., 1998; Giacometti et al., 1994). Following this brain atrophy, a widening of the temporal horns of the lateral ventricles, the anterior portions of the Sylvian fissure and of the third ventricle is seen (Giacometti et al., 1994; Kumar et al., 1991). Some have reported atrophy of the amygdala to be a sensitive indicator of AD, but others have not been able to confirm this finding (in Cummings et al., 1998).

Interestingly, it seems that the areas of the brain that show the earliest structural signs of AD are the areas that are the last to mature during childhood and adolescence (Moceri et al., 2000).

Studies on neuronal loss, plaques and tangles reveal the important contribution of the hippocampus in the development of AD. Hippocampal atrophy has been reported to take place very early in AD and is highly associated with impairment in neuropsychological functions such as delayed recall (Fox, Warrington, Seiffer, Agnew, & Rossor, 1996; Villareal & Morris, 1998).

There is severe neuronal loss in the entorhinal cortex in very early stages of AD probably before the onset of any clinical symptoms (Frisoni et al., 1999; Gómez-Isla et al., 1996). The cortical cholinergic system is another cortical system involved in the neural processing of memory which is vulnerable to degeneration in AD. It originates in neurons within the basal forebrain and innervates the entire cortex. AD leads to cell death in the transmitter source nuclei, including the nucleus basalis of Meynert, locus ceruleus, and the Raphé nucle in the midbrain leading to neurochemical deficiencies in acetylcholine, norepinephrine and serotonin respectively (Cooper, Bloom, & Roth, 1996; Cummings et al., 1998).

4.8   Neuroimaging and electrophysiology in AD

Neuroimaging techniques are used to detect and evaluate the progression of AD, and other causes of cognitive decline. At present, no imaging modality is considered the standard diagnostic test for AD. It is likely that a combination of both structural and functional imaging may in the future increase clinical diagnostic accuracy and specificity.

In mild AD about 50% of the patients may show slowing of the EEG and this slowing becomes characteristic as the disease progresses (e.g. in Morris & Kopelman, 1994). Green and Levey (1999) found that cognitively intact relatives of AD patients showed ERP changes similar to patients diagnosed as having AD. These results indicate that preclinical detection of AD may be possible in a group at increased risk for developing AD due to positive family history of the disease.

SPECT and PET studies indicate that patients with probable and definite AD show abnormal bilateral decrease of regional CBF in the temporal, parietal and cingulate regions. In more severely affected patients there are abnormally low prefrontal, occipital, and whole-brain levels

while the motor and the visual cortices as well as the subcortical structures are relatively well perfused (Reiman et al., 1996). SPECT perfusion deficits in parietal and temporal regions correlate with both neuropsychological impairments and neuropathology. It may be useful in distinguishing AD from other forms of dementia or as a component in prediction of the earliest sign of AD (see in Swartz et al., 1999). MRI studies on AD indicate some overall grey matter volume reduction in the brain, mostly in the basal forebrain, cingulate gyrus, and medial temporal lobe, e.g. hippocampus, amygdala and parahippocampal gyrus (reviewed in Giacometti et al., 1994).

Reiman et al. (1996) found an interesting relationship between the ApoE 4 allele status and brain glucose hypometabolism in cognitively normal subjects having a family history of AD. These metabolic changes occurred in the same brain regions as are typical for AD. They were most prominent in the posterior cingulate cortex but also in parietal, temporal, and prefrontal regions (Reiman et al., 1996; 1998). These authors suggest that the glucose metabolism in the posterior cingulate cortex, measured with PET, begins to decrease before the onset of memory decline. Furthermore, they found that MRI measurements of hippocampal volume show decrease in conjunction with long-term memory decline. Although the metabolic reduction was greatest in those ApoE 4 homozygotes that showed evidence of MCI on neuropsychological tests, it was also apparent in the remaining cognitively intact ApoE 4 homozygotes (Reiman et al., 1996). These results indicate that cognitively normal subjects who are homozygous for the ApoE 4 allele have reduced glucose metabolism in the same regions of the brain as in AD patients and the reduction increases as the disease progresses from a presymptomatic stage to more severe AD (Reiman et al., 1996).

A PET study by Bäckman et al. (1999) showed similar patterns of brain activation and deactivation in early AD patients compared to NC during cued recall. The main difference between the two groups were decreased activity in the left hippocampal formation during cued recall in the early AD patients, which they concluded could reflect AD-related failures in episodic processing. They, also, found increased activation of the cerebellum in the early AD group compared to NC group. They suggest that the reason for this increased activation of the cerebellum in the early AD group should be interpreted in context of retrieval failures, which is

concordant with recent theories where it is suggested that the cerebellum operates as an error-driven adaptive system for cognitive processing, particularly memory (Bäckman et al., 1999).

4.9   Neurochemical approaches

4.9.1   Acetylcholine and other neurotransmitters

Acetylcholine was the first known neurotransmitter, discovered in the 1920s. Its exact role in the brain is unclear, but it is known to be involved in memory, attention and cognition (Snyder, 1996). There are two kinds of cholinergic receptors in the human brain, that is muscarine receptors (M_1 and M_2) and nicotinic receptors (Whitehouse & Geldmacher, 1994). M_1 receptors are relatively preserved in AD, whereas M_2 and nicotinic receptors are markedly decreased. M_2 is mainly found in the brainstem and basal nucleus of Meynert and presumably acts as an inhibitory autoreceptor, limiting the release of acetylcholine (Cummings et al., 1998).

A reduction of cholinergic projection from the basal forebrain to the cerebral cortex and hippocampus is seen in AD. The cholinergic cell loss of the basal forebrain involves groups of neurones located beneath the globus pallidus, that is neural populations in the medial septum, the diagonal band and the basal nucleus of Meynert (Nolte, 1993). Cells arising in these areas innervate neocortex, hippocampus and amygdala (Nolte, 1993; Whitehouse & Geldmacher, 1994). Some studies have shown a relationship between the ApoE 4 alleles and cholinergic cortical and subcortical function, where one or two ε4 alleles cause reduced levels of acetylcholine (Swartz et al., 1999).

The degeneration of the cholinergic neurons and a decreased level of choline acetyltransferase activity are the most consistent neurochemical abnormalities in the brain of AD patients and generally thought to occur relatively early in the development of the disease (Cummings et al., 1998; Pirozzolo et al., 1989). There are, however, some who state that it is not apparent in individuals with mild AD and becomes apparent relatively late in the course of the disease (Davis et al., 1999). This is a very critical and important issue regarding when to start cholinergic treatment in AD. Is sooner the better or is it not?

There is also evidence for deficits in other neurotransmitters and modulators in AD such as serotonin, somatostatin, glutatmete, norepinephrine, and GABA (Cummings, et al., 1998;

Pirozzolo et al., 1989; Whitehouse & Geldmacher, 1994). The pyramidal cells that provide the substrate for formation of plaques and tangles appear to be primarily GABA-ergic (Pirozzollo et al., 1989).

4.9.2   Medication treatment

Some years ago there were no specific drug treatment for AD, comprising mainly antidepressants, neuroleptics, and hypnotics (Kelly, Harvey, & Cayton, 1997). Since then there have been some new treatments available for AD. Currently there are two types of AD drug therapies – that is symptomatic approaches based on enhancement of cholinergic function and neuroprotective approaches utilising antioxidant agents (Gauthier, 1999).

- **Cholinergic medication**

There are in principal four ways to increase the available acetylcholine in the AD patients' brain. That is by using acetylcholine precursors, acetylcholine releasers, acetylcholine agonists and most effectively acetylcholinesterase inhibitors (Holmes & Wilkinson, 2000). Drugs that inhibit acetylcholinesterase act by blocking the breakdown of acetylcholine, allowing it to remain at the synapse for a longer time. These acetylcholinesterase inhibitors include drugs as tacrine (Cognex), donepezil (Aricept), rivastigmine (Exelon), galantamine (Reminyl), and metrifonate (Shadlen & Larsen, 1999; Pryse-Phillips, 1999; Swartz et al., 1999). Of these drugs donepezil and rivastigmine have probably had the greatest impact (Holmes & Wilkins, 2000). Studies on galantamine have so far also shown evidence of cognitive and global functional improvement (Wilcock et al., 2000), but it is also an allosteric modulator of nicotinic receptors (Tariot, et al., 2000). Galantamine has recently been approved in many countries e.g. USA and Iceland.

Cognitive function of AD patients deteriorates over time, and it has therefore been an important treatment goal to slow or stabilize the cognitive decline. Studies have shown that by using the acetylcholinesterase inhibitors mentioned above decline in cognitive function can be delayed from 6 months up to 12 months. Although it only delays the deterioration for a relatively short time, it makes an important difference to patients and caregivers (reviewed in Tariot, 2001). This limited benefit of drug therapies shows that cholinergic deficit alone may not be the critical determinant of AD (Pirozzolo et al., 1989).

- **Free Radicals/Oxidative Stress**

There is growing evidence that free radical damage and oxidative stress play a pivotal role in the process of aging and in pathogenesis of AD, and are active in the formation of both plaques and tangles (Lovell & Markesbery, 2001). Free radicals (reactive oxygen species) are a particular type of molecule that easily reacts with other molecules. The production of too many is called oxidative stress, believed to be a major contributor to the aging process, resulting in nerve cell damage and death (NIA, 1999). The oxidative damage to proteins and membrane lipids and an up-regulation of antioxidant enzymes have led to several clinical trials of antioxidants and free radicals scavengers in treating patients with moderate to severe demetia, e.g. vitamin E (α-tocopherol) and ginko biloba (Munoz & Feldman, 2000; Pryse-Phillips, 1999).

- **Anti-inflammatory agents**

Some studies report a decreased prevalence of AD among those taking anti-inflammatory agents on a long-term basis (Munoz & Feldman, 2000; Veld et al., 2001). It has been reported that a high dose of anti-inflammatory agents is necessary for it to have positive effects on the impairments following the disease. As these agents have undesirable side-effects, most researchers do not recommend the use of anti-inflammatory drugs in AD (Holmes & Wilkinson, 2000). A recent study, however, showed positive effects of anti-inflammatory drugs although given only at low doses (Broe et al., 2000).

- **Estrogen replacement therapy**

Many researchers have examined the relation between postmenopausal estrogen replacement therapy and the risk of developing AD. Estrogen promotes the growth and survival of cholinergic neurons and may also decrease cerebral amyloid deposition (Greenfield et al., 1998). Estrogen has a number of beneficial functions against AD e.g. antioxidant, anti-amyloid and possible anti-inflammatory properties (Holmes & Wilkinson, 2000; Mulnard et al., 2000). The findings regarding estrogen replacement therapy have been inconsistent. Several epidemiological studies show that women on estrogen replacement therapy may have both a delayed onset and reduced risk for developing AD (Munoz & Feldman, 2000). There are

however other studies that failed to show a reduced risk of developing AD using estrogen replacement therapy (Seshadri et al., 2001). In a one year study of women with mild to moderate AD some modest benefit on MMSE after the first two months of estrogen replacement therapy was found, but the benefit did not persist with continued treatment (Mulnard et al., 2000).

- **Other treatments of AD**

Other drugs used by AD patients are often drugs that influence the behavior of the patients rather than the memory or the cognitive function. Drugs that can reduce the losses in the glutamatergic and serotonergic (e.g. clozapine) systems have been associated with reduction of behavioral and psychological disturbance in AD (Holmes & Wilkinson, 2000).

There have been reports of other treatments of AD. Some researchers hope that by using neurotrophin, which is an agent believed to promote the release of trophic factors and cytokines, they will be able to boost the levels of nerve growth factor for AD therapeutic purposes (Rattray, 2001). Recently it was reported that a group of scientists implanted genetically modified tissue into the brain of an AD patient. This procedure involved implanting autologous fibroblasts engineered to produce nerve growth factor into the nucleus basalis of Meynert. Although the technique is not considered a cure for AD it is hoped that it can prevent ongoing cell loss in the brain and possibly improve the functioning of remaining cells (Reuters Medical News, 2001).

It was recently published that scientists have been developing a new vaccine that blocks the development of AD in genetically engineered mice and reduces the helical form of amyloid plaques. Its potential as a therapeutic approach for humans in the future is very exciting (reviewed in Ingram, 2001).

Using the medications that are available today can sometimes slow the progression of the disease and even improve the patients' cognitive function for some time, but the most beneficial effects are probably seen on daily living and behavior which is very important for the patient and the caregivers (Kelly, et al., 1997). Early diagnosis allows an earlier opportunity for treatment. A current question is whether the use of cholinesterase inhibitors or high-dose

antioxidants in the preclinical stage of AD may delay the progression and conversion to dementia (Shadlen & Larson, 1999). The benefit of using the medications mentioned above requires further studies.

5.   NEUROPSYCHOLOGY AND PRECLINICAL AD

5.1   Investigations of preclinical AD

Investigation of the preclinical stages of AD can be categorized into longitudinal and cross-sectional study designs. In longitudinal designs a large cohort of non-demented older subjects are recruited and assessed longitudinally with neuropsychological tests until a sufficient number of subjects have been diagnosed clinically with probable or possible AD. The neuropsychological test performance of those developing AD is compared to those who remained healthy. In the cross-sectional design, a group of people with one or more of the known or putative risk factors for AD are compared to a group of matched controls that do not possess the same risk factor(s) (e.g. Collie & Maruff, 2000).

5.2   Longitudinal prospective community studies

Following is a short discussion of some longitudinal prospective community studies with an emphasis on the neuropsychological tests that were the best indicators of preclinical AD signs of the participants in the studies.

Masur, Sliwinski, Lipton, Blay, & Crystal (1994) reported the findings of a study on a cohort of initially healthy elderly people from the Bronx Aging Study. Tests that were found to be predictive of those later developing AD were in addition to two memory measures, the Digit Symbol subtest of the WAIS-R, and an Oral Word Fluency measure. Digit Span and Block Design did not contribute to the prediction of those developing AD later (Masur et al. 1994). In the North Manhattan Aging Project, Jacobs et al. (1995) reported the preclinical stage of AD to be characterized by impairments on confrontation naming (measured with Boston Naming), abstract reasoning (measured with Similarities) and memory (Immediate Recall on the Selective Reminding Test). The results from the PAQUID cohort in the Bordeaux area indicated that impaired processing speed, selective attention, and more controlled aspects of memory functioning (tested e.g. with Cancellation test, Similarities, and Associate Learning)

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correlates with increased risk of developed AD within two years (Fabrigoule et al., 1998). A limitation of the findings reported by Fabrigoule et al. (1998) is that they are based on rather few individuals, i.e. only 16 individuals out of 1159 developed AD and 25 developed dementia within two years. Other prospective community studies are the Framingham Cohort studies reported by Linn et al. in 1995 (after 13-year prospective study) and later by Elias et al. in the year 2000 (after 22-year of prospective study). Linn et al. reported that those who later developed AD (mean age 76 years) scored significantly lower, on most of the neuropsychological measures, than those not developing AD, on the initial testing. The preclinical phase of significant deficits preceded the clinical diagnosis of probable AD in some cases by more than six years. The test battery, used by Linn et al., included few tests and the administration took only 20 minutes. This limited assessment could therefore not cover a wide range of cognitive domains (Fox et al., 1998). The most sensitive tests of preclinical AD were e.g. Logical Memory (LM) retained, Associate Learning, and Similarities. Oral Word Fluency and Digit Span where not indicative of who would later develop AD. The group developing AD later scored even significantly higher on Digit Span. Elias et al., (2000) on the other hand, reported no difference between those developing AD versus those not developing AD on the Digit Span score. According to them memory (measured with LM-retained) and abstract reasoning (measured with Similarities) were predictive of those developing AD later, predicting AD after a dementia free period of as long as 10 years. Other tests, such as Oral Word Fluency, LM immediate recall, and Associate Learning, did not have association to those who developed AD later.

Rubin et al. reported in 1998 a longitudinal evaluation of participants with annual clinical and psychometric examinations for up to 15 ½ years. They found that before the onset of detectable clinical changes and global psychometric deterioration, people eventually developing dementia performed less well on LM. Chen et al. (2000) reported findings of a 10-year prospective community study where delayed recall of a Word List discriminated best between those manifesting AD 1.5 years later and those remaining non-demented. The second best indicator was Trails B, and the third was LM delayed and immediate recall. Those who later developed AD were, furthermore, significantly older and less educated than controls (Chen et al., 2000). Small et al. (2000) reported results from the Kungsholmen Project, a follow-up

study of a population-based sample. According to them the first indicator of AD is memory deficits. This study may not be very reliable since the results are only based on the MMSE test.

Many researchers have studied people complaining of memory impairment, with other cognitive function intact and therefore not clinically diagnosed as demented. A follow up study of these subjects can help researchers to understand better the preclinical stage of AD and how the disease develops. In a prospective longitudinal study Tierney, Szalai, Snow, Fisher, Nores et al. (1996) followed a group of memory impaired people without clinical diagnosis of dementia. Of 123 participants, 29 became demented within two years. Tests that predicted best those eventually developing AD were Rey Auditory Verbal Learning Test and Mental Control of WMS – predicting better than e.g. Associate Learning, LM, Oral Word Fluency, and Trails A and B.

Reid et al. (1996) reported a study with newly diagnosed AD participants. According to them impairment in memory (measured with e.g. LM) and frontal/executive function (measured e.g. with Similarities and letter and animal categories of the Oral Word Fluency) where the earliest signs of cognitive impairment in this group.

5.3   Familial studies

Familial studies on AD include in most cases subjects with autosomal dominant or a very strong family history of AD, mostly subjects from families with early-onset AD. La Rue, Matsuyama, McPherson, Sherman, & Jarvik (1992) reported a study on cognitive performance of 21 offspring and 11 siblings (mean age around 65 years) of patients with probable AD. They reported that relatives of patients with early onset dementia were more likely to show a decline in performance, over a four years interval, than relatives of patients with later onset dementia (La Rue et al., 1992). Later, in 1995, they reported a longitudinal study where they compared 40 first-degree relatives to 24 NC without a family history of AD (mean age around 57 years; La Rue, O'Hara, Matsuyama, & Jarvik, 1995). They reported that relatives of AD were more likely to show cognitive decline over an interval of six years. In this study the cognitive decline was observed in the late-onset relative subgroup as well as the early-onset relative subgroup.

