THE RELATIONSHIP OF NEUROPSYCHOLOGICAL FUNCTIONING WITH DEMOGRAPHIC CHARACTERISTICS, BRAIN IMAGING FINDINGS, AND HEALTH IN ELDERLY INDIVIDUALS

Raija Ylikoski

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Departments of Psychology and Neurology
University of Helsinki
Helsinki, Finland

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Supervisors

Hely Kalska, Ph.D.
Department of Psychology
University of Helsinki, Finland

Docent Timo Erkinjuntti, M.D.
Department of Clinical Neurosciences
University of Helsinki, Finland

Reviewers

Docent Matti Laine, Ph.D.
Department of Psychology
University of Turku, Finland

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

Opponent

Docent Eeva-Liisa Helkala, Ph.D.
Department of Public Health and
General Practice
University of Kuopio, Finland

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ABSTRACT

Identification of cognitive manifestations of neurological diseases in aged patients depends on our understanding of cognitive changes and their relationship with possible silent brain lesions, characteristic of normal elderly. The aim of present studies was to provide information on demographic factors, brain-behavior relationships, and health-related aspects in neurologically healthy elderly individuals in order to provide background information for clinical diagnostic decision making.

For the neurological investigation a random sample of persons living at home were invited. From the sample of 338 individuals, aged 55 to 85 years, 120 subjects underwent both magnetic resonance imaging of the brain and neuropsychological testing. A group of 37 individuals were invited to a five-year follow-up study.

Significant age-related decline was found in tests that measured speed of performance together with constructional, attentional or psychomotor functions, and visual memory. Most of the neuropsychological test performances were associated with education, especially verbal intellectual functions. Test performances of older subjects were heterogeneous. Besides a group performing on average level, we found a cognitively well-performing group and a group with cognitive impairment. In the follow-up study, memory decline was not related to mild hippocampal atrophy. Instead, white matter hyperintensities of the brain were associated with attention and speed of performance. White matter changes related to hypertension correlated with attention and flexibility. Subjects with white matter changes and cardiac failure were impaired in visual functions, attention and flexibility.

The determination of cognitive impairment relies on norms corrected for age and education. However, the results of well educated, and high performing subjects was comparable with performance of younger people. One should study further whether hippocampal atrophy is related to normal age-related memory decline. White matter changes, possibly related to hypertension and cardiac diseases, should be taken into account when differentiating acute cognitive impairment.

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications which are referred to in the text by their Roman numerals **I - V**:

I. Ylikoski R, Ylikoski A, Erkinjuntti T, Sulkava R, Keskivaara P, Raininko R, Tilvis R. Differences in neuropsychological functioning associated with education, neurological status, and magnetic resonance imaging findings in neurologically healthy elderly individuals. Appl Neuropsychol 1998;5:1-14.

II. Ylikoski R, Ylikoski A, Keskivaara P, Tilvis R, Sulkava R, Erkinjuntti T. Heterogeneity of cognitive profiles in aging: successful aging, normal aging, and individuals at risk for cognitive decline. Eur J Neurol 1999;6:645-652.

III. Ylikoski R, Salonen O, Mäntylä R, Ylikoski A, Keskivaara P, Leskelä M, Erkinjuntti T. Hippocampal and temporal lobe atrophy and age-related decline in memory. Acta Neurol Scand 2000;101:273-278.

IV. Ylikoski R, Ylikoski A, Erkinjuntti T, Sulkava R, Raininko R, Tilvis R. White matter changes in healthy elderly persons correlate with attention and speed of mental processing. Arch Neurol 1993;50:818-824.

V. Ylikoski R, Ylikoski A, Raininko R, Keskivaara P, Sulkava R, Tilvis R, Erkinjuntti T. Cardiovascular diseases, health status, brain imaging findings and neuropsychological functioning in neurologically healthy elderly individuals. Arch Geront Geriatr, in press.

ABBREVIATIONS

AACD	Aging-Associated Cognitive Decline
AAMI	Age-Associated Memory Impairment
AD	Alzheimer's Disease
ANCOVA	Analysis of Covariance
APOE	apolipoprotein E
BMDP	Bio-Medical Data Processing
CA	Central Atrophy
CDR	Clinical Dementia Rating
CF	Cardiac Failure
CHD	Coronary Heart Disease
CNS	Central Nervous System
CT	Computed Tomography
DF	Degrees of Freedom
DSM III R	Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised
D-TEST	Dementia Test Battery
EEG	Electroencephalogram
FAQ	Functional Activities Questionnaire
FULD OMT	FULD Object-Memory Test
GRADE S	Grade School
HA	Hippocampal Atrophy
HYP	Hypertension
KM	K-means clustering (BMDP-KM)
M	Mean
MBLOCK	Modified Block Design
MCI	Mild Cognitive Impairment
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
PET	Position Emission Tomography
SD	Standard Deviation
SE	Standard Error
TIME1	Time 1 measurement, first measurement point
TIME2	Time 2 measurement, second measurement point

WMHI	White Matter Hyperintensities
WAIS-R	Wechsler Adult Intelligent Scale -Revised
WMS	Wechsler Memory Scale
WMS-R	Wechsler Memory Scale -Revised
UPDRS	Unified Parkinson's Disease Rating Scale

1. INTRODUCTION

Declining cognitive functions threaten the well-being, independence, and longevity of elderly persons. Considerable scientific effort has been extended in attempts to understand age-related cognitive decline, its neural basis, and factors which may modify or delay it. At present there is no general agreement about which aspects of decline in cognitive abilities are due to ”normal” aging and which are due to ”pathological” processes. The central aim of most neuropsychological assessments of older persons is determining the presence or absence of cognitive impairment. In making this determination, the neuropsychologist typically relies heavily on normative data to make inferences about cognitive impairment. However, the growing heterogeneity with respect to many cognitive characteristics among older people complicates the interpretation of test results. One can find persons with minimal change in cognitive functions when compared to their younger counterparts. On the other hand, some cognitive decline will frequently occur prior to the onset of clinically manifest dementia.

There are many aspects of medical, biological and social-demographic domains that can be associated with, or even cause, declining cognitive functions in the elderly. Selective declines in cognition may be associated with structural alterations in the brain. The anatomic changes in the brain in healthy elderly subjects are minor, but increase with age. Clinically and neuropsychologically relevant aspects are the decreased volume in temporal regions and hippocampus, as well as white matter changes. These alterations are typical in many pathological processes, but are also frequently seen in neurologically healthy elderly individuals. Diseases occurring in elderly subjects may modify cognitive functions as well. The role of cardiovascular diseases and risk factors for cerebrovascular diseases are essential for their possible connection to brain pathology.

This study was designed to provide knowledge of variability in cognitive functions, as well as knowledge of basic factors that contribute to age-related cognitive decline, such as demographic factors, specific structural brain changes, and health-related aspects. The study sample constituted of non-neurologic and non-psychiatric elderly subjects living independently at home, screened for possible preclinical dementia cases. The general aim of the study was to give background knowledge of cognitive aging for clinical differentiation and diagnostic decision making.

2. REVIEW OF THE LITERATURE

2.1. Nature of cognitive functioning in the elderly

Age-related decline in intellectual abilities has been extensively documented throughout the adult life span by both longitudinal and cross-sectional studies. Longitudinal studies of aging have shown decline in measures of memory (Arenberg 1990; Mitrushina & Satz 1991; Taylor et al. 1992; Giambra et al. 1995; Zelinski & Burnight 1997), intelligence (Siegler 1983; Schwartzman et al. 1987; Giambra et al. 1995), verbal fluency (Schaie 1983; McCrae et al. 1987), spatial ability (Schwartzman et al. 1987), and speed of behavior (Siegler 1983; Schaie & Willis 1993; Fozard et al. 1994). Average decline in cognitive competence may begin in the mid-fifties, but it is typically of small magnitude until the seventies are reached (Schaie 1990; Schaie 1994; Giambra et al. 1995).

Cross-sectional studies have reported impairment in tests that are related to speed of performance together with constructional (Heaton et al. 1986; Ardila & Roselli 1989; Howieson et al. 1993), attentional (Bornstein et al. 1985; Heaton et al. 1986; Ardila & Roselli 1989; Elias et al. 1993a; Mazaux et al. 1995), or psychomotor components (Bornstein et al. 1985; Heaton et al. 1986; Ardila & Roselli 1989; Elias et al. 1993a). These cognitive functions have been documented to be most sensitive to changes associated with aging (Van Gorp et al. 1990). Numerous studies have also confirmed pronounced age-related decline in visual memory (Benton et al.1981; Haaland et al. 1983; Farmer et al. 1987; Ardila & Roselli 1989; Crook et al. 1992; Howieson et al. 1993; Janowsky & Thomas-Thrapp 1993). The results concerning age-differences in verbal memory in cross-sectional designs have been controversial. Some studies show differences between age groups in learning (Petersen et al. 1992) and in logical memory (Albert et al. 1987; Farmer et al. 1987; Ardila & Roselli 1989). However, after controlling for the effect of education (Farmer et al. 1987; Crook et al. 1992) or studying the results of the well-educated, healthy elderly (Benton et al. 1981), the differences in verbal memory between age groups may remain slight. Although learning may be impaired, the retention percentage of previously learned material has remained relatively stable (Petersen et al. 1992). The verbal intellectual functions have been reported to be maintained with age (Heaton et al. 1986). Similarly basic language skills have not shown age effects (Heaton et al. 1986). Some changes may occur in verbal tests that require flexibility (like fluency tests) or naming (Ardila & Roselli 1989, Howieson et al. 1993).

The mechanisms of the differential decline of cognitive functions remain an open question. The distinction between speeded visuospatial abilities and verbal intellectual functions resembles the classic aging pattern (Horn 1982; Cattel 1947). On the other

hand, the impact of age on tests that measure speed of performance together with attentional components support the theory of the age-related diminishing of the information-processing capacity (Salthouse 1991). There may be other mechanisms as well, such as efficient allocation of attention, working memory capacity and the ability to cope rapidly with novel situations (Rabbit 1993). Together with processing speed, executive functions related to frontal brain structures may also play a role, in decreasing cognitive functions related to the aging process (West 1996; Schretlen et al. 2000). Research in the neuropsychology of aging is concerned with changes in behavior with age that are related to corresponding changes in the nervous system (Moscovitch & Winocur 1992).

2.1.1. Norms for the clinical neuropsychological tests, and the effect of demographic characteristics

Neuropsychological information on cognitive functions in the elderly is crucial for both theoretical and practical reasons. The knowledge of underlying neuropsychological mechanisms helps to elucidate brain-behavior mechanisms in the aging process. On the other hand, information about test performance of healthy elderly subjects is needed in differential diagnosis. A common problem in clinical neuropsychological assessment is to determine whether a given set of test results is within normal limits, or whether it suggests brain pathology. The problem of discriminating between a normal aging course and pathology becomes increasingly difficult with age (Johansson 1991).

Knowledge of the influence of confounding variables such as gender and education, as well as the provision of an adequate range of norms is still needed (Erickson & Eimon 1992; Loewenstein et al. 1994; Tuokko & Woodward 1996). Together with age, education effects have been found in numerous tests (Bornstein 1985; Heaton et al. 1986; Farmer et al. 1987; Ardila & Roselli 1989; Nielsen et al. 1989; Crook et al. 1990; Ganguli et al. 1991; Mortensen & Gade 1993). Especially tests of verbal skills and past accumulated knowledge have been shown to be education-related (Benton et al. 1981; Heaton et al. 1986; Farmer et al. 1987; Howieson et al. 1993). Research comparing males and females in ability tests has found no difference in general intelligence, although sex differences have appeared in a few specific areas of ability. Men have tended to be better in tests that involve manipulating spatial relationships, quantitative skills, and physical strength (Heaton et al. 1986), whereas women have shown better results in tests of verbal abilities, like fluency or verbal memory tests (Heaton et al. 1986; Mortensen & Gade 1993).

