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AGE-ASSOCIATED MEMORY IMPAIRMENT

A neuropsychological and epidemiological study

Doctoral Dissertation

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ABSTRACT

The aim of this study was to characterize the neuropsychological and epidemiological aspects involved in diagnosing age-related changes in cognition. The properties of the diagnostic criteria for age-associated memory impairment (AAMI) proposed by the National Institute of Mental Health and for age-associated cognitive decline (AACD) proposed by the International Psychogeriatric Association were evaluated in a large random sample and in smaller select groups of elderly subjects.

According to the high prevalence of AAMI found in the present study, AAMI appeared likely to be a phenomenon of normal aging rather than a continuum from normal aging to a pathologic state such as Alzheimer's disease. As in some previous studies, the neuropsychological methods used for AAMI diagnosis also appeared ambiguous in this study. The follow-up of AAMI subjects suggested that AAMI, in general, is nonprogressive, but that the AAMI population also includes subjects with very early dementia. However, these subjects can be differentiated by means of a more detailed neuropsychological evaluation. In comparison with age-matched controls, AAMI subjects appeared to be impaired not only in tests assessing memory, but also in tests of executive functions associated with frontal lobe function. This finding agrees with previous reports suggesting an important role for frontal lobe dysfunction in the memory loss of elderly people. The comparison of subjects with high and low frequencies of subjective complaints of memory loss suggested that these subjective feelings of memory impairment are more closely associated with personality traits than with actual memory performance in normal elderly people. This complicates the use of memory complaints in the inclusion criteria for AAMI and AACD diagnosis.

The prevalence of AACD was found to be lower than that of AAMI. As AAMI tends to identify a very heterogeneous subject group, the AACD diagnosis might prove superior to AAMI for differentiating a meaningful subgroup from the elderly population, both for research purposes and in clinical settings. This remains to be confirmed in follow-up studies. This study demonstrated that the AAMI diagnosis appears to identify a very heterogeneous group of subjects of only vague clinical or theoretical significance. The significance of the AACD diagnosis remains to be confirmed in follow-up studies. Nevertheless, more reliable diagnostic approaches are needed in studies trying to identify risk factors for dementia or to find treatments for very early dementia.

National Library of Medicine Classification: WT 100, WL 103.5, WL 359

Medical Subject Headings: aging; memory; memory disorders; dementia; Alzheimer’s disease; neuropsychological tests; risk factors; epidemiology; diagnosis; classification; personality; frontal lobe/physiopathology.

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Kuopio, November 1996

Tuomo Hänninen

ABBREVIATIONS

AACD	Aging-associated cognitive decline
AAMI	Age-associated memory impairment
AD	Alzheimer's disease
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BSF	Benign senescent forgetfulness
BSRT	Buschke Selective Reminding Test
BVRT	Benton Visual Retention Test
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
GDS	Geriatric Depression Rating Scale
ICD-10	International Classification of Diseases, 10th revision
IPA	International Psychogeriatric Association
LM	Logical memory subtest from the WMS
MAC-Q	Memory Complaint Questionnaire
MCD	Mild Cognitive Disorder
MMPI	Minnesota Multiphasic Personality Inventory
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
MTL	Medial temporal lobe
NIMH	National Institute of Mental Health
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
PAL	Paired Associated Learning subtest from the WMS
PET	Positron emission tomography
rCBF	Regional cerebral blood flow
SD	Standard deviation
SPECT	Single photon emission computed tomography
SPSS-PC+	Statistical package for social sciences - personal computer
ST	Stroop Test
TMT	Trail Making Test
VFT	Verbal Fluency Test
VRT	Visual Reproduction Test
V-WAIS	Vocabulary subtest from the WAIS
WAIS	Wechsler Adult Intelligence Scale
WCST	Wisconsin Card Sorting Test
WHO	World Health Organization
WMH	White matter hyperintensity
WMS	Wechsler Memory Scale

LIST OF ORIGINAL PUBLICATIONS

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

(The publications are not included in the internet version of this thesis due to copyright reasons. Reprints of the publications ma be inquired both from the author and from http://www.uku.fi/laitokset/neuro/publicat.htm)

I Koivisto K, Reinikainen KJ, Hänninen T, Vanhanen M, Helkala E-L, Mykkänen L, Laakso M, Pyörälä K, Riekkinen PJ Sr. Prevalence of age-associated memory impairment in a randomly selected population from eastern Finland. *Neurology* 45:741-747, 1995.

II Hänninen T, Hallikainen M, Koivisto K, Partanen K, Laakso MP, Riekkinen PJ Sr, Soininen H. Decline of frontal lobe functions in subjects with age-associated memory impairment. *Neurology*, in press (January 1997).

III Hänninen T, Reinikainen KJ, Helkala E-L, Koivisto K, Mykkänen L, Laakso M, Pyörälä K, Riekkinen PJ. Subjective memory complaints and personality traits in normal elderly subjects. *Journal of the American Geriatrics Society* 42:1-4, 1994.

IV Hänninen T, Hallikainen M, Koivisto K, Helkala E-L, Reinikainen KJ, Soininen H, Mykkänen L, Laakso M, Pyörälä K, Riekkinen PJ Sr. A follow-up study of age-associated memory impairment: Neuropsychological predictors of dementia. *Journal of the American Geriatrics Society* 43:1007-1015, 1995.

V Hänninen T, Koivisto K, Reinikainen KJ, Helkala E-L, Soininen H, Mykkänen L, Laakso M, Riekkinen PJ Sr. Prevalence of ageing-associated cognitive decline in an elderly population. *Age and Ageing* 25:201-205, 1996.

CONTENTS

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1. INTRODUCTION

Aging causes deterioration of various aspects of memory performance in normal adults (Craik and Jennings 1992). Kral (1958, 1962) introduced the term "benign senescent forgetfulness" to categorize age-associated changes in memory. However, Kral did not operationalize this concept. To characterize the phenomenon more precisely, a National Institute of Mental Health (NIMH) work group proposed research criteria for "age-associated memory impairment" (AAMI) (Crook et al. 1986). Briefly, these criteria include the presence of complaints of gradual memory loss in everyday problems in persons over the age of 50 years, objective evidence of impairment on a standardized memory test as compared to young adults, evidence of adequate intellectual function, and absence of dementia or any medical condition that could produce cognitive deterioration.

The data about AAMI that has been accumulating during the decade since the proposition of these criteria is limited and controversial. Very little is known about the prevalence of AAMI. Recent estimates vary from 18% to 85%, depending on the subjects' age and the population studied (Larrabee and Crook 1994, Barker et al. 1995). The clinical course of AAMI is not known. It has been debated whether AAMI could be viewed as an intermediary state in a continuum from normal aging to dementia (especially Alzheimer's disease, AD), or whether it just reflects an increased variability of cognitive performance in the elderly population. The gradually progressive cognitive decline and other clinical manifestations of AD are preceded by a long preclinical phase with specific changes taking place in the patient's brain (Hardy and Allsop 1991). Accordingly, very mild stages of dementia appear to merge with AAMI when assessed with memory tests or with cognitive and behavioral scales (Youngjohn et al. 1992, Brayne 1994). If AAMI turned out to be a clinical entity which predisposed to AD, this could open possibilities for therapeutic interventions aimed at interfering with the disease in its very early phases.

Previous reports have suggested some neurophysiological, structural and metabolic factors in the brain as characteristic for AAMI subjects (Soininen et al. 1994 and 1995, Parnetti et al. 1996), but these findings are not quite established yet. Moreover, the neuropsychological profile, i.e., the possible coexistence of other cognitive deficits with the memory impairment, has not been studied in AAMI subjects.

The whole construct of AAMI has also been criticized. The relevance of specific portions of the criteria (Blackford and La Rue 1989, Rosen 1990) and the reliability of the methodology used (Smith et al. 1991, Barker et al. 1995) have been challenged. In particular, the use of subjective memory complaints as part of the inclusion criteria has been criticized (Wilson and Evans 1996). On the whole, the subject group identified by the criteria has been considered too heterogeneous to be a clinically meaningful entity (O'Brien and Levy 1992). In addition to AAMI, various other constructs for the classification of age-related cognitive changes have been introduced (Dawe et al. 1992, Ebly et al. 1995). Recently, diagnostic criteria were specified for "aging-associated cognitive decline" (AACD) (Levy 1994). For AACD diagnosis, a broader assessment of cognitive domains is required and, also differing from AAMI, AACD classification utilizes age- and education-specific cutoff points for neuropsychological tests.

The purpose of the present series of studies was to characterize some of the neuropsychological and epidemiological aspects involved in diagnosing age-related changes in cognition. The prevalence rates for AAMI and AACD were studied in a randomly selected sample of elderly subjects. The clinical course of AAMI, the incidence of dementia in the AAMI population and the value of neuropsychological tests in predicting the development of dementia in AAMI were evaluated by a follow-up study. The neuropsychological profile of AAMI subjects was evaluated by comparing their performance in tests assessing frontal lobe functions with that of age-matched controls. The associations between the tests assessing frontal lobe functions and frontal lobe volumes as measured by magnetic resonance imaging were also examined. The relevance of subjective memory complaints as part of AAMI diagnosis was evaluated by examining the relationship of personality traits and affective state to these subjective complaints of memory loss.

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2. REVIEW OF LITERATURE

2.1. MEMORY IN AGING

2.1.1. Neuropsychology of memory in aging

Age-related alterations are observed in human memory performance. Although age differences in memory are seen in diverse experimental conditions (Verhaeghen et al. 1993), the effect of aging is not identical in all aspects of memory (Craik and Jennings 1992). Various models and schemes have been proposed to describe human memory function. The terminology used in different theories has also varied a lot. Research stemming from different traditions has produced a body of data which is mainly divided into two categories (Tulving 1995). The functional view of memory performance based on the information-processing approach in cognitive psychology describes human memory in terms of processing operations: encoding, storage and retrieval. The theory based on cognitive neuroscience and neuropsychology categorizes distinct memory systems. This theory originates in the functional dissociations between memory domains observed in humans with brain lesions and also in experimental animal models. The most significant distinctions are made between declarative and nondeclarative (procedural), and between semantic and episodic memory systems.

Memory processes

With regard to how aging affects various memory processes, Light (1991) reviewed research from four perspectives. These included theories attributing memory impairment to failures in metamemory (strategy use and memory monitoring), or to impoverished semantic encoding (due to problems in language comprehension), or to failures of deliberate retrieval (as opposing automatic, nonconscious recollection), or to diminished processing resources (due to reduced attentional capacity or cognitive slowing). Light argued that, so far, none of these research traditions provides enough evidence to explain the observed pattern of impaired function in old age. However, Craik and Jennings (1992) emphasized the value of these theories in generating relevant empirical questions. The functional approach suggests that age-related decline occurs in memory tasks requiring self-initiated, effortful processing (e.g., free recall), whereas in tasks involving stronger external support (e.g., recognition), smaller effects of aging on performance are implicated (Huppert 1991).

Primary, secondary and working memory

Both of the aforementioned research traditions make a principal distinction in memory function according to the time period involved. Primary memory (short-term memory) refers to the holding of information in the conscious awareness for a short period of time. Secondary memory (long-term memory) refers to material which is removed from conscious awareness but which is retrievable after longer periods of time. A concept closely related to primary memory is working memory which, however, refers to the somewhat more complex attentional capacity for simultaneously storing and processing the information needed during cognitive performances. The main effects of aging have been shown to take place in secondary memory (e.g., Kazniak et al. 1986). However, although primary memory is well preserved, working memory is strongly affected by aging. This dissociation has been explained in terms of the secondary memory component involved in working memory (Craik and Jennings 1992). According to Baddeley's (1992) model, working memory comprises multiple components: the "central executive" and several modality specific slave systems (e.g., "articulatory loop", "visuo-spatial sketchpad") for the temporary maintenance of information. It has been suggested that central executive resources undergo a specific decrease, whereas

the storage capacities remain unaffected by aging (Van der Linden et al. 1994).