In 1994 Small et al. reported a study with 29 participants having at least one first-degree relative with documented AD and 14 without AD history in the family (mean age 60 years). All the participants in the study complained of memory difficulties. They compared these two groups without finding any cognitive differences. One year later Small, La Rue et al. (1995) reported another study with similar results. In this study they used two cognitive measures, one measure of verbal memory (Buschke-Fuld Selective Reminding Test) and one of visual-spatial memory (Benton Visual Retention Test). They followed 42 subjects who volunteered to participate because of their concerns about mild memory complaints. The mean age of the group was 60 (*SD* 9.9) years. As in the earlier study they found no difference between participants with a family history of AD (*n*=28) and those without such a history (*n*=14), in any of the baseline demographic, neuropsychological, or metabolic measures (Small, La Rue et al., 1995).

In 1994 Bondi et al. reported a study where 28 subjects with a positive family history of progressive dementia were compared to 25 subjects with a negative family history of dementia (mean age around 70 years old). They studied the group over three annual evaluations on the California Verbal Learning Test (CVLT). They found that those with positive family history of dementia were more likely to undergo changes in diagnostic status over time and that memory difficulties measured with CVLT could predict those developing AD later. They did not report how many of these first-degree relatives were siblings or offspring. Hom, Turner, Risser, Bonte, & Tinter (1994) did a similar study where they tested 20 asymptomatic first-degree relatives of AD patients and 20 age-, education-, and gender-matched NC subjects without a family history of AD. Mean age for the first-degree relatives was 54.5 (*SD* 5.7) years (2 siblings and 18 offspring) and for the NC group 57.7 (*SD* 6.3) years. About 50% of the first-degree subjects showed a pattern of significant neuropsychological deficits compared to only 20% of the NC. The first-degree relatives performed significantly worse on several cognitive domains, compared to the NC group, e.g. on measures of verbal intelligence, verbal short-term memory, and attention and concentration. None of the first-degree relatives fulfilled the criteria of AD and their performance was within normal expectations for their age and education and they were apparently functioning well without showing or reporting any significant clinical signs or symptoms of AD (Hom et al., 1994).

Díaz-Olavarrieta et al. (1997) assessed neuropsychological changes in 14 subjects at risk of inheriting AD in a one-year follow up study. The group was a mixture of siblings of AD patients and offsprings selected from three families with very strong history of AD, with the mean age of 36 ± 4 years. The comparison group was 14 age and education matched subjects with a negative family history of AD. Subjects having a positive family history of AD showed impairments on tests of delayed recall of verbal material compared to the NC.

In a longitudinal study on familial AD Fox et al. (1998) reported that memory tests make the largest contribution in discriminating early AD from healthy aging. They recruited asymptomatic at-risk members of early-onset familial AD with mean age of 44.7 ± 8.1 years. Participants included in the study were those with a strong family history of AD. They included 63 participants and of them 10 developed AD. About six years prior to the clinical diagnoses of AD they showed impairments on verbal memory and performance IQ, the performance on verbal subtests were not impaired.

5.4   Neuropsychological predictors of AD

Researchers have been trying to study the preclinical signs of AD for some time to find some reliable technique to diagnose the disease earlier and with greater accuracy. Some follow-up studies have documented the length of preclinical signs of AD, before clinically diagnosed, to be around 3 years (Fabrigoule et al., 1998; Jacobs et al., 1995; Tierney, Szalai, Snow, Fisher, Tsuda et al., 1996), 5 years (Fox et al., 1998; Linn et al., 1995), 7 years (Small et al., 2000), and at lest 10 years (Almkvist et al., 1998; Elias et al., 2000). La Rue and Jarvik (1987) demonstrated that significant differences in cognitive performance might be identified up to 20 years before AD is diagnosed. Furthermore, reports from the NUN-study have stated that linguistic ability in early life, measured as the grammatical complexity in autobiographies, can be indicative of those developing AD more than 60 years later (Snowdon et al., 1996).

Neuropsychology is a cornerstone in the assessment of early AD and the most sensitive indicator of the preclinical stage of the disease (Goldman et al., 2001). Measures of verbal and non-verbal memory performance are, according to most studies, the first indicators to

demonstrate deficits in preclinical AD (Almkvist, 1996; Bäckman et al., 1999; Chen et al., 2000; Fox et al., 1998; Linn et al., 1995; Locascio, Growdon, & Suzanne, 1995; Masur et al. 1994; Newman, Warrington, Kennedy, & Rossor, 1994; Perry & Hodges, 2000; Petersen et al., 1999; Reid et al., 1996; Schmitt et al., 2000; Small, Herlitz, et al., 1997;Small et al., 2000; Tierney, Szalai, Snow, Fisher, Nores et al. 1996; Tierney, Szalai, Snow, Fisher, Tsuda et al., 1996).

Although generally there is an agreement of memory impairments being the first signs of AD, researchers disagree to some extent which cognitive impairments come second to memory impairments. Many studies indicate that attention is the first non-memory domain to be affected in AD patients and to be affected before deficits in language and visuo-spatial functions. According to the study by Rizzo, Anderson, Dawson, Myers, & Ball (2000) mild AD was characterized by impairment of visual attention and slow processing speed which both correlated strongly with other cognitive deficits. Divided attention and selective attention are found to be particularly vulnerable, while sustained attention is relatively preserved in the early stages of AD (Perry & Hodges, 1999). Some studies show that sustained attention is mainly controlled by frontal areas, which as stated earlier, deteriorates rather late in the disease. Selective attention is, however, controlled by the parietal lobes (in Almkvist, 1996) which deteriorate early in the disease course. According to Reid et al. (1996), on the other hand, frontal/executive deficits were second after memory impairment to indicate AD in the newly diagnosed AD patients.

Other cognitive abilities that have been associated with the subsequent development of AD are verbal abilities, measured e.g. with Oral Word Fluency (Fabrigoule et al., 1998; Small, Herlitz et al., 1997) and visuo-spatial and executive functioning (Jacobs et al., 1995; Small et al., 1997). In a study of Bozoki et al. (2001) on non-demented patients with MCI they determined that those with impairments in several cognitive domains, in addition to memory, were more than twice as likely to develop AD, over a period of 2 to 5 years, than those with memory impairments alone. In this study deficits in Block Design was the most frequent abnormality other than memory loss (Bozoki, Giordani, Heidebrink, Berent, & Foster, 2001).

The above studies show that memory impairment, measured with immediate and delayed recall, is the best indicator of subsequent AD. This locus of impairment is consistent with both histopathological and morphologic evidence on the medial temporal lobe including the hippocampus and neighboring regions, but as mentioned above the role of the hippocampal formation is pivotal in acquiring new memories.

5.5   The AD research effort

The clinical diagnosis of AD is not difficult once the disease is established, while the detection of the illness in the preclinical stages is more difficult. Early and accurate diagnosis of AD and improved ways to determine causes and assess risk factors are essential because of somewhat effective treatments available today and hopefully more effective ones in the future. It is likely that treatment cannot significantly reverse AD once is it overt and for that reason is it likely that the treatment will be most effective in the early stages of the illness. Therefore, it is important to determine the time line and the earliest evidence of cognitive decline measured with neuropsychological tests signaling the preclinical stage of AD.

The importance of identifying specific neuropsychological tests that have clinical utility in the prediction of AD, is beneficial not only for treatment purposes but also for social and psychological purposes. Early diagnosis is vital to provide the AD patient an opportunity to participate with legal and financial planning while decision-making capacity is still preserved, and to counsel the patient and the family about the course and prognosis of the disease.

PART II: NEUROPSYCHOLOGICAL DEFICITS IN AD

6. AIMS OF THE STUDY

In the present study subjects (Sibs), who had a sibling with AD and another AD relative within six meiotic events, were compared to a group of people (NCs) without any first-degree relatives with known dementia and group of AD patients. The participants in the Sib and NC groups were all living in the community and had not been referred because of memory problems. The aims of this study were threefold:

1) To see if siblings of AD patients show any cognitive impairment compared to a group of people without any known demented first-degree relative.
2) To see if there are some individuals among the siblings that resemble mildly demented AD patients, on the neuropsychological tests.
3) Furthermore, to see which neuropsychological tests best differentiate mildly impaired siblings from normal controls.

7. METHOD

The study was conducted at the Genetic Research Service Center in Reykjavik, Iceland, between June 1998 and April 2001. This study is a part of large genetic research project where the aim is to locate the genetic markers of AD. This genetic study is performed on Icelandic pedigrees with medically diagnosed dementia by deCODE genetics INC, Geriatric department of Landspitali University Hospital, and the Genetic Research Service Center.

7.1 Subjects

The subjects in the study were AD patients, siblings of AD patients, and an NC group. The AD patients had been clinically diagnosed according to the NINCDS-ADRDA criteria for AD (McKhann et al., 1984), supplemented by complete medical and geriatric examination, neuropsychological assessment and CT scans. The patient group consisted of probable or possible AD patients who scored 3 or 4 on Reisberg's Scale for Global Deterioration (Reisberg, Ferris, de Leion, & Crook, 1982), considered to have mild or moderate AD. They

were selected from pedigrees with a history of dementia, which is connected by at least two AD patients within six meiotic events or less (see figure 1). The Sibs were drawn randomly from the same pedigrees. The Sibs were not referred for a medical evaluation of dementia.
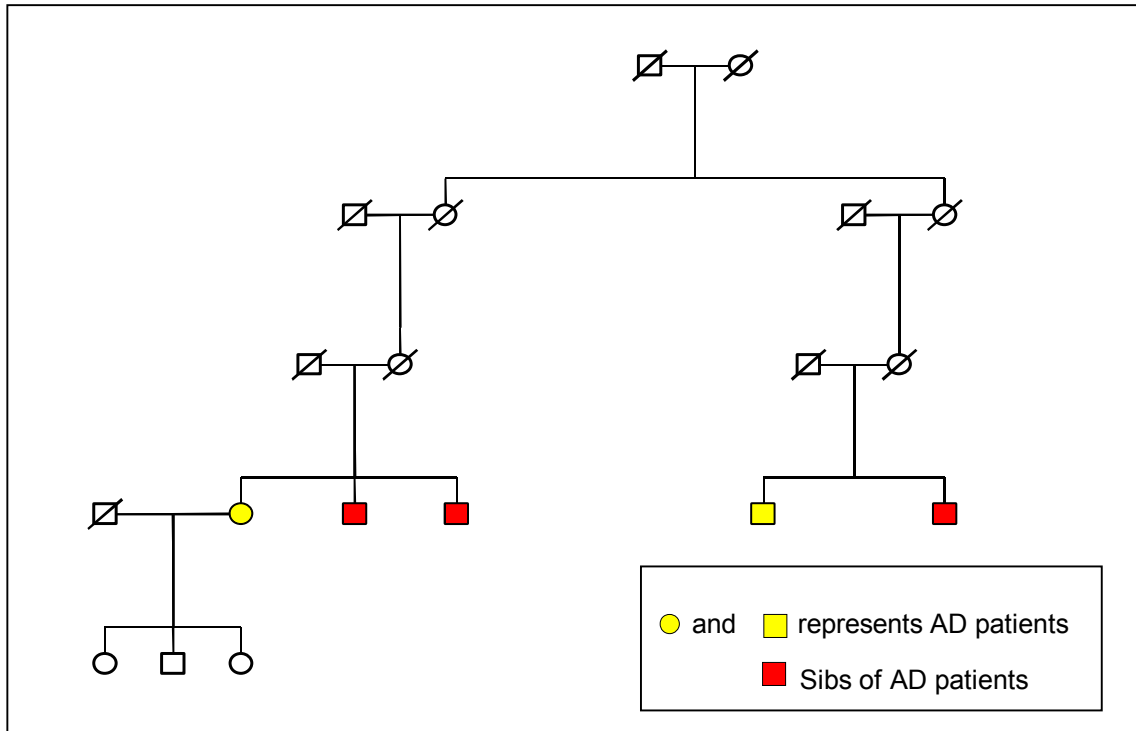
Figure 1.
An example of the pedigree definition used in the study. Cluster of individuals that are connected by at least two AD patients within six meiotic events or less.

In the initial project 85% of the AD patient cohort and 82% of their siblings consented to participate. The participants in the current study were randomly selected from this research cohort. Only one AD patient and two siblings refused to participate in the neuropsychological part of the study after having taken part in the initial genetic research by giving a blood sample. The NC group consisted of spouses of the siblings and people volunteering after seeing an advertisement. Spouses were in the majority in the NC group and of those contacted 15% refused to participate.

Exclusion criteria in this study were the following: Known central or peripheral nervous system disorders; psychiatric illness; chronic drug or alcohol abuse; significant or uncorrected impairment of hearing, vision, or movement; or other physical disabilities or impairments that

would preclude or hinder appropriate completion of the neuropsychological test battery (except for Alzheimer's disease in the AD patient group). The total number of subjects tested were 281, but 15 AD, 5 Sibs, and 10 NC participants met the exclusion criteria and were left out of the statistical analyses. There were two Sibs and two NCs with some impairment of vision who were therefore excluded from tests that make heavy demands on vision, e.g. Letter Cancellation and Rey Complex Figure. Finally, one participant in the Sib group and two in the AD patient group were excluded from all data analysis, being statistically extreme cases on more than two neuropsychological measures.

The NC group included mainly the spouses of the participants in the study, and the remaining 29 participants were volunteers that came after seeing an advertisement. The NC subjects had no known demented first-degree relatives.

Data analysis was based on 85 AD patients, 95 Sibs, and 68 NC. The AD group was significantly older than the NC group (table 2), but other demographic variables revealed no differences between the three groups.

Table 2.
Demographics for the AD, Sib, and NC groups.

	AD n = 85		Sibs n = 95		NC n = 68	
Age (years)						
M	75.1*		73.3		71.8	
SD	5.4		6.3		5.4	
Range	60-85		60-85		60-85	
Gender:						
Male	37	(43.5%)	50	(52.6%)	28	(41.2%)
Female	48	(56.5%)	45	(47.4%)	40	(58.8%)
Education (yrs.):						
≤8	44	(57.1%)	51	(55.4%)	38	(59.4%)
>8	33	(42.9%)	41	(44.6.%)	26	(40.6.%)

* The AD group was significantly older than the NC group, ($F(2,247) = 6.50, p < .01$).

7.2   Material/Instruments

7.2.1 Neuropsychological assessment

Many researchers use Mini Mental State Examination (MMSE; Folstein et al., 1975) as a screening test for AD. Studies have however shown that the Icelandic version of the MMSE test (Tomasson, 1986) has some flaws due to linguistic differences (Palsson, 1995). The Icelandic version of the test is more difficult than the English version, especially for older women who score significantly lower than men in this test (Palsson, 1995). Although a newer and perhaps better version is used today, it have not been standardized and was therefore not used in this study.

The following neuropsychological tests and behavioral scales were used in the study and administered in the following order:

Orientation where the subject has to say his name, year and date of birth (orientation to person); the name of the street or the city we are located in (orientation to place); and the present day, month, year, and time (orientation to time and date).

Letter Cancellation is a vigilance test that requires sustained, focused attention. It consists of ten 31-capital letter rows in which the target character, the Icelandic letter "Þ", is randomly interspersed 52 times. The subject has to cross out all target letters (Þ) in as short a time as possible. The performance is scored for errors and for time of completion (Lezak, 1995).

In the Rey Osterrieth Complex Figure Test (Rey Complex Figure) the participant copies a figure and without prior warning is asked to reproduce it both from immediate (brief delay about 30 sec) and delayed (45 min later) memory (Lezak, 1995; Spreen & Strauss, 1998).

Wechsler Memory Scale (WMS) subtests
The Logical Memory (LM) of the WMS consists of two stories. The examiner reads the stories aloud for the participant for immediate recall. After a 45 minute delay the subject is asked to reproduce the stories from memory (Wechsler, 1945, Wechsler, 1974). The score used was the mean number of details recalled in both stories. The GIST scoring criteria was used to score the LM test (Abikoff & Alvir, 1987; Spreen & Strauss, 1998).

The Associate Learning Test of the WMS (Wechsler, 1974) is administered with immediate recall of items. The participant listens to 10 word pairs trying to make an association between each pair. Then the first word of each pair is provided as a cue and the subject has to recall the correct responses to the stimulus words over three trials (Spreen & Strauss, 1998). In six of the word pairs, the second word has an obvious association with the first (easy pairs). In the other four pairs, there is little or no evident association (hard pairs). Half a credit is given for the easy associations and a full credit for the difficult ones (Wechsler, 1945).

The Wechsler Adult Intelligence Scale (WAIS) subtests

In the Similarities of the WAIS the subject must explain what pairs of words have in common. There are 13 word pairs where the difficulty ranges from the simplest ("orange-banana") to the most difficult ("praise-punishment" or "wood-alcohol"). The test begins with the first item and is discontinued after four consecutive failures. Items are passed at the two-point level if an abstract generalization is given and at the one-point level if a response is a specific concrete similarity (Lezak, 1995).

The Digit Span of the WAIS is administered in both forward and backward versions. In the forward span, the examiner reads aloud digits at the rate of one per second and the subject's task is to repeat each sequence exactly as it is given. It starts with two digits forward and continues until the subject fails a pair of sequences or repeats a nine-digit sequence correctly. Two trials are given for each item (i.e. at each span length) and the subject receives one raw score point for each correct trial. Digit backwards is administered in the same way as forward digit but instead of repeating the digits forward the subject has to recall the digit-sequence in reverse order (Lezak, 1995). Because of the difference between digits backward and forward the scores are not collapsed into one score. However, repeating digits backward places more demand on mental control and symbol transformation than does repeating them in the same order presented (Nelson, Dean, & Lucas, 1995).

The Block Design test of the WAIS is a construction test where red and white blocks are presented to the subject. Each block has two white and two red sides, and two half-red half-white sides with the colours divided along the diagonal. The subject uses the blocks to construct replicas of two block constructions made by the examiner and eight designs printed in smaller scale. There are four blocks used in the first six designs (time limit one minute) and

in the next four designs all nine blocks are used (time limit two minutes). The subject can earn one or two bonus points for speed on the last four designs of the test. All subjects begin with the first item, which is presented and demonstrated as a block-copying test. The first and second items can be repeated if the subject fails to produce a correct design within the time limits. The testing is discontinued after three consecutive failures (Lezak, 1995).