2.1.2. Heterogeneity of cognitive functioning

Identification of the cognitive manifestations of neurological diseases in the aged patients, as well as their interpretation, depends on our understanding of the cognitive changes characteristic of normal elderly. It appears that the elderly population is far from being homogeneous with respect to cognitive decline. There is considerable individual variability (Ivnik et al. 1995) and interindividual variability in performance tends to increase with advancing age (Benton & Sivan 1984; Christensen et al. 1994a; Morse 1993). Subgroups of "successful aging" and "usual aging" have been introduced to explain the heterogeneity of the elderly population (Rowe & Kahn 1987). The reasons for the decline in some individuals are not known. One explanation is that studies include individuals who develop pathological disorders, or that such decline is part of the normal aging process (Storandt 1990). It is well established that subtle cognitive impairment can be present for several years before the clinical diagnosis of probable Alzheimer's disease (Masur et al. 1990; Flicker et al. 1991; Jacobs et al. 1995; Linn et al. 1995). It has been found that studies of normal aging include individuals affected by early and preclinical dementia that is, pathologic aging (Dal Forno & Kawas 1995; Lipton et al. 1996; Sliwinsky et al. 1996). Contamination of elderly "normative" samples by preclinical dementia causes underestimation of the true level of cognitive function and overestimation of the effect of age on cognition. Other diseases occuring frequently in elderly subjects may modify cognitive functions as well. Cardiovascular diseases could be one of the most important entities (Hertzog 1978; Schultz et al. 1989; Tranel et al. 1997) because they coincide with cerebral lesions (Schmidt et al. 1995).

In order to identify subjects at risk for dementing diseases, the National Institute of Mental Health work group proposed the concept of Age-Associated Memory Impairment (AAMI) as a diagnostic entity (Crook et al. 1986). However, AAMI has been found to constitute a highly heterogeneous group, where many individuals remain stable in cognitive functioning and a small subgroup may deteriorate (Koivisto et al. 1995; Hänninen et al. 1995; Ritchie et al. 1996). Aging-Associated Cognitive Decline (AACD) (Levy 1994) was proposed to define and diagnose possible preclinical dementia more closely. A diagnosis of AACD is based on a more comprehensive evaluation of cognition than that of AAMI, and could define a more homogeneous group of individuals (Hänninen et al. 1996). Recently, a third definition concentrating on memory functions has emerged: the Mild Cognitive Impairment (MCI). Subjects with MCI have been found to be at an increased risk of developing dementia (Petersen et al. 1995; Smith et al. 1996). Currently the concept is moving to Alzheimer type MCI, a border between non-symptomatic and mildly demented patients with AD pathology; i.e. towards earliest clinical AD (Petersen et al. 1999).

2.2. The relationship of age-related cognitive decline with MRI findings

Parallel changes in the brain structure and cognitive functions could indicate that at least part of the age-related cognitive changes are the result of anatomical, neurochemical and functional alterations in the brain. The anatomic changes in the brain in healthy elderly subjects are mild but increase with age. Both weight and volume of the brain decrease as age increases (Wisniewski & Terry 1976; Creasey & Rapoport 1985). Ventricles and cortical sulci increase in size, reflecting both peripheral and central atrophy (De Leon et al. 1984; Jernigan et al. 1991; Matsubayashi et al. 1992; Salonen et al. 1997). These changes may occur in up to 80 % of healthy elderly individuals (Laffey et al. 1984). In volumetric studies age-related decrease in brain volumes has been found especially in frontal, temporoparietal and parieto-occipital areas and in the ventricular area (Coffey et al. 1999). Temporal and hippocampal atrophy has been found in one-third of healthy elderly subjects (Colomb et al 1993, DeLeon et al. 1997; Kaye et al 1997) .

White matter changes of the brain are shown as hyperintensity on MRI (WMHI, white matter hyperintensity). The presence of white matter changes varies from 27 % to 95.6 % in different studies (Fazekas 1989; Breteler et al. 1994a; Lindgren et al. 1994; Longstreth et al. 1996). Silent infarcts can be found from 10 % (Mirsen et al. 1991) to 33 % of elderly subjects (Longstreth et al. 1996; Matsubayashi et al. 1992). The frequency of white matter changes increases with age, and is more frequent in demented patients (Fazekas et al. 1987; Mirsen et al. 1991, Almqvist et al. 1992; Skoog et al. 1994; Barber et al. 1999). The etiology of WMHI remains uncertain. However, the evidence from studies on cerebrovascular diseases indicates that evolving changes are related to vascular risk factors and presence of cerebrovascular disease (Awad 1986; Lechner et al. 1988; Breteler et al. 1994a; Longstreth et al. 1996; Fukuda et al. 1995; Pantoni et al. 1999). For example, midlife high arterial blood pressure has been significantly associated with later-life WMHI (DeCarli et al 1999). In the healthy elderly, the lesions have been related to reduced cerebral blood flow (De Reuk et al. 1992), and especially reduced frontal lobe metabolism (DeCarli et al. 1995).

2.2.1. Memory performance and temporal lobe regions

The role of medial temporal structures affecting memory functions has been well established with various diagnostic entities causing amnesia (Sass et al. 1990; Squire et al. 1990; Bigler et al. 1996; Gleizner et al. 1998). Deteriorating memory (Petersen et al. 1994; Tierney et al. 1996; Mori et al. 1997) and increasing hippocampal atrophy (Deweer et al. 1995; Laakso et al. 1995; DeLeon et al. 1997; Jack et al. 1997;

Juottonen et al. 1999) are also frequently found in Alzheimer's disease. Both hippocampal volumetric measures and delayed recall of visual memory have shown high diagnostic accuracy in differentiating Alzheimer patients from control subjects (Laakso et al. 2000). Among older patients with Mild Cognitive Impairment (MCI), hippocampal atrophy has predicted subsequent conversion to AD (Jack et al. 1999). In addition, reduced hippocampal asymmetry between right and left hippocampus has been observed in subjects with Age-Associated Memory Impairment (AAMI) (Soininen et al. 1994). Whether changes in temporal lobe structures contribute to memory performance in healthy subjects is still a matter of controversy. Some studies have found a positive correlation between delayed recall and hippocampal atrophy or volume (Colomb et al. 1993, De Leon et al.1997) or that hippocampal size predicts the performance in paragraph recall (Colomb et al. 1996), while other studies have found no statistically significant association (Sullivan et al. 1995; Raz et al. 1998). Longitudinal studies relating hippocampal atrophy to declining memory have been few (Colomb et al. 1996). So far there has been no studies where possible pre-clinical dementia cases were excluded.

2.2.2. White matter changes and cognitive functioning

Neurological diseases causing demyelination of white matter, like multiple sclerosis, have been characterized neuropsychologically by slowing of cognitive processes (Rao et al. 1989a; Kujala et al. 1995; Kail 1998). Patients with extensive periventricular demyelination have shown a neuropsychological syndrome that resembles subcortical dementia (Anzola et al. 1990). Similarly, WMHI is typically seen in patients with subcortical vascular dementia (Kinkel et al. 1985; Roman et al. 1987; Filley et al. 1999; Rossi et al. 1999; Erkinjuntti & Pantoni in press). The neuropsychological key features of the patients include memory impairment and slowing of mental processes (Cummings & Benson 1984). WMHI has been shown to be an independent risk factor in the development of vascular dementia (Pohjasvaara et al. in press). WMHI may also contribute to cognitive decline in patients with AD (Steingart et al. 1987, Diaz et al. 1991; DeCarli et al. 1996), but to demonstrate a correlation once the dementia is fully developed is difficult.

The clinical significance of WMHI in healthy elderly remains incompletely understood. However, it has been systematically shown to be part of the aging process (Lindgren et al. 1994). Hyperintensities found in neurologically healthy individuals are usually of minor magnitude, but may specifically influence cognitive functions that are mediated by subcortical and frontal circuits (Bowler & Hachinski 1997). Especially tests that measure flexibility, attention and speed of performance have been related to WMHI (Breteler et al. 1994b; DeCarli et al. 1995). In addition, visuoconstructional

functions and picture memory have correlated with WMHI (Skoog et al. 1996). However, some studies have not found an association between white matter changes and cognitive functions in small samples (Rao et al. 1989b, Hunt et al. 1989). WMHI may cover different concepts. Benign lesions do not necessarily affect cognitive functioning unless they are strategically situated (Tatemichi et al. 1995). Both in healthy aging (Boone et al. 1992) and dementing disorders (Fukuda et al. 1990) frontal WMHI may contribute to cognitive impairment. Boone et al. (1992) have suggested that a threshold of WMHI area must be present before cognitive deficits can be observed.

2.3. Do health-related aspects influence cognitive functioning in elderly subjects?

There are many aspects of medical, biological and social-demographic domains that can be associated with, or even causal to, declining cognitive functions in the elderly. One of the most frequently studied aspects has been general health status (Benton & Sivan 1984; Perlmutter & Nyquist 1990; Christensen et al. 1994b; Earles and Salthouse 1995; Emery et al. 1995). Although it is assumed that poor health contributes to accelerated decline in intellectual functioning (Benton & Sivan 1984), the results are still contradictory. For example self-rated health status does not explain cognitive decline in some studies (Christensen et al. 1994b; Earles & Salthouse 1995). However, other studies show a significant relationship between health status and cognitive decline (Perlmutter and Nyquist 1990; Emery et al. 1995).

Cardiovascular diseases are essential for their possible connection to brain pathology (Shimada et al. 1990). The type and mechanisms of cognitive difficulties in neurologically healthy subjects with cardiovascular diseases is less studied, although up to 40 % of cardiac patients have exhibited clear difficulties in cognitive functions and 30 % of such patients have evidenced mild cognitive difficulties (Barclay et al. 1988). Cardiovascular diseases or risk factors have been related to poorer memory and attentional performance (Farina et al. 1997; Vingerhoets et al. 1997), to lower abstraction and visuospatial skills (Desmond et al. 1993), or to lower cognitive status (Kilander et al. 1998). Likewise, patients with peripheral vascular disease have demonstrated cognitive deficits (Phillips & Mate-Kole 1997). Little is known about the morphological basis of the cognitive difficulties in neurologically healthy cardiac patients. Schmidt et al. (1991) found that in middle-aged patients with cardiomyopathy, cognitive test performance was significantly worse in patients with ventricular enlargement and cortical atrophy.

3. AIMS OF THE STUDY

The general objective of the present study was to provide information on relevant demographic factors, brain-behavior relationships and health-related aspects in neurologically healthy elderly individuals, in order to provide background information for clinical diagnostic decision making.

The specific aims of the study were as follows:

1. To evaluate the effects of age, education, and gender on neuropsychological test performance in neurologically healthy elderly people who have been screened for possible preclinical dementia and given a detailed neurological description (Study I).
2. To analyze the variability of cognitive functions in the study sample and to investigate whether subgroups with superior or impaired cognitive profiles could be found (Study II).
3. To test the hypothesis whether age-related memory decline is related to hippocampal and temporal lobe atrophy in a follow-up study design (Study III).
4. To study the relationship between white matter changes detected by MRI and cognitive functions (Study IV).
5. To evaluate the association of health-related factors, particularly cardiovascular diseases, with cognitive functioning (Study V) .

4. SUBJECTS AND METHODS

4.1. Subjects

The Helsinki Aging study began in 1989 in order to examine sex-balanced, random cohorts of persons aged 75, 80, and 85 years living in the city of Helsinki (300 in each cohort). For the Aging Brain Study a random sample of persons living at home were invited. These new cohorts included 52, 63 and 50 persons, respectively. The study was extended for younger age groups adding random samples from similar cohorts aged 55, 60, 65, and 70 years. These younger cohorts included 40, 43, 37, and 53 subjects respectively. From this sample of 338 individuals 50 refused to participate, 13 died and seven moved away. A neurologist clinically examined all the 268 subjects (Ylikoski et al 1995). Of these 37 (13.8%) suffered from conditions affecting the central nervous system or had psychiatric disorders: 12 had had strokes, 8 mild dementia (DSM III-R), 3 Parkinson's disease, 4 epilepsy, 3 severe head trauma, 3 CNS infection, 2 operated on brain tumour, and 2 had psychiatric disorders. Out of the neurologically intact subjects 120 consecutive cases underwent both magnetic resonance imaging (MRI) of the brain and a complete neuropsychological investigation. The number of subjects studied in the age groups of 55, 60, 65, 70, 75, 80, 85 years, were 20 (10 males), 18 (11 males), 19 (8 males), 18 (7 males), 17 (7 males), 17 (6 males) and 11 (5 males), respectively. In the normative study (Study I) and in the study relating health factors to cognitive functioning (Study V), the possible preclinical dementia cases were excluded. According to neurological investigation (CDR 0.5) and memory-test performance (Logical Memory or Visual Reproduction performance 1.5 SD below mean according to age-specific norms), or the presence of apolipoprotein E allele E4 and difficulties in memory tests (Logical Memory or Visual Reproduction performance less than 1.5 SD compared to age specific norms). The exclusion was not based on single criteria; instead both decline in memory tests and presence of apolipoprotein E allele E4 were required. Seven cases were suspected to have early AD or dementia. All subjects participating in the study gave their informed consent. The Ethics Committee of the Helsinki University Central Hospital approved of the study.