Declarative and nondeclarative memory

The further classification of secondary memory creates another principal distinction in memory systems. Declarative memory (explicit memory) accounts for the conscious recollection of facts and information acquired through learning. Nondeclarative memory (procedural memory, implicit memory) describes memory involved with learned skills or modifiable cognitive operations which is not expressed by conscious recollection, but rather through modified performance. Simple classical conditioning and also the phenomenon of priming (nonconscious identification of a previously perceived item) are commonly included in the nondeclarative system (Squire et al. 1993). However, Tulving and Schacter (1990) proposed that priming might constitute a subsystem of its own: the perceptual representation system. The literature suggests a marked age-related decline in declarative but only minimal decline in nondeclarative memory tasks (Craik and Jennings 1992), although age differences in priming have been found which are, however, smaller than those found by direct measures of memory (recall, recognition) (La Voie and Light 1994).

Semantic and episodic memory

Declarative memory has been divided further into episodic and semantic memory (Tulving 1983). Episodic memory refers to memory for autobiographical events related to particular temporal contexts. Ordinary memory tests of free recall, cued recall and recognition involve this type of memory. A special aspect of episodic memory is source (context) memory: the recollection of the source of acquired information (e.g., in which situation one learned a particular fact or item) (Schacter et al. 1994). Semantic memory includes general knowledge about the world not associated with specific learning situations. The age differences in episodic memory are obvious, whereas in semantic memory they appear only if tasks, in addition to memory, also involve conceptual or inferential processing (Craik and Jennings 1992). Moreover, age differences have been shown to be particularly pronounced in source memory (Spencer and Raz 1995). Schacter et al. (1995) suggested that source memory impairment in the elderly reflects difficulties in the recollection of the perceptual aspects of episodes.

Tulving (1995) has proposed a model for converging the concepts of memory processes together with the concepts of multiple memory systems. According to this model, the relationships among memory systems are process-specific. The encoding occurs in a serial manner (from perceptual representation system via semantic to episodic memory), different systems being dependent on one another. After encoding, different kinds of information about the same initial event are stored in different systems in parallel. This information is then retrievable from each memory system independently of the other systems. Tulving also proposed this model as compatible with what is known about the contribution of different brain regions to different memory systems.

Comprehensive neuropsychological framework for cognitive aging

Various attempts have been made to establish a comprehensive neuropsychological framework to account for the general factors behind age-related changes in memory and other cognitive functions. A frequently cited distinction of age-related cognitive changes has been made between "fluid intelligence" and "crystallized intelligence" (Horn 1982). Fluid functions include those which challenge new learning, inductive reasoning or speed of processing. The decline in these functions during aging has been well documented (Salthouse 1992). Crystallized functions which operate with previously acquired information, general knowledge and comprehension tend to be preserved late in aging. For example, Baltes (1991) reviewed studies showing that in measures of "wisdom" (i.e., "good judgement and advice about important but uncertain matters of life"), no evidence can be found for lower performance in older adults. With regard to memory systems, the distinction between fluid and crystallized functions appears to relate to the dissociation between episodic and semantic memory.

Veroff (1980) proposed that the cognitive changes which occur during aging resemble those seen in patients with frontal lobe dysfunction. Mittenberg et al. (1989) found evidence for this with an extensive battery of neuropsychological tests. Salthouse (1990) proposed that a reduction in working memory processing, which is dependent on the frontal lobes, is the crucial factor for age-related changes not only in memory but in various other cognitive domains. Later, Salthouse (1994) emphasized reduction in processing speed as the general factor behind various cognitive decrements. Also considering the frontal lobes, Dempster (1992) suggested that a reduction in the capacity to inhibit of irrelevant influences might be an explanation for various age-associated cognitive changes. This view was been later supported by others (Arbuckle and Gold 1993, Kramer et al. 1994). Daigneault and Braun (1993) also suggested that frontal lobe function is the first to decline during normal aging, and attributed this decline to "defective attentional monitoring within high-level working memory". Close functional associations appear to exist between working memory, source memory and episodic memory, which may explain the more pronounced age-related decline in all of these systems in comparison to semantic memory.

2.1.2. Neuroanatomy of memory in aging

The description of the neurobiology of learning and memory varies depending on the level of biological organization in observation. At the basic level, memory is dependent on the function of individual neurons. Initial memory storage (lasting minutes to hours) involves the changes in the strength of synaptic connections. Longer-term memory storage, however, involves growth of new synaptic connections between neurons. The proposed mechanism inducing these changes is long-term potentiation: a long-lasting increase in the strength of synaptic response along a neural pathway after electrical stimulation (Bliss and Collinridge 1993). The most crucial neurotransmitter for these neuromodulatory effects is acetylcholine (Hasselmo and Bower 1993). Various changes which occur at the cellular level of brain function during aging affect these basic and modulatory systems (Ivy et al. 1992). In the following, however, the neural mechanisms of memory in aging are considered on a more general neuroanatomical level.

The prominent changes shown to occur in the brain during aging are: a decrease in brain weight, gyral atrophy, ventricular dilation, and selective loss of neurons within different brain regions (Kemper 1994). The relevance of these changes to behavioral measurements is still largely ambiguous (e.g., Lezak 1995). In addition to biological changes, environmental contexts are reflected in age-related cognitive changes (Arbuckle et al. 1992). Recent studies with advanced brain imaging methods (especially PET and functional MRI) have elucidated the neuroanatomical localization of cognitive functions (e.g., Frackowiak 1994, Moscovitch et al. 1995, Schacter et al. 1996). So far, very few of these studies have considered the effects of aging (Eustache et al. 1995, Grady et al. 1995). However, some associations between age-related cerebral and cognitive changes have been suggested.

Medial temporal lobe and diencephalon

Declarative memory is dependent on the integrity of the medial temporal lobe (MTL) structures, including the hippocampus together with adjacent, anatomically-related cortex (entorhinal, perirhinal and parahippocampal cortices). The MTL is not the eventual site of memory storage, but it operates for a limited period of time in the consolidation of memory traces, binding together the different neocortical structures involved in memory representations (Squire and Zola-Morgan 1991, Alvarez and Squire 1994). Another structure crucial for memory is the diencephalon, with a special role for the medial thalamus (more specifically, the anterior thalamic nucleus, the mediodorsal nucleus, and the connections within the internal medullary lamina). It has been hypothesized that the diencephalic structures and the MTL would contribute somewhat differently to memory functions, but no convincing evidence of such differences has been offered (Squire et al. 1993).

Neuropathological studies show that during normal aging, the hippocampus loses some of its neurons (20% - 30% by the age of 80 years), and the

remaining neurons develop signs of pathology (senile plaques and neurofibrillary tangles) (Squire 1987). These findings suggest that forgetfulness in elderly individuals might at least in part be due to hippocampal dysfunction. Albert et al. (1987) found that age-related decline in memory performance correlated with regional EEG changes in the frontal and temporal areas. Recent MRI studies of the MTL (Launer et al. 1995) and the hippocampus (Golomb et al. 1993) have further confirmed that atrophy in these regions is common in elderly persons and might contribute specifically to memory dysfunction. However, Barnes (1994) reviewed evidence indicating that the hippocampal changes associated with normal aging are not simply degenerative but selective, including deterioration, preservation and also functional compensation. Decreased hippocampal volume has been shown to be as a rather accurate diagnostic measure for AD (de Leon et al. 1993, Laakso et al. 1995), and it also correlates with declarative memory performance in AD patients (Riekkinen et al. 1995). Considering the entorhinal cortex, recent findings also suggest that no distinct neuron loss occurs during normal aging whereas a marked decrement is present even in very mild AD (Gómez-Isla et al. 1996).

Eustache et al. (1995) demonstrated concomitant age-related declines in brain oxidative metabolism (in the resting condition) and tests of episodic memory, which also suggests that neurobiological changes within the neural network for episodic memory (which includes the hippocampus and the thalamus) may underlie the memory impairments of normal aging. Accordingly, Grady et al. (1995) found age-related reductions in regional cerebral blood flow within the network including the hippocampus and the anterior cingulate cortex during the encoding phase of a face recognition task.

Frontal lobe

The frontal lobe has been associated with the performance of higher-level cognitive functions such as organization and the executive control of complex mental processes (Mesulam 1990). Frontal lesions themselves do not cause amnesia in the way that MTL and diencephalic lesions do. However, the frontal lobes contribute to various aspects of memory processes: the spatial and verbal working memory (Joyce and Robbins 1991, Petrides et al. 1993), the organization of retrieval processes requiring deliberate mental effort (Janowsky et al. 1989, Incisa della Rocchetta et al. 1993), and the temporal organization of memory (Milner et al. 1985). Source memory has also been associated with executive processes controlled by the frontal lobes (Spencer and Raz 1995). Frontal dysfunction has been proposed as an explanation for the characteristics previously attributed to diencephalic amnesia on the basis of studies of memory disorders associated with Korsakoff's syndrome (Squire et al. 1993). Grady et al. (1995) found increased regional cerebral blood flow activation (rCBF) in the left prefrontal cortex during encoding and the right prefrontal cortex during the recognition phase of a face recognition task. Moreover, they observed that age-related disruption in rCBF activation during the encoding phase was associated with inferior memory performance.

The greatest loss of neurons (Haug et al. 1983) and reduction in brain volume (Coffey et al. 1992) during aging is seen in the frontal lobes (but also in subcortical structures, the thalamus and the basal ganglia (Haug et al. 1983)). Another view is that the number of cells is not dramatically reduced, but they shrink in size (Terry et al. 1987). Dempster (1992) suggested that similar patterns of inefficiency in frontal lobe function occur in young children, older adults, and subjects with frontal lobe lesions. The integration of neuropsychological and neuroanatomical evidence suggests that these regions are the last to develop during maturation and the first to undergo involution in later life. These suggestions also agree with the pattern of memory changes found in aging.

Brain white matter

In demented patients, studies have suggested that white matter hyperintensity (WMH) in the brain is related to greater impairment of verbal abilities and attention and to slowing of mental processes (Kertesz et al. 1990, Almkvist et al. 1992). In normal healthy elderly subjects, findings have been controversial. Ylikoski et al. (1993) found a negative correlation between WMH and measures of attention and speed of mental processing in healthy elderly subjects. Skoog et al. (1996) suggested that WMH affects various cognitive functions in both nondemented (verbal and spatial ability, memory, speed, arithmetic ability and global cognitive rating) and demented (spatial ability, memory and global rating) subjects. However, Almkvist et al. (1992) and Fein et al. (1990) found no cognitive changes associated with WMH in normal elderly subjects. Boone et al. (1992) suggested that decline is evident in attention and select frontal lobe functions only after a "threshold" of sufficient severity in WMH has been overcome. Mittenberg et al. (1989) speculated that the frontal lobe disconnection syndrome caused by WMH might be a possible explanation for age-related changes in frontal lobe function. Thus, WMH might be associated with age-related decline in working memory and other frontal lobe- mediated aspects of memory.

2.1.3. Successful aging

Some longitudinal studies have demonstrated a rather high stability of intelligence during aging (Schwartzman et al. 1987). Variability in neuropsychological test scores is greater in older subject groups (Morse 1993). Thus, a large proportion of aged persons also show cognitive performance comparable to the standards of younger adults, at least in some domains. The term "successful aging" has been introduced to take into account this heterogeneity among the elderly population. In "usual aging", extrinsic factors heighten the effects of aging alone, and in successful aging, extrinsic factors play a neutral or positive role (Rowe and Kahn 1987). Thus, cognitive changes might be better explained in terms of such factors as life style, habits, diet and psychosocial factors than by aging per se.

By using a structural equation model, Jones et al. (1991) found evidence for a causal relationship between age-related changes in the brain (as measured by CT and EEG) and cognition in healthy individuals. However, their model also suggested other causal contributors to cognitive function. Favourable circumstances, according to psychosocial measures relating to general psychiatric symptomalogy and social support, and also measures of stress were associated with better cognitive performance. Arbuckle et al. (1992) found that in addition to being younger, healthier and having higher education, also such factors as being more introverted, more intellectually active, and more satisfied with social support predicted less intellectual decline and better memory performance. Several studies suggest that a high educational level together with continuing mental activity may protect against aging effects (Orrell and Sahakian 1995). A high mental activity level may also, to some extent, moderate the unfavourable effects associated with low education (Christensen et al. 1996).