The Picture Arrangement of the WAIS consists of eight sets of cartoon pictures that make up stories. Each set is presented to the subject in scrambled order with instructions to rearrange the pictures to make the most sensible story. Testing is discontinued after three consecutive failures. Time limits range from one minute on the easiest items to two minutes on the two most difficult ones. The subject can earn time bonuses on the last two sets of the test (Lezak, 1995).

The Trail Making Test is given in two parts, A and B. The subject has to draw a line to connect circles as fast as he can without lifting the pencil from the paper. In part A the subject has to connect consecutively numbered circles from "1" to "25" in a sequence. Part B is similar but there the circles are both numbered and lettered and the subject has to shift in connecting numbers and letters. First they have to connect the number "1" to letter "A" and then letter "A" to number "2" etc. The numbers are from one to thirteen and the letters are in alphabetic order from A to L. The subject gets the chance of short practice before starting the time-measured tests (Lezak, 1995, Reitan, 1958). Those who made more than three errors in Trail Making Test A and four errors in Trail Making Test B, without correcting them, were considered unable to finish the tests and therefore excluded from the analyses of this test. The scores were the time required to complete each trial.

Verbal Fluency Tests

In Oral Word Fluency the subject is asked to name as many words as possible beginning with the letter "s", excluding proper names or different forms of the same word. Performance was scored by counting the total number of correct words produced in one minute (Lezak, 1995).

In Category Fluency the subject is asked to name as many animals as he can think of within one minute. Performance was scored by counting the total number of correct words produced (Lezak, 1995).

In the Boston Naming Test the subject has to name 30 large ink drawings of items ranging from familiar ones such as "bed" and "pencil" in the beginning and ending with more unfamiliar items such as "compasses" and "pyramid". When the subject is unable to name a drawing, the examiner gives a semantic cue; if still unable to give a correct name, a phonetic cue is provided. The examiner notes how often cues are needed and which ones are successful. The subject gets one point for each picture correctly named, with pictures named upon semantic and phonemic cues counted separately (Lezak, 1995).

In the Gestalt Closure Test (Kaufmans ABC) the subject has to decipher a set of incomplete pictures. The test consists of 25 pictures and the subject gets one point for each picture correctly identified (Lezak, 1995).

Recognition tests
The following recognition tests were specially designed for this study to add some short form of recognition to the memory tests.

In the Recognition of the Rey Complex Figure the subject has to recognize which one of six figures presented on a single sheet is the original Rey Complex Figure copied 45 minutes earlier. The subject gets one point for the correctly recognized figure, but when the figure is wrongly recognized the number of the wrong figure is recorded. The figures are different regarding the inner and outer structure, and angle (see appendix I; Palsson & Jonsdottir, unpublished).

The Recognition of the Logical Memory test consists of ten questions regarding the stories read 45 min earlier. The examiner states the questions in a multiple-choice form, and the subject has to choose the right answer from three possibilities. For each story the subject is able to score a maximum of five points. The total score from story A and story B is divided by two to obtain the final score. Because there is no formal measure of recognition of the LM test a special version of multiple-choice recognition test was made for the present study (see appendix II, Palsson & Jonsdottir, unpublished).

In the Reading and understanding test the subject has to read a short story and answer three questions regarding the content of the story. The understanding and short term memory of the story are scored. The subject can gain points for the accuracy/quality of reading and for answering the questions right (see appendix III, Palsson & Jonsdottir, unpublished).

- **Functional traits assessed by neuropsychological tests**

The tests used in the present study are divided into six functional domains, where each test can measure more than one functional trait (see table 3).

Table 3.
Functional domains and neuropsychological assessment

Neuropsychological tests and functional domains	
Orientation	*Language*
Orientation to person, place and time	Oral Word Fluency
Verbal and nonverbal memory:	Boston Naming Test
Logical Memory (LM) delayed and immediate recall	Reading and understanding
Recognition of LM	*Attention and mental speed*
Associate Learning, Easy pairs and hard pairs	Letter Cancellation
Rey Complex Figure – delayed and immediate recall	Trails A and B
Recognition of Rey Complex Figure	Digit Span
Abstract reasoning and executive function	*Visuo-spatial and constructional abilities*
Similarities	Block Design
Oral Word fluency	Gestalt Closure (Kaufmann-ABC)
Picture Arrangement	Rey Complex Figure, copy
Trails B	

7.2.2 The Global Deterioration Scale

The AD patients included in the study were those who according to a geriatrician scored 4 or lower on the Global Deterioration Scale (GDS; Reisberg et al., 1997). The GDS is a 7-point scale that rates the subject's global cognitive status according to criteria based on subjective

complaints and objective evidence. A higher score indicates a more global impairment. The patient group consisted of mild AD (GDS 3) and moderate AD (GDS 4) paitents. Patients with a GDS rating of 3 have exhibited at least two of the following symptoms: (1) getting lost when travelling to an unfamiliar place, (2) decline in work performance apparent to co-workers, (3) word- and name-finding deficits apparent to intimates, (4) relatively little retention of material read in a passage or book, (5) decreased facility remembering the names of newly introduced people, (6) losing or misplacing an object of value, or (7) a concentration deficit apparent upon clinical testing. Subjects with a GDS of 4 exhibit more apparent deficits which manifest as (1) decreased knowledge of current and recent events; (2) a concentration deficit on serial subtraction tasks; (3) decreased ability to travel, handle finances, or perform complex tasks; and (4) possibly deficient memory of their own personal history (Reisberg et al., 1982).

7.3   Procedure

Cognitive functions were assessed by a comprehensive neuropsychological test battery measuring a broad range of cognitive functions aimed to detect subtle cognitive impairments. The test battery needed to be as short as possible, yet comprehensive, being a part of a bigger study. The neuropsychological assessment was administered in one session lasting about one and a half-hours, with a suitable rest period if needed.

An informed written consent was obtained from all subjects or a close family member as in the AD group. A health information questionnaire was also filled out. The study received ethical approval from the Data Protection Commission of Iceland and the Bioethics Committee of the Icelandic Health Ministry. All study participants were informed that the study results would be based on group analysis and that it was hence not possible to provide information regarding individuals. However, if the participants in the Sib or NC groups were concerned about becoming symptomatic a referral to specialized dementia clinic was provided.

7.3.1 Statistical analysis

The differences between the Sib and NC groups on the test variables were examined parametrically and categorically using Student t-tests and Chi-square (X^2) analyses respectively. Because of multiple comparisons and the risk of Type I error the *Bonferroni*

correction[13] was used and the *p*-value in each *t*-test was corrected. The level of statistical significance was set at $p < .05$. All tests were two-tailed. Discriminant analysis was used to group the participants according to their scores on the neuropsychological measures. The differences between the groups were assessed by univariate (ANOVA) or multivariate analysis of variance (MANOVA) when the study groups exceeded two. *Post hoc* comparison of Tukey HSD (honestly significant difference) was used when there were three study groups and because of unequal sample size Dunnett's comparison was used when comparing four study groups (Howell, 1997). Statistical analyses were performed by using computerized statistical software (SPSS 10.0 for Windows software).

8.   Results

The NC consisted of two groups, spouses who were in the majority (58%) and those recruited after seeing advertisement in a social center for elderly. There was no difference between these two control groups on neuropsychological or clinical variables with one exception. Those who joined the study by advertisement had significantly more errors on the Letter Cancellation test ($t(67) = 2.82, p < .05$) when compared to the spouses. Because there was no other difference found between these groups they were considered as one homogenous control group.

Exclusion criteria were used to minimize the effect of central or peripheral nervous system disorders other than AD, excluding 15 AD patients, 5 Sibs, and 10 NCs. Furthermore, one statistical outlier in the Sib group and two in the AD patient group were excluded from the analysis.

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[13] The Bonferroni correction for multiple comparisons is as follows:

$\alpha^1 = \alpha/c$ (α^1 = corrected alpha level; α = alpha level (.05); c = number of functional domains; Howell, 1997). Instead of changing the level of significance in each comparison the *p*-value in the *t*-tests was corrected according to following formula ($\alpha = \alpha^1 * c$). The number of functional domains was defined in the study as six, and they were equal to the number of factors according to factor analysis.

The result section is divided into two parts, study I and II. In study I the Sib and NC groups are compared on various different cognitive domains, including orientation, memory, abstract reasoning and executive function, language, attention and mental speed, and visuo-spatial and constructional abilities. In study II the Sib and NC groups are compared to the AD patient group. Finally, the neuropsychological measures shown to be the best discriminator of cognitively impaired and intact participants were used to divide the Sibs into two groups. Those Sibs with neuropsychological scores similar to the AD patients were considered impaired and grouped together and labeled as ImpSib group, others in the Sib group were classified as IntSibs (shortening of intact siblings). All four-study groups were then compared on the rest of the neuropsychological measures to see how they scored.

8.1 Study I: Comparison of Sib and NC groups

In this study, siblings (Sibs) of AD probands and NC without known first-degree AD probands matched for gender, age, and education were compared.

There was no difference between the Sibs and NC groups on clinical variables obtained by the health questionnaire such as blood pressure, metabolic diseases, head trauma, alcohol consumption, and exposure to toxic material. About 69% of Sibs and 64% of NC admitted memory impairment when asked, the difference beeing non-significant.

8.1.1 Neuropsychological assessment

Sibs scored significantly lower than NC on the following seven neuropsychological measures (table 4): Orientation $t(161) = 3.28$, $p < .001$; Immediate and delayed recall of the Rey Complex Figure, $t(159) = 2.75$, $p < .05$ and $t(159) = 3.56$, $p < .05$, respectively; Immediate recall of the WMS LM $t(161) = 4.65$, $p < .001$; Delayed recall of the WMS LM $t(161) = 2.86$, $p < .001$; Hard Pairs of Associate Learning, $t(161) = 2.86$, $p < .05$; Trails A time in seconds $t(154) = 2.73$, $p < .05$ (table 4, and figures 2 to 4).

Table 4.
Means (*M*), standard deviations (*SD*), and significant differences (*p*) of Sibs and NC on neuropsychological test variables.

Test	Sibs		NC		t-test/sig.
	M	(*SD*)	*M*	(*SD*)	
Orientation	9.63	(0.70)	9.90	(0.31)	*
Letter Cancellation					
Time in seconds	108.4	(36.5)	104.0	(32.2)	n.s.
Number of errors	5.41	(6.37)	3.18	(5.03)	n.s.
Rey Complex Figure:					
Copy	28.78	(8.06)	31.02	(5.54)	n.s.
Immediate Recall	10.73	(7.32)	13.96	(7.40)	*
Delayed Recall (45 min)	9.93	(7.37)	13.49	(7.59)	*
Wechsler Memory Scale:					
Logical Memory:					
Immediate Recall[a]	9.84	(3.44)	12.27	(3.07)	***
Delayed Recall[a] (45 min)	7.31	(3.83)	9.81	(3.13)	***
Recognition of LM	3.34	(1.00)	3.63	(0.75)	n.s.
Associate Learning:					
Easy Pairs[b]	7.52	(1.38)	8.04	(1.29)	n.s.
Hard Pairs	3.51	(2.53)	4.69	(2.71)	*
WAIS:					
Similarities[c]	14.05	(3.74)	15.01	(3.08)	n.s.
Digit Span[c]					
Forward[d]	5.41	(1.15)	5.91	(1.24)	n.s.
Backward[d]	3.74	(1.01)	3.75	(1.13)	n.s.
Block Design[c]	12.16	(2.64)	13.04	(2.52)	n.s.
Picture Arrangement[c]	9.88	(3.31)	10.69	(3.46)	n.s.
Trails A:					
Time in seconds	60.0	(25.4)	49.8	(18.9)	*
Trails B:					
Time in seconds	136.6	(54.1)	119.9	(42.9)	n.s.[f]
Oral Word Fluency:					
Letter "s"	12.00	(5.11)	12.76	(5.44)	n.s.
Semantic category (animals)	17.18	(5.28)	19.28	(5.74)	n.s.
Boston Naming Test[e]					
Without cue	26.27	(3.98)	27.03	(3.18)	n.s.
With semantic cue	27.02	(3.29)	27.81	(2.73)	n.s.
Gestalt Closure (K-ABC)	15.62	(4.78)	15.79	(4.51)	n.s.
Reading test:					
Score	2.81	(0.45)	2.87	(0.39)	n.s.
Comprehension	2.62	(0.63)	2.78	(0.52)	n.s.

[a] Wechsler Memory Scale, Logical Memory (stories) – Gist Scoring. Story A +B divided by two.
[b] Score divided by two.
[c] Age-related WAIS scores.
[d] WAIS raw scores.
[e] The Boston Naming Test short (30 item) version.
[f] Significantly fewer Sibs completed the Trails B test.

Higher scores indicate better performance on all tests except for time measures where the opposite holds true.
All values expressed as means (SD).
Significance level
    * < .05
    ** < .01
    *** < .001
n.s. non-significant (p>.05)

In the Trails B test the Sibs were somewhat slower in completing the test, although the difference was not significant. However, there were significantly fewer Sibs that could complete Trails B than NC. In the Sib group 69% completed the Trails B test compared to 84% of the NC, $\chi^2(1, N = 160) = 4.53, p < .05$ (figure 2). Furthermore, Sibs scored almost significantly lower on Digit Span forward ($t(161) = 2.65, p = .054$) compared to NC, but there was no difference in Digit Span backward.
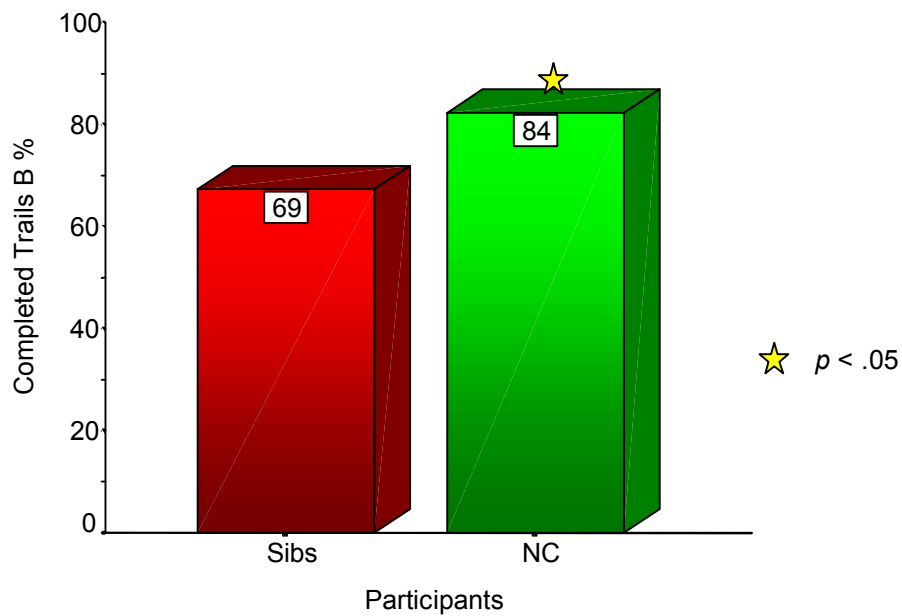

Figure 2.
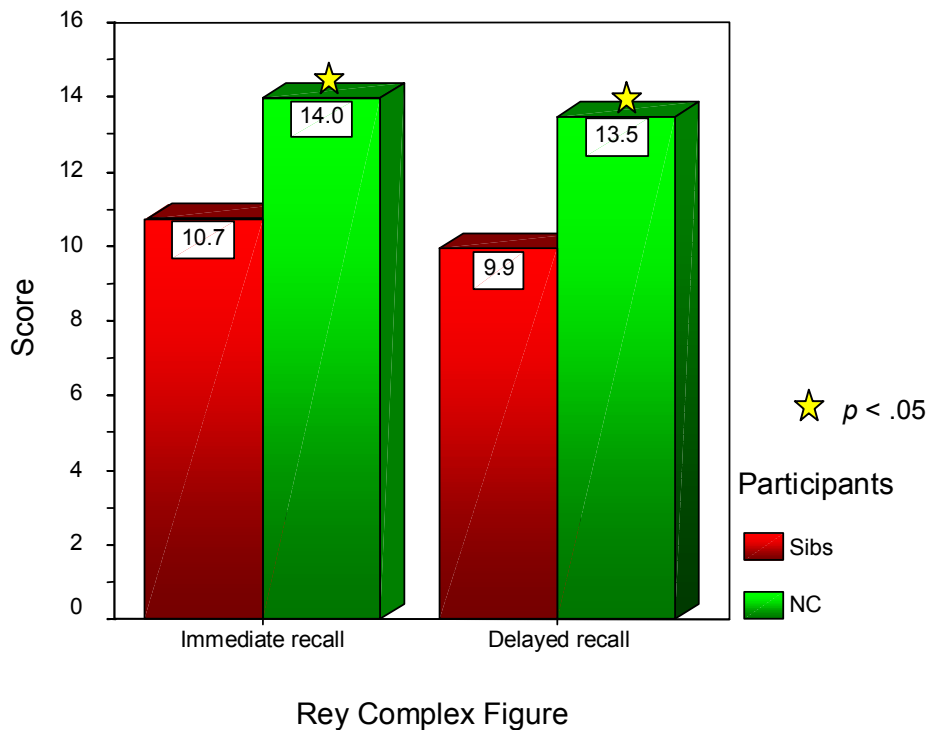Comparison of how many Sibs and NC completed Trails B test.

Figure 3.
Comparison of Sibs and NC on immediate and delayed recall of the Rey Complex Figure. Sibs scored significantly lower on both immediate and delayed recall.

About 70% of the Sibs recognized the Rey Complex Figure after-45 min delay when given a multiple choice. The respective value in the NC group was 83%. Although approaching significance the difference was not significant, $\chi^2(1, N = 158) = 3.58$, $p = .059$.

Participants that were unable to copy the Rey Complex Figure also gained zero score in the immediate and delayed recall of the figure. About 14% of the Sibs could not recall anything of the figure in immediate recall compared to only 6% of the NC. In delayed recall of the Rey Complex Figure 24% of the Sibs could not recall anything of the figure after 45 min compared to only 10% of the NC group.