Table 1. Characteristics of the Helsinki Aging Brain Study Cohorts

Subjects	Age Group, years 55	60	65	70	75	80	85	Total
Eligible random cohort	--	--	--	--	274	266	255	
Invited unselected sample	40	43	37	53	52	63	50	338
Refused	--	2	--	21	7	12	8	50
Died	--	--	--	--	--	7	6	13
Moved	--	--	--	--	2	4	1	7
Examined neurologically	40	41	37	32	43	40	35	268
Disease affecting CNS	4	5	2	5	6	6	9	37
Neuropsychological examination	20	18	19	18	17	17	11	120

The five-year follow-up study (Study III) included age cohorts of 55, 60, 65 and 70 years of age. 75 consecutive cases of the neurologically intact subjects underwent a complete neuropsychological investigation from March 1990 to April 1991. During the follow-up, 10 subjects had died or moved away, two individuals could not be reached, and 3 refused to participate. Among the remaining 60 individuals, 10 subjects had developed neurological or psychiatric diseases. The 5-year follow-up MRI and neuropsychological evaluation was administered to 37 subjects during the period of April 1995 to May 1996. The possibility of preclinical dementia was evaluated according to memory test scores (test scores 1.5 standard deviations (SD) below mean according to age and education adjusted norms) and subjective memory complaint at the first measurement. Mild cognitive impairment (MCI) (Petersen et al.1995) was found in five subjects, and two of them showed deterioration in follow-up memory tests (the average decline being more than 1.5 SD below the mean). These two subjects, being at risk for pathological memory decline, were excluded from the sample. The remaining sample size was 35 individuals.

4.2. Methods

4.2.1. Clinical and Neurological examination

Clinical and neurological evaluation included detailed medical history using all available files and an interview of a close informant when available, structured medical and neurological examination, screening laboratory tests, electrocardiogram, Mini-Mental State Examination (MMSE) (Folstein & Folstein 1975), and the Clinical

Dementia Rating (CDR) (Hughes et al. 1982). Cortical disinhibition signs were examined in each subject according to the standardized techniques described by Tweedy et al. (1982). These included evaluation of resistance to habituation of the glabellar reflex, paratonia, and six reflexes: grasp, palmomental, snout, suck, root, and jaw jerk. The summary scores of primitive reflexes were used in the analysis. Extrapyramidal signs were assessed using a section of the Unified Parkinson's Disease Rating Scale (UPDRS) (motor examination) (Stern 1978). Item scores range from 0 to 4, with the total score ranging from 0 to 56. Higher scores indicate more severe impairments.

Data were gathered about major diseases by referring to clinical diagnosis. Medical history was obtained regarding arterial hypertension and any cardiac disorder including coronary heart disease, myocardial infarction, cardiac failure, and cardiac arrhythmias. The criteria for these conditions included a previously documented diagnosis, a permanent medication, systolic blood pressure > 160 or diastolic blood pressure > 95, and atrial fibrillation on an electrocardiogram. Diabetes was defined by a previously documented diagnosis, current use of insulin or oral hypoglycemic medication, fB-gluc > 6 or 7 mmol/L. None of the subjects had undergone coronary bypass surgery or had suffered from cardiac arrest. Other systemic diseases, based on previous clinical diagnosis according to medical files, included asthma, chronic bronchitis, emphysema, locomotor system disease, cancer, or others. A summary score of presence of any cardiovascular diseases and presence of any systemic diseases was obtained. Clinicians rated subjects' health status according to all information available as healthy, quite good, or poor; in statistical analyses a dichotomous score of healthy or not healthy was used.

Daily living activities were obtained from a close informant by the Functional Activities Questionnaire (FAQ) (Pfeffer et al. 1982). All participants were asked whether their memory had deteriorated during the past six months, and similarly a close informant was asked whether the subject's memory was impaired. Subjects were also asked about their activities, such as organizational activities, cultural activities, studying, sports, travelling and hobbies requiring special skills like handicrafts. Activities were scored as one or more activities in a week and no activities. Depression was evaluated by the Zung self-rating scale (Zung 1962).

4.2.2. Magnetic resonance imaging (MRI)

In the first phase of the research project all the participants included in the neuropsychological study were examined by a low field MRI. It was performed with an ultralow field imager operating at 0.02T (Acutscan, Instrumentarium Corp., Helsinki, Finland). Axial T2-weighted images (repetition time 2000 milliseconds, time

to echo 150 milliseconds) were obtained without gaps between the 10 mm thick sections. The field of view was 30 cm, and the matrix 128x256. The images were analyzed by an experienced radiologist blinded to the clinical and neuropsychological findings. Peripheral (widening of cortical sulci and cisterns) and central (widening of ventricles) atrophy were visually rated as none, mild, moderate or severe. In the statistical analyses the scores were reduced to dichotomic variables indicating the presence or absence of atrophy (Study I and V). White matter hyperintensities (WMHI) were rated as periventricular hyperintensities around frontal horns, ventricular body, trigones, and occipital horns, and hyperintensities in the centrum semiovale including the watershed areas (see Study IV). The total scores reflecting WMHI were calculated by summing up all the scores in different areas. In studies I, IV and V we also used a dichotomic score of presence (any white matter change in any of the areas measured) or absence (no changes in any of the areas measured) of white matter changes.

In the follow-up study (Study III) MRI was performed with a superconducting MRI system operating at 1.0 T (Siemens Magnetom) at follow-up (TIME2) measurement. Transaxial T2-, (proton density) PD- and T1-weighted images were obtained using the SE-technique. For the assessment of temporal atrophy, a three dimensional gradient echo sequence (TR, 30 ms; TE 5 ms, alpha 40; NEX, 1) with 64 3-mm-thick coronal sections was used. Peripheral (widening of cortical sulci and cisterns), temporal (neural loss in temporal neocortex, entorhinal cortex and hippocampus) and central (widening of ventricles) atrophy were visually rated from T1-weighted images and scored as none, mild, moderate or severe. For the rating of temporal atrophy, a coronal slice passing through the dorsal part of the third ventricle and anterior part of the pons was chosen to represent both neocortical, entorhinal and hippocampal parts. The neocortex included gyrus temporalis superior, medialis and inferior. The entorhinal cortex was composed of gyrus parahippocampalis. The hippocampus included the gyrus dentatus and the cornis Ammonis separated by the hippocampal sulcus. White matter lesions were obtained from the proton density images (Mäntylä et al. 1997). The reliability of the visual rating has been tested in another study sample using the same rating systems. The weighted Kappa values for inter-observer agreement ranged from 0.72 to 0.84 for white matter ratings (Mäntylä et al. 1997). The inter-observer reliability was from 0.71 to 0.74 for neocortical, from 0.63 to 0.69 for entorhinal, and from 0.61 to 0.62 for hippocampal atrophy (weighted Kappa scores).

4.2.3. Neuropsychological examination

Due to the nature of cognitive functions in the elderly individuals and the various differential diagnostic problems, a clinical neuropsychological test battery should assess both specific and general cognitive abilities, like attention, language, memory, visuospatial ability, and conceptualization (Albert 1984, Naugle et al. 1990, Reitan & Wolfson 1986). The tests used should meet the requirements of measuring both very able and very frail individuals along the same continuum of performance (Rabbit 1993).

Memory: Learning was examined by the Fuld Object-Memory Test (OMT) (Fuld 1982). Verbal memory was assessed by the Logical Memory story A (of the non-standardized Finnish version) the Wechsler Memory Scale-revised, WMS-R. Visual memory was measured by the Visual Reproduction of the WMS-R (Wechsler 1987). Delayed recall (after 15 to 20 minutes) was administered, and retention percentages of Logical Memory and Visual Reproduction were calculated. The Digit Span forward and backward were performed according to the Wechsler Memory Scale, WMS (Wechsler 1945). Interference effects (both heterogeneous and homogeneous) and ability to use Logical Retrieval with visual aid were derived from the D-test (Christensen 1975; Erkinjuntti et al. 1986).

Verbal intellectual functions: General knowledge and conceptualization were evaluated by the Information and Similarities subtests of Wechsler Adult Intelligence Scale-revised, WAIS-R (Wechsler 1981).

Constructional functions: visuoconstructional functions and visuospatial reasoning were assessed by the Block Design of the WAIS-R (Wechsler 1981). Together with the original scoring system, the performances were evaluated in each item without strict time limit (for each item 10 minutes was allowed) with a score ranging from 0 to 4 (4 = all cubes are correct, 3 = one of the cubes is wrong; 2 = at least half of the cubes are correct; 1 = less than half of the cubes are correct, but the form is square; 0 = none of the cubes is correct and also the form is wrong, or the item was not attempted because of a failure in previous items). The score of the modified Block Design (Mblock) was the summary score of all the items.

Language: Comprehension of language was assessed by a shortened version of the Token test (de Renzi et al. 1978). Parts four and six were performed and the total amount of correct responses were calculated. Confrontation naming was assessed by the non-standardized Finnish version of the Boston Naming test (last 30 items), (Borod et al. 1980; Laine et al. 1993). Verbal fluency was evaluated both by semantic category (animal naming in one minute) and letter generation (naming words beginning with the letter "s" in half a minute) (Fuld 1982).

Speed and attention, speed of mental processing: In Trail Making A (Reitan 1958, Reitan 1986) the time to complete the test was scored; no corrections were made for wrong answers. Mental speed and capacity of shifting mental set were evaluated by the modified Stroop test (Perret 1974). It was done in two sets: with colored dots and colored color-names. Both time and the number of correct responses were scored. No corrections were made for incorrect answers. In addition, speed of mental processing was assessed by subtracting the time spent on reading colored dots from the time spent on reading conflicting color-names (Stroop, difference/time).

Simple psychomotor speed was assessed by the Finger Tapping test.

Visuoperceptual functions: Visuospatial analysis was measured by the Clock test, both recognition of time and setting the time were studied. In Copying Designs both one-dimensional (flag) and two-dimensional (cube and cross) figures were used (Christensen 1975, Erkinjuntti et al. 1986).

Calculation: Automatic calculations, complex arithmetical calculation and verbal arithmetical problems (discursive ability) were assessed according to Christensen's version of the Luria's Neuropsychological Investigation (Christensen 1975, Erkinjuntti et al. 1986).

For clustering techniques (Study II) eleven measures of cognitive functioning were chosen. The Logical Memory and the Visual Reproduction of the WMS-R represented the memory tests, both immediate recall and retention percentages were used. The other tests were the Similarities and the Block Design subtests of the WAIS-R, the Boston Naming test, Verbal fluency by semantic category, the Trail Making A test, the interference effect of the Stroop test, and the Finger Tapping test.

For the diagnosis of AACD, and MCI as well as for the validation of the cluster analysis, several other neuropsychological tests were used. The tests were the Fuld OMT, delayed recall (raw scores) from Logical Memory and Visual Reproduction of the WMS-R, the Information subtest of WAIS-R, the Token test, letter fluency, the Stroop test (the time spent on reading dots and color-names), the Clock test, Copying Designs, and Calculation.

In Study V, the tests were grouped according to clinically and theoretically relevant domains. The summary scores were calculated from the standardized z-scores as follows. *Verbal Memory* consisted of immediate and delayed recall of the Fuld OMT, the Logical Memory, story A, of the WMS-R, Digit Span forward and backward, Interference tasks and Logical Retrieval from the D-test. *Visual Memory* was measured by the Visual Reproduction of the WMS-R, including both immediate and delayed recall. *Intellectual and Verbal Functions* included Information and Similarities subtests of WAIS-R, the Token test, and the Boston Naming test. *Visuoconstructional and Spatial Functions* were assessed by the Block Design of the WAIS-R, the modified Block Design (Mblock) score, the Clock test, and Copying Designs. *Mental*

Flexibility consisted of number of correct responses on the Stroop test part B. The interference effect was also measured by dividing the time spent on reading colored dots by the time spent on reading conflicting color names, a ratio score was used in order to minimize the effect of age-related slowing (Graf et al. 1995). Flexibility and the ability to organize thinking were also evaluated by Verbal fluency. *Speed and Attention* included Trail Making A, and the speed of reading part A and B on the Stroop test.