Much of the variability found in the cognition of aged individuals has been regarded as a consequence of health-related factors (Perlmutter and Nyquist 1990, Houx et al. 1991). Accordingly, Howieson et al. (1993) found many cognitive functions to be relatively well-preserved in a sample of optimally healthy "oldest old" (84 to 100 years of age) subjects as compared to "young old" (66 to 74 years of age) subjects. However, Christensen et al. (1994) disagreed with this, and found only a minor role for health in age-related cognitive decline. The obvious age-associated changes emerging in most of the sensory modalities are commonly not regarded as major contributors to cognitive aging (Ivy et al. 1992). However, Lindenberger and Baltes (1994) found that visual and auditory acuity in combination contributed strongly to the age-related variance in intelligence measures in very old persons (70 to 103 years of age). In interpreting this result, the authors preferred the "common cause" hypothesis, which implies that the negative effects in both the sensory and cognitive domains may reflect an age-related loss in the integrity of brain function. However, they could not rule out the possibility that the result might reflect "sensory deprivation", prolonged sensory underload, which could reduce an individual's engagement in cognitively-stimulating interaction with his/her environment. Furthermore, a role for genetic factors as modificators of cognition during aging has been suggested (Finkel and McGue 1993, Helkala et al. 1996). Rapp and Amaral (1992) emphasized the value of studies combining behavioral and neurobiological assessments in the same subjects to define the neural basis of age-related cognitive changes and to identify the factors that promote successful aging.

2.2. AGE-ASSOCIATED MEMORY IMPAIRMENT (AAMI)

Kral (1958, 1962) was the first to introduce diagnostic terminology for age-associated changes in memory. He used the term "benign senescent forgetfulness" (BSF) to distinguish subjects with mild memory decline from those with more severe, "malignant" changes, and also from those with normal memory functions. However, Kral did not operationalize the concept of BSF. A National Institute of Mental Health (NIMH) work group, which was set up to describe this phenomenon more precisely, proposed the concept of "age-associated memory impairment" (AAMI) as a diagnostic entity (Crook et al. 1986). In brief, the criteria of AAMI include the presence of subjective memory decline, objective evidence of memory loss (in a well-standardized memory test, a score at least one standard deviation below the mean of younger adults), adequate intellectual function, and the absence of dementia or other memory-affecting disease (e.g. stroke) in a person aged 50 years or older. Thus, the AAMI diagnosis identifies persons with subjectively and objectively evidenced memory loss without cognitive decline impairing enough to warrant the diagnosis of dementia. The criteria leave open the question of progression in the condition. The detailed AAMI criteria are presented in Table 1.

Some researchers have regarded both neurobiological and neuropsychological observations in aging studies as evidence of a continuum between normal aging, mild cognitive impairment, and dementia (Von Dras and Blumenthal 1992). Drachman (1994) argued that strong evidence suggests that dementia might be an inevitable concomitant of advanced aging "if we live long enough". In agreement with this theory, AAMI (or BSF) could be viewed as an intermediate state between so-called successful aging without marked cognitive decline and states diagnosed as dementia, especially AD (Brayne and Calloway 1988, Brayne 1994). Moreover, Youngjohn et al. (1992) suggested that some subjects in the AAMI category may actually be in the early stages of AD. On the other hand, if AAMI turned out to be a separate and stable entity, that would provide a means of reassurance for that large proportion of elderly which is worried about age-related memory loss as a sign of possible incipient dementia.

Since the proposition of the criteria, a substantial body of research has been conducted involving subjects with AAMI. The construct of AAMI has been utilized in studies aiming to characterize age differences in memory (Larrabee and Crook 1989), brain structure (Reisberg et al. 1988, Parnetti et al. 1996), neuroimmunology (Reisberg 1988) and cerebral metabolism (Small et al. 1994, Parnetti et al. 1996). Various pharmacological treatment trials have been conducted to find out means to improve the memory function in AAMI subjects (e.g., Crook et al. 1991, McEntee et al. 1991, Neri et al. 1995, and reviews: McEntee and Crook 1990, Sarter 1991, McEntee and Crook 1992).

McEntee and Crook (1990) estimated that AAMI might affect most of the over 50 population to some degree. However, Lane and Snowdon (1989) reported a prevalence rate of 35% for AAMI in subjects aged 65 years or over. The results are somewhat hampered by the low participation rate (58%) of the study population, and by the fact that the methodology used did not strictly follow the propositions of the NIMH work group. On the basis of memory test performance alone, Larrabee and Crook (1994) estimated the prevalence of AAMI to vary from 39% in the age group 50 to 59 years to 85% in the age group over 80 years. In that study, no exclusion criteria were employed. Barker et al. (1995) recently reported much lower prevalence rates for AAMI. They found a 15.8% prevalence of AAMI in 50- to 64-year-old and 24.1% in 65- to 79-year-old subjects. The low figures were mainly explained by the high proportion of subjects meeting some of the exclusion criteria, since memory test performance identified as many as 79% of the participants in the AAMI category.

The presence of memory complaints is an essential part of the AAMI criteria, which has been a controversial issue in the AAMI literature. Various studies have assessed whether such complaints are related to objective findings in memory tests or to some other factors, such as personality traits or affective state of the subjects. A number of studies has provided evidence for a significant relationship between memory complaints and memory performance as assessed by memory tests (Zelinski et al. 1980, Riege 1982, Dixon and Hultsch 1983, Larrabee et al. 1991). In many other studies, however, no association or only a minor association has been found between subjects' performance in memory tests and ratings on memory complaint questionnaires. In these studies, investigators have considered memory complaints to be associated with a depressed mood (Kahn et al. 1975, Plotkin et al. 1985, Larrabee and Levin 1986, McGlone et al. 1990, Bolla et al. 1991) or with depression combined with other factors such as anxiety, stress (Broadbent et al. 1982), poor social network, negative stereotypes of aging, poor affective state (Derouésne 1990), indecisiveness, impaired concentration, mental slowing (O'Connor et al. 1990), neurotic tendencies (Poitrenaud et al. 1989) or somatic complaints and feelings of inadequacy (Zonderman et al. 1989). Heaton and Pendleton (1981) found that patients' self- ratings were much more strongly associated with their scores in a personality inventory than with their neuropsychological test performance. Flicker et al. (1993) reported that elderly subjects with subjective perceptions of cognitive decrements but without clear evidence of impairment on clinical interview were not at a high risk for progressive cognitive deterioration during a three- to four-year follow-up. It has been suggested that the criterion based on subjective memory loss should be abolished from the AAMI diagnosis (Smith et al. 1991, Caine 1993). However, some investigators have emphasized that memory complaints should be taken seriously as a possible sign of early dementia (O'Brien et al. 1992, Grut et al. 1993).

The terminology for classifying age-related changes in memory performance has been used rather inconsistently. Sometimes BSF and AAMI have been used as interchangeable terms (Crook et al. 1986, Buschke and Grober 1986, Bamford and Caine 1988, Lane and Snowdon 1989). In other papers, BSF has been considered to indicate more profound memory loss relative to one's age peers, as AAMI is defined relative to younger adults (Larrabee et al. 1986, O'Brien et al. 1992). However, BSF has also been presented as a milder condition, and AAMI has been diagnosed only when there is clear evidence of cognitive decline which is not severe enough to warrant the diagnosis of dementia (O'Neill et al. 1992, Coria et al. 1993). Due to these differences in definitions, all studies using AAMI and BSF concepts are not directly comparable.

Although many studies have supported the theoretical construct of AAMI (Buschke and Grober 1986, Larrabee and Crook 1989, Lane and Snowdon 1989, Youngjohn et al. 1992), other investigators have doubted the usefulness of the AAMI diagnosis, and have suggested that there should be revisions made in the defining criteria to reduce the variability in the AAMI population and to enhance the reliability of the diagnosis (Bamford and Caine 1988, Blackford and La Rue 1989, Smith et al. 1991, O'Brien and Levy 1992, Caine 1993). In spite of partly promising results, the rationale for conducting pharmacological treatment studies with AAMI subjects has been strongly criticized (O'Brien and Levy 1992, Barker and Jones 1993, O'Brien 1994). Moreover, Rosen (1990) considered the concept of AAMI to be a potential hindrance to research into aging. The controversies in the AAMI literature are obvious. However, much of the criticism has been based on theoretical reasoning and not so much on empirical evidence. Thus, further research on this topic is warranted. In particular, follow-up studies of AAMI subjects have been recently recommended by many investigators (e.g., O'Brien 1994, Nicholl 1995).

2.3. AGING-ASSOCIATED COGNITIVE DECLINE (AACD)

A task force of the International Psychogeriatric Association (IPA) in collaboration with the World Health Organization (WHO) recently proposed diagnostic criteria for "aging-associated cognitive decline" (AACD) (Levy 1994). The diagnosis of AACD is based on a more comprehensive evaluation of cognition than that of AAMI. Deterioration in any major cognitive domain is sufficient for identifying AACD. The cognitive domains specified in the AACD criteria are memory and learning, attention and concentration, thinking, language and visuospatial functioning. Also differing from the AAMI criteria, the subject with AACD is required to score one standard deviation below of age- and education-specific standards (not those of younger adults) in neuropsychological tests assessing cognitive abilities. Thus, the AACD diagnosis identifies persons with subjectively and objectively evidenced cognitive decline which is not impairing enough to warrant the diagnosis of dementia. In presenting the AACD criteria, the IPA task force recognized the possible variability in individuals identified as having AACD. For some of them it may precede dementia, and for some it may be a relatively stable condition. The criteria for AACD diagnosis are presented in Table 2.

AACD and AAMI must also be differentiated from the various other diagnostic classifications which have been proposed (Dawe et al. 1992, Ebly et al. 1995). The best established of these classifications are "mild cognitive disorder" (MCD) and "age-related cognitive decline" (ARCD). MCD is included

in the research criteria for ICD-10 (World Health Organization 1993). This diagnosis is used only when there is an indication of a disease or condition known to cause cerebral dysfunction. The epidemiology of MCD has been considered in two recent studies with contradictory results. Christensen et al. (1995) found a prevalence rate of only 4% for MCD and concluded that the diagnosis lacks validity. Ebly et al. (1995) wanted to add the presence of subjective complaints, but otherwise agreed with the ICD-10 criteria for MCD. ARCD is included in the DSM-IV (American Psychiatric Association 1994) defined as "an objectively identified decline in cognitive functioning consequent to the aging process that is within normal limits given the person's age". However, no more detailed criteria are included in the DSM-IV, and no studies employing this construct have been conducted.

Table 1. Proposed criteria for the diagnosis of Age-Associated Memory Impairment - National Institute of Mental Health Work Group (Crook et al. 1986)

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1. Inclusion criteria

a. Males and females at least 50 years of age.
b. Complaints of memory loss reflected in such everyday problems as difficulty remembering names of individuals following introduction, misplacing objects, difficulty remembering multiple items to be purchased or multiple tasks to be performed, problems remembering telephone numbers or zip codes, and difficulty recalling information quickly or following distraction. Onset of memory loss must be described as gradual, without sudden worsening in recent months.
c. Memory test performance that is at least 1 SD below the mean established for young adults on a standardized test of secondary memory (recent memory) with adequate normative data. Examples of specific tests and appropriate cutoff scores are listed below, although other measures with adequate normative data are equally appropriate.

Test Cutoff score
Benton Visual Retention Test (A) 6 or less
Logical Memory Subtest of the Wechsler Memory Scale (WMS) 6 or less
Associate Learning Subtest of the WMS 13 or less

d. Evidence of adequate intellectual function as determined by a scaled score of at least 9 (raw score of at least 32) on the Vocabulary subtest of the Wechsler Adult Intelligence Scale.
e. Absence of dementia as determined by a score of 24 or higher on the Mini-Mental State Examination.