In delayed recall of the LM test (after 45 minutes) some participants could not remember the story at all. They were given a cue regarding the story to help them to remember it. The cue was only minimal (in story A: "the story was about a woman"; story B: "the story was about a boat"). About 44% of the Sibs needed such a cue compared to only 31% of the NC. Cue was mostly given regarding the story B.
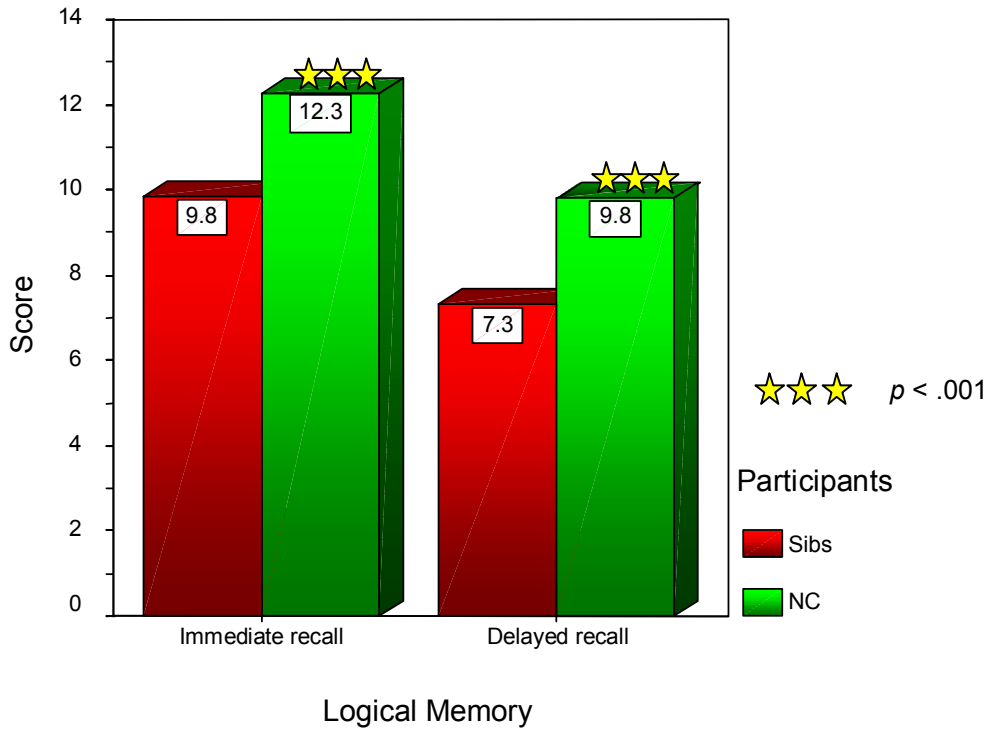
Figure 4.
Comparison of Sibs and NC on immediate and delayed recall of Logical Memory. Sibs scored significantly lower on both immediate and delayed recall.
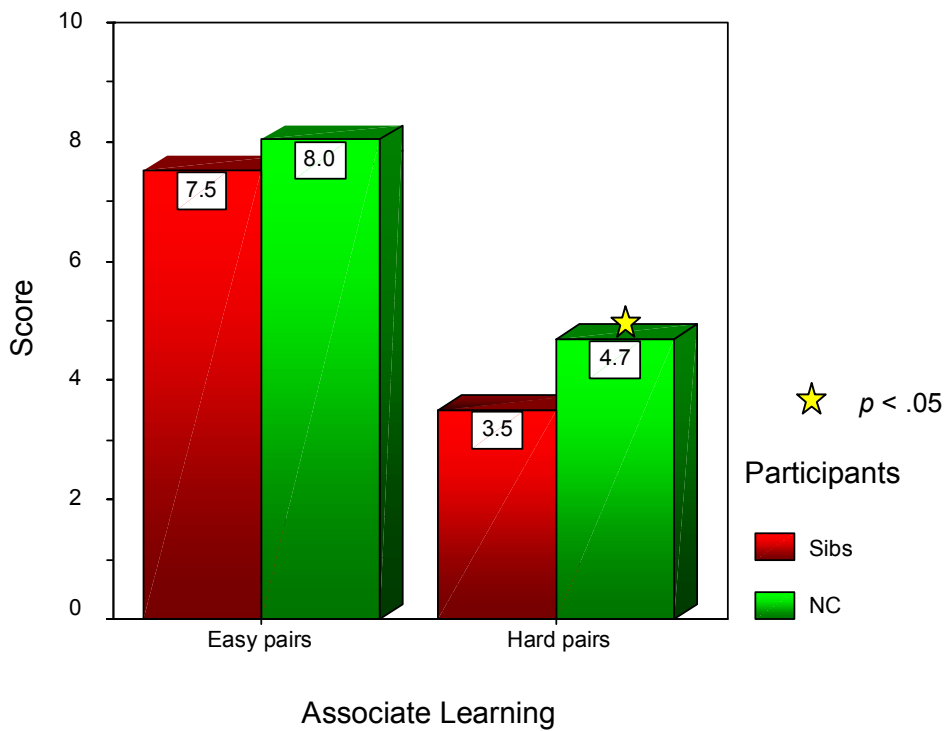

Figure 5.
Comparison of Sibs and NC on easy and hard word pairs of the Associate Learning. Sibs scored significantly lower on hard pairs.

8.1.2   Comparson of known risk factors for AD

Age

The Sib and NC groups were divided into three age groups with 10 year intervals, e.g. 55-64, 65-74, and 75-85 years old. The Sibs and NC groups were then compared on the neuropsychological measures in each age group. In the youngest age group, the 55-64 years old, there was no significant difference between the Sibs and NC groups on the neuropsychological measures. There was, however, a significant difference between the groups on LM immediate and delayed recall in the age group 65-74 years old, $t(84) = 2.59$, $p < .05$ and $t(84) = 2.82$, $p < .05$, respectively, with Sibs scoring lower than NC. In the oldest group, 75-85 years old, only a barely significant difference was detected between Sibs and NC on LM immediate recall, $t(84) = 2.73$, $p = .05$.

Gender

Comparison of the sexes within each group showed that women in the Sib group scored significantly lower than men in the Sib group on Boston Naming ($t(93) = 3.83$, $p < .001$) and Block design (($t(93) = 3.36$, $p < .01$). Women in the Sib group scored, on the contrary, higher than men on hard pairs of the Associate Learning ($t(93) = 3.74$, $p < .001$), and on other memory tests, although not significantly. There was no differences between the sexes in the NC group on the neuropsychological measures.

Education

The Sib and NC groups had received similar education, more than half of the individuals having only elementary education.

Based on the educational status the participants in each group were divided into two educational groups. One group consisted of those having 8 years of education or less and the other of those having education beyond 8 years. These two educational groups were compared within each study group.

No difference was found within the NC group when comparing participants with short education (≤8 years) to those with longer education (>8 years of education). There were, however, some differences in the Sib group. Those in the Sib group who had longer education (>8 years) scored significantly higher than those with less education (≤8 years) on the

following tests: Rey copy ($t(48) = 2.34$, $p < .05$); Rey immediate ($t(48) = 2.96$, $p < .05$); Rey delayed ($t(48) = 3.84$, $p < .001$); Trails A ($t(47) = 2.88$, $p < .001$); and Reading score ($t(48) = 2.08$, $p < .05$).

8.2   Study II. Comparison of AD, Sib, and NC groups

The comparison of Sib and NC groups revealed some differences between the groups on the neuropsychological measures. The next step in the analysis was to compare the Sib and NC groups to a group of AD patients to see if and how they differed.

There was no difference between the AD, Sib, and NC groups on gender and education. The only difference between the three groups on demographic variables was that the AD group was significantly older than the NC group ($F(2,247) = 6.50$, $p < .01$).

Post Hoc comparison showed, as expected, impairments in the AD patient group on all neuropsychological measures compared to Sibs and NC, with two exceptions. The difference between the AD patients and the Sib group were non-significant on Digit Span forward and on numbers of errors in the LC test.

8.2.1   Sibs divided into impaired and intact groups

As stated earlier the Sibs scored significantly lower than the NC group on Orientation, Trails A, hard pairs of the Associate Learning test, and immediate and delayed recall of LM and Rey Complex Figure. The AD patients, Sibs, and NC were compared according to how they scored on these seven neuropsychological measures by using discriminant function analysis. These variables were selected for the discriminant analysis because the Sibs were impaired on these measures and they should therefore be the most reliable predictors of cognitive impairment in the group.

The canonical correlation analysis yielded a highly significant difference between the three group centroids, which indicates that the group means differ (Wilk's Lambda of .385, $p < .001$; see figure 6).

The canonical variables are two[14]. The eigenvalue for the first canonical discriminant function is very high (1.479) and corresponds to the maximum spread of the group means or as high as 96.8% of the variance, but the second eigenvalue (0.049) accounted only for very little of the total dispersion or 3.2% of the variance.
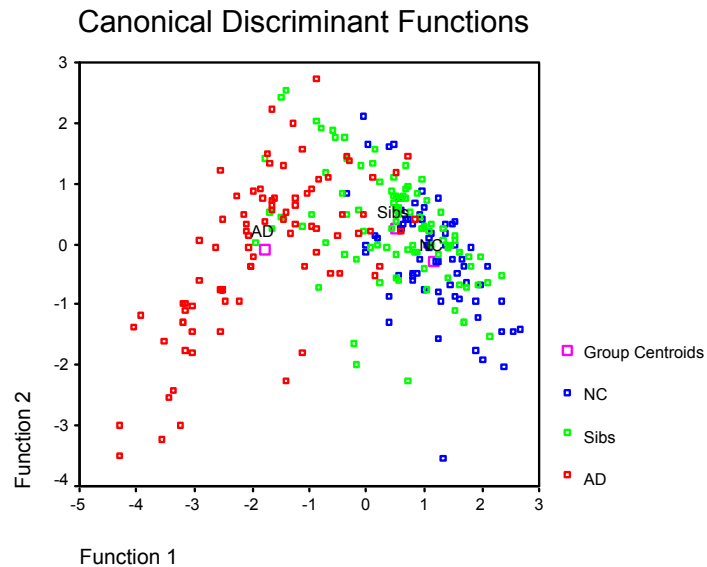
Figure 6.
Canonical analysis of how the participants of the AD, Sibs, and NC groups fall within a two-dimensional scales on tests of verbal and non-verbal immediate and delayed recall, orientation, and mental speed and attention.

Delayed recall of the LM test had the largest absolute correlation within the canonical discriminant functions. Second come the immediate recall of the LM and test of orientation (table 5).

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[14] Canonical variables/functions = k-1 (k is the number of groups).

Table 5.
Largest absolute correlation between each variable and the canonical discriminant functions ordered by the size of the correlation.

	Function 1	Function 2
Delayed recall of LM	.826	.403
Immediate recall of LM	.759	.502
Orientation	.755	.539
Delayed recall of Rey Figure	.542	.306
Hard pairs of Associate Learning	.485	.304
Immediate recall of Rey Figure	.470	.309
Trails A	.332	.034

The discriminant analysis revealed that about 12% of the Sibs had more resemblance to the AD group than to the Sib group (see table 6). Their scores on the neuropsychological tests had more correlation to those of the AD group, than to the rest of the Sib group.

Table 6.
Predicted group membership of the AD, Sibs, and NC groups according to discriminant analysis.

	Predicted group membership					
Participant	AD		Sibs		NC	
	n	(%)	n	(%)	n	(%)
AD	68	(80.0)	17	(20.0)	0	(0)
Sibs	11	(11.6)	49	(51.6)	35	(36.8)
NC	0	(0)	23	(33.8)	45	(66.2)

No one in the NC group should be considered AD according to the discriminant analysis and, vice verse, no one in the AD group should be considered NC. Twenty percent of the AD patients had more resemblance to the Sibs than to their own group. The analysis showed 65.3% of originally grouped cases to be correctly classified.

The Sibs were divided into two groups according to the discriminant analysis. The 11 Sibs that had more resemblance to the AD group were labeled as ImpSibs and the rest of the groups as IntSibs (n = 84). The Impaired and IntSib groups were then compared to the AD patient and NC groups on the demographic variables (table 7). The ImpSib group was slightly older than the IntSib group and the NC group, although not significantly. The AD group was as stated earlier significantly older than the NC group. There was no difference between the four groups regarding gender or education.

Table 7.
Demographics for the AD, ImpSibs, IntSibs, and NC groups.

	AD $n = 87$		ImpSibs $n = 11$		IntSibs $n = 84$		NC $n = 68$	
Age (yrs.)								
M	75.1*		76.5		72.8		71.8	
SD	5.4		6.7		6.2		5.4	
Range	61-85		63-85		60-85		60-85	
Gender:								
Male	37	(43.5%)	4	(36.4%)	46	(54.8%)	28	(41.2%)
Female	48	(56.5%)	7	(63.6%)	38	(45.2%)	40	(58.8%)
Education (yr.):								
8 ≤	44	(57.1%)	9	(90.0%)	42	(51.2%)	38	(59.4%)
8 >	33	(42.9%)	1	(10.0%)	40	(48.8%)	26	(40.6.%)

* The AD group was significantly older than the NC group ($F(3,247) = 5.67$, $p < .01$).

In Table 8 is age and gender distribution of the participants in the ImpSib group shown, there were slightly more females than males in the group.

Table 8.
Age and gender distribution of the ImpSib group.

ImpSibs	
Age	Gender (M/F)
63	F
70	F
72	M
74	F
75	M
76	F
80	F
81	F
82	F
83	M
85	M

Note: M = Male; F = Female

Post hoc comparison on the four groups showed much resemblance between the ImpSibs and the AD patients on the neuropsychological measures (table 9). The IntSib group, on the other hand, showed much resemblance to the NC group on the neuropsychological measures with no significant difference.

The ImpSib group scored significantly lower than the NC group on several neuropsychological measures in addition to those tests used to divide the Sib group into two parts. These tests were the Easy Pairs of the Associate Learning test, Similarities, and Semantic category of Oral Word Fluency. Furthermore, the ImpSib group scored significantly lower than both the NC and the IntSib groups on the Recognition of the LM test and significantly lower than IntSib group on Digit Span backward (see table 9).

Table 9.

Comparison of AD, ImpSibs, IntSibs, and NC groups on the neuropsychological measurement. Mean (*M*), standard deviation (*SD*), significant difference (*p*), and Dunnett's post hoc comparison.

Test	AD M	AD SD	ImpSibs M	ImpSibs SD	IntSibs M	IntSibs SD	NC M	NC SD	P	MANOVA Post Hoc
Letter Cancellation:										
Time in seconds	146.6	69.7	120.1	44.5	106.8	35.3	104.0	32.2	***	AD<IntSibs,NC
Number of errors	6.65	7.57	8.00	8.52	5.06	6.00	3.18	5.03	**	AD<NC
Rey Complex Figure:										
Copy	20.42	10.3	23.41	10.8	29.49	7.41	31.02	5.54	***	AD<IntSibs,NC
Wechsler Memory Scale:										
Logical Memory:										
Recognition of LM[a]	1.70	1.39	2.28	1.91	3.48	0.80	3.63	0.75	***	AD,ImpSib<IntSibs,NC
Associate Learning:										
Easy Pairs[b]	5.45	2.31	6.54	1.49	7.65	1.32	8.04	1.29	***	AD<IntSibs,NC & ImpSibs<NC
WAIS:										
Similarities[c]	11.13	4.53	11.55	3.42	14.38	3.56	15.01	3.08	***	AD<IntSibs,NC & ImpSibs<NC
Digit Span										
Forward[d]	5.20	1.32	5.45	1.21	5.40	1.15	5.91	1.24	**	AD<NC
Backward[d]	3.18	1.02	3.18	0.60	3.81	1.04	3.75	1.13	***	AD< IntSibs,NC & ImpSibs<IntSibs
Block Design[c]	9.19	4.33	10.73	2.41	12.35	2.63	13.04	2.52	***	AD<IntSibs,NC
Picture Arrangement[c]	7.75	3.67	9.00	2.24	10.00	3.42	10.69	3.46	***	AD<IntSibs,NC
Oral Word Fluency:										
Letter "s"	8.89	4.85	10.00	5.88	12.26	4.98	12.76	5.44	***	AD<IntSibs,NC
Semantic category[e]	12.08	5.83	12.27	5.71	17.82	4.90	19.28	5.74	***	AD<IntSib,NC & ImpSibs<NC
Boston Naming Test[f]										
Without cue	20.92	6.03	23.73	4.22	26.61	3.85	27.03	3.18	***	AD<IntSibs,NC
With semantic cue	21.88	5.68	25.18	3.66	27.26	3.19	27.81	2.73	***	AD<IntSib,NC
Gestalt Closure (K-ABC)	11.29	4.94	13.91	4.81	15.85	4.76	15.79	4.51	***	AD<IntSibs,NC
Reading test:										
Score	2.40	0.92	2.64	0.67	2.84	0.40	2.87	0.39	***	AD<IntSibs,NC
Comprehension	1.86	1.03	2.36	0.92	2.65	0.57	2.78	0.52	***	AD<IntSibs,NC

ImpSibs = ImpSib group
IntSibs = IntSib group

[a] Recognition of the Logical Memory (WMS stories).
[b] Score divided by two.
[c] Age-related WAIS scores.
[d] WAIS raw scores.
[e] Semantic category (animals).
[f] The Boston Naming Test short (30 item) version.

Higher scores indicate better performance on all tests except for time measures.
All values expressed as means and SD.
Significant difference between groups according to Dunnett's post hoc comparison.
Significance level of the MANOVA
    * < .05
    ** < .01
    *** < .001
    n.s. non-significant (p>.05)

Note – the neuropsychological measures on which Sib group was impaired compared to NC in the initial analysis are not in the table as these tests were used to divide the Sib group into Impaired and IntSib groups.

Only 36.4%[15] of ImpSibs and 44.0%[16] of the AD patients could successfully recognize the Rey Complex Figure compared to 74.4% of the IntSibs and 83.1% of the NCs. Only 22.4% of the AD patients and 45.5% of ImpSibs completed Trail B test, compared to 72.0% of the IntSibs and 83.6% of the NCs.

When the groups are compared on memory complaints 66.3% of IntSibs and 63.5% of NCs complained of memory loss, compared to 90.6% of those in the ImpSib group.