4.2.4. Criteria for Aging-Associated Cognitive Decline (AACD), and Mild Cognitive Impairment (MCI) (Study II)

Subjects were regarded as having AACD if they reported subjective memory or cognitive decline and scored one standard deviation below age and education-adjusted test results of this sample on at least in one neuropsychological test (Levy, 1994). Memory was measured by the Fuld OMT, attention by the Stroop test, thinking by Calculation and the Information test (WAIS-R), language by the Token test, and visuospatial functions by the Clock test and by Copying Designs.

Diagnosis of MCI was based on the following set of criteria: memory complaint corroborated by an informant, normal general cognitive function, normal activities of daily living, memory impairment defined as more than 1.5 standard deviations below mean in Fuld OMT, delayed recall of Logical Memory (WMS-R), or delayed recall of Visual Reproduction (WMS-R) based on age- and education-matched test results of this sample (Study II) (Petersen et al. 1995; Petersen et al. 1997; Smith et al. 1996). In study III, the performance in immediate recall of Logical Memory and Visual Reproduction was also taken into account.

4.2.5. Statistical Analysis

4.2.5.1. Data screening

The neuropsychological investigation was quite extensive, and although the majority of subjects completed all the tests, some missing data still occurred. A few individuals did not perform the Visual Reproduction test (WMS-R), the Information and Block Design tests (WAIS-R), the Token test, the Boston Naming test, Finger Tapping, Copying Designs, the Clock test and Calculation. The missing data was replaced by the mean value of the corresponding age group. The normality of the variables was evaluated by frequency distributions and by computing the skewness and kurtosis of the variables. Nine of the tests (Fuld OMT, Interference task (D-test), Logical Retrieval (D-test), modified Block Design, the Trail Making test, the Stroop test, the Clock test,

Copying Designs, and Calculation) had skewed frequency distributions, and they were transformed towards normality according to the rules by Tabachnick and Fidell (1989), after which skewness and kurtosis were near zero value. After transformations the possible outliers were screened by computing the Mahalanobis distance of each case to the group mean. The analysis revealed one outlier; however, the subject was not excluded from the analysis. The data were analyzed by using the BMDP (Bio-Medical Data Processing) programs (Dixon et al. 1990).

4.2.5.2. Statistical methods

The association of education, gender, health status, frequency of subjects with systemic diseases, cardiovascular diseases and MRI findings between the three age groups were evaluated by Chi-square analysis. Because of the small cell frequencies in some of the categories, delta was used and a constant (0.5) was added to compensate for small expected values (Dixon et al. 1990). Depression score was analyzed by one-way analysis of variance in three age groups (Study V).

Age-related decline in cognitive functions was analysed by one-way analysis of covariance (ANCOVA), where the effects of education and gender were controlled for (Study I). The effect of education was evaluated by ANCOVA, controlling for age and gender. Both age and education were controlled for when the effects of gender were analyzed. The transformed test scores were used in analysis; however, the results were given as raw scores in the tables.

Before undertaking the cluster analyses, scores on all tests were standardized as z scores with respect to the mean and standard deviation of the entire sample (Study II). Standardized scores were subjected to a BMDP-KM (Dixon, 1990) K-means clustering procedure, using an iterative partitioning method. Classification of cases was based on the Euclidean distance as a measure of similarity. The optimal number of clusters was determined using the procedure described by Hair et al. (1987). Several runs of analysis were made attempting classification into a different number of clusters (between two and seven). A five-cluster solution had high discriminating power and provided relevant clinical interpretability. The discriminative power between three-, four- and five-cluster solutions was analyzed in two ways, by discrimative analysis and multivariate analysis of variance. In three-cluster solution the discriminative analysis correctly classified (jacknifed classification) 91 % of subjects in cluster one, 87 % of subjects in cluster 2, and 86 % of subjects in cluster three. The results in four-cluster solution were as follows, 86 % in cluster one, 91 % in cluster two, 83 % in cluster three and 84 % in cluster four. The five-cluster solution showed the highest classification percentages: 94 % in cluster one, 96 % in cluster two, 92 % in cluster three, 88 % in cluster four, 91 % in cluster five. In multivariate analysis of variance, the relationship

between different cluster solutions and the eleven cognitive tests used in cluster analyses were compared by calculating the effect size. It measures the strength of association between the effects (main effects of grouping variable) and the set of dependent variables. In three-cluster solution the effect size was 0.85, in four cluster solution 0.92, and in five-cluster solution the effect size was 0.97.

In assessing the stability and reliability of the cluster solution, the analyses were systematically replicated 11 times, with one of the 11 variables being removed during each of the replications (see Study II). In order to validate the cluster solution, its discriminability in other neuropsychological tests were analyzed. One-way analyses of variance with cluster membership as an independent variable were performed with eleven variables which were not used in initial cluster analyses (Study II). In all eleven analyses the results proved to be statistically significant (Degrees of Freedom 4,115; F value ranging from 7 to 77; all p values being less than .001).

The characteristics of age, education, gender, health factors, activity level, AACD and MCI in five different clusters were cross-tabulated, and Chi-square was calculated. The relationship of the Depression test score and the Information test score with cluster solution was analyzed by one-way analysis of variance.

Hotelling's T test was used to evaluate the differences in cognitive functions between the longitudinal sample and those subjects who were not followed (Study III). The longitudinal changes in different memory tests were compared between the groups of subjects who did not have hippocampal atrophy (HA-) and a group that had hippocampal atrophy (HA+), with repeated measures analysis of covariance (ANCOVA), adjusting for education. The association of hippocampal atrophy with TIME2 memory test performance was examined by analysis of covariance, adjusting for education. We also analyzed whether a subgroup that had both hippocampal and temporal neocortex atrophy differed from those who did not have any atrophy.

Means of the total score of WMHIs were used as a continuous variable reflecting the white matter changes (Study IV). The relationship between WMHI and cognitive functioning was evaluated by partial correlation where the effect of age and education was controlled. Subjects with and without white matter changes were also evaluated by t-test (pairwise mean differences with Bonferroni-adjusted significance levels).

In Study V, the summary scores of different neuropsychological domains were calculated by summing up the standardized scores of individual tests. The normality of the distributions was examined, and skewed distributions were not observed among cognitive domains. The relationships between health-related variables and cognitive domains were analyzed by covariance analysis, with age and education as covariates. Partial correlation, adjusting for age and education, was used to study relationships between the depression score and cognitive variables. Subjects having coronary heart disease, arterial hypertension or cardiac failure vs. subjects having white matter

changes or central atrophy on MRI were further compared on cognitive functions with covariance analysis, employing education and age as covariates.

5. RESULTS

5.1. Characteristics of the sample and correlations of demographic variables with cognitive functioning (Study I).

In statistical analysis the age cohorts were combined in three age groups: 55 to 60 years, 65 to 70 years, and 75 to 85 years. Most of the subjects had only grade school education. Significant differences between the age groups in education and gender were not found (Study I). The frequency of primitive reflexes was low and it was not related to age. The number of extrapyramidal signs was quite low, but increased significantly with age (Study I). The frequency of white matter changes, as well as central and peripheral atrophy increased significantly with age (Study I). The number of systemic diseases increased and overall health status deteriorated with age (Study V). Coronary heart disease, cardiac failure and myocardial infarction were more common in the older age groups (Study V). Depression score increased slightly in the older cohorts, but not statistically significantly (Study V).

In covariance analysis (controlling for the effects of education and gender), age-related decline was highly significantly related to speed of performance and attention (Trail Making A, Stroop, Finger Tapping) (Table 2). Constructional functions (Block Design) declined with age in both timed and non-timed performance. Visual memory impairment was clearly related to aging. In verbal memory, learning (Fuld OMT), delayed Logical Memory and the Interference tasks were slightly declined with age (Table 2). Some language tests also showed age-related decline, especially comprehension of long sentences (the Token test). In addition, Boston Naming, Verbal fluency and Calculation showed a tendency to decline with age.

Table 2. Neuropsychological test results in 113 neurologically healthy individuals; statistical relationship with age (analysis of covariance, controlling for education and gender).

Neuropsychological test	AGE GROUPS			
	55/60 years MEAN (SD) (N=38)	65/70 years MEAN (SD) (N=37)	75/80/85years MEAN (SD) (N=38)	F
SPEED AND ATTENTION				
Trail Making A, time	53.6 (21.5)	70.7 (39.2)	92.9 (48.5)	15.1***
Stroop, dots, time	15.4 (2.9)	17.7 (3.3)	19.5 (6.7)	10.7***
Stroop, words, time	33.6 (14.8)	42.3 (18.8)	53.2 (29.1)	13.5***
Stroop,difference, time	18.2 (14.2)	24.6 (17.5)	33.6 (27.1)	12.3***
Finger tapping, right	47.5 (7.5)	43.0 (7.4)	38.4 (8.2)	12.3***
left	43.9 (7.3)	39.6 (5.4)	36.2 (8.2)	10.7***
CONSTRUCTIONAL FUNCTIONS				
WAIS-R Block Design	28.8 (9.7)	24.8 (7.8)	18.4 (8.0)	13.8***
VISUAL MEMORY				
Visual Reproduction immediate	33.3 (4.5)	28.9 (6.0)	27.2 (7.3)	9.5***
Visual Reproduction delayed	30.0 (6.0)	23.6 (8.8)	20.3 (9.3)	13.3***
VERBAL MEMORY				
FULD OMT total retrieval	44.2 (3.3)	41.9 (5.5)	40.0 (6.1)	5.8**
WMS-R Logical Memory delayed	13.6 (3.4)	13.4 (4.5)	11.8 (3.8)	3.6*
Interference (D-test)	13.1 (2.3)	12.9 (2.4)	10.9 (3.0)	8.6***
LANGUAGE				
Token Test	15.5 (1.4)	15.0 (1.6)	13.8 (1.6)	12.9***
Boston Naming Test	23.6 (3.5)	23.1 (4.6)	21.2 (3.9)	4.1*
Verbal fluency, animals (60sec)	22.1 (4.5)	21.1 (5.1)	19.3 (5.6)	3.3*
CALCULATION	28.9 (3.8)	27.7 (5.5)	26.7 (4.6)	3.5*

Analysis of covariance (F), Degrees of Freedom 2. Significance * = p<.05; ** = p<.01; *** = p<.001

The verbal intellectual tests (Information and Similarities), all language tests (Token, Boston, Fluency tests) and Calculation showed significant education effects (Table 3). Education correlated with verbal memory tests, except for learning and Interference tasks. Visual memory performance correlated slightly with education. Tests assessing speed and attention like Trail Making and Stroop timed tests were related to education, especially the task measuring speed of reading (Stroop dots, time, Table 3). Also Copying Designs performance differed significantly between the educational groups. (See appendix for more detailed results.)

Table 3. The relationship of education with neuropsychological tests (N=113). The results are based on an analysis of covariance, where effect of age and gender are adjusted.

Neuropsychological test	EDUCATION		
	Grade School	More than grade S	
	Mean (SD)	Mean (SD)	F
	N = 82	N = 31	
VERBAL INTELLECTUAL FUNCTIONS			
WAIS-RInformation	23.3 (5.2)	29.2 (4.8)	28.6***
Similarities	24.6 (4.8)	28.3 (2.8)	15.5***
LANGUAGE			
Token Test	14.5 (1.7)	15.6 (1.4)	12.7***
Boston Naming Test	21.8 (4.1)	24.9 (3.4)	13.8***
Verbal fluency, animals (60 sec)	20.3 (4.8)	22.4 (5.9)	4.2*
Verbal fluency, letter s (30 sec)	6.8 (2.6)	8.8 (3.3)	10.7***
CALCULATION	26.8 (5.0)	30.2 (3.0)	20.3***
VERBAL MEMORY			
WMS-R Logical Memory immediate	13.8 (3.4)	16.4 (3.7)	13.9***
Logical Memory delayed	12.4 (3.6)	14.7 (4.5)	9.4**
WMS Digit Span forward	5.6 (0.9)	6.4 (1.0)	16.1***
backward	4.0 (0.8)	4.5 (0.8)	7.5**
Logical Retrieval (D-test)	4.3 (0.9)	4.8 (0.6)	7.9**
VISUAL MEMORY			
WMS-R Visual Reproduction immediate	29.1 (6.5)	31.8 (6.5)	4.1*
Visual Reproduction delayed	23.6 (9.4)	27.3 (8.0)	4.2*
SPEED AND ATTENTION			
Trail Making A, time	77.6 (44.9)	59.2 (25.8)	5.8*
Stroop, dots, time	18.5 (5.1)	15.2 (3.4)	14.3***
Stroop, words, time	44.7 (20.4)	38.9 (29.0)	5.5*
VISUOPERCEPTUAL FUNCTIONS			
Copying Designs	61.3 (6.8)	64.1 (6.8)	9.4**

Analysis of covariance, (F) (significance * = p<.05; ** = p<.01; *** = p<.001). Degrees of Freedom 1.