2. Exclusion criteria

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

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Table 2. Diagnostic criteria for aging-associated cognitive decline (AACD) -Working Party of the International Psychogeriatric Association in collaboration with the World Health Organization (Levy 1994)

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1. A report by the individual or a reliable informant that cognitive function has declined.
2. Onset of decline must be described as gradual and must have been present for at least 6 months.
3. Difficulties in any one of the following areas: memory and learning; attention and concentration; thinking (e.g., problem- solving, abstraction); language (e.g., comprehension, word finding); visuospatial functioning.
4. Abnormality of performance on quantitative cognitive assessments (for example, neuropsychological tests or mental state evaluations) for which age and educational norms are available for relatively healthy individuals. Performance must be at least 1 SD below the mean value for the appropriate population.
5. Exclusion criteria: None of the abnormalities listed above of a degree sufficient for the diagnosis of mild cognitive disorder or dementia to be made. (There must be no objective evidence from physical and neurological examination or laboratory tests, and no history of cerebral disease or damage, or of systemic physical disorder known to cause cerebral dysfunction.) Other exclusion criteria would be as follows: (a) depression, anxiety or other significant psychiatric disorder that may contribute to the observed difficulties; (b) organic amnestic syndrome; (c) delirium; (d) postencephalitic syndrome; (e) postconcussional syndrome; (f) persisting cognitive impairment due to psychoactive substance use or the effects of any centrally acting drug.

2.4. NEUROPSYCHOLOGICAL METHODOLOGY IN THE STUDIES OF AGING

2.4.1. Studying age differences in cognition

A frequently debated weakness in the research of age differences in cognition is the lack of longitudinal data and the unreliability of cross-sectional data for describing longitudinal change. Subject cohorts of different ages probably differ also in many other dimensions critical for cognitive performance. Possible intervening factors increasing the effect of aging are, for example, differences in early health care and nutrition, educational and occupational opportunities, and sociocultural expectations (Albert 1988). Moreover, the age ranges in different studies are very variable depending on how "old age" is defined. The generalization of data from early to late stages of old age appears to be problematic (Nilsson et al. 1987). The definition of "normal aging" is also problematic, since the typical "normal" control group of elderly individuals is also likely to include a few subjects with some brain disorder (Lezak 1995). Accordingly, a recent study suggested that excluding individuals with established dementia is not enough, because preclinical dementia may account for a large proportion of the apparent age-related decline in cognition (Lipton et al. 1996). The suggested separation between "usual" and "successful" aging may further complicate the definition of normality in the elderly (Calne et al. 1991).

Cohort differences may also occur in test taking characteristics. Older subjects may be unfamiliar with standardized testing making them more anxious or less motivated in test sessions. They might also be more vulnerable to fatigue (Albert 1981). However, some problems are also evident in longitudinal studies. A selective loss of subjects during follow-up because of, for example, death, physical illness or severe cognitive dysfunction could lead to the underestimation of aging effects (Albert 1988). Moreover, the repeated administration of neuropsychological tests appears to result in significant practice effects, at least in subjects up to 75 years of age (Mitrushina and Satz 1991).

2.4.2. Differentiating dementia from normal aging

The variability has been commonly thought to increase with age (Rowe and Kahn 1987). A meta- analysis of a remarkable number of studies demonstrated this for measures of reaction time, memory, and fluid intelligence, but not for measures of crystallized intelligence (Morse 1993). Several subgroups of elderly persons with different cognitive profiles (with relative weaknesses and strengths in different domains) have been described. Some controversy exists regarding how these subgroups possibly relate to the cognitive subgroups found among AD patients (Valdois et al. 1990, Leibovici and Ritchie 1995, Mitrushina et al. 1995)

The research into the relationship of "normal" changes with those resulting from degenerative diseases (especially AD) relates to the aforementioned debate about the continuum from normal aging to dementia. In spite of some preliminary suggestions of qualitative differences between normal aging and AD, the evidence is not compelling (Nebes 1992). Reviewing memory studies, Huppert (1994) concluded that "there appears to be a continuity in the memory performance of normal elderly subjects and those with mild dementia or whose dementia is in the early stages". Furthermore, evidence from studies of visuospatial functions (Filoteo et al. 1994) as well as personality and behavior (Hope 1994) does not indicate qualitative differences. However, the studies of language functions reviewed by Kempler and Zelinski (1994) do suggest some qualitative differences.

On the basis of cross-sectional comparisons of normal and demented elderly individuals, various cognitive screening scales and neuropsychological tests have been proposed to be both sensitive and specific for the detection of dementia. The most widely used scale in population-based dementia screening studies has been the Mini-Mental State Examination (MMSE) (Folstein et al. 1975). In studies aiming to find a single neuropsychological test suitable for the detection of dementia, tests for such memory functions as logical memory (Storandt et al. 1984), list learning with the selective reminding method (Christensen et al. 1991), cued recall (Grober et al. 1988), and delayed recall (Welsh et al. 1992) have been found applicable. Also, tests of verbal fluency and psychomotor speed (Storandt et al. 1984), confrontational naming (Storandt and Hill 1989, Welsh et al. 1992), visuo-constructive function (Wolf-Klein et al. 1989), and queries of memory complaints from relatives (McGlone et al. 1990, Morris et al. 1991) have been suggested as reliable methods for differentiating dementia from normal aging. Several authors have suggested that a short battery of neuropsychological test should be used for dementia screening instead of a cognitive scale or only one individual test (Storandt and Hill 1989, Morris et al. 1989 Stern et al. 1992) However, despite satisfying results in case-control studies, it has been difficult to establish a method for dementia screening which would be at the same time sensitive and specific enough at the population level (Koivisto 1995).

The validity of neuropsychological methods varies according to the purposes of the assessment (Heinrichs 1990). The most important kind of validity for the memory assessment of older adults is construct validity. According to Cunningham (1986), the "test must be anchored in a structural theory of memory functioning that is reasonably comprehensive in identifying broad common factors". Schaie and Schaie (1977) noted that a test may assess different constructs in older and in younger adults due to various cohort effects. However, the establishment of construct validity is in many cases a very abstract endeavour (Cunningham 1986). Predictive (external) validity is more concrete. In dementia screening studies, tests or scales have been assessed in reference to their ability to detect subjects for whom the clinical dementia diagnosis (external criterion) has been established. Age, education, gender and cultural background have been shown to affect scores in tests and scales and, therefore, various adaptations to scoring have been suggested to increase diagnostic accuracy (e.g., Stern et al. 1992, Ylikoski et al. 1992). Face validity (a test appears to measure what it is said to measure) is of the essence in testing older people (Cunningham 1986) and in voluntary population screening (Ritchie 1988). Older subjects may not want to participate in test sessions if tests appear incomprehensible or illogical.

Ritchie (1988) criticized available cognitive screening scales for poorly established reliability. The consistency and stability of these screening instruments have not been considered properly. However, for example, the MMSE has been shown to have good test-retest and interrater reliability (Tombaugh and McIntyre 1992). In various individual tests of cognitive performance, the reliability appears to be good also for elderly populations (Cunningham 1986, Chouinard and Braun 1993).

2.4.3. Predicting dementia

Longitudinal studies have suggested that the mild cognitive impairment determined by clinical evaluation and neuropsychological tests is useful in predicting dementia from two to three years before the condition is manifest clinically (Flicker et al. 1991, Bickel and Cooper 1994). Observed mild cognitive decline also appears to be associated with a greater risk of mortality in very old age groups (Johansson et al. 1992). Mortality has also been associated with psychiatric symptoms both in middle-aged and elderly populations (Huppert and Whittington 1995).

Specific neuropsychological test scores have been suggested to be of value for predicting cognitive deterioration. Linn et al. (1995) found low performance in tests of verbal memory to be related to AD by seven years or more. Interestingly, they also found that subjects later diagnosed with AD performed at higher levels in a test of primary memory (the Digit Span), and speculated that this might reflect a response in this memory system to the deterioration of secondary memory. Masur et al. (1994) also demonstrated that low performance in tests of delayed recall may predict dementia. Moreover, Masur et al. suggested that a test of complex visuomotor performance (the Digit Symbol) and a verbal fluency score predicted the development of dementia over four years. In studies involving asymptomatic subjects known to be mutation carriers of familial AD, a gradual impairment of long- term episodic memory has been found several years before a clinical diagnosis can be made (Almkvist 1996). It has also been suggested that subjective memory complaints, even without manifest psychometric evidence of cognitive decline, may be associated with an elevated risk of dementia (O'Brien et al. 1992), but conflicting longitudinal data also exist (Flicker et al. 1993).

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3. AIMS OF THE STUDY

The present series of studies is a part of a larger project to investigate the nature of cognitive decline in aging and the relationships between normal aging and dementia. The general purpose of these studies was to characterize the neuropsychological and epidemiological properties involved in diagnosing age- related cognitive changes as proposed in the research criteria for age-associated memory impairment (AAMI) and aging-associated cognitive decline (AACD).

The specific aims of the study were:

1) To evaluate the prevalence rate of AAMI in a randomly selected sample of elderly subjects (Study I).

2) To characterize the neuropsychological profile of AAMI by evaluating the performance of AAMI subjects in neuropsychological tests assessing frontal lobe functions as compared to the performance of age-matched control subjects with intact memory, and by examining the associations between test performance and frontal lobe volume as measured on MRI scans (Study II).

3) To evaluate the relevance of subjective memory complaints as part of AAMI and AACD diagnosis by examining the association of personality traits and affective state with these subjective complaints of memory loss (Study III).

4) To examine the clinical course of AAMI and to evaluate the value of neuropsychological tests in predicting cognitive decline in AAMI subjects during a follow-up period of more than three years (Study IV).

5) To evaluate the prevalence rate of AACD, and to examine the value of a neuropsychological test battery for characterizing AACD subjects (Study V).

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4. SUBJECTS AND METHODS

4.1. SUBJECTS

The study was conducted in the Memory Research Clinic of the Department of Neurology in the University of Kuopio between January 1989 and October 1994. The study was approved by the Ethics Committee of the University of Kuopio and Kuopio University Hospital. All subjects gave informed consent before participating in the study.

The study included three different samples of subjects aged 60 to 81 years at the time of the investigations. The samples were randomly drawn from the population register of the city of Kuopio.

Population 1: A random sample of 592 persons born between 1912 and 1921 was drawn from the Kuopio population register, which included all 5,286 inhabitants of Kuopio in this age group on January 1, 1986. Of the 592 persons randomly selected, a total of 79 subjects had died before the investigation, and 11 had moved outside the study area. Of the remaining 502 subjects, 403 (80.3 %) were evaluated. Of the nonparticipants, 17 reported being too ill to participate, 55 refused to participate and 27 could not be contacted. Because the data for the assessment of AAMI were missing for one patient, 402 completely evaluated subjects were included for analysis. The examinations were carried out from January to August 1989.

Population 2: Another random population sample of 250 persons born between 1922 and 1930 was drawn from the Kuopio population register to evaluate the prevalence rate for AAMI in a younger age group. Of the 250 randomly selected, 176 (70.4%) participated. No data on nonparticipants were collected. Examinations were done during January and February of 1990.

Population 3: To increase the power of the study on the prevalence of AAMI, we also examined a third population sample of 667 subjects born between 1917 and 1927. This random population sample was also taken from the Kuopio population register; however, all persons included in Subpopulations 1 and 2 described above were excluded. Eventually, 482 (72.7%) persons of this sample participated. A total of 108 were not willing to participate, 62 could not be contacted, 11 were too ill to participate and 4 had died before the study. Of those who participated, data for the assessment of AAMI was available from 471 subjects (97.7%). These examinations were done from May to September 1992.