Seven measures were used to divide the Sib group into ImpSib and IntSib groups. In table 10 the mean scores of the AD patients, ImpSibs, IntSibs, and NC groups on these seven measures are listed. The significante differences between the AD and ImpSibs vs. IntSibs and NCs is of no surprise, because these variables were used to differentiate among the Sibs. The most interesting finding shown in table 10 is that IntSibs scored significantly lower than NCs on the immediate and delayed recall of the LM. This is the only test that reveals some difference between the NC and IntSib groups. Another notable finding is in the test of Orientation which was the only one showing some significant difference between the AD and the ImpSib groups. The only test where ImpSibs score not significantly lower than ImpSibs is on the Trails A.

---

[15] There are only 11 individuals in the ImpSib group and only 4 of them represent this 36.4 percentage and this number could easily be skewed due to small sample size. This small sample size in the ImpSib group is also limiting the results of other nominal variables, which should therefore be taken with precaution.

[16] It should be noted that 11.5% of the AD patients could not copy anything of the Complex Figure in the initial testing and were therefore excluded from the recognition test.

Table 10.
Comparison of AD, ImpSibs, IntSibs, and NC groups on the neuropsychological measurement that were used to divide the Sibs into Impaired and Intact groups. Mean (*M*), standard deviation (*SD*), significant difference (*p*), and Dunnett's post hoc comparison.

Test	AD		ImpSibs		IntSibs		NC			MANOVA
	M	*SD*	M	*SD*	M	*SD*	M	*SD*	*P*	Post Hoc
Orientation	7.35	*1.97*	8.36	*0.50*	9.80	*0.53*	9.90	*0.31*	***	AD < SibImp,SibInt,NC & SibImp < SibInt,NC
Rey Complex Figure:										
Immediate recall	3.74	*5.64*	3.91	*4.95*	11.64	*7.11*	13.96	*7.40*	***	AD,SibImp < SibInt,NC
Delayed recall	2.04	*4.99*	2.73	*4.12*	10.94	*7.11*	13.49	*7.59*	***	AD,SibImp < SibInt,NC
Wechsler Memory Scale:										
Logical Memory:										
Immediate recall	4.73	*3.06*	4.63	*2.93*	10.52	*2.89*	12.27	*3.07*	***	AD,SibImp < SibInt,NC & SibInt < NC
Delayed recall	1.57	*2.48*	1.23	*1.57*	8.10	*3.28*	9.81	*3.13*	***	AD,SibImp < SibInt,NC & SibInt < NC
Associate Learning:										
Hard Pairs	0.94	*1.93*	1.09	*1.51*	3.82	*2.47*	4.69	*2.71*	***	AD,SibImp < SibInt,NC
Trail Making Test:										
Trail A	91.6	*70.0*	68.8	*26.3*	58.8	*25.2*	18.9	*2.37*	***	AD < SibInt,NC

ImpSibs = ImpSib group
IntSibs = IntSib group
  Higher scores indicate better performance on all tests except for time measures.
  All values expressed as means and SD.

Significant difference between groups according to Dunnett's post hoc comparison.
Significance level of the MANOVA
    * < .05
    ** < .01
    *** < .001
    n.s. non-significant (p>.05)

Note – the Sib group was divided into Impaired and Intact according to how the individuals scored on these seven measures. Significant differences between the AD and ImpSibs vs. IntSibs and NC is therefore expected.

8.2.2 Dividing the Sib group according to the LM test

There was a highly significant difference between the Sib and NC groups on the immediate and delayed recall of the LM. These two measures weighted the most in dividing the Sibs into Impaired and Intact groups. It is interesting to notice the significant difference between the IntSib and NCs on the immediate and delayed recall of the LM, despite the discrimination of the Sibs into impaired and intact individuals. The immediate and delayed recall of the LM were the only measures showing significant differences between the IntSib and NC groups. The next logical step in the analysis was therefore to repeat the discriminant analysis on all the groups

(the Sib group as a whole, as well as the AD patient and NC group), but now only using the LM immediate and delayed recall to divide the Sib group, instead of all the seven measures used earlier.

The AD patient, Sib, and NC groups were analysed according to the discriminant functional analysis by using only the LM immediate and delayed recall. The canonical correlation analysis yielded a highly significant difference between the three group centroids, which indicates that the group means differ (Wilk's Lambda of .470, $p < .001$; see figure 7).
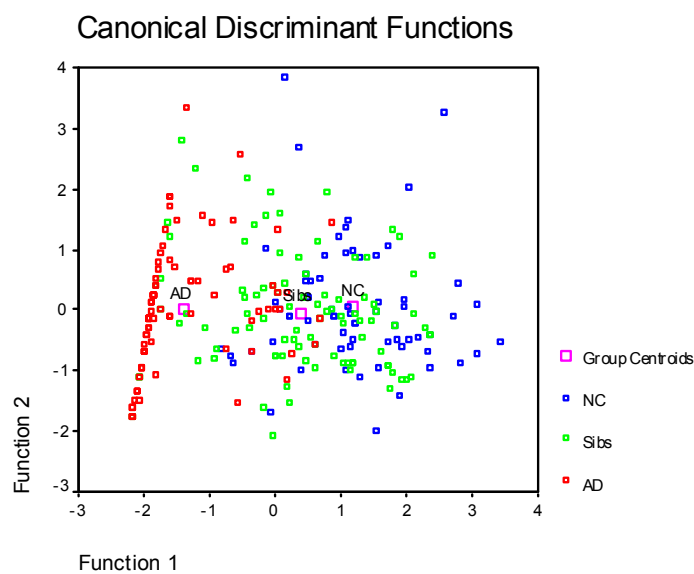
Figure 7.
Canonical analysis of how the participants of the AD, Sibs, and NC groups fall within a two-dimensional scale on tests of immediate and delayed recall of the LM test.

When using only the LM test, the eigenvalue for the first canonical discriminant function was very high (1.127), corresponding to the maximum spread of the groups mean or as high as 99.9% of variance. The second eigenvalue (0.001) had no influence on the total dispersion, or only 0.1% of the variance.

The discriminant analysis revealed that according to the scoring on immediate and delayed recall of LM test 20% of the Sibs had more resemblance to the AD group than to the rest of the Sib group (see table 11).

Table 11.
Predicted group membership of the AD, Sib, and NC groups according to discriminant analysis on immediate and delayed recall of the LM test.

Participant	Predicted group membership					
	AD		Sibs		NC	
	n	(%)	n	(%)	n	(%)
AD	70	(82.4)	14	(16.5)	1	(1.2)
Sibs	19	(20.0)	39	(41.1)	37	(38.9)
NC	3	(4.4)	19	(27.9)	46	(67.6)

Three (4.4%) NCs recalled so little on the immediate and delayed LM that they had more resemblance to the AD group than to the rest of the NC group. On the contrary one AD patient scored as high as the NC group on the LM test. Furthermore, 14 (16.5%) AD patients had more resemblance to the Sib group than the rest of their own group. The analysis showed 62.5% of original grouped cases being correctly classified.

As before the Sib group was divided in two on basis of the discriminant analysis, this time according to the LM immediate and delayed recall alone, instead of the seven neuropsychological measures before. There were no differences between the four groups (divided Sib group, AD and NC groups) on the demographic variables. Those who scored more similar to the AD patient group on the LM test were labeled NewImpSibs and the rest of the Sibs as NewIntSibs[17]. The AD patient and NC groups were, as before, still unchanged.

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[17] To avoid confusion it is important to notice that the group names "ImpSibs" and "IntSibs" refer to the older analysis where seven neuropsychological measures were used to divide the Sibs. When using the terms "NewImpSibs" and "NewIntSibs" it refers to the newer analysis where only two neuropsychological measures were used to divide the Sibs.

Table 12.

Demographics for the Sib group when divided according to discriminant analysis on the LM immediate and delayed recall.

	NewImpSibs *n* = 11		NewIntSibs *n* = 84	
Age (years)				
M	75.5		72.7	
SD	6.2		6.3	
Range	63-85		60-85	
Gender:				
Male	9	(47.4%)	41	(53.9%)
Female	10	(52.6%)	35	(46.1%)
Education (yrs.):				
≤8	13	(72.2%)	38	(51.4%)
>8	5	(27.8%)	36	(48.6%)

NewImpSibs - Siblings of AD patients that scores similar to the AD patient group on the LM test

NewIntSibs - Siblings of AD patients that scores dissimilar to the AD patient group on the LM test

Post hoc comparison of the NewImpSibs, NewIntSibs, AD patient, and NC group showed hardly any difference from how the groups differed when the Sib group was divided earlier, according to the seven neuropsychological measures (in table 9 and 10). The only difference was that the distinction between the healthy individuals (NewIntSibs and NCs) and the impaired ones (NewImpSibs and AD patients) was more obvious. The only differences, when dividing the Sibs according to only the LM instead of seven neuropsychological measures, were that both NewIntSibs and NC groups, instead of only either group, scored significantly higher than the NewImpSibs on Digit Span backward ($F(3,246) = 7.99$, $p < .05$) and semantic

category of the Oral Word Fluency (F(3,247) = 28.18, p < .01). The NewImpSib group scored, furthermore, significantly lower than the NC group on Block Design (F(3,246) = 21.14, p < .05).

The results of dividing the Sib group into impaired and intact groups according to the LM test alone, without the other five neuropsychological measures, seem to increase the number of individuals in the Sib group that are considered impaired. Furthermore, it indicates that there are some individuals in the NC group who should be considered cognitively impaired. This new division also showed some sharpening of the groups in the direction of NewImpSibs being more impaired on other neuropsychological measures compared to the NC and the rest of the Sib group.

9. DISCUSSION

In the present study a group of individuals having a sibling with AD and another AD relative within six meiotic events were compared to a group of individuals without a first-degree relative with known dementia and to a group of AD patients. The aim of the study was: 1) To examine if siblings of AD patients are at higher risk of having cognitive impairment than are NCs; 2) To compare the siblings to a group of AD patients on neuropsychological tests to find out if some individuals in the sibling group, on purely neuropsychological evidence, should rather be classified with the AD patients; 3) To determine which combination of cognitive measures was best suited to detect subtle cognitive impairments. The groups were compared on neuropsychological measures widely used and standardized, and shown to be sensitive to preclinical signs of AD. Previous studies have found first-degree relatives of AD patients to have an increased risk of developing AD which can be detected on neuropsychological tests before overt clinical signs appear. The results of the present study showed that Sibs scored significantly lower than NC on immediate and delayed recall of LM of the WMS, immediate and delayed recall of Rey Complex Figure, hard pairs in Associate Learning of the WMS, Orientation, and Trails A. There were also significantly fewer Sibs that completed the Trails B test compared to NCs. The Sibs showed no impairment on other neuropsychological measures. In addition, the Sib group was compared to a group of mild or moderate AD patients

(according to the GDS scale of Reisberg et al., 1997) participating in the study. This comparison on the neuropsychological measures revealed that at least 12% of the Sibs had stronger resemblance to the AD group than to the rest of the Sib group. Concordant with results of other studies the cognitive impairments, manifested by the Sibs, might be indicators of AD in the preclinical stage.

Like the result section, the discussion is divided between two studies. In study I the comparison of the Sib and the NC groups on the various measures are discussed. In study II the comparison of divided Sibs (ImpSibs and IntSibs), AD patients, and NCs is discussed.

9.1   Study I: Comparison of Sib and NC groups

The Sibs and NCs were homogenous in terms of gender, age, and education. Furthermore, they did not differ on health variables that might have affected cognitive abilities such as blood pressure, metabolic diseases, head trauma, alcohol consumption, or exposure to toxic material. No difference was found between the Sib and the NC groups on self-reported memory impairments, with about 69% of the Sibs and 64% of NCs complaining of memory impairment.

Sib and NC groups were compared on various neuropsychological measures including cognitive domains of orientation, memory, abstract reasoning and executive function, language, attention and mental speed, and visuo-spatial and constructional abilities. The Sib group scored significantly lower than NCs on memory, orientation, and one test of mental speed and executive function. Below the results on each cognitive domain are discussed separately.

9.1.1. Verbal and non-verbal memory

Rey Complex Figure

No difference was found between the Sib and the NC groups on the copying of the Rey Complex Figure. The Sibs, on the other hand, showed impairments in both immediate and delayed recall of the figure. Furthermore, Sibs showed some difficulties in recognizing the figure compared to NCs. Only 70% of the Sibs could recognize the correct picture compared to 83% of NCs, the difference approaching significance level ($p = .059$).

Logical Memory and Associate Learning

Verbal memory was assessed with LM and Associate Learning tests. Sibs showed more apparent deficits in the LM test, performing significantly worse both on immediate and delayed recall of prose passages compared to NCs. The difference between the groups was highly significant.

The hard pairs and the easy pairs of the Associate Learning test were calculated separately in the analysis. It is recognized that pairing unrelated words and new unfamiliar verbal material, as in hard pairs, place much more demand on cognitive function and is therefore more vulnerable to many kinds of brain damage than pairing semantically related words and well-learned verbal associations, as in easy pairs (Lezak, 1995).

The ability to learn the easy pairs was similar between the groups. On the other hand, Sibs scored significantly lower on hard pairs than the NCs.

Summary on memory

The Sib group demonstrated evidence of memory impairment when compared to the NCs. Their scores were significantly lower on free recall test of the LM and Rey Complex Figure and hard pairs of the Associate Learning. The present results would seem to suggest that the Sibs have memory deficits as measured with verbal and non-verbal recall, with the verbal memory impairments being highly significant. The findings of Sibs scoring in the normal range on the recognition tests of LM and Rey Complex Figure and the easy pairs of Associate Learning indicate that the subtle memory impairments found in the Sib group are only apparent on the more difficult memory tests. Many studies have found tests of free recall to be the best indicator of preclinical signs of AD (e.g. Tuokko, Vernon-Wilkinson, Weir, & Beattie, 1991). The present results of impaired free recall of the Sibs could therefore indicate AD in the preclinical phase.

9.1.2   Other neuropsychological domains

In the current study, tests of general cognitive functions in addition to memory were assessed. These are tests of orientation, abstract reasoning and executive function, language, attention

and mental speed, and visuo-spatial and constructional abilities. The Sib group showed memory impairments and only some orientation and attention and mental speed deficits, whereas other cognitive functions were intact.

- **Orientation**

As described earlier the Orientation test is combined of orientation to person, place, and time. The Sibs scored significantly lower on the Orientation tests compared to NCs. The difference between the groups was due to orientation to time and mainly because Sibs could not remember the day of the month. There was no difference between the groups regarding orientation to person or place.

Orientation impairments have been related to earliest signs of late-onset AD (Koss et al., 1996) and, furthermore, it has been reported that orientation deficits in time and place increase the odds of patients having AD rather than frontotemporal dementia (Varma et al., 1999). The impaired orientation of the Sibs therefore would seem to support the assumption that the Sibs are in the preclinical phase of AD.

- **Attention and mental speed**

The assessment of attention and mental speed included tests of Letter Cancellation, Trails A and B, and Digit Span.

Results of the present study showed no significant difference between the Sib and NC groups on the Digit Span test forward and backward, although the Sibs showed a trend toward a lower score than NCs on Digit Span forward ($p = .054$). No difference was found between the two groups in the time it took the participants to complete the Letter Cancellation test. The Sibs, however, performed slightly worse on the test. The Sibs had a mean of 5.4 errors compared to 3.2 errors in the NC group, although the difference was far from significant.

Trail Making Test

Participants having more than three errors on Trails A and more than four errors on Trails B were excluded from time measure analysis on the Trail Making Test. This was due to timesaving and because participants with so many errors were usually unable to finish the tests.

All participants in the two groups were able to complete the Trails A test, except for three Sibs and four NCs excluded from the test due to impaired sight.

It took the Sibs significantly longer time to finish the Trails A test compared to NCs. This test requires attentional tracking of the participant (Perry & Hodges, 1999). The Trails B test requires however both attentional tracking and concurrent manipulation of information (Perry & Hodges, 1999). Therefore it was much more difficult for both groups than Trails A. It was therefore a surprise to find out that although Sibs were somewhat slower than NCs in Trails B the difference was not significant. It is however interesting that significantly fewer Sibs could complete the Trails B test compared to NC, 69% and 84% respectively.

The above results indicate some attentional deficits in the Sibs, at least on the more demanding tests as Trails A and B – whereas easier tests as e.g. Letter Cancellation did not reveal any impairment on attention or mental speed. These results indicate some minor attentional and mental speed impairment in the Sib group, which can only be detected by using tests that are cognitively demanding and not too easy.

Many studies have reported attentional impairments in the preclinical stage of AD or early in the AD process measured with Trails A and B. Daly et al. (2000) reported that the time it took NCs and those who converted later to AD to complete Trails B differed by more than 2 *SD*. This is a much greater difference than observed in the present study. Chen et al. (2000) reported that a combination of delayed recall and executive function measured with the Trails B test, to discriminate best those manifesting AD within 1.5 year and those remaining non-demented.

Mild AD has been characterized by impairment of visual attention and processing speed, measured e.g. with Trail Making tests (Rizzo et al., 2000), and as the disease progresses the difficulties with the Trails A and B increases, particularly Trails B (Amieva et al., 1998).

The studies mentioned above show the Trail Making Test to be sensitive to impairments indicating AD in the preclinical phase. Concordant with these studies, it is likely that the impairment observed in the Sib group, compared to NCs, on Trails A and B, could have a predictive role of an early manifestation of AD, coupled with memory dysfunction.

- **Other cognitive domains**

Abstract reasoning and executive function

The domain of abstract reasoning and executive function was assessed with neuropsychological measures of Similarities, Picture Arrangement, and letter and category fluency of the Oral Word Fluency test.

There was no difference found between the Sibs and NCs on Oral Word Fluency. This result is concordant with other studies indicating that the Oral Word Fluency is not a sensitive test to cognitive impairments in the preclinical phase of AD (Farlow et al., 1994; Linn et al., 1995). According to Elias et al. (2000) Oral Word Fluency was a predictor for AD for the age group of 75-94 years old, but not for individuals 65-74 year of age. The current results show no difference between the Sibs and NCs on the Oral Word Fluency test. In accordance with the results of Elias et al. it could be due to the relatively young mean age (around 73 years old) of the participants in the present study. No difference was found between the Sib and the NC groups on the Similarities or Picture Arrangement tests.

The results of the present study indicate therefore intact abstract reasoning and executive function in the Sibs compared to the NCs. Other studies show, on the other hand, that impairment in these domains may develop later when the disease becomes more prominent (e.g. Locascio et al., 1995).

Visuo-spatial and constructional abilities

The results of the present study revealed intact visuo-spatial and constructional abilities among the Sibs, compared to NCs, assessed by tests of Block Design, Gestalt Closure and copying of the Rey Complex Figure.