Statistical differences according to gender were obtained in a few cognitive functions (Table 4). After controlling for education and age in covariance analysis, men scored significantly higher in Information and Block Design subtests, in Finger Tapping, and Calculation tasks. Slight differences were obtained in the Clock test, Copying Designs, and Boston Naming.

Table 4. The relationship of gender with neuropsychological test results (N=113). Analysis of covariance, where effects of age and education are adjusted. Results are mean and standard deviation.

Neuropsychological test	GENDER		
	Women	Men	F
	N = 62	N = 51	
SIMPLE PSYCHOMOTOR SPEED			
Finger Tapping, right	40.5 (7.9)	46.1 (1.0)	16.9***
left	37.2 (7.3)	43.2 (6.7)	24.3***
CONSTRUCTIONAL FUNCTIONS			
WAIS-RBlock Design	21.6 (9.3)	27.1 (8.7)	12.3***
Mblock	29.3 (8.3)	33.9 (3.7)	9.4**
VISUOPERCEPTUAL FUNCTIONS			
Visuospatial/Clock test	6.9 (1.4)	7.5 (0.4)	8.5**
Copying Designs	60.7 (7.9)	63.7 (4.9)	4.9*
CALCULATION	26.6 (5.4)	29.2 (3.3)	10.1**
MEMORY			
WMS-R Logical Memory immediate	15.1 (3.4)	13.9 (3.9)	3.8
Visual Reproduction immediate	28.7 (7.2)	31.2 (5.3)	4.8*
VERBAL INTELLECTUAL FUNCTIONS			
WAIS-RInformation	23.2 (5.4)	27.0 (5.5)	18.3***
LANGUAGE			
Boston Naming Test	21.9 (4.3)	23.5 (3.7)	5.4*

Analysis of covariance, F statistics (significance * = p<.05; ** = p<.01; *** = p<.001). Degrees of Freedom 1.

5.2. Heterogeneity of cognitive profiles in elderly individuals (Study II)

The heterogeneity of subjects reflected by cluster membership was influenced by age, education, activity level, and intellectual level (measured by the Information test) (Study II), but not with health status. One subgroup was identified to be at risk for cognitive decline, as most of the subjects had diagnosis of AACD and MCI.

Subjects classified in Cluster 1 (N=34) demonstrated above average performance on all measures respective to the performance of the entire sample (Figure 1). The older subjects in this cluster took part in weekly activities, had high scores on the Information test, and more than half of them had higher education. Cluster 2 (N=23) comprised subjects who performed in the average range on most of the measures. Cluster 2 represented all age groups equally. Cluster 3 (N=26) represented subjects who performed a little below the average level. These subjects had lowest scores on

visual memory, visuoconstructional functions and tests measuring speed of performance. Fifty-eight percent of the subjects came from the oldest age group. Those younger subjects whose cognitive performance was comparable to the oldest age group (75 to 85 years) had a lower intellectual level and approximately half of them could be diagnosed as having AACD or MCI. Cluster 4 (N=26) was another cluster that represented the average level, with the exception of good language functions. It represented all age groups equally. The 8 subjects from the oldest age group took part in weekly activities and had a higher intellectual capacity. Cluster 5 (N=11) clearly represented a group of the oldest subjects who had difficulties in all of the cognitive domains tested. They also had the lowest Information scores, and the highest scores in the depression inventory. Almost all of them (82%) could be diagnosed as having AACD, and half of them (54%) were diagnosed as having MCI.

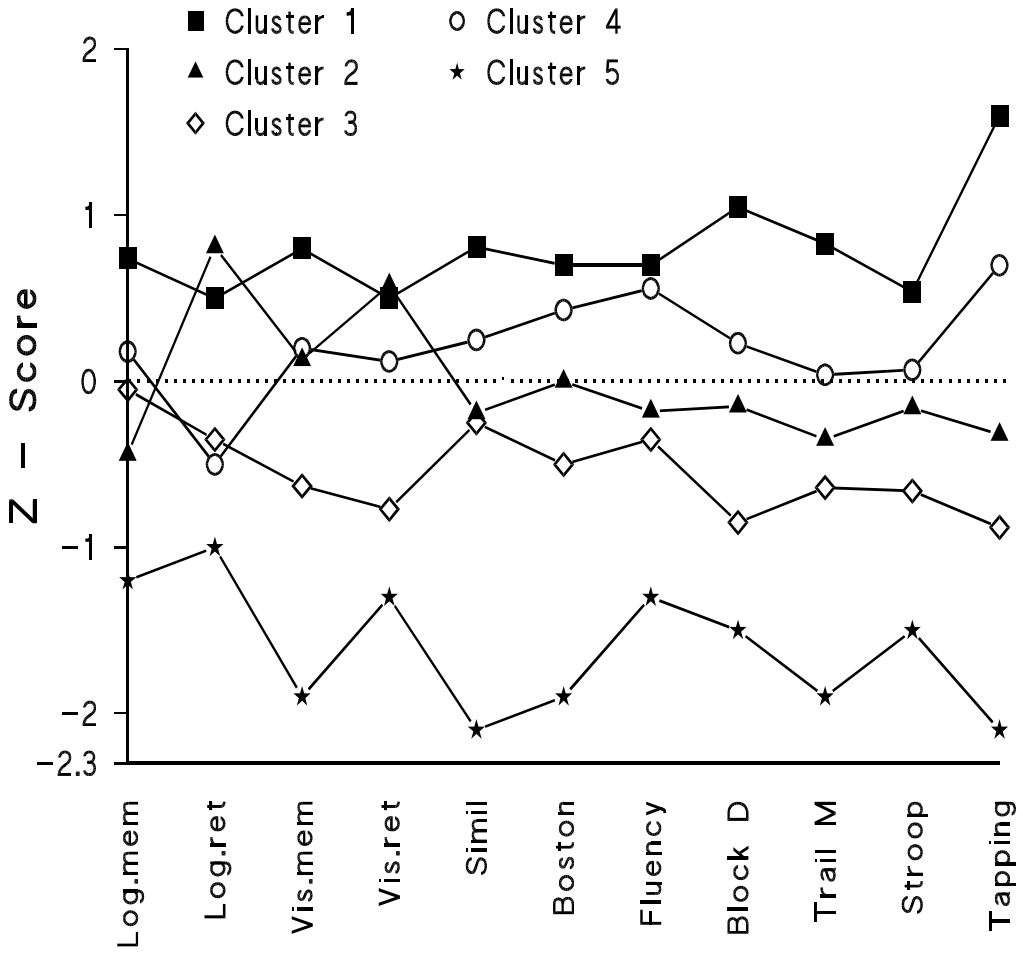

Figure 1. Cognitive profiles (in standard scores) for five clusters, Cluster 1 (N=34), Cluster 2 (N=23), Cluster 3 (N=26), Cluster 4 (N=26), Cluster 5 (N=11). Abbreviations and one-way analysis of variance between clusters (degrees of freedom 4,115): log.mem = Logical Memory immediate recall (WMS-R), F=16, p<.001; log.ret = Logical Memory retention percentage (delayed recall), F=16, p<.001; vis.mem. = Visual Memory immediate recall (WMS-R), F=58, p<.001; vis.ret = Visual Memory retention percentage, F=32, p<.001; Simil = Similarities (WAIS-R), F=35, p<.001; Boston = the Boston Naming test, F=47, p<.001; Fluency = Verbal Fluency (animals), F= 14, p<.001; Block D = Block Design (WAIS-R), F=56, p<.001; Trail M = Trail Making A, F=38, p<.001; Stroop = the Stroop test, Interference effect, F=16, p<.001; Tapping = Finger Tapping, F=17, p<.001.

5.3. Temporal lobe atrophy and age-related decline in memory (Study III)

The study sample of 35 follow-up subjects included 18 female and 17 male participants; 25 subjects had gone to grade school, and 10 had continued beyond grade school. MRI was performed at the follow-up (TIME2) measurement point. Hippocampal atrophy was found in 15 (43 %) subjects, and 11 (31 %) of these had bilateral hippocampal atrophy. The hippocampal atrophy was rated as mild except for two cases who showed moderate atrophy. The 11 subjects who had bilateral hippocampal atrophy also had mild atrophy of the temporal neocortex, and six of them had entorhinal atrophy. Of those 20 individuals who did not have hippocampal atrophy, four had temporal lobe atrophy.

Four memory tests showed decline during the follow-up in the whole group. Logical Memory immediate recall (repeated measures analysis of variance, $F=3.9$, $DF=1,33$, $p=.05$) and delayed recall ($F=6.0$, $p=.02$) declined significantly during follow up. Both immediate ($F=4.5$, $p=.04$) and delayed recall of Visual Reproduction deteriorated significantly ($F=7.6$, $p=.009$). Retention percentage of the Logical Memory test, the Visual Reproduction test, and the Fuld OMT did not decline significantly over a period of five years.

In the repeated measures analysis of covariance the decline in test performance was correlated with hippocampal atrophy scores measured at follow-up (TIME2) time. Longitudinal decline in memory test performance was not related to developing hippocampal or temporal atrophy (Table 5). Similarly at the follow-up measurement point (TIME2) the memory test performance did not differ between those who had hippocampal and temporal lobe atrophy (HA+) and those who did not (HA-), as tested by covariance analysis adjusting for education (Table 5). Analyses were repeated comparing the 16 subjects with no hippocampal or temporal atrophy with those 11 with both hippocampal and temporal neocortex atrophy, but no statistically significant differences were obtained.

Table 5. Memory performance in subjects without hippocampal atrophy (HA-, N=20) and with hippocampal atrophy (HA+, N=15). Adjusted means (M) and standard errors (SE).

	HA - TIME1 M (SE)	TIME2 M (SE)	HA + TIME1 M (SE)	TIME2 M (SE)	F1 Follow-up	F2 Between TIME2
Logical Memory Immediate	15.0 (0.9)	13.7 (0.8)	15.4 (1.1)	14.3 (0.9)	0.35	0.72
Logical Memory Delayed	14.0 (0.9)	12.8 (0.7)	14.4 (1.1)	13.4 (0.8)	0.20	0.43
Logical Memory Retention	93.2 (2.8)	94.6 (3.7)	93.2 (3.3)	92.3 (4.2)	0.26	0.17
Visual Reproduction Immed	32.5 (1.3)	30.0 (1.3)	33.1 (1.4)	32.3 (1.3)	0.81	1.70
Visual Reproduction Delayed	28.3 (1.8)	25.0 (1.6)	29.8 (2.1)	27.0 (1.8)	0.90	0.73
Visual Reproduction Retent	86.5 (4.2)	79.0 (4.3)	89.5 (4.8)	85.0 (4.9)	1.50	1.20
Fuld OMT	43.6 (1.0)	43.0 (1.0)	44.4 (1.2)	43.9 (1.0)	0.46	0.43

F1= Analysis of covariance (education as covariate) with repeated measures (TIME1 vs TIME2) between subjects with or without hippocampal atrophy. DF=1,32.
F2= Analysis of covariance (education as covariate) between subjects with or without hippocampal atrophy in TIME2 measurement point. DF = 1,32.
Fuld OMT= Fuld Object Memory Test

5.4. White matter changes, attention and speed of mental processing (Study IV)

The total score of WMHI tended to increase with age. The subjects showed only a mild degree of white matter changes. Even in the age-group of 85 years of age, the mean total WMHI score was 7.8 of the maximum 48.