After combining the three subpopulations, a total of 1,049 randomly selected subjects aged 60 to 78 years were completely evaluated, giving an overall participation rate of 74.4 %. All three subpopulations were used in the study of the prevalence of AAMI (I). In the study of the prevalence of AACD (V), only Subpopulation 1 was used. The population in the follow-up study (IV) consisted of 229 AAMI subjects identified in Subpopulations 1 and 2. Of them, 176 (76.9%) subjects participated in the follow-up. The clinical characteristics of the evaluated subjects in the prevalence studies and follow-up are presented in Table 3.

Table 3. Clinical characteristics of study populations and tests used in evaluation (I, IV, V)

	Study 1	Study 2	Study 3	Total in screening	Follow-up for AAMI subjects
Random sample	592	250	667	1509	229 (From 1 and 2)
Subjects examined (%)	402 (80.1)	176 (70.4)	471 (71.6)	1049 (74.4)	176 (76.9)
Sex: female	245 (60.9)	101 (57.4)	287 (60.9)	633 (60.3)	103 (58.5)
Age, years	71.3+/-3.1	63.5+/-2.3	68.6+/-2.7	68.8+/-3.9	71.7+/-5.0
-range	68-78	60-67	64-75	60-78	63-81
Education, years	6.7+/-3.4	6.9+/-2.7	7.8+/-3.4	7.3+/-3.3	6.6+/-2.5
-range	0-18	2-19	2-25	0-25	1-17
Tests					
BVRT	X	X	X		X
PAL	X	X	X		X
MMSE	X	X	X		X
MAC-Q	X	X	X		X
BSRT	X				X
VRT	X				X
VFT	X				X
TMT	X				X
ST					X
WCST					X
DSp-WAIS					X
DSy-WAIS					X
BD-WAIS					X
V-WAIS			X		X

BVRT = Benton Visual Reproduction Test; PAL = Paired Associated Learning subtest from the Wechsler Memory Scale; MMSE = Mini-Mental State Examination; MAC-Q = Memory Complaint Questionnaire; BSRT = Buschke Selective Reminding Test; VFT = Verbal Fluency Test on letters and category; TMT = Trail-Making Test; ST = Stroop Test; WCST = Modified Wisconsin Card Sorting Test; DSp-WAIS = Digit Span; DSy-WAIS = Digit Symbol; BD-WAIS = Block Design; V-WAIS = Vocabulary from the Wechsler Adult Intelligence Scale.

The AAMI subjects and age-matched controls for the study of frontal lobe functions (II) were randomly selected from Subpopulations 1 and 2. The subjects were included in the study if they were willing to complete the entire study protocol. The participants were examined between August 1992 and October 1994. The clinical data for the subjects in this study are presented in Table 4.

Table 4. Clinical data for subjects in the study of frontal lobe functions in AAMI (II)

	Controls	AAMI	*p*
Number of Subjects	47	43	
Gender (women /men)	24/23	31/12	0.041
Age (years)	71.1+/-4.0	69.9+/-5.4	0.249
Education (years)	9.9+/-3.7	8.2+/-3.2	0.023
MMSE	28.3+/-1.4	27.6+/-1.6	0.031
BVRT	7.7+/-0.8	5.2+/-1.0	0.000
PAL	17.8+/-2.0	14.1+/-1.8	0.000
V-WAIS	50.4+/-6.9	42.3+/-7.5	0.000
MAC-Q	26.6+/-3.0	2.8+/-3.1	0.005
GDS	4.6+/-3.3	6.7+/-4.2	0.020

Results are mean+/-SD. Chi-square test for gender, Student's t-test for age and education, ANCOVA adjusted for age and education for other variables. AAMI = age-associated memory impairment; BVRT = Benton Visual Reproduction Test; PAL = Paired Associated Learning subtest from the Wechsler Memory Scale; MMSE = Mini-Mental State Examination; MAC-Q = Memory Complaint Questionnaire; V-WAIS = Vocabulary from the Wechsler Adult Intelligence Scale; GDS = Geriatric Depression Rating Scale.

Subjects for the study of memory complaints (III) were selected from the participants of Subpopulation 1 according to Memory Complaint Questionnaire scores (MAC-Q, see 4.2.2.). The cutoff points were set so that subjects scoring 30 or higher (the highest quartile) were classified as "complainers" (C-group) and subjects scoring 24 or less (the lowest quartile) were classified as "noncomplainers" (nonC-group). With these criteria, 28 "complainers" and 34 "non-complainers" were identified for closer evaluation. After matching by age and education, 18 subjects remained in both groups. In both groups, 16 subjects (88.9%) returned the questionnaire (see 4.2.1.). When the subjects completed the MAC-Q in the questionnaire for the second time, their ratings showed some differences compared to their answers in the initial screening phase. Now, only 10 (62.5%) subjects from the C-group reached the score of 30 or higher necessary to classify them as complainers (the mean was 31.4 points in the screening and 30.4 points in the follow-up). Also, only 10 subjects in the nonC-group now achieved the score of 24 or less necessary to classify them as noncomplainers (mean: 22.1 points in the screening and 23.2 points in the follow-up). The mean age was 71.7 in the C- group and 71.5 years in the nonC-group. The mean education was 6.5 and 7.5 years, respectively. The mean MAC-Q score was 31.9 in the C-group and 21.9 points in the nonC-group. These study groups did not differ from one another or from the larger screening sample, except for their incidence of memory complaints (Table 5). The questionnaire was sent to the study groups in November 1989, an average of eight months after the screening.

Table 5. Clinical data for subjects in the study of memory complaints (III)

	Population 1	Complainers	Noncomplainers
Nr of subjects	403	10	10
Men/women	157/246	2/8	3/7
Age (years)	72.0+/-3.0	71.7+/-2.31	71.5+/-2.84
Education (years)	6.7+/-3.4	6.5+/-2.27	7.5+/-4.06
MAC-Q	26.8+/-3.74	31.9+/-1.6	21.7+/-0.95
MMSE	26.0+/-2.81	27.8+/-1.4	28.3+/-1.42
BVRT	5.1+/-1.9	6.1+/-0.99	6.5+/-1.51
PAL	13.8+/-3.8	16.6+/-2.27	16.8+/-2.35

Results are mean +/- SD. MAC-Q = Memory Complaint Questionnaire (in the screening); MMSE = Mini-Mental Status Examination; BVRT = Benton Visual Retention Test; PAL = Paired Associated Learning from Wechsler Memory Scale. No statistically significant differences (Student's t-test) between the study groups or between the total population and the study groups except for MAC-Q (p. < 0.001) between all groups.

4.2. METHODS

4.2.1. Study program

All respondents in the random sample-based study phases (I,V) underwent a structured interview which included demographic information, medical history and current medication. The NIMH criteria with suggested cutoff points for the neuropsychological tests were used for the classification of AAMI (Crook et al. 1986). Subjective complaints of memory loss were rated with the Memory Complaint Questionnaire (MAC-Q). A score of 25 or higher was considered to indicate subjective memory impairment (Crook et al. 1992). Objective memory capacity was assessed with the Benton Visual Retention Test, form C, administration A (BVRT) and with the Paired Associated Learning subtest of the Wechsler Memory Scale (PAL). The cutoff scores for AAMI in these tests were 6 or less in the BVRT and 13 or less in the PAL. A score below the cutoff point in either test was considered as

evidence of objective memory impairment. To examine mental capacity and to rule out the presence of dementia, the subjects were tested with the Mini-Mental State Examination (MMSE) in which a score less than 24 was used to exclude possibly demented subjects. Table 3 presents the neuropsychological methods used in the different phases of the study, which are described in detail in Chapter 4.2.2.

Subpopulation 1 was also examined with four other tests: the Buschke Selective Reminding Test (BSRT), Russell's adaptation of the Visual Reproduction Test also including the copying of figures after delayed recall (VRT), the Verbal Fluency Tests on letters P, A and S, and category (animals) (VFT-L, VFT-C), and the Trail Making Test versions A, B, C (TMT). Those subjects scoring poorly in these tests received a further evaluation and a clinical examination to diagnose dementia according to the DSM III-R criteria (American Psychiatric Association 1987). The methods of these evaluations and the results including prevalence rates of dementia have been reported previously (Koivisto 1995).

The following diseases with possible direct negative effects on cognitive functions were considered exclusions for AAMI and AACD: stroke, brain hemorrhage, diabetes, psychiatric disorders and malignancy.

In the follow-up evaluation (IV), the classification of AAMI was accomplished by the same methods as described above. Furthermore, a comprehensive neuropsychological test battery including the BSRT, VRT, VFT, TMT and also the Stroop Test (ST), the modified Wisconsin Card Sorting Test (WCST), and four subtests from the WAIS: the Digit Span (DSp-WAIS), Digit Symbol (DSy-WAIS), Block Design (BD-WAIS) and Vocabulary (V-WAIS) was performed. A clinical neurological examination similar to that administered in normal practice was also done. Again, dementia was diagnosed according to the DSM III-R criteria (American Psychiatric Association 1987).

The subjects participating in the follow-up were classified into six subgroups: 1) AAMI subjects, 2) dementia patients (dementia group), 3) subjects with MMSE scores of less than 24, but without any other evidence of dementia (mild decline group), 4) subjects with no objective evidence of memory loss (normal memory group), 5) subjects with a disease potentially affecting memory during the follow-up (disease exclusion group), 6) subjects with no subjective memory complaints (no complaints group). A subject could be excluded from a diagnosis of AAMI by more than one criteria, e.g., someone could simultaneously be demented and rate no complaints in the MAC-Q. Therefore, when the subjects were classified, the exclusion criteria were applied in the order of importance. The presence of dementia was considered to be the most meaningful exclusion criterion, and the others in the same order as they are presented above.

In the study of frontal lobe functions (II) in AAMI, the test battery included, in addition to tests for the assessment of AAMI, four tests assessing frontal lobe function: the VFT, TMT (Parts A and C), WCST, and ST. The subjects also received a full neurological examination and scanning of the brain by Magnetic Resonance Imaging (for details, see Publication II). A score below 15 was required in the Geriatric Depression Rating Scale (GDS) to exclude depression.

In the study of memory complaints (III), a memory complaint and personality self-rating questionnaire was posted to the subjects classified as Complainers or NonComplainers in the screening of Subpopulation 1. This questionnaire included the MAC-Q, Hypochondriasis- and Psychasthenia-scales from the Minnesota Multiphasic Personality Inventory (MMPI) and the GDS.

In the study of the prevalence of AACD (V), five test variables were selected as indicators of performance on the cognitive domains essential for AACD diagnosis (Levy 1994). The following scores were used: 1) Memory: in the BSRT, the score was the total recall in six trials (max. 60), 2) Attention: in the TMT, version A, the score was the time in seconds (max. time limit 150 s.), 3) Effortful cognitive processing: in the TMT, version C, the score was the time in seconds (max. time limit 300 s.), 4) Verbal ability: in the VFT, animal category, the score was the total number of animals generated during one minute, and 5) Visuoconstructive function: in the copying of figures of the VRT, the score was the number of components present in the drawings (max. 21). A score inferior to the cutoff in one test was sufficient for a diagnosis of AACD.

To determine the education-specific cut-off points for the neuropsychological tests in the study of AACD prevalence, a subgroup of 278 healthy subjects without diseases which could potentially affect cognitive functions (see above) was identified from Subpopulation 1. The cutoff points for the TMT-A and TMT-C were calculated as the mean score plus one SD, and for the BSRT, VFT and VRT (copying) as the mean minus one SD in each of three educational subgroups of these healthy subjects: minimal education (three years or less), elementary school education (four to six years) and secondary school or high school education (seven years or more). The prevalence of AACD was calculated separately for each educational subgroup. The effect of age on the prevalence of AACD was also evaluated within three categories: subjects of 67-70, 71-74 and 75-78 years of age. Table 1 in Publication V presents the cutoff points for these tests.

The subjective report of cognitive decline was acquired with the MAC-Q. The same cutoff score (25 points or higher) as used in the study of AAMI prevalence was considered to indicate subjective cognitive decline. The medical exclusion criteria were evaluated with an interview about medical history and current medication. No laboratory test data or neurological examination data were available.