Language

The language domain was measured with Boston Naming, Oral Word Fluency, and Reading and understanding. The results of the Oral Word Fluency have been discussed earlier in the section of abstract reasoning and executive function. No difference was found between the Sibs and NCs on any of the language measures.

- **Summary of Sibs and NCs comparison on neuropsychological measures**

Comparisons of Sibs and NCs in the present study reveal some cognitive deficits in the Sibs. The Sibs showed impaired memory, tested with delayed verbal and non-verbal recall, defective orientation to date, short attention span and low mental speed as tested with the Trail Making Test. However, other tests of attention and mental speed, such as Letter Cancellation and Digit Span, showed no difference between the two groups. There was, furthermore, no difference found between the two groups on tests of visuo-spatial and constructional abilities, language, abstract reasoning and executive function.

9.1.3 Comparisons of known risk factors for AD

As illustrated in the introduction chapter various factors are thought to increase the risk of developing AD. The most common are growing age, female gender, short education, and positive family history of AD. Following is comparison of the Sib and the NC groups on these risk factors.

- **Age affect**

The increased risk of developing AD with growing age is a well-documented finding (e. g. Chen et al., 2000; Hy & Keller, 2000; Kawas et al., 2000).

The present findings indicate that the memory impairments are most likely to be evident in the Sib group in the age range of 65-74 year. In the youngest Sib group impairments seem not to be manifest and regarding the oldest age group it is possible that the neuropsychological tests have lost the discrimination power because of normal aging effects. The present results differ from what La Rue et al. reported 1992 that first-degree relatives showing tendency toward cognitive decline were on the average older than those with more stable performance.

- **Gender**

Some studies show that females with AD manifest greater deficits on tasks requiring semantic memory, confrontation naming (Boston Naming), and category fluency, but on the other hand not on letter fluency and word recognition (McPherson, Back, Buckwalter, & Cummings, 1999). The results of the present study show that females in the Sib group scored significantly

lower than males in the Sib group on Boston Naming and Block Design. The females, on the contrary, scored higher than males on hard pairs of the Associate Learning test (also on other memory tests although not significantly). This is in concordance with what others have reported (cited in Lezak, 1995). Interestingly, no gender difference was observed in the NC group.

The present study revealed that the females in the Sib group scored lower on some measures of cognitive function, but on the contrary scored higher on the memory measures most sensitive to preclinical AD. If individuals in the Sib group are truly in the preclinical stage of AD the current findings indicate no gender difference in the tendency to develop AD. This is concordant with some other studies (e.g. Small et al., 2000; Zubenko et al., 1999).

- **Education**

As stated in the introduction researchers disagree on the affects of education in the development of AD. Several studies have reported that individuals with minimal formal education stand a higher risk of developing AD than those with longer education (e.g. Letenneur et al., 1999; Munoz & Feldman, 2000).

In the present study there was no difference between the Sib and NC groups in terms of education.

According to the study of Filley and Cullum (1997) verbal skills of AD patients, as measured with reading tests, correlate strongly with level of education, whereas other language tests showed no correlation with education, e.g. tests of Oral Fluency and Boston Naming. Additionally, nonverbal cognitive abilities showed no correlation with education, that is Block Design, Digit Symbol, and Clock Drawings. The results of the present study are in part similar to those of Filley and Cullum. Sibs with shorter education (≤8 years) tended to score lower on Reading test than Sibs with longer education (>8 years). The present results also showed that Sibs with shorter education tended to score lower than those with longer education on all aspects of the Rey Complex Figure tests, that is copying, and immediate and delayed recall of the figure and on other motor tests such as Trails A. Interestingly, no difference was found within the NC group on the effects of education on the same variables.

9.1.4　Summary of Sib and NC groups comparison

The comparison of the Sib and NC groups on demographic and neuropsychological variables show that those who have a family history of AD within six meiotic events are at greater risk of having impaired recall of verbal and non-verbal information from memory, impaired orientation regarding day of the month, and difficulties in attention and mental speed measured with Trails A and B. Other studies have found impairments on these tests to be related to preclinical phase of AD. The Sibs showed, however, intact performance on other tests that are found to be less sensitive to cognitive impairments in the earliest stages of AD.

These results raise the following questions. Are these cognitive deficits found in the Sibs only limited to a group of individuals within the Sib group or do individuals in the Sib group score generally lower than the NCs? Are these impairments seen in the Sib group indicators of a preclinical phase of AD? In the hope of answering these questions a group of AD patients was added to the comparative analysis of the Sib and NC groups. The results of this comparison are discussed below.

9.2　Study II. Comparison of AD, Sib, and NC groups

How is it possible to see if all the participants in the Sib group are cognitively impaired, compared to the NCs, or to see if these impairments are only limited to a group of individuals lowering the mean score of the whole group? Are the cognitive impairments found in the Sibs an indicator of preclinical phase of AD? The best way of answering these questions is probably to perform a follow up study to see if or how the individuals in the Sib group change over time and who will develop AD and who not. Another way of finding the answer to these questions, without waiting a couple of years, is to test a group of mild or moderate AD patients and to see if the scores of some individuals in the Sib group correlate to the scores of the AD patients. Other possible explanations such as head trauma or other diseases resulting in cognitive impairments had earlier been ruled out in the initial exclusion of subjects participating in the study. The next step was to find out if those impaired on these selected tests showed some other cognitive impairments in addition.

In the following the comparison of the AD patients, Sibs and NCs is discussed and from the viewpoint to determine if some individuals in the Sib group are possibly in the preclinical phase of AD.

9.2.1 Comparsons of AD patients, Sibs and NCs.

The only difference found between the AD patients, Sibs, and NCs on the demographic variables (gender, age, and education) was that the AD were significantly older than the NCs. Post hoc comparison on the neuropsychological measures showed, as expected, impairments in the AD group on almost all measures compared to Sibs and NCs. The only exceptions were the scores on Digit Span forward and numbers of errors in LC tests where the difference between the AD patients and the Sib group was non-significant. It is well established in the literature that clinically diagnosed AD patients score significantly lower on most cognitive measures compared to healthy elderly individuals living in the community. Therefore it is not necessary to discuss results of impaired cognitive performance in the AD patients any further.

9.2.2 Sibs divided into impaired and intact groups

In this part of the study the AD patients, Sibs and NC groups were compared by using discriminant analysis on the neuropsychological measures of Orientation, Trails A, hard pairs of the Associate Learning test, and immediate and delayed recall of LM and Rey Complex Figure. These were the tests where Sibs showed deficits in comparison to NCs. By using the discriminant analysis the individuals were regrouped according to how they scored on these seven selected measures.

The canonical analysis indicated that the immediate and delayed recalls of the LM tests were the largest contributor to the discriminant function analysis. The test of LM had the strongest weight when the individuals in the three study groups are recruited into new groups according to how they scored on these seven selected tests. Secondly is the Orientation test and then the immediate and delayed recall of the Rey Complex Figure and hard pairs of the Associate Learning. The Trails A had the least impact of these seven tests in the discriminant analysis.

According to the discriminant analysis the score of 11 Sibs was so impaired, on these seven selected neuropsychological measures, that it had more resemblance to the AD patients than to the rest of the Sib group. As seen in figure 6 and table 6 there was a great overlap between Sibs and NCs, and between Sibs and AD patients. Interestingly there was no overlap between the NC group and the AD patient group. Although only 12% of individuals in the Sib group are considered to score similarily to the AD patient group, 20% of the AD patients are considered to score more similar to the Sibs than to their own group, indicating great overlap between these groups on the neuropsychological tests. It seems, however, that these 20% of the AD patients did not score normally on these tests, because their score did not correlate with the NCs. If the AD patients are correctly diagnosed it would perhaps be more correct to interpret these results vice verse and assume that the ratio of Sibs scoring similar to the AD patients is most likely exceeding the 12%. The number of individuals in the Sib group likely to be in the preclinical phase of AD could therefore possibly be as large as 20 to 30% instead of only 12%.

The next step in the analysis was to divide the Sib group into Impaired and IntSib groups according to how the participants' score correlated on the discriminant analysis to the score of the AD patients or the NCs, respectively. The NCs and the AD patients were unchanged but the Sibs were divided into ImpSibs and IntSibs. The 11 participants in the Sib group that scored similar to the AD patients were grouped together as ImpSibs and the rest of the Sibs as IntSibs. The next step was to compare the four study groups on the rest of the neuropsychological measures and on the demographic variables.

The only difference found on demographic variables was that the AD patient group was significantly older than the NC group. Age and gender comparisons were not reliable because of the small sample size in the ImpSib group. No difference was found on the neuropsychological measures between the IntSib and NC groups. As expected, the AD patients scored significantly lower than the NC group on all neuropsychological measures. The AD patients also scored significantly lower than IntSibs on all neuropsychological measures, except on number of errors in Letter Cancellation and Digit Span forward.

The most interesting results of the present study are how the ImpSibs scored on the neuropsychological measures compared to the other groups. The ImpSibs did not differ from the AD patients on any of the neuropsychological measures, showing the same cognitive deficits. The ImpSibs scored, on the other hand, significantly lower than NCs on several neuropsychological measures in addition to those used to divide the Sibs into two groups. These tests were the copy of the Rey Complex Figure, Easy Pairs of the Associate Learning test, Similarities, and Semantic category of Oral Word Fluency. Furthermore, the ImpSibs scored significantly lower than both the NC and IntSib groups on recognition tests of LM and Rey Complex Figure, and significantly lower than IntSibs on Digit Span backward.

When looking at how the groups scored on the seven measures used to divide the Sibs into ImpSib and IntSib groups it is of no surprise that the ImpSibs, compared to the NC group, showed greater deficits on these tests. These tests were after all used to divide the group in two. Interestingly, and surprisingly, the IntSibs scored significantly lower than the NCs on the immediate and delayed recall of the LM. This result was obtained despite the fact that this test was used among five others to divide the Sibs into intact and impaired groups. It is especially interesting, as also found in some other studies, that the test of LM is very sensitive to detecting AD in the preclinical phase (e.g. Elias et al., 2000; Linn et al., 1995; Reid et al., 1996).

These results indicate that although dividing the Sibs into two groups, according to how the participants scored on the seven selected neuropsychological measures, the group who scored normally on most of the tests still showed some memory impairments on the LM immediate and delayed recall. This indicates that some individuals in the IntSib group should perhaps have been classified as ImpSibs – at least according to their memory performance on the LM test. These findings are discussed further in the following section.

9.2.3 Dividing the Sib group according to the LM test

It is interesting that both immediate and delayed recall of the LM were the neuropsychological measures weighting the most in dividing the Sibs into impaired and intact groups of the seven measures used. Nevertheless, after the division there was still a significant difference between

the IntSibs and the NCs on the LM measures. These results indicate that although the division of the Sibs into ImpSib and IntSib groups, according to these seven neuropsychological measures, some individuals in the IntSib group still have impaired verbal memory compared to the NCs. These results might seem to suggest that perhaps the LM test alone is able to distinguish the individuals in the Sib group showing cognitive impairments from the healthy ones. To address this question a discriminant analysis on the three original study groups (Sibs, NC, and AD) was performed, as before, but now using only the immediate and delayed recall of the LM test. The discriminant analysis showed greater overlap between the three groups than before when also using the neuropsychological measures of immediate and delayed recall of Rey Complex Figure, hard pairs of the Associate Learning test, Orientation, and Trail Making Test. This new discriminant analysis showed 19 (20%) participants in the Sib group to score identical to the AD patient group on the LM measures, instead of 11 before when the other five measures were also used. This group was labeled as NewImpSibs to distinguish it from the older one. The rest of the Sibs were labeled as NewIntSibs. What is more, when only the LM immediate and delayed recall were used in the discriminant analysis, 3 (4.4%) individuals in the NC group were found to score more in resemblance to the AD group than the other two groups, instead of none when all the seven measures were used. Although the number of NewImpSibs had increased from 12% to 20% by using this new analysis, the rest of the results, regarding group comparisons on the neuropsychological and demographical variables, were very similar. The only difference found was the NewImpSibs scoring lower on most neuropsychological measures and the NewIntSibs higher. So the difference between the impaired and intact groups seems to have increased when only the LM measures were used to divide the Sibs, instead of the seven neuropsychological measures used before. These results raise the following question: Is LM alone a sensitive predictor of preclinical signs of AD, perhaps even better than when using also the neuropsychological tests of immediate and delayed recall of the Rey Complex Figure, hard pairs of the Associate Learning, Orientation, and Trail Making Test? It is quite possible that out of 95 siblings of AD patients, with the mean age of 73.3 years (ranging from 60-85 years old), 20% have cognitive impairments and are possibly in the preclinical phase of AD. It is also likely that out of 68 NCs, with the mean age of 71.8 years (ranging age of 60 to 85 years old), 4.4% have cognitive deficits and are possibly in the preclinical phase of AD. These results are concordant with the incidence rate of

AD in the community and in first-degree relatives of AD patients. Therefore it is quite possible that these cognitive impairments evident in a 20% of the Sibs are an indicator of preclinical phase of AD.

Only a follow up study on the Sibs and the NCs can tell us which of the neuropsychological tests are the most sensitive in detecting persons in the preclinical phase of AD. The results of this study nevertheless indicate that siblings of AD patients that also have another AD relative within 6 meiotic events apart are in greater risk of having some cognitive deficits compared to a group of NC who have no known first-degree relative with dementia. The present results, in the following section, are compared to other studies on preclinical AD, in order to find out if the ImpSibs are likely to be in the preclinical phase of AD or not.

9.2.4 The neuropsychological assessment

The AD patients' scored significantly lower on the neuropsychological tests than individuals who are considered normal such as IntSibs and NCs. The impairments found in the AD group are well documented in the literature and need no further discussion. More interestingly is the performance of the ImpSibs, a group of people who are considered to be normal and who have not been referred to a clinician due to memory or other cognitive impairments. The comparisons of the ImpSibs to the groups of the IntSibs and NCs are discussed in greater depth below.

9.2.5 Verbal and non-verbal memory

- **Recognition of the Rey Complex Figure and LM**

Free recall is a cognitively demanding task whereas recognition and cued recall are relatively easy and better preserved in those beginning to develop AD (Small, Herlitz et al., 1997). Free recall was significantly impaired in the Sib group as a whole, compared to the NC group, whereas recognition was not. After dividing the Sib group into ImpSibs and IntSibs, the differences on verbal and non-verbal recognition memory were significant. The ImpSibs recognized significantly less of the LM test compared to IntSibs and NCs. Furthermore, significantly fewer ImpSibs (36.3%) could correctly recognize the Rey Complex Figure compared to IntSibs and NCs, 74.0% and 83.1% respectively. These recognition difficulties

observed in the ImpSibs indicate some problem of storing information in the memory. This storing impairment could lead to or be in addition to the retrieval or retention impairments in the immediate and delayed recall of the verbal and non-verbal materials that was noticed in the Sib group in the initial analysis.

- **Associate Learning**

The hard pairs of the Associate Learning was one of the tests used to divide the Sib group, but not the easy pairs. However, after dividing the Sibs into two groups, the ImpSib group showed significant deficits on the easy pairs of the Associate Learning test compared to NCs. The ImpSibs showed, therefore, great difficulties in learning to pair semantically related words and well-learned verbal association.

- **Summary on memory**

The ImpSibs showed significant impairments on all memory measures compared to the IntSibs and NCs. ImpSibs showed even impairments in memory tasks that place much less demand on cognitive function than free recall, as the easy pairs of the Associate Learning and recognition of the LM and Rey Complex Figure. Impairments on these tests are usually seen later in the AD course than impairment on tests of free recall. The current results indicate therefore deficits in the ImpSibs on immediate and delayed recall of verbal and non-verbal information as well as recognition.

It is difficult to decide what in the memory process is impaired in the ImpSib group. Is it the encoding, storage, or retrieval process, or a combination of these processes?
When only the retrieval process is impaired, individuals are assumed to show poor free recall with intact recognition (Lezak, 1995). Current results showed impaired free recall of the ImpSibs and in addition problems of recognition on both verbal and non-verbal memory. This general memory difficulty indicates problems of the ImpSib group in encoding, storage, and retrieval. More memory tests are needed to state which aspect of memory is most impaired in the ImpSib group. These results would have been strenghtened by the use of another non-verbal memory test not as difficult as the Rey Complex Figure, thereby reducing the risk of floor effect. It would also have strengthened the results of the present study, if another verbal

memory tests had been used in addition to those used, especially those tests which have standardized recognition tests, e.g. Rey Auditory Verbal Learning Test or California Verbal Learning Test.

9.2.6 Results of other studies on memory impairments in preclinical AD

It is certainly well established that deficits in verbal and non-verbal memory are the first signs of preclinical AD. According to some studies, verbal memory impairments precede the clinical diagnosis of dementia by an average of 2.8 years (Howieson et al., 1997; subjects aged < 80 years) or around 6 years (Linn et al., 1995; subjects with mean age of 76 years). Many longitudinal studies have reported impairments in memory measured by using immediate and delayed recall of LM or Associate Learning to be the best predictor of those eventually developing AD. In a longitudinal study of the PAQUID cohort, Fabrigoule et al. (1998) reported that Associate Learning test in addition to some other tests was a good indicator of this. Similar results were found in the prospective study of the Framingham Cohort reported by Linn et al. (1995) where scores in the tests of Associate Learning and LM, among others, were significantly lower for those developing AD later. Later, Elias et al. (2000) reported another study of the Framingham Cohort where they only found impairments on LM-retained and Similarities to be predictors of those developing AD later. Chen et al. (2000) reported a 10 years prospective study where Word List delayed recall discriminated best between those who manifested AD 1.5 years later, second came tests of Trails B and LM delayed and immediate recall. Studies on newly diagnosed AD patients also showed memory impairment as measured with LM to be the first indicator of the disease (e.g. Reid et al., 1996). As reviewed earlier many other studies have reported memory impairments to be one of the first indicators of AD (e.g. Almkvist, 1996; Farlow et al., 1994; Fox et al., 1998; Jacobs et al., 1995; Kumar, et al., 1991; Masur et al., 1994; Newman et al., 1994; Perry & Hodges, 2000; Schmitt et al., 2000; Small, et al., 2000; Tierney, Szalai, Snow, Fisher, Nores et al., 1996).