The tests reflecting attention and speed of mental processing had a significant association with WMHI, even after controlling for age and education. Partial correlations between WMHI and the Trail Making test was .24 ($p<.05$), for Stroop dots/words time .30 ($p<.01$), for Stroop/difference time .32 ($p<.01$) and for the summary score of Trail Making and Stroop/words time .32 ($p<.01$). A score of speed of mental processing was composed by summing up the time spent on the Trail Making A test and reading color names on the Stroop test. Despite the statistically significant correlations, the overall level of correlations remained quite low. The differences between the groups with or without white matter changes are presented in table 6.

Table 6. Speed and attention in neurologically healthy elderly (N=113) with or without WMHI. Mean(sd).

Variable	WMHI		t-test
	Absent (N=70)	Present (N=43)	
Trail Making A			
time	60.4 (26.6)	92.7 (55.1)	-4.2***
Stroop			
dots/time	16.9 (5.0)	18.5 (4.5)	-1.7
words/time	38.2 (16.2)	51.0 (29.8)	-2.9**
difference/time	21.2 (13.9)	32.4 (28.2)	-2.8**
Summary score of speed and attention +)	98.6 (33.9)	143.7 (71.4)	-4.5***

** = p<.01; *** = p<.001
+) Trail Making A/time + Stroop words/time

5.5. The relationship between health factors and cognitive functioning (Study V)

This unselected, home-dwelling sample consisted of subjects who were relatively healthy, although physicians' rating of health status deteriorated and frequency of systemic diseases increased with age (Study V). Approximately half of the subjects had at least some cardiovascular diseases. Arterial hypertension, cardiac arrhythmias and diabetes were equally common in all three age groups, while coronary heart disease, myocardial infarction and cardiac failure were more common in the two older age groups (Study V).

The relationship between health-related factors and neuropsychological domains was examined using covariance analysis, with age and education as covariates (Table 7). General health status or presence of systemic diseases were not related to cognitive functions. Depression score was not correlated to test performances. Subjects with cardiovascular diseases had lower scores on visuoconstructional and spatial functions (Analysis of covariance: 1: no diseases, mean (SD) = 0.5 (3.3); 2: subjects with diseases, mean (SD) = -0.5 (3.0); F-statistics = 3.82; p = 0.05).

Table 7. The relationship of health-related variables with cognitive functions. Covariance analysis, with age and education as covariates (F statistics, Degrees of Freedom 1, N=113). Partial correlations between Depression score and test results (r), adjusting for age and education.

	Health Status			Systemic Diseases			Depression
	Healthy	Not Healthy		No	Yeas		
	Mean (SE) N=66	Mean (SE) N=47	F	Mean (SE) N=50	Mean (SE) N=63	F	r
Verbal Memory	1.1 (0.6)	-0.5 (0.6)	0.14	0.3 (0.5)	0.03 (0.7)	0.67	-0.12
Visual Memory	0.4 (0.2)	-0.3 (0.2)	0.14	0.2 (0.2)	-0.3 (0.2)	0.11	-0.11
Intellectual Verbal Functions	0.5 (0.4)	-0.4 (0.3)	0.42	0.2 (0.3)	-0.3 (0.4)	0.38	0.10
Visuoconstructional and Spatial functions	0.6 (0.4)	-0.4 (0.3)	0.07	0.2 (0.3)	-0.3 (0.4)	0.54	-0.02
Flexibility	0.4 (0.3)	-0.3 (0.3)	0.003	0.1 (0.3)	-0.4 (0.3)	1.16	-0.19
Speed / Attention	0.6 (0.3)	-0.6 (0.2)	1.5	-0.3 (0.2)	0.7 (0.3)	0.29	0.11

Means as standardized scores; SE = standard error. Tests measuring cognitive functions are described in the Methods section.

More detailed analyses regarding the relationship between cardiovascular diseases, MRI findings and cognitive functioning were conducted with specific diagnostic entities, coronary heart disease, cardiac failure, and arterial hypertension. Other diagnostic groups (myocardial infarction, cardiac arrhythmias and diabetes) were not evaluated in this study due to small sample sizes and lack of relationships with MRI findings. In a covariance analysis adjusting for age and education, coronary heart disease had no relationship with any of the cognitive variables. Subjects who had coronary heart disease (CHD) and white matter changes (WMHI) or subjects who had CHD and central atrophy (CA) did not differ from those who did not have these MRI changes or coronary heart disease in cognitive functions (Study V, Figure 1). Cardiac failure (CF) was significantly related to Visuoconstructional and Spatial functions (means: no CF / CF = 0.09 / -2.2; F= 9.6; p= .003, evaluated in subjects between 65-85 years of age). Cardiac failure and MRI changes were together related to cognitive functioning. Those subjects who had white matter changes and cardiac failure (CF) differed significantly from persons without MRI changes and cardiac failure in visuoconstructional and spatial functions (covariance analysis, F = 7.8, p=.009), in flexibility (F=4.9, p=.03), and in speed and attention (F = 5.8, p=.02) (Table 8).

Subjects who had cardiac failure and central atrophy performed more poorly in speed and attention tests than subjects who did not have MRI changes and cardiac failure (F=8.2, p=.008; Study V, Figure 2). Arterial hypertension (HYP) was related to Visuoconstructional and Spatial functions (means: no HYP / HYP = 0.5 / - 0.8; F= 5.8; p = .02), and to Flexibility (means: no HYP / HYP = 0.4 / -0.6; F=4.5; p=.03). Arterial hypertension (HYP) together with white matter changes on MRI were related to flexibility (F=10.3, p= .004) (Table 8).

Table 8. White matter changes (WMHI), cardiac failure (CF), and hypertension (HYP), and their relationships with cognitive functioning in a sample of 65 to 85 years of age. Analysis of covariance, with age and education as covariates.

	No WMHI No CF Mean (SE) N=21	WMHI+CF Mean (SE) N=12	F	No WMHI No HYP Mean (SE) N=16	WMHI+HYP Mean (SE) N=12	F
Verbal Memory	-0.2 (1.3)	-0.8 (1.8)	0.06	-0.1 (1.5)	-0.8 (1.7)	0.08
Visual Memory	-0.0 (0.4)	-1.7 (0.6)	3.72	-0.1 (0.5)	-0.4 (0.6)	0.08
Intellectual						
Verbal Functions	0.03 (0.6)	-0.8 (0.8)	0.53	-0.3 (0.7)	-0.5 (0.8)	0.03
Visuoconstructional and						
Spatial functions	0.1 (0.5)	-2.8 (0.8)	7.78**	-0.0 (0.7)	-1.6 (0.8)	1.98
Flexibility	0.7 (0.6)	-1.8 (0.8)	4.91*	0.8 (0.6)	-2.2 (0.7)	10.3**
Speed / Attention	0.1 (0.5)	-2.0 (0.6)	5.77**	0.1 (0.6)	-1.9 (0.7)	3.67

Means as standardized scores, adjusted for age and education; SE = standard error
Tests measuring cognitive functions are described in the methods section.

6. DISCUSSION

6.1. Why are norms still needed?

6.1.1. Defining the study population

To identify the necessary concomitants of brain aging, one must study a selected healthy non-neurologic and non-psychiatric sample, and not just a representative sample of the elderly in whom diseases which can interfere with brain function are prevalent (Creasey & Rapoport 1985). Many population-based or epidemiological studies on age-related cognitive decline include neurological patients (see e.g.

Gallacher et al. 1999; Laursen 1999), or it is not mentioned whether neurological patients have been excluded (see e.g. Ganguli et al. 1991; Fozard et al. 1994; Tuokko & Woodward 1996). In neuropsychological studies a slightly different picture of the aging process has emerged. In some longitudinal studies with neurologically healthy subjects, cognitive decline has been selective rather than diffuse, involving memory, the ability to acquire new information and retrieval of this information shortly after acquisition (Small et al. 1999). Tranel et al. (1997) found that healthy elderly individuals exhibited little cognitive decline over a period of ten years. They concluded that aging per se may not have a major negative impact on higher order cognitive capacities. Accordingly, no change in cognitive functions between 3- and 5-year follow-up was observed (Malec et al. 1996; Wilson et al. 1999).

In addition, elderly normative samples include subjects with preclinical dementia, which causes underestimation of the true level of cognitive function and overestimation of the effect of age on cognition (see e.g. Welsh et al. 1994; Giambra et al. 1995; Tuokko & Woodward 1996). Identification of subgroups with a high risk of Alzheimer's disease or other dementing disorders has increased our knowledge of age-related cognitive decline, and also of the development of pathological processes (see e.g. Hänninen et al. 1995; Petersen et al. 1995; Hänninen et al. 1996; Petersen et al. 1999).

Our sample constituted a random sample of individuals living independently at home and free of neurological or psychiatric disorders. We also excluded subjects with probable or preclinical dementia meeting two criteria, either CDR score or APOE genotype together with low scores on memory tests.

6.1.2. Considering the demographic variables

In line with previous studies, we found (Study I) that age cohorts from 55 to 85 years differed significantly in tests that measure speed of performance together with constructional, attentional or psychomotor components. Neuropsychological tests like the Block Design (Heaton et al. 1986; Ardila & Roselli 1989; Howieson et al. 1993), the Digit Symbol Substitution test (Heaton et al. 1986; Ardila & Roselli 1989; Mazaux et al. 1995), the Trail Making test (Bornstein 1985; Van Gorp et al. 1990; Ganguli et al. 1991; Elias et al. 1993a), and Finger Tapping (Bornstein 1985; Heaton et al. 1986; Ardila & Roselli 1989; Elias et al. 1993a) have shown significant age-related decline. There are contradictory results concerning tests of mental speed and flexibility, like the Stroop test. After controlling for the speed effect, Graf et al. (1995) found no differences between age groups in the Stroop test. Other studies have revealed impairment, especially in color naming and in the interference effect (Cohn et al. 1984; Houx et al. 1993). Our results confirm the latter findings.

The differences in Visual Reproduction scores between age groups were marked, like in previous studies (Haaland et al. 1983; Farmer et al. 1987; Ardila & Roselli 1989; Crook et al. 1992; Howieson et al. 1993; Janowsky & Thomas-Trapp 1993). In verbal memory, differences between age cohorts were more selective. We found age-related decline in Fuld OMT, the Interference test which reflects working memory capacity, and less so in delayed Logical Memory. No changes were observed in Logical Memory immediate recall and in Digit Span. Several previous studies have shown differences between age groups in verbal Logical Memory (Albert et al. 1987; Ardila & Roselli 1989; Ganguli et al. 1991; Petersen et al. 1992; Howieson 1993).Verbal learning has shown to be sensitive to age-related changes (Ardila & Roselli 1989; Ganguli et al. 1991; Petersen et al. 1992; Howieson et al. 1993; Small et al. 1999).

The verbal intellectual functions have been reported to hold up with age. In our study the relationship with age and the Information and Similarities subtests (WAIS-R) did not reach significance, after controlling for education. However, in some elderly samples the Similarities subtest has shown age-related decline (Heaton et al. 1986; Farmer et al. 1987; Ardila & Roselli 1989). More complex language functions that also require use of mnemonic or semantic processes have been found to deteriorate (Albert et al. 1987; Ardila & Roselli 1989;Ganguli et al. 1991; Howieson et al. 1993). Similarly, we found age-related differences in the Boston Naming test, the Token test and a slight difference in category based Verbal fluency.

The clear age-related changes in certain cognitive functions emphasize the need for normative data from different age cohorts. The knowledge of differential decline also helps in clinical decision making.

Although especially verbal intellectual functions have been found to be more education-related than age-related, in many studies most of the tests administered have been related to educational level (Bornstein 1985; Heaton et al. 1986; Farmer et al. 1987; Ardila & Roselli 1989; Nielsen et al. 1989; Crook et al. 1990; Ganguli et al. 1991; Mortensen & Gade 1993). Similarly, in our study, performance on most of the tests was associated with education, indicating that education should be taken into account when interpreting test scores in older individuals. In our series, the tests which did not discriminate between educational groups were the Fuld OMT, the Interference test (D-test), Block Design and Finger Tapping, the Stroop test (parts Word and Difference) and the Clock test; all other tests were significantly related to education.