All of the evaluations in Studies I and V were carried out by a trained nurse, physician, or psychologist in the Memory Research Unit of the Department of Neurology in Kuopio University. An instructional manual was used to standardize the interview and the presentation of the tests. In the follow-up phase (IV) and in the study of frontal functions (II), the neuropsychological evaluations were performed by a psychologist (the presenting author) only. In the follow-up study (IV), the medical records of nonparticipating subjects were surveyed to find out possible dementia diagnoses and, if present, the cause of dementia.

4.2.2. Neuropsychological tests and behavioral scales

The following neuropsychological tests and behavioral scales were used during the different phases of the study as described above:

In the Benton Visual Retention Test (BVRT) (Benton 1974), the subject is required to copy from memory ten different figures after a presentation of ten seconds for each. The score used in the present study was the number of correctly reproduced figures.

In the learning phase of the Paired Associate Learning (PAL) subtest from the Wechsler Memory Scale (WMS) (Wechsler 1974), ten pairs of words are read out by the examiner. Then, the subjects are required to recall the second word of each pair when the first one is presented as a cue. This procedure is repeated three times. The total score was calculated according to the WMS manual.

The Logical Memory (LM) subtest from the WMS (Wechsler 1974) includes two stories which are read by the examiner. Immediately after hearing each story, the subject must recall as many details as possible. The score used was the mean number of details recalled in two trials.

The Mini-Mental State Examination (MMSE) (Folstein et al. 1975) includes a selection of short items testing different aspects of cognitive function: orientation, repetition and recall of words, attention, language (several items), and constructional ability (drawing). The score used was the sum of the scores of all items.

In the Vocabulary subtest from the Wechsler Adult Intelligence Scale (V-WAIS) (Wechsler 1955), subjects are required to explain the meaning of 32

words. A score of two points was given for each complete answer, and one point for each partly correct answer, from which the sum score was counted.

In the Buschke Selective Reminding Test (BSRT) (Buschke and Fuld 1974), subjects have to recall as many as possible of the ten words that have just been read out by the examiner. On the second trial, the examiner repeats only those words which the subjects have not recalled, and the subjects are asked to try to recall all ten words again. This procedure is repeated six times. The scores obtained are the total number of words, and the number of words in long-term memory (i.e., those words which were recalled in consecutive trials without being repeated).

In Russell's adaptation of the Visual Reproduction Test (VRT) (Russell 1975), subjects must reproduce geometric figures from memory immediately after seeing them for ten seconds. To measure long-term retention, the subject is asked to reproduce the figures again after 30 minutes of unrelated testing. The same figures were also used as a visuo-constructive task by asking the subjects to copy them after the delayed recall task.

In the Finnish version of the Verbal Fluency Test on letters (VFT-L) (Borkowski et al. 1967), the subjects are given 60 seconds to produce as many words as possible beginning with each of the letters P, A, and S, excluding proper names or different forms of the same word. The Verbal Fluency Test on category (VFT-C) (Butters et al. 1987) requires producing as many animal names as possible in 60 seconds. The performance was scored by counting the total number of correct words produced for each letter or category.

In Part A of the Trail Making Test (TMT-A) (Reitan 1958), the subjects must to draw a line to connect consecutively numbered circles. In Part B (TMT-B), subjects have to draw a line alternating between numbers (1-13) and letters from the beginning of the alphabet (A-L). In Part C (TMT-C), the letters are replaced with the names of the twelve months. Part C was developed because many elderly persons in Finland do not know the alphabet correctly (Koivisto et al. 1992). The scores were the time required to complete each trial, and the difference between parts A and C (in Publication II), which reflects the time of cognitive processing subtracted from the psychomotor speed involved in both tasks.

In the Modified Wisconsin Card Sorting Test (WCST) (Nelson 1976), subjects are required to deduce the card sorting principle (form, color or number of symbols) and to modify their response strategy according to feedback from the examiner. The scores recorded were the number of completed categories (six consecutive correct responses), the total number of correct responses and the number of perseveration errors.

In the Stroop Test (ST) (Golden 1978), two naming trials are used. The first trial requires the naming of colored dots on a sheet of paper, and the second requires the naming of a color when color names are printed in a color different from the word itself (interference condition). The shortened versions involving 50 dots and words were used in both naming trials. The scores in the test were the time used to complete each naming trial and the difference between the scores for the interference condition and the simple naming of colored dots (interference effect).

Three subtests from WAIS (Wechsler 1955) were used in the comprehensive test battery of the follow- up (IV) to accomplish the dementia diagnosis (test data not shown). These subtests were the Digit Span (DSp-WAIS), which requires attention and primary memory; the Digit Symbol (DSy-WAIS), which requires perceptual organization, sustained attention and visuomotor coordination; and the Block Design (BD-WAIS), which is a test of visuospatial construction.

Subjective complaints of memory loss were recorded by the Memory Complaint Questionnaire (MAC-Q) (Crook et al. 1992). It includes six questions concerning one's ability to remember everyday matters (e.g., the names of other people or phone numbers) as compared to a time when the person was young. The score used was the sum of six questions rated with a five-point scale.

The Geriatric Depression Rating Scale (GDS) (Yesavage et al. 1983) was used to assess depressive symptoms. This scale includes thirty questions concerning different aspects of mood and activity. The answers are rated as true or false. The sum score of those answers indicating symptoms or feelings of depression was used.

The Hypochondriasis-scale of the MMPI (Hs-scale) is designed to assess somatic complaints and anxiety about physical health. The Psychasthenia-scale of the MMPI (Pt-scale) evaluates personal feelings about competence and capabilities and as well as phobias, obsessions and compulsions. The scales include 33 (Hs) and 48 (Pt) items which are rated as true or false (Dahlstrom et al. 1990). The sum score was used for each scale.

4.3. Statistical analysis

The data were analyzed by using the SPSS-PC+ software (II, III, IV and V) and the SPSS programs at the Computer Center of the University of Kuopio (I).

The results for continuous variables are given as a mean +/- SD and, for categorical data, as percentages (I-V). The analysis of covariance (ANCOVA) adjusted for age and education was used to compare the means of clinical and neuropsychological data between AAMI subjects and controls, for assessing the frontal lobe functions in AAMI (II). The correlations between neuropsychological test results and frontal lobe volumes were tested with Pearson's correlation two-tailed analysis test. Student's two- tailed t-test for independent samples was used to examine for group differences in the scores of MAC- Q, GDS and MMPI (III). The correlations between the MAC-Q and memory tests and personality scales were also analyzed with Pearson's correlation two-tailed analysis test. The differences between subgroups in the follow-up (IV) were analyzed with analysis of variance (ANOVA) and the post hoc analyses with Duncan method. The stepwise discriminant function analysis (Wilk's method) was used to examine the accuracy of the tests administered during the baseline evaluation for distinguishing the AAMI and demented subjects of the follow-up. The chi-square test was used to evaluate the differences in AACD prevalence between the subgroups of the study population (V). The level of statistical significance was set at $p < 0.05$ (I-V).

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5. RESULTS

5.1. PREVALENCE OF AAMI IN AN ELDERLY POPULATION

A total of 1,049 subjects aged 60 to 78 years (mean 68.8 +/- SD 3.9) were completely evaluated to determine the prevalence of AAMI. Table 3 lists the clinical characteristics of the participants in the three screening studies. (The illnesses reported by participants are shown in Table 2 in Publication I). A total of 564 subjects (239 men, 325 women) from the entire population were classified as having AAMI by using the inclusion criteria alone; i.e. they had subjective memory impairment, memory test performance below the cutoff score for AAMI in at least one of the tests, and no dementia, resulting in a prevalence rate of 53.8 % (men, 57.4 %, women, 51.3 %) (Table 6). The prevalence rate was highest (58.6 %) in the youngest age group of 60-64 years (men, 58 %; women, 59.1 %) and lowest (48 %) in the oldest age group of 75 to 78 years (men, 53.8 %; women, 45.9 %). The prevalence rate for men was higher than that for women in all age groups except for the youngest age group of 60 to 64 (men, 58.0 %; women, 59.1 %).

When the exclusion criteria for AAMI were taken into account, including illnesses that could cause memory impairment, the prevalence of AAMI decreased to the rates presented in Table 7. Thus, the prevalence rate for AAMI in the total study population was 38.4 % (men, 42.5 %; women, 35.7 %). Also, by these criteria the prevalence rate was highest (45.7 %) in the youngest age group of 60 to 64 years (men, 50.0 %; women, 42.4%) and lowest (33.0 %) in the oldest age group of 75 to 78 years (men, 34.6 %; women, 32.4 %).

The subjects from the samples who did not participate in the AAMI prevalence screening were older than those who participated in Study 1 (nonparticipants: 72.3±2.9 years vs. participants: 71.3±3.1 years, $p < 0.000$) and in Study 3 (69.1±3.1 years vs. 68.6±2.7 years, $p = 0.041$) but not in Study 2 (62.8±2.9 years vs. 63.5±2.3 years, $p = 0.056$). The sex distribution of the nonparticipants was not different from that of the participants in any of these studies.

Table 6. Number of cases and age- and sex-specific prevalence rates for AAMI in various age groups according to neuropsychological criteria only in different subpopulations and in the total population

Table 6. Number of cases and age- and sex-specific prevalence rates for AAMI in various age groups according to neuropsychological criteria only in different subpopulations and in the total population

Age	Study 1		Study 2		Study 3		Total Population	
	Cases	Rate%	Cases	Rate%	Cases	Rate%	Cases	Rate%
			Men					
60-64	-	-	29	58.0	-	-	29	58.0
65-69	33	55.9	13	52.0	66	51.6	112	52.8
70-74	47	61.8	-	-	37	71.1	84	65.6
75-78	12	54.5	-	-	2	50.0	14	53.8
Total							239	57.4
			Women					
60-64	-	-	39	59.1	-	-	39	59.1
65-69	40	56.3	22	62.8	82	44.6	144	49.6
70-74	55	50.9	-	-	53	55.8	108	53.2
75-78	32	48.5	-	-	2	25.0	34	45.9
Total							325	51.3
			Combined					
60-64	-	-	68	58.6	-	-	68	58.6
65-69	73	56.1	35	58.3	148	47.4	256	51.0
70-74	102	55.4	-	-	90	61.2	192	58.0
75-78	44	50.0	-	-	4	33.3	48	48.0
Total							564	53.8

Table 7. Number of cases and age- and sex-specific prevalence rates for AAMI according to National Institute of Mental Health Work Group criteria in different subpopulations and in the total population

Age	Study 1		Study 2		Study 3		Total Population	
	Cases	Rate %	Cases	Rate %	Cases	Rate (%)	Cases	Rate %
			Men					
60-64	-	-	25	50.0	-	-	25	50.0
65-69	26	44.1	10	40.0	58	40.1	88	41.5
70-74	31	40.8	-	-	24	46.1	55	43.0
75-78	7	31.8	-	-	2	50.0	9	34.6
Total							177	42.5
			Women					
60-64	-	-	28	42.4	-	-	28	42.4
65-69	31	43.7	17	48.6	53	28.8	101	34.8
70-74	38	35.2	-	-	35	36.8	73	36.0
75-78	23	34.8	-	-	1	12.5	24	32.4
Total							226	35.7
			Combined					
60-64	-	-	53	45.7	-	-	53	45.7
65-69	57	43.8	27	45.0	105	33.6	189	37.6
70-74	69	37.5	-	-	59	40.1	128	38.7
75-78	30	34.1	-	-	3	25.0	33	33.0
Total							403	38.4

Table 8 presents the percentages of subjects meeting AAMI test criteria in various tests in different subpopulations and in the total population.