It is evident from the above findings that memory impairments measured with LM and Associate Learning are found to be reliable indicators of AD in the preclinical phase. In the current study, the cognitive impairment evident in the ImpSib group, could therefore in accordance with these studies indicate AD in the preclinical phase.

9.2.7 Other neuropsychological domains

There is a great deal of evidence that memory tasks have the greatest sensitivity of detecting AD in the preclinical stage. The longitudinal and epidemiological studies mentioned above indicate several different cognitive domains to be affected secondly after memory in the preclinical stage of AD. In the present study tests of other cognitive functions in addition to memory were assessed. These were orientation, abstract reasoning and executive function, language, attention and mental speed, and visuo-spatial and constructional abilities. This comprehensive test battery was designed to delineate the cognitive domains implicated in the preclinical and earliest stages of AD. Following are the comparison of ImpSibs, IntSibs, and NCs on cognitive domains other than memory discussed.

- **Attention and mental speed**

According to Fabrigoule et al. (1998) preclinical impairments of AD are detected with impaired processing speed and selective attention, assessed with tests of Letter Cancellation and Digit Span. Perry and Hodges (1999) reported attention to be the first non-memory domain to be affected in AD and to be manifested before deficits in language and visuo-spatial functions are evident. Divided attention and some form of selective attention were impaired in the early stages of AD and in mildly demented patients, while sustained attention was relatively preserved (Perry & Hodges, 1999). Somewhat similar is a study presented by Rizzo et al. (2000) who reported that mild AD patients performed significantly worse than NC on attention and processing speed. The difficulties were in all aspects of attention, that is sustained-, divided-, and selective attention.

Digit span

The problem with the Digit Span test is that some researchers have combined the forward and backward scores and used it as a one measurement. There is a great risk of loosing information by dealing with these two tests as one (Lezak, 1995), and in the present study they were used as divided tests of forward and backward span.

In the present study no difference was found in ImpSibs, IntSibs and NCs on the Digit Span forward test, which is a simple test of attention. However, there was a significant difference on

Digit Span backward where ImpSibs scored significantly lower than IntSibs, but not between the ImpSibs and NCs.

Some researchers have reported Digit Span to be an early indicator of AD and one study indicated impairment twenty years prior to diagnosis (La Rue & Jarvik, 1987). Several other follow up studies, on the other hand, failed to show impaired score on the Digit Span test in the preclinical phase of AD (Elias et al., 2000; Newman et al., 1994; Small, Herlitz, et al., 1997) and even in mild AD patients (Perry & Hodges, 2000). One study by Linn et al. (1995) showed contradictory result were those who later diagnosed as AD patients performed at higher levels than NCs on Digit Span test at initial screening. Flicker et al. (1993) found a difference between moderate AD patients and NCs on the Digit Span test, but not between mild AD patients and NCs, indicating that the Digit Span test can be a potential marker for the transition from mild to moderate dementia.

Letter Cancellation

There was no difference observed between the ImpSibs, IntSibs and NCs in number of errors on the Letter Cancellation test and in the time it took to finish the test. The present results, therefore, indicates that the attention in the ImpSib group is not impaired enough to influence the Letter Cancellation test, although they had at mean more errors than all the other groups, even more than the AD patients. The reason for the non-significant difference between the groups was probably due to very large SDs in the groups.

Summary on attention and mental speed

The results of the current study indicate some attention and mental speed impairments in the ImpSibs, at least on the more demanding tests as Trails A and B, and on Digit Span backward–where more easy tests as Letter Cancellation and Digit Span forward revealed no impairments in the ImpSibs. Other studies have found impairments on these tests to be related to preclinical signs of AD. The present results therefore support the assertion that ImpSibs could be in the preclinical stage of AD.

- **Abstract reasoning and executive functions**

The domain of abstract reasoning and executive function was assessed with neuropsychological measures of Similarities, Picture Arrangement, and letter and category fluency of the Oral Word Fluency test.

Similarities

In the present study ImpSibs scored significantly lower than NCs on the test of Similarities. Some studies show impairment on Similarities in the preclinical phase of AD. According to La Rue and Jarvik (1980; 1987) the test of Similarities, among other tests, indicates which individuals will develop AD 20 years before clinical diagnosis. Elias et al. (2000) reported that abstract reasoning measured with Similarities was predictive of AD for a group of people who developed the disease after a dementia-free period of 10 years after baseline neuropsychological assessment. Jacobs et al. (1995) reported that impairments in verbal reasoning (Similarities) in addition to two other tests could predict individuals later developing dementia and Fabrigoule et al. (1998) reported that impairments of Similarities among other test were predictive of AD after an interval of two years. In accordance with these findings it is possible that these impairments evident in the ImpSibs on Similarities in addition to other tests could indicate preclinical AD.

Picture Arrangement

No difference was found on the groups on test of Picture Arrangement. One study, performed by Fox et al (1998), reported impairments of Picture Arrangement in first-degree relatives of AD patients six years before they were clinically diagnosed as AD.

Oral Word Fluency

Category fluency is often considered to depend on the integrity of the structure of semantic knowledge, whereas letter fluency is believed to depend on phonemic or lexical cues (Monsch et al., 1994). No differences were observed between the ImpSib, IntSib and NC groups on letter fluency of the Oral Word Fluency test. The ImpSibs, however, scored significantly lower than NCs on category fluency of the Oral Word Fluency test.

Monsch et al. (1994) and Masur et al. (1994) found that category fluency provides better discriminative ability between normal aging and AD than letter fluency, particularly in the early stages of AD. Monsch et al. concluded that semantic knowledge deteriorates early in the course of AD. Small et al. (1997) reported letter fluency to be associated with an increased risk of AD. Moreover, Masur et al. (1994) reported that verbal fluency in addition to two memory measures and the Digit Symbol subtest of the WAIS-R independently contributed to the prediction of later dementia in their cohort of initially healthy elderly people from the Bronx Aging Study. In accordance with these studies the deficits evident in the ImpSibs on category fluency test could indicate AD in the earliest stage. Later as the disease develop into mild AD it is characterized by impairment of processing speed as measured with Oral Word Fluency (Rizzo et al., 2000) and according to Locascio et al. (1995) Verbal Fluency along with Boston Naming discriminated best mild or moderate AD from severe AD.

Summary on abstract reasoning and executive function

Tests of Picture Arrangement and letter fluency of the Category Fluency test revealed no difference between ImpSibs, IntSibs, and the NC groups. The ImpSib group scored, however, significantly lowers than NCs on Similarities and semantic category of the Oral Word Fluency test, which in accordance with other studies are strong indicators of AD in the preclinical phase. Therefore these results indicate mild impairments in the general intelligence domain of abstract reasoning and executive function in the ImpSibs, which is only evident in some neuropsychological tests. Other studies show that impairments in abstract reasoning and executive function may most likely become more prominent as the AD develops.

- **Visuo-spatial and constructional abilities**

Visuo-spatial and constructional abilities were assessed with tests of Block Design, Gestalt Closure and copying of the Rey Complex Figure. Some researchers have found visuo-spatial and constructional abilities to be preserved relatively long as the AD progresses (Perry & Hodges, 2000). The present study revealed neither impairment in the Sib group as a whole in the initial analysis, nor in the ImpSibs on any of the visuo-spatial and constructional tests. However, some studies have found impairments of Block Design in the preclinical stage of AD. Bozoki et al. (2001) studied how mild cognitive impairments predicted dementia and

found that deficits in Block Design were the most frequent abnormality after memory loss. Fox et al. (1998) reported that impairments of Block Design with some other tests could be detected some six years prior to clinical diagnoses of AD.

- **Language**

The language domain was measured with Boston Naming and Reading and understanding. No difference was found between the ImpSibs, IntSibs, and NCs on these tests. Some studies reported performance on Boston Naming to be largely spared in the early course of AD (Farlow et al., 1994; Fox et al., 1998; Kennedy et al., 1993). According to Touchon and Ritchie (1999) verbal function was not one of preclinical deficits of AD (measured with Naming and Verbal Fluency). This argues against an impairment of semantic memory being an early feature of AD. Jacobs et al. (1995), on the other hand, found impairments in Boston Naming, in addition to impairments in memory and verbal reasoning, to be prominent in the early stages of dementia and to be detected before functional impairment is evident and dementia is diagnosed. Other studies stated scores on the Boston Naming test, along with Verbal Fluency test, to be the best in discriminating mild or moderate AD from severe AD (Locascio et al., 1995).

In the current study no difference was found between the groups on test of Reading and understanding. This is of no surprise as the impaired reading have been related to more advanced AD (Almkvist, 1996; Kennedy et al., 1995; Reid et al., 1996). It therefore supports the idea of the ImpSibs being possible in the preclinical stage of dementia, but not with advanced disease.

Summary on language

The present study revealed no difference between the groups on the language measures of Boston Naming and Reading and understanding. This intact verbal function found in the ImpSibs, compared to the IntSibs and NCs, could indicate intact verbal function in the preclinical stage of AD. Although, according to other studies, deficits in the language domain will develop as the disease progresses.

9.2.9 Summarizing the neuropsychological group comparison

When other studies are examined and their results reviewed it is clear that most of the tests used in the present study have earlier been related to preclinical signs of AD. The ImpSibs scored significantly lower than IntSibs and NCs on some of these tests, but not on all. These tests which did not reveal any difference between the groups were Letter Cancellation, copy of the Rey Complex Figure, Picture Arrangement, letter fluency of the Oral Word Fluency test, and Digit Span forward. Perhaps these results weaken the hypothesis of the ImpSibs being in the preclinical stage of AD. However, on the other hand, if the ImpSibs had shown deficits on all the neuropsychological measures used in the study it would indicate more than just preclinical AD. It has been repeatedly reported in the literature that difficulties on the same neuropsychological tests as evident in the ImpSibs are indicators of AD in the preclinical phase. These tests were the immediate, delayed, and recognition of the LM and Rey Complex Figure, easy and hard pairs of the Associate Learning, Orientation, Trail Making Test, Digit Span backward, Similarities, and category fluency of the Oral Word Fluency. When the present results from the neuropsychological assessment as a whole are compared to other studies it strongly indicates ImpSibs to be in the preclinical stage of AD (see figure 8).
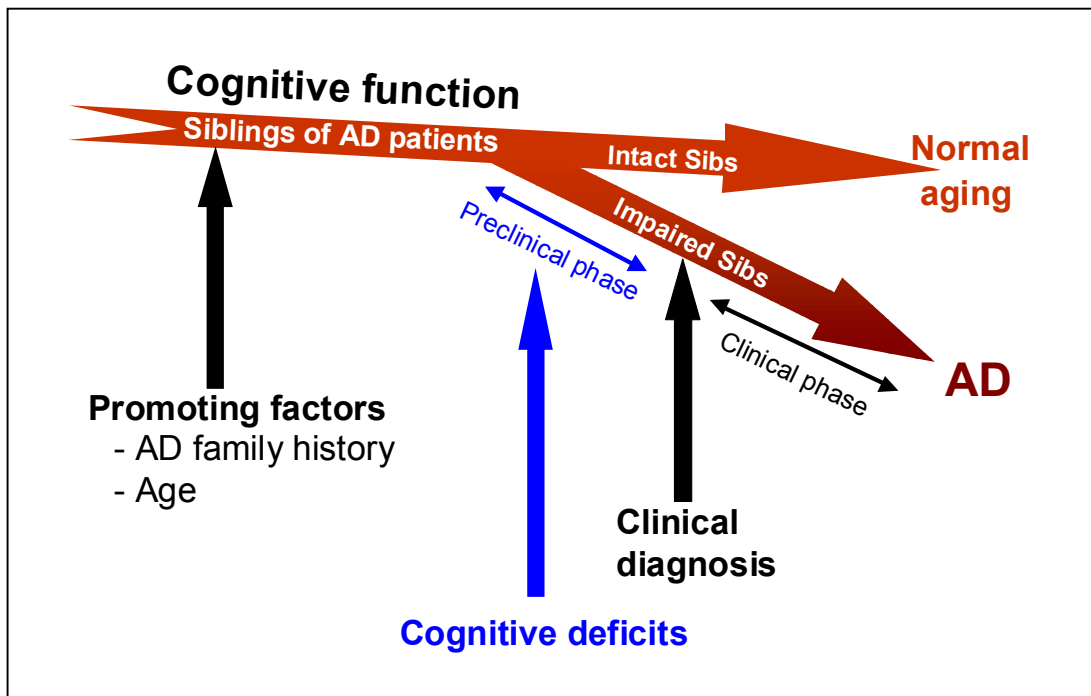
Figure 8.
Schema of how ImpSibs deviate from normal aging, possible being in the preclinical phase of AD developing later into AD.

In figure 8 it is shown how the ImpSibs deviate from normal aging and maybe in the preclinical phase of AD. Although the schema divides the Sibs into healthy and those developing AD it is possible that some of those considered likely to develop AD (ImpSibs) can stay unchanged for the rest of their lives without developing AD. It is even more likely that some of those considered healthy elderly (IntSibs and NCs), at the time of the testing, will develop AD in the future. They could even already be in the preclinical phase of AD and the analysis or the neuropsychological tests have just not identified them. Only longitudinal follow up study can answer the questions of which individuals will develop AD for sure. Despite all the modern technique it is almost impossible or at least very difficult to predict, with some reliability, which individuals in the community will develop AD and impossible to find out who will not. This will perhaps change in the next decade due to extensive research on AD and its genetic mysteries.

9.2.10 Self-report of memory impairment

Some researchers have shown that AD patients' self-report of memory function has no relation to their cognitive performance, whereas the informants' judgment provides a reliable guide (Morris, 1994). This lack of insight into own cognitive impairment is named anosognosia and is common in AD (e.g. Kotler-Cope & Camp, 1995). The Sibs in the current study had not been referred to clinician because of memory complaints and therefore filled out the health questionnaire them selves. About 66% of the IntSibs and 64% of NCs complained of memory loss compared to 91% of those who were in the ImpSib group. These findings indicate that most people at the age between 60 and 85 years old consider their own memory to be impaired. But interestingly, almost all in the ImpSib group complained of having impaired memory, indicating that those who are in the preclinical stage of AD can often notice their memory difficulties although they might lack this insight into their own condition as the disease develops. These results, however, raise the question of the reliability of self-reported memory impairments as the majority of the participants in the study complained of memory loss, at least when asked directly.

9.2.11 AD risk factors and the ImpSibs

Below is a discussion of those risk factors in the ImpSib group that have been related to AD as increased age, female gender, short education, and positive family history of AD.

The age of the ImpSibs was normally distributed from 63 to 75 years old. Although the mean age of the ImpSib group was slightly higher than the rest of the groups it was not significant. There were four males and seven females in the ImpSib group. Although the females outnumber the males in the ImpSib group it is not reliable because it is such a small group. According to the study of Wilson, Beckett, Bennett, Albert, & Evans (1999) and Chen et al. (2000) those who developed AD were older and less educated than those who did not develop AD. Nine individuals in the ImpSib group had only elementary schooling (8≤ years of education) compared to only two individuals with more education. All participating groups included greater amount of individuals with only elementary schooling or around 60%. The ratio of individuals with only elementary schooling was little higher in the ImpSib group compared to the other groups, but could easily be skewed because of the small sample size.

According to the study of Bowler, Munoz, Merskey, & Hachinski (1998) education does not influence the age of onset or the rate of progression of AD.

When the results of the current study are summarized regarding demographical risk factors it seems that higher age does not lead to increased risk of developing memory or other cognitive impairments. The results regarding increased risk of having cognitive difficulties due to female gender or short education were unreliable due to a small sample size in the ImpSib group.

- **Family history of AD**

The current findings of increased risk of impaired cognitive function, especially memory, in those who are siblings of AD patient replicate other findings (Bondi et al., 1994; La Rue et al., 1992). Mendez et al. (1992) found that the risk of developing AD is greater for siblings than for other first-degree relatives at similar age, and the risk is greater for first-degree relative than for second-degree relatives. They reported that 33% of AD patients had a first-degree relative with dementia, in comparison with only 21% of those who had other dementia and 12% of unaffected older people. The risk of developing dementia appears to increase when a person has two or more first-degree relatives affected by dementia. Rocca and Amaducci (1988) reported a 3 to 8 fold increased risk of AD in subjects with at least one family member affected with AD. The current study indicates that 12-20% of individuals having sibling with AD and another AD family member within six meiotic events apart are at increased risk of developing memory and other cognitive impairments, compared to 0-4% of those without any known first-degree AD relative. These present findings indicate therefore that AD siblings, with same AD family history as in the present study, are in at least 3 to 5-fold increased risk of developing cognitive impairments than those without any known first-degree AD relative. These cognitive impairments are, furthermore, very similar to those found in individuals in the preclinical stage of AD and usually considered an indicator of AD in the earliest stage.

Regardless of whether the increased familial incidence of dementia in AD is due to an autosomal dominant gene with variable penetrance, a polygenic inheritance, shared exposure to some environmental agent, or some combination of these, the increased familial frequency of AD appears in most studies. In the current study an effort was made to rule out the environmental factor by having the Sibs' spouses as a control group. That does hovewer not

rule out possible environmental factor from childhood or at occupation – at least in most cases. The current results therefore indicate some genetic promoting factor in the development of memory and other cognitive impairments that possibly will later become clinically diagnosed as AD.

9.2.12 ImpSibs and Mild Cognitive Impairment

Should the ImpSibs be diagnosed as MCI? The ImpSib group shows some memory impairments exceeding 1.5 SD below NC mean necessary for the diagnosis of MCI. However, according to the MCI criteria of Petersen et al. (1999) it is necessary that those diagnosed as MCI should have normal general cognitive function aside from memory. The ImpSibs were impaired, as a group, on some other cognitive domains, as well as memory, not quite falling under the criteria of MCI. Another diagnostic criterion in MCI is a self-reported memory complaint, preferably corroborated by family member. Most of the individuals in the ImpSib group complained of memory impairment when asked, as in fact around 60% of other Sibs and NCs. The current study lack information from a family member to corroborate these memory complaints of the ImpSibs. It is interesting to notice that this statement, if taken literally, in the MCI criteria excludes those who are unaware of their memory impairments due to lack of insight (anosognisia), a well known symptom in AD. Its also excludes those who deny or minimize their memory impairments in hope of concealing their impairments and deceiveing others or simply because they believe that their symptoms are related to normal aging. The results from the current study are based on a group comparison, but not on individual basis. It is therefore not suitable to label a group MCI without looking separately at each individual in the group.