The gender differences on Finger Tapping are consistently supported (Ardila & Roselli 1989; Heaton et al. 1986). In addition to this we found gender-differences in calculation like Ardila & Roselli (1989). In contrast to other studies, we obtained gender-based differences also in Block Design and Information (WAIS-R). This is not consistent with some other studies (Ardila & Roselli 1989, Heaton et al. 1986). Except

for younger subjects, where gender has been associated with the Information subtest (Saykin et al. 1995). Ardila & Roselli (1989) also found significant gender differences in Visual Reproduction (WMS) and the Boston Naming test. Ganguli et al. (1991) found that females were better on learning, the Boston Naming, story recall and the Trail Making A test. We found less strong relationships with the Clock test, Copying Designs and Boston Naming.

6.1.3. Diagnostically significant subgroups in neurologically healthy elderly samples

The division of populations into diseased versus normal, and the division of research findings into disease-related and age-determined, has serious limitations. A main problem is the neglect of heterogeneity among older people in the nondiseased group with respect to many cognitive characteristics. One can find persons with minimal change in cognitive functions when compared to their younger counterparts. These people might be viewed as having aged successfully with regard to the particular variable under study (Rowe & Kahn 1987). The same authors have recommended that gerontological research should incorporate the distinction between usual and successful aging (Rowe & Kahn 1987; Schultz & Heckhausen 1996). However, successful aging can be viewed as a complex phenomenon, and it has been suggested that the definition of successful aging should consist of multiple criteria, such as length of life, biological health, mental health, cognitive efficacy, social competence and productivity (Baltes et al. 1990). Neuropsychological study on age-related changes can only address the cognitive aspects of successful aging. Our study, together with previous studies, confirmed the fact that a subgroup of a cognitively well-performing individuals can be found with relation to "successful aging" (Study II). It constitutes of high-performing younger subjects together with cognitively successfully aged older persons. Our cluster analyses showed a group (Cluster 1) with an above average level of cognitive performance. This group was also characterized by a high activity level and a high intellectual level measured by the Information test (WAIS-R). Especially the 12 subjects from the two older age groups (65 to 85) were active, and most of them had higher education. There was also a cluster of subjects (Cluster 5) where 82 % were diagnosed as having AACD, and 54 % were diagnosed as having MCI. Cluster 3, which included most of the younger subjects with AACD or MCI, had the lowest scores on visual memory, visuoconstructional functions (Block Design) and speed of performance, all of which have been reported to be sensitive to the aging process (Van Gorp et al. 1990). The remaining two clusters (Cluster 2,4) performed at a near average level on cognitive functions, representing normal or usual aging.

Heterogeneity within cluster membership was more pronounced among the oldest individuals. The oldest age group (75 to 85 years) was divided over several clusters. One subgroup (44%) performed according to the average level (Cluster 2 and 4). Another subgroup (33%) had difficulties in cognitive functions that are sensitive to aging (Cluster 3). Finally there was a group (22%) of individuals with cognitive decline (Cluster 5). Similarly, 65 or 70 year-olds were classified into a group of successfully aged (Cluster 1), groups representing average aging (Clusters 2 and 4) and in a group exhibiting decrement of performance in age-sensitive tasks (Cluster 3). Subjects aged 55 or 60 years were mostly classified into successful (Cluster 1) or average performers (Clusters 2 and 4).

The subgroups identified here differed mainly according to their overall degree of performance. Similar findings have been reported in other studies using clustering techniques. Valdois et al. (1990) found six clusters which were divided into two clusters with the best performers, two clusters with average performers, and two clusters with the worst performers. Mitrushina et al. (1995) also arrived at a six-cluster solution, where two clusters exhibited an above average level of performance, one an average level, one a variable level (average, but difficulties in learning and memory), and two clusters had mild to moderate difficulties in test performance. Ritchie et al. (1996) studied elderly subjects with cognitive complaints. In a five-cluster solution they found two highly performing clusters (representing successful aging), one medium performance cluster (normal aging group), and two clusters which were at risk for subclinical pathology (one with overall poor performance and one with difficulties in memory functions). Previous studies together with our results summarize observed characteristics among groups of elderly individuals. The internal validity of the cluster solution was evaluated by alternative cognitive tests and multiple comparisons, while the systematic findings with other similar studies and association with diagnostic concepts consolidated the external validity (descriptive and clinical validity and generalizability) (Morris 1988). However, a cluster analysis is merely a statistical method. Showing that subjects can be placed into groups does not validate the groups (Morris 1988). Although the subgroups may be clinically relevant and add to our knowledge of heterogeneity of normal aging, it does not mean that the subgroups are biologically meaningful.

Individuals with more pronounced age-related cognitive deficits are of particular interest as they may be at high risk for the subsequent development of dementia. Results from longitudinal studies indicate that members of these at-risk clusters have a higher chance for a subsequent diagnosis of dementia or other cognitive disorders (Malec et al. 1996; Ritchie et al. 1996). In our study the at-risk cluster also represented individuals who could be diagnosed as having AACD, and half of them were characterized as having MCI. The individuals with MCI have been found to have an

increased risk for developing Alzheimer's disease (Petersen et al. 1995; 1999).

6.2. The problem of differentiating age-related brain changes and their contribution to cognitive functions from pathological processes

In a five-year follow-up study (Study III), we evaluated a group of 35 neurologically non-diseased subjects between 55 and 70 years of age at initial examination. The sample was psychometrically screened for possible preclinical dementia cases. The purpose of this study was to evaluate the relationship between memory functions and medial temporal lobe atrophy, and the association between longitudinal decline in memory and temporal lobe atrophy. Contrary to expectations we did not find statistically significant associations between hippocampal and temporal lobe atrophy with memory test performance. Neither did the longitudinal decline in memory show a relationship with temporal lobe atrophy. However, the relationship between age-related memory decline and hippocampal and temporal lobe atrophy, should be verified in future studies. There could be other factors influencing memory functions besides age-related structural changes in temporal lobes.

An important question concerning age-related brain lesions is to ascertain when these naturally occurring silent lesions in the brain actually took place. A longitudinal volumetric MRI study could reveal more precisely the association between insidious brain alterations and cognitive changes. In positron emission tomography studies, episodic memory functions have been related to temporal lobe activation in healthy subjects (Nyberg et al. 1996), and there has been evidence of age-related change in brain activation (Grady et al. 1995). It has also been suggested that a link exists between the cholinergic system, EEG slowing, and memory problems in old age (Hartikainen et al. 1992). Whether structural brain changes could be related to cognitive functions in healthy elderly individuals and whether they might explain age-related memory impairment, is still an open question. In a population-based sample a group of clinically healthy elderly individuals showed a relationship between cognitive screening tests and temporal lobe atrophy; however, the sample consisted of subjects with minimal cognitive impairment (Launer et al. 1995). Colomb et al. (1993) have suggested that those healthy subjects exhibiting both hippocampal atrophy and decline in delayed memory tests in their clinic-based study sample could be at increased risk for subsequent decline in the transition between healthy aging and the earliest stages of Alzheimer's disease. It is well established that subtle cognitive impairment, especially in delayed memory, can be present for several years before the clinical diagnosis of probable Alzheimer's disease (Jacobs et al. 1995; Linn et al. 1995). In order to avoid the confusion between normal aging and preclinical dementia we excluded those individuals having mild cognitive impairment, and who deteriorated during follow-up,

according to psychometric criteria (Petersen et al 1995). Our results were similar to those previous studies (Sullivan et al. 1995; Raz et al. 1998) which did not find a significant relationship between mild structural temporal lobe changes and age-related decline in memory. This finding has implications for clinical differential diagnostics concerning preclinical dementia. It is possible that explicit memory is affected only by extensive damage to the limbic circuit. Whether that indicates a pathological rather than a normal aging process remains to be verified in longitudinal studies. Other aspects influencing memory decline in healthy elderly subjects should be studied in the future. There has been evidence that certain aspects of memory could be related to frontal lobe functioning (Mesulam 1990, Hänninen et al. 1997) and these features have been sensitive to changes in normal aging (Craik et al. 1990; Daigneault & Braun 1993). It has been hypothesized that deficits in recall in elderly people could be a function of both hippocampal and frontal system deterioration (Moscowitch & Winocur 1992).

Another issue concerning the clinician, is whether slowness of behavior is the result of white matter changes or whether it is due to some acute neurological disease. We found that age-related WMHI could be related to certain alterations in cognitive functioning in the healthy elderly (Study IV), namely tests that measure attention and speed of behavior. Similar results have been found in many other studies (Schmidt et al. 1993; Breteler et al. 1994b; DeCarli et al. 1995). However, some studies have not found association between white matter changes and cognitive functions in small samples with a narrow age range (Rao et al. 1989b, Hunt et al. 1989). In a larger series of 100 healthy volunteers a decline in so-called frontal lobe tests was associated with a volume of WMHI on MRI greater than 10 cm^3 (Boone et al 1992). The results were significantly lower in Digit Span forward, Auditory Consonant Trigrams, in the Stroop test and in the Wisconsin Card Sorting test (Boone et al 1992). Similarly, De Carli et al. (1995) found that subjects with large WMHI volumes had significantly more brain atrophy, reduced cerebral metabolism and lower scores on tests of frontal lobe functioning. Minor changes in white matter may not be relevant in clinical neuropsychological decision making, while large (confluent) changes should be taken into account when evaluating slowness of behavior.

6.3. The association of health with neuropsychological performance

Our results indicated that the effect of health-related aspects on cognitive functions was manifold. Crude health status registered by a physician or presence of systemic diseases or depression did not have any substantial association with cognitive functions in our subjects, who were independently living at home and were relatively healthy. Health evaluations based on one categorial variable may, however, be too insensitive

for measuring general health, as studies using more refined scales have found significant relatioships with cognitive functioning (Perlmutter & Nyquist 1990). Our results verified the previous findings that those hypertensive subjects who develop white matter changes also deteriorate in distinctive cognitive functions (Van Swieten et al. 1991; Schmidt et al. 1995). In our sample cardiovascular diseases, especially cardiac failure, together with white matter changes and central atrophy, had special importance in regard to cognitive functions.

Previously, diabetes has been correlated with decline in abstract reasoning and visuospatial functions (Desmond et al. 1993); risk for diabetes has also been related to cognitive impairment (Vanhanen et al. 1997). Chronic atrial fibrillation has been related to poorer memory performance and attention (Farina et al. 1997), or to low cognitive status (Kilander et al. 1998). Hypercholesterolaemia has been related to memory difficulties (Desmond et al. 1993). According to our results, cardiac failure may also contribute to cognitive decline, especially in visuoconstructional and spatial functions and flexibility. We did not find a correlation between coronary heart disease and cognitive functions. The impact of cardiac diseases on cognitive functions may be differential as myocardial infarction, too, has not been related to cognitive status (Kilander et al. 1998).

Untreated hypertension has been associated with speed of behavior and overall cognitive decline (Elias et al. 1993b; Farmer et al. 1990; Goldstein et al. 1990). The results of treated hypertension and its relation to cognitive functions have not been consistent. While some samples (Elias et al. 1990; Parnetti et al. 1989; Kuusisto et al. 1993) have shown a relationship between hypertension and cognitive functions, other samples (Desmond et al. 1993; Farmer et al. 1990; Goldstein et al. 1990), have not found correlations. It is possible that arterial hypertension per se is not the only cause for hypertension-related cognitive alteration. In addition, the coexisting silent brain damage may contribute to neuropsychological impairment.

Cardiovascular diseases, especially silent infarcts and white matter changes, have been reported to be a possible risk factor for brain pathology (Shimada et al. 1990). The relationship between arterial hypertension or blood pressure and MRI abnormalities has been confirmed by many studies, including stroke patients (Manolio et al. 1994; Longstreth et al. 1996; Awad et al. 1986; Fukuda & Kitani 1995). White matter hyperintensities have been related to hypertension and heart disease also in stroke-free cohorts (Lindgren et al. 1994; Goldstein et al. 1998). Moreover a subsample of hypertensive subjects exhibiting confluent lesions in white matter have shown to be impaired in attention (Schmidt et al. 1995) and memory functions (Van Swieten et al. 1991). In our study, those subjects who had both arterial hypertension and white matter changes had difficulties in mental flexibility. The role of other cardiovascular diseases in developing brain abnormalities in relation to cognitive impairment is less studied in

neurologically healthy individuals. We found that subjects who had both cardiac failure and white matter changes had difficulties in visuoconstructional and spatial functions, mental flexibility, and speed and attention. Some of these subjects had also developed central atrophy, which correlated with speed and attention. However, although coronary heart disease had a slight correlation with central atrophy, no relationships with cognitive functions were found. Our findings have implications for both neuropsychological aging research, and for clinical management of elderly persons.