Table 8. Percentage of subjects meeting AAMI test criteria (cutoff points in parenthesis) in various tests in different subpopulations and in the total

population

	Study 1 (n=402)	Study 2 (n=176)	Study 3 (n=471)	Total Population (n=1049)
MAC-Q	79.8	79.0	73.9	76.3
Memory tests				
BVRT (Less or equal to 6)	78.4	67.4	70.9	72.8
PAL (Less or equal to 13)	43.6	31.9	36.7	38.1
LM (Less or equal to 6)	NE	NE	36.3	-
WAIS-V (Greater or equal to 32)	NE	NE	57.7	-
MMSE (Greater or equal to 24)	85.8	97.7	91.3	91.2

MAC-Q = Memory Complaint Questionnaire; BVRT = Benton Visual Retention Test (administration A); PAL = Paired Associate Learning subtest of Wechsler Memory Scale; LM = Logical Memory subtest of the Wechsler Memory Scale; WAIS-V = Vocabulary subtest of the Wechsler Adult Intelligence Scale; MMSE = Mini-Mental Status Examination, NE = not evaluated

5.2. FRONTAL LOBE FUNCTIONS IN SUBJECTS WITH AAMI

Compared to controls, the AAMI subjects showed impaired performance in three of four tests assessing frontal lobe functions (ANCOVA adjusted for age and education) (See Table 2 in Publication II). In the ST, the speed of color naming was not different, but performance in the interference condition was worse and the importance of the interference effect was greater in the AAMI subjects. In the TMT, inferior performance was found in the AAMI subjects for all three speed variables, reflecting impairment in both psychomotor speed and in more complex executive processing. In the WCST, a difference between groups was also found for all three variables. The groups did not differ significantly in the VFT.

The mean volumes of the frontal lobes were similar in the AAMI subjects (right: 120.51±21.35 cm3; left: 116.79±20.04 cm3) and controls (right: 120.62±19.61 cm3; left: 116.82±20.19 cm3). No differences between groups were found either when the analysis was repeated using the relative volumes adjusted for intracranial area (data not shown).

Three significant correlations were found between test performance and volumetric measures of the frontal lobe. In the AAMI subjects, the number of correct responses in the WCST correlated positively with the volume of the right frontal lobe ($r = 0.28$, $p = 0.047$). In the controls, the number of perseverative errors in the WCST correlated negatively with the volume of the right frontal lobe ($r = -0.28$, $p = 0.043$), and the score of the VFT category naming correlated positively with the volume of the left frontal lobe ($r = 0.25$, $p = 0.048$).

5.3. PERSONALITY TRAITS OF SUBJECTS WITH MEMORY COMPLAINTS

The mean score of the MAC-Q in Subpopulation 1 (N = 403) in the screening phase was 26.79±3.74 (SD). The mean score in the BVRT was 5.10±1.93, and in the PAL 13.83±3.77. No significant correlation was found between memory complaints in the MAC-Q and memory performance in the BVRT ($r = -0.03$, $p = 0.29$) or PAL ($r = -0.10$, $p = 0.45$). The clinical data of the subjects are presented in Table 5.

In the questionnaire, the C-group had significantly higher scores than the nonC-group in the Hypochondriasis-scale. Also, in the Psychasthenia-scale, the difference was significant. The complainers scored slightly higher in the GDS, but this difference was not statistically significant (Table 9).

Table 9. Comparison of scores in the Hypochondriasis and the Psychastenia scales from the MMPI between subjects complaining and not complaining of memory loss.

	Complainers (n=10)	Noncomplainers (n=10)	*p*
MAC-Q	31.90+/-1.37	21.3+/-1.42	0.000
MMPI-Hs	12.00+/-3.71	5.22+/-4.66	0.003
MMPI-Pt	15.00+/-9.13	6.00+/-5.43	0.019
GDS	9.10+/-8.28	4.10+/-4.77	0.120

MAC-Q = Memory Complaint Questionnaire (the questionnaire phase); MMPI-Hs = Hypochondriasis scale of the MMPI; MMPI-Pt = Psychasthenia scale of the MMPI; GDS = Geriatric Depression Rating Scale

Scores on the MAC-Q correlated significantly with scores on the subscales of the MMPI: Pearson's correlation coefficient between the Hs-scale and MAC-Q was 0.73 ($p < 0.001$) and between the Pt- scale and MAC-Q 0.62 ($p < 0.01$). The correlation between the GDS and MAC-Q scores (0.45) was not statistically significant.

To determine whether the final study groups in the analysis differed from those whose MAC-Q scores in the later questionnaire no longer classified them as belonging to the C- or nonC-groups, we compared these subjects with the final C-group and nonC-group and the total screening sample. This analysis did not, however, reveal significant differences between the study groups and the subjects excluded from the final evaluation, except for their MAC-Q scores. For details, see Publication III, pages 2 and 3.

5.4. FOLLOW-UP OF SUBJECTS WITH AAMI

Of the 229 AAMI subjects who had been screened an average of three years eight months (3.6 years) earlier, 176 (76.9%) (73 men, 103 women) participated in the follow-up. Of the 53 nonparticipants, 15 (6.5%) had died, 2 (0.9%) had moved, 15 (6.5%) reported being too ill to be able to participate, and 21 (9.1%) refused to take part. The mean age of the participants in the follow-up was 71.7±5.0 years (range 63 - 81 years). The mean duration of formal education was 6.6±2.5 years (range 1 - 17).

The subjects who did not participate in the follow-up were significantly older (69.8±4.6 years at baseline) than the participants of the follow-up (68.1±4.7 years at baseline) ($p < 0.05$). However, this difference disappeared when those who had died before the follow-up (71.2±3.8 years at baseline) were excluded from the nonparticipant group. No statistically significant difference in education was found between the participants and nonparticipants. The only differences in baseline test data between the participants and nonparticipants of the follow-up were found in the VRT: the participants scored better than the nonparticipants in both the immediate (9.0*3.5 versus 7.0±2.5, $p < 0.001$) and delayed recall (6.0±3.8 versus 4.3±2.9, $p < 0.01$) sections. The only difference in baseline health status was a higher frequency of intermittent claudication in the nonparticipants (7/53, 13.2%) than in the participants (3/176, 1.7%) ($p < 0.01$) of the follow-up. The differences in these test and health variables remained, even when those who had died during the follow-up period were excluded.

The clinical course of AAMI

A total of 104 (59.1%) subjects still met the criteria for AAMI at the time of follow-up. The classification of the other subjects to various "cognitive subgroups" in the follow-up assessment was done by applying the exclusion criteria in the order of importance as described in Subjects and Methods, Chapter 4.2.1. Thus, after the 3.6 years follow-up period, sixteen (9.1%) subjects showed a decline in cognition severe enough to fulfil the DSM-III-R criteria for dementia (dementia group). Alzheimer's disease was diagnosed in 13 cases, vascular dementia in one case, and the cause of dementia could not be defined in two cases. The age-specific annual incidence rates for dementia are presented in Table 10.

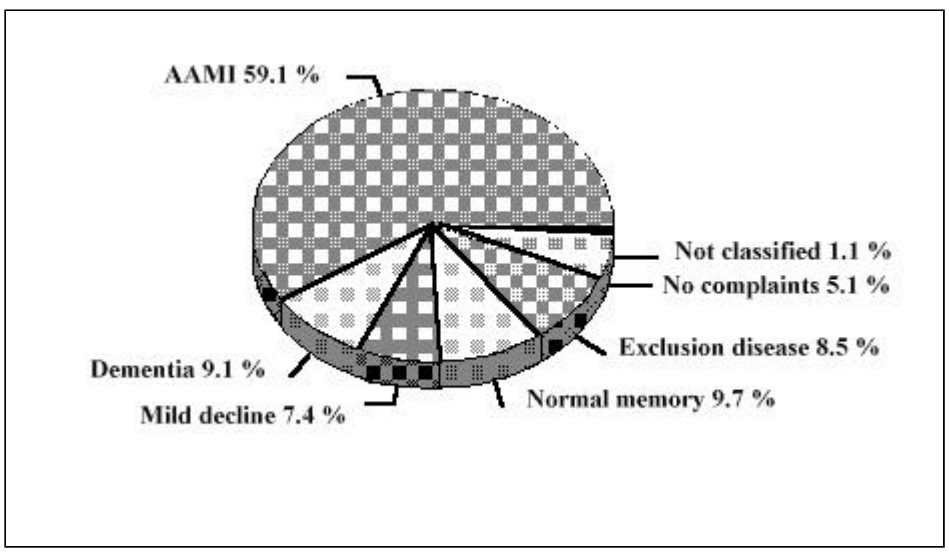
Table 10. The incidence of dementia in different age groups of subjects with age-associated memory impairment.

Age range (years)	Number of the subjects in the study	Number of demented subjects	Incidence rate per year	Incidence per year in normal population*
60-64	24	2	2.31%	0.5%
65-69	37	2	1.50%	0.5%
70-74	53	4	2.10%	1.5%
75-81	62	8	3.58%	3.0%
Total	176	16	2.53%	

*According to the estimation by O'Brien et al. (1992)

A decline in the MMSE score unaccompanied by any other indication of dementia was detected in 13 (7.4%) subjects (mild decline group). The performance of seventeen (9.7%) subjects was superior to the cutoff scores in the criterion memory tests (normal memory group). Fifteen (8.5%) subjects were now suffering from a disease causing exclusion from AAMI diagnosis (diabetes eight, cancer five, and stroke two cases) (disease exclusion group). Finally, nine (5.1%) subjects were excluded solely on the basis of MAC-Q ratings indicating that they now considered their memory to be as good as it was in their youth (no complaints group). Two subjects (1.1%) could not be classified because of incomplete neuropsychological data. These two subjects, however, showed no signs of dementia in the clinical neurological examination. See Figure 1 for the classification of the subgroups at the follow-up visit.

Figure 1. The distribution of different subgroups in AAMI population after a 3.6-year follow-up.



The dementia group was significantly inferior to the AAMI and other subgroups in most neuropsychological measures of the follow-up evaluation. The mild decline group was inferior and the normal memory group was superior to the AAMI group in many variables. The groups with other AAMI exclusions, i.e., the disease exclusion or no complaints groups, did not differ significantly from the AAMI group (Table 11).

The prediction of dementia in AAMI

We also analyzed whether the different diagnostic subgroups classified in the follow-up differed in the neuropsychological tests already at the time of the baseline evaluation. The dementia group had had poorer performance than the AAMI subjects in most tests already at baseline (Table 12). An even more pronounced difference was found between the dementia and normal memory groups. The normal memory group was superior to the dementia group in almost all neuropsychological measures at the baseline assessment. The mild decline, normal memory, disease exclusion, and no complaints groups did not differ significantly from the AAMI group (Table 12).

To examine the value of the test scores of the baseline evaluation for predicting cognitive decline, we performed discriminant function analysis between the AAMI and dementia groups. We included all the test variables from the baseline, as well as sex, age, and education. Only 12 of the demented and 61 of the AAMI subjects from the first, older sample had complete neuropsychological data from the baseline and could be included in this analysis. The most efficient predictors of dementia were the total recall portion of the Buschke Selective Reminding Test (BSRT-TOT), the immediate recall portion of the Visual Reproduction Test (VRT1), the Verbal Fluency Test on category (VFT-C), the Benton Visual Retention Test (BVRT), the Paired Associated Learning Test (PAL), and the Verbal Fluency Test on letters (VFT-L) (Table 5 in Publication IV). These tests correctly classified 52 of 61 (85.2%) AAMI subjects and 10 of 12 (83.3%) demented subjects ($p < 0.001$). The age or education level were not significant discriminators between the groups. Table 6 in Publication IV presents the sensitivity, specificity and positive predictive value for various cutoff points of each test for differentiating between the AAMI and demented subjects at the baseline evaluation. The memory tests, the BSRT- TOT and the VRT1, had rather high

sensitivity/specificity ratios, but the best result was achieved when the six tests were combined as defined in the discriminant function analysis.