In the current study the ImpSibs had a positive family history of AD and scored very similar to the AD patient group, and in accordance with other studies the cognitive impairments evident in the ImpSibs are indicators of preclinical AD. Therefore it is possible that individuals in the ImpSib group will develop AD later, currently being in the preclinical phase of AD.

9.3   Comparison to other studies

Many earlier studies only include first-degree relatives of autosomal dominant familial AD (e.g. Newman et al., 1994), unlike the current study, and are therefore not discussed here. Many of

the studies mentioned in the introduction chapter, on preclinical AD, are population based long-term studies or studies where the participants are assembled because of complaints of memory problems, not severe enough to be clinically diagnosed as AD. In many studies, where the aim is to detect the earliest changes of normal aging developing into AD, subjects with memory complaints or even memory performance that is lower than NC are used (Daly et al., 2000; Petersen et al., 1999).

In other studies, more similar to the current study rather than to longitudinal community based studies, subjects with a positive family history of AD were used. The definition of familial AD is usually the existence of at least two first-degree relatives with AD in two different generations (Fox et al., 1998; Lehtovirta et al., 1996). The present study can therefore not be categorized as a typical familial study since the inclusion of participants having AD in the family is much wider. Small et al. (1994) tested people with a history of mild memory impairments. They compared 29 participants with a positive family history of AD with 14 without such a history. The assessment took 3-hours and included various neuropsychological tests. Tests used in the study of Small et al. as well as in the present study were Block Design, Picture Arrangement, Similarities, Digit Span, Boston Naming, Logical Memory, Associate Learning, and Rey Complex Figure. Unlike the present study Small et al. found no difference between those who had positive family history of AD and those with negative family history of AD. One-year later they reported another study also showing no increase in cognitive deficits of individuals with a positive family history of AD compared to those with a negative family history of AD (Small, La Rue et al., 1995). The later study included however only two tests, one of verbal memory and the other non-verbal memory. Although memory impairments are generally reported as the first indicator of AD the lack of tests of other cognitive domains limits the results of Small, La Rue et al., (1995). Both above studies of Small et al. (1994; 1995) included rather few subjects, only 29 with positive family history of AD and 14 NC with negative family history of AD. The subjects in these studies were also younger (mean age of 60 years) than the subjects in the current study and, additionally, all the participants in their studies had a history of mild memory impairments.

La Rue et al. reported familial studies in 1992 and 1995. These were longitudinal studies and therefore included smaller samples of participants than in the current study. In the study reported in 1992 were 32 participants, 21 offsprings and 11 siblings. Unlike the present study the study by La Rue et al. is a longitudinal study where they followed the group of first-degree relatives over a four-year interval. The limitation of this study is the lack of comparison with a group of NCs with a negative family history of AD. In the study reported later, La Rue et al. (1995) compared 40 first-degree relatives of AD patients and with 24 NCs. The mean age of the participants was almost 13 years younger than in the current study. The cognitive impairments found in the first-degree relatives of AD patients reported in both studies of La Rue et al. were more related to relatives with early-onset dementia in the family rather than of late-onset dementia. Both studies included a comprehensive neuropsychological assessment and some of the neuropsychological tests used are the same as used in the current study e.g. tests of Associate Learning, Similarities, Boston Naming, and Oral Word Fluency. In the latter study (1995) impaired scores of Boston Naming, Similarities and immediate recall of Selective Reminding Test correlated with later diagnoses of AD.

Bondi et al. (1994) reported a study where subjects with a positive family history of dementia (at least one first-degree relative with dementia; $n = 28$) were compared to subjects with negative family history of dementia ($n = 25$). The mean age was similar to that in the present study, i.e. around 70 years old. They found that those with a family history of dementia were more likely to undergo changes in diagnostic status over time and that memory difficulties measured with California Verbal Learning Test (CVLT) could predict those developing AD later. These results are somewhat limited since they are only based on five subjects who developed AD 3 years later. Of those subjects three had a positive family history of dementia and developed AD, one developed questionable dementia and one developed AD but had uninformative family history of dementia. Furthermore, the five participants who developed AD within 3 years, were compared to the rest of the subjects on 34 neuropsychological measures that resulted in significant differences on 11 variables. The above study of Bondi et al. is somewhat similar to the present study, although the researchers failed to report how many of the first-degree relatives were siblings or offspring. Hence, the results are not quite comparable to the present study. The results by Bondi et al., nevertheless, indicate that

individuals with a positive family history of AD are at greater risk of developing AD. In addition, their results indicate that impairments on immediate and delayed recall of the LM, Oral Word Fluency, and Similarities and intact Boston Naming and Block Design are indicators of AD in the preclinical phase. However, unlike the present study they found no difference on Trails A and B between those who developed AD later and those who did not.

Fox et al. (1998) reported a six years follow up study on familial AD where they found memory tests to make the largest contribution to discriminating early AD from healthy aging. Second after memory test was the performance IQ consisting of Block Design, Picture Completion and Picture Arrangement in best discriminating early AD from healthy aging. Although they found memory tests to be the largest contribution in discriminating preclinical AD from healthy elderly, which is similar to the present results, their study differed from the current one in many ways. Their results were based on 10 subjects out of 63 who developed AD over a six-years period with the mean age 44.7 ± 8.1 years. The mean age is much lower than in the present study (around 70 years old). Their selection of participants was also quite different from the present study, only including those having at least two family members in two different generations, including a first-degree relative, affected with AD. In addition the participant had to be within 5 years of the historical age at onset for their family and the age of onset had to be before the age of 65 years. In the current study only one first-degree relative and another within six meiotic events apart were enough to include the participant in the study. Furthermore, no exclusion regarding age of onset of the AD relatives was used in the present study as in the study of Fox et al.

The results from a family study by Díaz-Olavarrieta et al. (1997) were similar to the current study, that is first-degree AD relatives were found to be impaired on memory measures of LM, Associate Learning, and Rey Complex Figure compared to those with negative family history of AD. The study of Díaz-Olavarrieta et al., however, included much younger participants compared to the present study, with a mean age of 36 ± 4 years. Furthermore, their study was only based on 14 subjects, both including siblings and offsprings of AD patients. Also the participants were from three families selected for the study because of a very strong family history of AD.

Hom et al. (1994) reported a study where half of the first-degree AD relatives, participating in the study, showed some impairments, compared to a group of NCs, on verbal intelligence, verbal short-term memory, attention and concentration. They only reported statistical comparisons of the groups on each cognitive domain as a whole, but not of each test that constituted the domain. The result of this study are perhaps somewhat similar to the current study where first-degree AD relatives showed memory impairments. Although the study by Hom et al. differs from the present study as they had fewer participants, and a mixture of siblings and offspring of AD patients, 2 and 8 respectively. The mean age of the participants in the study of Hom et al. was also much younger (54.5 ± 5.7 years) than in the present study.

Comparison to other studies reveals some differences of the present study regarding the selection of participants. The definition of AD within a family is different from other studies. The number of participants in the current study is also greater than in most of the studies reported above, although the neuropsychological assessment is thorough, taking 1 ½ hour and measuring many aspects of cognitive function. Another difference is also the selection of participants in the current study, as they were not selected due to history of memory difficulties or memory complaints as in many other studies.

10. CONCLUSION

The selection of participants in the current study is somewhat different from studies reported earlier. The familial or pedigree definition in this study is unique. We selected siblings of AD patients with another relative with clinical diagnosis of AD within six meiotic events apart (sharing the same great-grandfather or great-grandmother), whereas NCs consisted mainly of spouses of the Sibs without any known demented first-degree relative. The subjects in the Sib group are therefore not specifically selected due to a very strong family history of AD, as in many studies where the Sibs had to have at least two first-degree relatives with AD or autosomal dominant AD in the family. In the present study participants in the Sib and NC groups had not been referred to a clinician because of memory or cognitive difficulties, which is rather common in studies on the preclinical phase of AD. Furthermore, the total number of

participants was rather large (250 individuals) compared with many other studies. The age range of the participants was 60 to 85 years and the study can therefore be considered to be on late-onset AD, whereas most familial studies are on early-onset AD.

Based on information gathered from neuropsychological measures and health history the findings of the current study show that siblings of AD patients are more likely to manifest significant memory impairments, impaired orientation and some difficulties in attention and mental speed than an age, gender, and education matched group of individuals without first-degree AD relatives. The results also show that the siblings of AD patients with this family history of AD are in approximately five-fold increased risk of cognitive impairments compared to those without first-degree AD relatives. According to other studies these cognitive impairments in the siblings may be predictors of AD in the preclinical phase. Furthermore, the results indicate that the neuropsychological tests of immediate and delayed recall of the LM, immediate and delayed recall of the Rey Complex Figure, hard pairs of the Associate Learning test, Orientation, and the Trail Making test can be used to find individuals living in the community who show cognitive impairments similar to those shown by AD patients and which are most likely indicators of AD in the preclinical phase. The results also raise the question of whether immediate and delayed recall of LM stories alone could detect the individuals likely to show cognitive impairments, compared to NCs, which are severe enough to be similar to those shown in clinically diagnosed AD patients. When using the seven neuropsychological measures 12% of the Sibs were found to have cognitive impairments, similar to those found in mild or moderate AD patients. However, when using only the LM measures the ratio was as high as 20%, and the individuals showed significant impairments on the same cognitive domains as the mild or moderate AD patients, although the impairments were a little less severe than in the AD patient group.

The neuropsychological tests used in the current study are standardized and widely used, especially in studies on earliest sign of AD in relatively healthy participants living in the community. In accordance with other studies on preclinical AD it is likely that the impairments found in the Sib group are indicators of preclinical stage of AD and only bound to a subgroup of the siblings, but not to the group as a whole. It is unlikely that methodological issues

account for these findings of impaired score of the Sibs as all possible confounders have been tested or eliminated. These results can only indicate which individuals are the most likely to develop AD in the future. It does not rule out that the others may develop AD as time passes.

Some shortcomings can be found in the current study. Firstly, because of the time limit of each testing the study included rather few memory tests. The results would have gained more power by including another non-verbal memory test in the assessment, in addition to Rey Complex Figure, and also a verbal memory tests of e.g. Rey Auditory Verbal Learning Test or California Verbal Learning Test. Secondly, and most importantly, it is not certain that these findings of cognitive impairments represent preclinical stage of AD and not indisputable that subjects in the ImpSib group will develop AD or other kind of dementia in the future.

10.1 Future research

A follow up study is needed to confirm that these memory impairments found in the Sib group will develop into AD. In midyear of 2002 it is four years since the Sibs in the study were tested, and it is therefore the proper time to retest them.

Another interesting aspect regarding this study is to see if cognitive deficits are detectable earlier than reported here and if it can also be found in the offspring of AD patients. Together with the participants presented in the current study we tested 199 offspring, 40 years old and older, and in addition to the NC group presented here an age matched group of 65 subjects with a negative family history of AD (total number of NCs are therefore 133 individuals). Furthermore, we have assembled blood samples and studied the genotype of almost all of those tested with the neuropsychological assessment (only exception were those NCs that participated in the study after seeing an advertisement). It would therefore be interesting to compare the ApoE and the Cystatin C status of the subjects to their performance on the neuropsychological measures.

Finally, most important is the genotype work of the deCODE company on these subjects. If the company will successfully locate the genetic markers of AD it would be a great opportunity to compare those who have the particular gene/genes to those who do not on the neuropsychological measures.

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FIGURES AND TABLES

APPENDIX

Appendix I

Rey Osterrieth Complex Figure Recognition Test

In the recognition of the Rey Osterrieth Complex Figure Test the subject has to judge which one of following six pictures (see appendix I) is the original Rey Osterrieth Complex Figure that he copied 45 minutes earlier.

If he fails to recognize the right picture the number of the wrong picture is written down, because the picture selected can be useful in identifying the deficits (Palsson & Jonsdottir, unpublished).

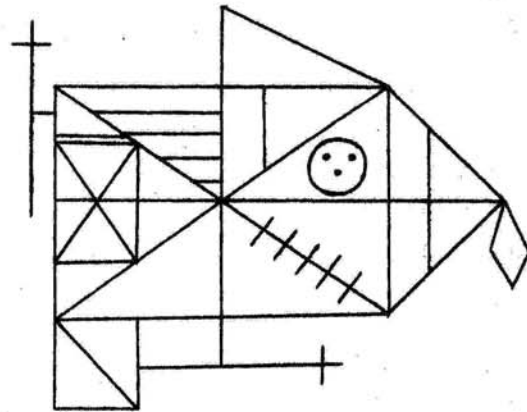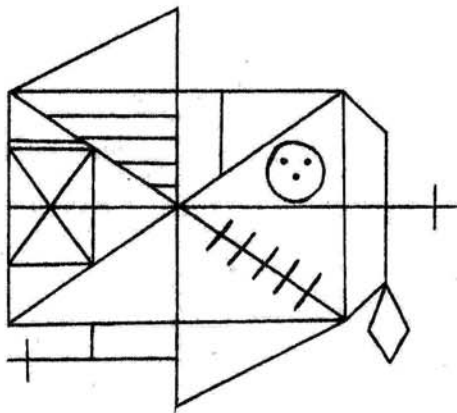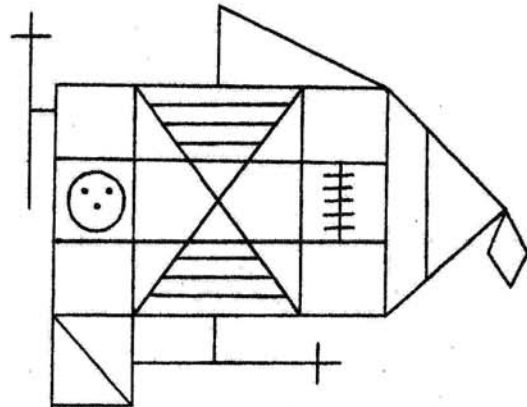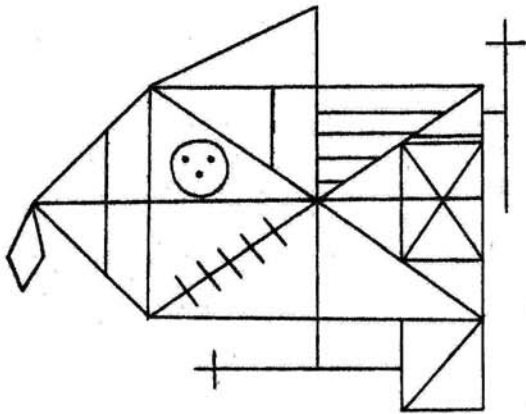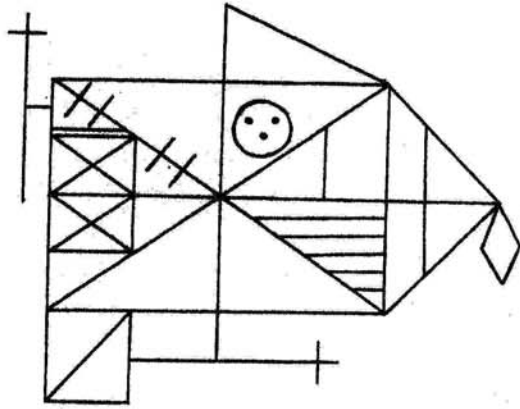**Appendix II**

Logical Memory Recognition

The recognition of the Logical Memory consists of ten questions regarding the stories read 45 min earlier. The examiner states the questions in a multiple choice form, and the subject has to choose the right answer from three possibilities (see appendix II). For each story the subject can score a maximum of five points. The total score for story A and story B is divided by two to obtain the final score (Palsson & Jonsdottir, unpublished).

Appendix III

The Reading and understanding test

In the reading test the subject has to read a short story. After the subject has read the story, the examiner asks three questions regarding the story. The subject can gain points for the accuracy/quality of reading and for answering the questions right (Palsson & Jonsdottir, unpublished).

Logical Memory (WAIS) Recognition
Correct answer is underlined – each correct answer gives one point

Story a)   **Answer**

1) Was the name of the woman attacked:

     Violet   <u>Anna</u>   Susan   _____

2) Was she employed as:

     Waitress   Baby sitter   <u>House cleaner</u>   _____

3) She was attacked and robbed of:

     <u>$ 15</u> $ 1,015 $ 50   _____

4) Did she have:

     2 children   <u>4 children</u>   6 children   _____

5) They had not eaten for:

     7 days   4 days   <u>2 days</u>   _____

Correct answers in story a) _____

Story b)

1) The liner that perished was:

     British   Norwegian   <u>American</u>   _____

2) Did it struck a:

     Iceberg   <u>Mine</u>   Submarine   _____

3) The accident occurred last:

     <u>Monday evening</u>   Tuesday noon   Saturday evening   _____

4) The number of passengers saved were:

     18   <u>60</u>   350   _____

5) The British ship that saved the passengers and brought into port was:

     Fishing ship   Liner   <u>Steamer</u>   _____

Correct answers in story b) _____

Total correct answers in both stories (a + b)/2 _____

128

Reading and understanding

(Note this text is originally in Icelandic and this English version is just for giving some idea of the text).

The couple Isaac and Dorothy were in their Sunday drive when their car suddenly began to make some strange noises and then stopped. The car would not start although many attempts were made. Equipped with tire iron and a pocked knife Isaac struggled with the engine in hope of finding the cause for the breakdown. When he was about to give up, Dorothy noticed that the car was out of gas. The fact that the car was out of gas, instead of out of order, did not make Isaac a bit happier, and it also did not make his mood better that this was all a great amusement for his wife.

Score for reading

0= Could not read the text at all.
1= Could read the text with some serious difficulties.
2= Could read the text with minor difficulties or it took longer time than 70 seconds.
3= Could read the text with no difficulties and within a 70 seconds.

Reading score

0   1   2   3

Questions regarding the understanding of the story

1.   Was it Isaac or Dorothy that could find out why the car stopped? (Answer: Dorothy).
2.   Why did the engine stop? (Answer: out of gas).
3.   Why do you think that Isaac was not happy although the car was only out of gas but not out of order? (Answer: he made a effortless attempt to repair the car when he was all the time out of gas; he should had known better to look at the gas meter first; and Dorothy laughed at him for trying to repair the car when it was only out of gas).

Understanding score

0   1   2   3