6.4. Limitations of the study and implications for future research

When evaluating the cognitive functions in a cross-sectional aging study there are methodological problems that need to be noticed. Cross-sectional studies can address only age differences; they cannot deal with changes in psychological function with age, because age and cohort are confounded (Storandt 1990). The demographic characteristics of these cohorts should be emphasized, and comparisons the results with other cohorts should be approached with caution. A crucial limitation of this study is the small sample size, which is, however, quite a common problem with normative studies including extensive clinical investigations (e.g. Bornstein 1985, Nielsen et al. 1989, Petersen et al. 1992, Saykin et al. 1995). Although many research projects gather normative data of cognitive tests, the standardized versions of WAIS-R and WMS-R tests in Finnish have limited range of norms. The WMS-R standardization sample does not include older subjects. The oldest age group in WAIS-R sample was from 55 to 64 years of age (38 subjects studied). The results of Information and Similarities subtests are quite similar between our sample and the standardization sample. The results from the Block Design test, however, differ from each other (mean in our sample 28, in WAIS-R sample 23). This could in part be do to sample characteristics, the subjects in WAIS-R standardization came from rehabilitation programs or were customers of employment service.

Selection of criteria for possible preclinical dementia is a difficult problem in aging research. A highly selected group of normal sample would make it difficult to interpret the test results in subjects who perform in the lower range of the average level. The diagnostic entities introduced so far constitute a heterogeneous group. In AAMI many individuals remain stable in cognitive functions and a small subgroup may deteriorate (Koivisto et al. 1995; Hänninen et al. 1995; Ritchie et al. 1996). MCI may prove to be more promising concept in clinical work. In a longitudinal study on MCI subjects, hippocampal MRI-based volume measurements were predictive of subsequent conversion to AD: 34 % of the MCI subjects developed AD dementia during the follow up of 2.5 years (Jack et al. 1999). In a four-year annual follow-up study the

conversion rate was 12% per year from MCI to AD (Petersen et al. 1999). In order to avoid excluding low performing subjects with no risk of developing dementia, we used criteria based on memory performance together with an outer criteria (CDR and APOE genotype). Allele E4 of apolipoprotein has been shown to be a risk factor for Alzheimer's disease (Kuusisto et al. 1994; Soininen & Scheltens 1998).

Another limitation of our study was that the WMHI was examined with an ultra-low-field MRI unit. Compared to a 1.5 T unit, the 0.02 T unit is expected to reveal about half the tiny incidental focal hyperintensities, but an equal number of the more extensive changes (Raininko et al. 1992). The MRI we used is still much more sensitive than CT (Erkinjuntti et al. 1987; Raininko et al. 1992). When selecting for the measures of temporal and hippocampal atrophy, we preferred visual rating for volumetric analysis on a 1.0 T MRI unit. The major reason is that volumetric measurements are time consuming for clinical work. In addition, visual ratings have correlated with volumetric measures (Vermersch et al. 1994) and differentiated normal controls from Alzheimer patients (Wahlund et al. in press).

In the future, norms from other age cohorts are needed, especially from cohorts with different social demographic characteristics. In light of the current knowledge of the aging process, in normative studies more emphasis should be given to characterization of clinically relevant subgroups, like MCI, or those that have aged successfully. Specific norms for different subgroups would make the clinical decisions more accurate. The diagnostic specificity of age-related brain changes remains to be more clearly described in future studies. The role of hippocampal atrophy in the development of Alzheimer's disease has been well documented. However, the specificity of hippocampal atrophy causing memory impairment should be studied further, since other dementing disorders also exhibit temporal lobe atrophy (Laakso et al. 1996; Pohjasvaara et al. in press). Longitudinal studies evaluating the relationship between age-related memory decline and temporal lobe atrophy are needed. Despite memory being one of the most common neurologic complaints among the elderly, age-related memory decline remains controversial. Similarly, the direct role of WMHI in causing cognitive deterioration has not been established, although it is associated with specific cognitive difficulties. Differentiating the impact of WMHI in dementing disorders (Pantoni et al. 1999) or in patients with cerebrovascular diseases (Sabri et al. 1999) is difficult. The associations between possible cardiovascular disease causing silent lesions in the brain and certain cognitive impairments remain to be more specifically characterized. Impaired cardiac output might be expected to be an important pathogenetic factor. The relationship between cognitive functions and brain changes are more complicated in very old persons. More refined methods like Position Emission tomography (PET) or high resolution MRI studies could be used to analyze specific relationships with cognitive functioning. The mechanisms underlying the

individual variability and the brain-behavior relationships in healthy elderly individuals require more research, and greater definition of specific patterns of change. Overall function can be maintained at high and effective levels because of plasticity and redundancy in the human brain.

7. CONCLUSIONS

Neuropsychological assessment of older individuals in whom there is an indication of decreased mental abilities is one of the most challenging tasks for the clinical neuropsychologist. Making decision on this requires an awareness of the neuropsychological correlates of normal aging and patterns of deficit that are associated with various incipient dementing disorders. Age and education are the most important demographic characteristics that should be considered when evaluating the normal range of test results. The present findings caution against treating samples of elderly individuals as homogeneous. Even those three clusters performing at a near average level showed different cognitive profiles according to memory or language functions, or those cognitive functions sensitive to aging. The main findings were, however, the identification of a subgroup with successful aging and a subgroup with cognitive decline. Individual variability in test performance should be considered in establishing norms. The cognitively successfully aged (with higher intellectual level and good education) should be compared to a group of younger subjects. On the other hand, individuals performing below the expected level of performance and obtaining a diagnosis of AACD or MCI could be subjected to follow-up to check for further cognitive decline.

Other factors besides medial temporal lobe atrophy should be studied when defining the mechanisms affecting age-related memory decline. Mild structural temporal lobe changes are not necessarily associated with age-related decline in memory. Measures of brain activation may provide more accurate descriptions than structural changes. More research is needed to evaluate the structure-function relationships in normal aging and especially in preclinical dementia stages.

Our results confirm that WMHI could explain some intellectual impairment in the elderly, especially the slowing of mental processing. However, there is variability among individuals. The factors related to different type, location, and extent of WMHI are not known in detail, although they are likely to be related to vascular risk factors and cerebrovascular disease. Whether slowness of behavior and attentional difficulties associated with WMHI are early signs of a pathological process remains to be clarified in the future. There may be critical central nervous system functions or threshold effects (Boone et al. 1992) in which a certain extent of damage or dysfunction leads to vulnerability of cognitive functions.

General health status may not be associated with cognitive functioning in neurologically healthy elderly persons. There are, however, certain cardiovascular diseases or risk factors and clinical entities besides diabetes and hypertension that could contribute to certain cognitive functions. The relationship between hypertension, white matter changes and difficulties in attention and flexibility is well established. More knowledge is needed about the morphological basis of cardiovascular diseases in relation to cognitive functioning. We found that cardiac failure correlated with white matter changes and central atrophy, and that together they were associated with low scores on visual functions, flexibility and attention.

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10. APPENDIX

Test results by age and education groups, GradeS (grade school), MoreS (more than grade school). Results are mean (standard deviation).

Neuropsychological test	AGE GROUPS					
	55/60 years		65/70 years		75/70/85 years	
	GradeS	MoreS	GradeS	MoreS	GradeS	MoreS
FULD OMT						
total retrieval(1-5)	44.0(3.0)	45.0(4.0)	42.2(8.0)	40.5(8.0)	40.1(6.7)	39.7(4.7)
Trial 5	9.6(0.7)	9.8(0.6)	9.1(1.0)	8.7(1.6)	8.6(1.7)	9.3(1.0)
delayed recall	9.5(0.7)	9.6(0.7)	9.3(0.8)	8.8(0.9)	8.8(1.5)	9.0(1.0)
Retention (delayed/trial 5)	99.0(9.1)	98.5(11.0)	102 (9.6)	104 (18.0)	105(19)	97.0(10.6)
WMS-R						
Logical Memory immediate	14.0(3.0)	17.0(3.0)	14.7(3.4)	17.4(5.0)	13.0(3.4)	15.2(3.2)
Logical Memory delayed	13.0(3.1)	16.0(3.3)	13.0(3.2)	16.1(6.0)	11.5(4.0)	12.6(3.4)
Retention Logical Memory	92.0(13.6)	94.0(7.0)	89.0(16.0)	89.0(16.7)	88.2(16.0)	82.0(13.2)
Visual Reprod. immediate	33.2(4.5)	33.5(5.0)	28.5(4.8)	32.5(5.3)	26.3(7.0)	29.0(8.0)
Visual Reprod. delayed	29.7(6.5)	31.0(5.0)	23.0(8.0)	27.5(8.8)	19.1(9.7)	23.0(8.3)
Retention Vis. Reprod.	88.5(13.6)	93.0(9.3)	80.0(20.8)	82.7(16.8)	68.8(25.5)	77.3(17.1)
WMS Digit Span						
forward	5.7(1.0)	6.5(1.0)	5.5(1.0)	6.3(1.3)	5.6(0.7)	6.4(0.9)
backward	4.1(0.8)	4.5(0.8)	4.0(1.0)	4.3(1.0)	4.0(0.6)	4.6(0.8)
D-Test						
Interference	12.8(2.5)	13.7(2.0)	13.3(1.7)	12.5(2.9)	10.5(3.1)	12.1(2.5)
Logical retrieval	4.5(0.6)	5.0(0.3)	4.5(0.7)	4.8(0.4)	4.1(1.1)	4.7(0.7)
WAIS-R						
Information	23.7(6.0)	27.8(5.6)	24.1(5.0)	31.0(3.7)	21.9(4.6)	28.7(4.7)
Similarities	25.3(5.0)	28.0(3.0)	26.0(4.0)	29.1(2.5)	23.2(4.7)	27.7(3.0)
Block Design	28.4(10.0)	30.0(9.0)	24.0(8.0)	27.4(7.8)	17.7(8.4)	20.0(7.2)
Token Test	15.3(1.5)	16.1(1.0)	15.0(1.3)	16.1(1.2)	13.5(1.5)	14.6(1.4)
Boston (naming)	22.6(3.4)	26.4(2.0)	23.0(3.6)	25.2(3.5)	20.4(4.0)	23.0(3.7)
Verbal fluency, animals (60s)	21.5(4.2)	23.7(5.0)	21.0(5.0)	23.0(5.0)	18.6(4.7)	20.7(7.1)
Verbal fluency, letter s (30s)	7.2(2.2)	9.4(3.7)	7.2(2.8)	9.3(2.5)	6.4(2.7)	7.8(3.5)
Trail Making A, time	55.0(21.5)	50.1(19.0)	77.4(42.3)	50.0(15.5)	99.5(55.0)	78.7(26.0)
Stroop, dots, time	16.2(2.7)	13.1(2.1)	18.1 (2.8)	15.7(3.0)	20.7(7.5)	17.0(3.4)
Stroop, words, time	35.6(16.0)	28.0(9.6)	45.0(20.0)	32.5(10.8)	52.5(22.2)	54.5(41.6)
correct	23.7(0.6)	23.9(0.3)	23.7 (0.7)	23.8(0.4)	22.3(3.9)	23.3(1.4)
Stroop,difference, time	19.4(15.6)	15.0(9.0)	27.0(19.1)	17.0(10.0)	31.8(17.7)	37.5(41.6)
Finger Tapping, right	47.1(7.3)	48.5(8.4)	43. 0(7.8)	44.1(6.4)	37.7(9.1)	39.8(5.8)
left	43.8(7.0)	44.0(9.0)	39.1 (5.5)	41.7(4.8)	34.8(8.2)	39.0(8.0)
D-test						
Visuospatial/Clock test	7.4(0.6)	7.4(0.5)	7.0 (1.7)	7.5(0.5)	7.1(10.9)	7.4(0.5)
Copying Designs	61.9(5.9)	63.8(6.0)	63.4 (5.0)	66.7(1.0)	60.0(6.9)	62.0(9.3)
Calculation	28.0(4.0)	31.4(1.0)	27.8 (4.2)	29.8(3.9)	25.5(4.8)	29.1(3.1)