Table 11. The results of neuropsychological tests in the follow-up evaluation for the subgroups classified according to the AAMI criteria

	AAMI	Dementia	Mild decline	Normal memory	Exclusion disease	No memory complaints	F	*p*
AAMI TESTS								
BVRT	4.6+/-1.3	1.8+/-1.3#	4.7+/-1.5	7.4+7-0.7	3.9+/-1.7	4.3+/-1.2	27.5	.0000
PAL	13.2+/-3.3	9.6+/-4.1##	11.6+/-3.0	16.5+/-2.2	12.6+/-2.7	12.3+/-3.4	6.5	.0001
MMSE	26.9+/-1.6	21.3+/-3.3##	22.3+/-1.0###	27.4+/-1.5	26.5+/-1.4	27.0+/-1.2	44.8	.0001
MAC-Q	28.2+/-2.3	29.1+/-3.6	26.9+/-3.3*	27.9+/-2.8	27.6+/-3.0	22.6+/-1.0#	9.1	.0000
MEMORY (Other than AAMI tests)								
VRT1	8.9+/-2.6	5.2+/-2.5##	6.9+/-2.2	11.2+/-3.2#	8.4+/-3.0	8.6+/-2.1	8.7	.0000
VRT2	6.8+/-2.9	1.5+/-2.0#	4.5+/-2.1	9.2+/-4.5#	5.8+/-3.4	4.9+/-2.5	11.2	.0000
BSR-TOT	32.9+/-8.2	20.9+/-5.7#	28.3+/-5.5	36.6+/-7.1**	29.7+/-7.6	32.7+/-9.7	7.5	.0000
BSR-LONG	25.6+/-12.3	7.6+/-8.4#	19.4+/-10.8	30.4+/-10.5***	22.7+/-8.5	23.9+/-15.1	7.1	.0000
COPYING								
VRT3	15.4+/-1.1	12.6+/-2.9#	13.7+/-1.8#	15.9+/-1.3	15.2+/-1.0	15.0+/-1.3	12.1	.0000
FRONTAL FUNCTION								
TMT-A	62.4+/-20.5	103.8+/-36.6#	71.3+/-20.3	50.1+/-15.4**	74.7+/-33.5	64.1+/-20.6	9.4	.0000
TMT-B	207.3+/-74.5	300.0+/-0.0#	204.3+/-94.5	130.6+/-60.0	200.6+/-83.9	272.5+/-29.8	5.0	.0004
TMT-C	160.8+/-75.3	253.2+/-78.8##	222.3+/-78.8	133.9+/-77.9	195.0+/-85.4	184.6+/-96.9	4.4	.0028
VFT-L	32.0+/-12.1	24.3+/-7.5	32.2+/-9.7	41.2+/-19.8*	31.9+/-12.5	39.3+/-12.5*	2.9	.0246
VFT-C	17.3+/-4.7	10.5+/-3.2#	17.6+/-5.2	19.5+/-5.6	16.2+/-5.5	17.0+/-5.0	6.0	.0002

= different from all other groups (ANOVA/Duncan), ## = different from all but Mild decline, ### = different from all but Dementia, * = different from Dementia, ** = different from all but AAMI and No complaints, *** = different from Dementia and Mild decline groups; BVRT = Benton Visual Reproduction Test; PAL = Paired Associated Learning subtest from WMS; MMSE = Mini-Mental State Examination; MAC-Q = Memory Complaint Questionnaire; VRT1 = Visual Reproduction Test, immediate recall; VRT2 = Visual Reproduction Test, delayed recall; BSRT-TOT = Buschke Selective Reminding Test, total recall; BSRT-LONG = Buschke Selective Reminding Test, long-term memory; VRT3 = Copying the figures of Visual Reproduction Test; TMT-A = Trail-Making test A; TMT-B = Trail-Making test B; TMT-C = Trail-Making test C; VFT-L = Verbal Fluency Test on letters; VFT-C = Verbal Fluency Test on category

Table 12. The neuropsychological test scores in the screening evaluation for the groups classified according to AAMI criteria in the follow-up evaluation

	AAMI	Dementia	Mild decline	Normal memory	Exclusion disease	No memory complaints	F	*p*
AAMI TESTS								
BVRT	5.0+/-1.2	4.0+/-1.2#	5.0+/-1.4	5.7+7-1.6	4.9+/-1.5	5.0+/-1.1	2.9	.0160
PAL	14.5+/-3.1	11.8+/-4.3##	12.9+/-3.0*	15.6+/-2.7	14.3+/-3.1	14.1+/-3.1	3.2	.0083
MMSE	26.8+/-1.6	25.8+/-1.6	26.1+/-2.0	27.8+/-1.4###	26.9+/-1.5	27.4+/-1.8###	5.5	.0048
MAC-Q	28.2+/-2.5	29.6+/-2.9	27.4+/-2.1**	27.7+/-2.3	28.1+/-2.9**	26.6+/-1.4	2.1	.0620
MEMORY (Other than AAMI tests)								
VRT1	9.4+/-3.0	5.7+/-3.2***	7.9+/-2.7*	12.0+/-4.1	9.8+/-4.0	8.7+/-2.4*	2.1	.0007
VRT2	6.2+/-3.5**	2.8+/-3.2	5.9+/-3.5	9.9+/-2.9#	5.6+/-4.7	6.6+/-3.7**	4.2	.0017
BSR-TOT	33.4+/-7.0	23.2+/-6.8#	29.6+/-5.2	34.9+/-5.2	35.2+/-7.6	35.7+/-6.1	5.8	.0001
BSR-LONG	23.3+/-10.7	9.0+/-10.4***	18.0+/-10.1	24.6+/-9.9	26.9+/-10.8	23.2+/-15.3	4.3	.0013
COPYING								
VRT3	16.8+/-2.3	15.3+/-2.4!	15.9+/-1.8!	18.1+/-2.3	16.8+/-2.3	15.1+/-2.7*	2.3	.0470
FRONTAL FUNCTION								
TMT-A	68.9+/-30.7**	96.1+/-32.0	77.9+/-24.6	50.7+/-11.6###	71.0+/-25.7	74.9+/-20.3	3.0	.0136
TMT-B	197.6+/-79.9	250.0+/-77.4*	277.5+/-45.0*	152.5+/-75.2	204.5+/-86.7	254.8+/-49.1*	2.5	.0390
TMT-C	166.3+/-72.8**	235.9+/-74.8*	210.7+/-48.5*	118.7+/-54.9	188.5+/-60.0*	178.3+/-86.9	3.6	.0048
VFT-L	30.5+/-11.9	24.9+/-10.2*	32.1+/-5.0	36.0+/-14.4	27.9+/-11.5	35.0+/-9.5	1.4	.2823
VFT-C	17.4+/-4.7	11.9+/-6.0#	16.4+/-2.4	21.4+/-8.1#	16.3+/-3.3	14.7+/-7.1	4.4	.0012

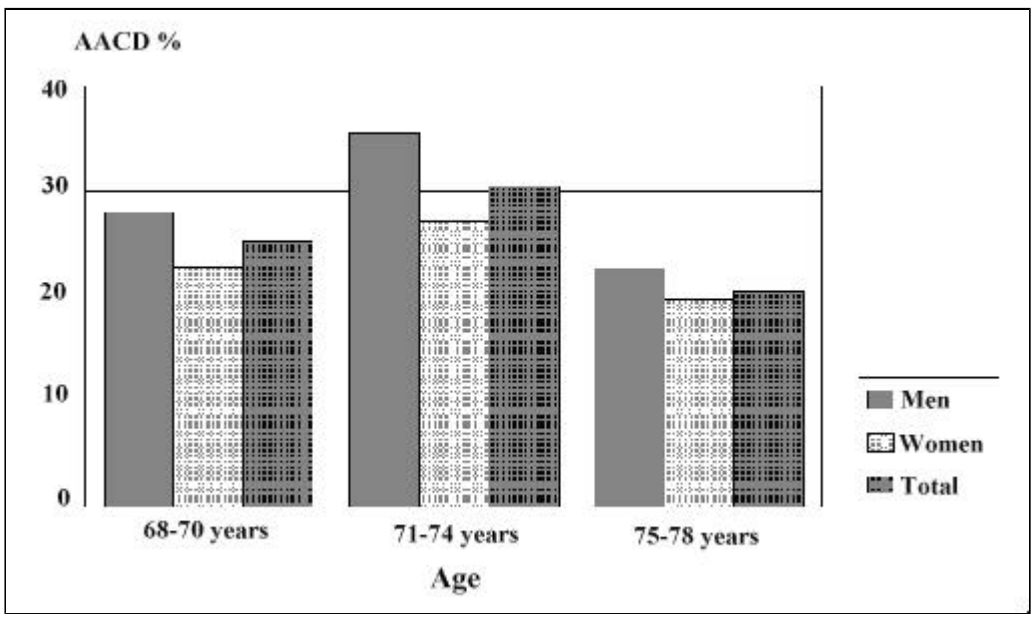
= different from all other groups (ANOVA/Duncan), ## = different from all but Mild decline and No complaint, ### = different from Dementia and Mild decline, * = different from Normal memory, ** = different from Dementia, *** = different from all but Mild decline group; BVRT = Benton Visual Reproduction Test; PAL = Paired Associated Learning

subtest from WMS; MMSE = Mini-Mental State Examination; MAC-Q = Memory Complaint Questionnaire; VRT1 = Visual Reproduction Test, immediate recall; VRT2 = Visual Reproduction Test, delayed recall; BSRT-TOT = Buschke Selective Reminding Test, total recall; BSRT-LONG = Buschke Selective Reminding Test, long-term memory; VRT3 = Copying the figures of Visual Reproduction Test; TMT-A = Trail-Making test A; TMT-B = Trail-Making test B; TMT-C = Trail-Making test C; VFT-L = Verbal Fluency Test on letters; VFT-C = Verbal Fluency Test on category

5.5. THE PREVALENCE OF AACD IN AN ELDERLY POPULATION

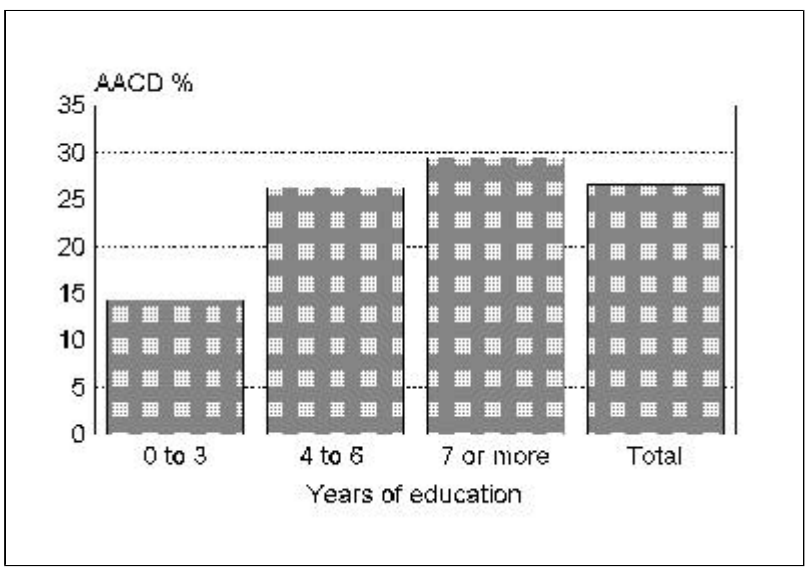
According to the cutoff points defined in five test variables, a total of 107 (26.6%) of 402 subjects fulfilled the AACD criteria. The prevalence of AACD tended to be higher in men (30.1%) than in women (24.4%). Age-specific prevalence rates were: 25.2% in the age group of 68-70 years, 30.5% in the age group of 71-74 years, and 20.5% in the age group of 75-78 years. The prevalence rates did not differ significantly in the various age groups (Table 2 in Publication V and Figure 2).

Figure 2. The prevalence rates for AACD in different age groups.



Prevalence rates varied among the three education groups formed by using the education-specific cutoff points in the neuropsychological tests, but these differences were not statistically significant. The subjects with three years or less of education had a prevalence rate of 14.3%, the subjects with 4-6 years of education, 26.2%; and the subjects with 7 years or more education, 29.4% (Figure 3).

Figure 3. The prevalence rates for AACD in subgroups with different educational levels



No major differences in the sensitivity of neuropsychological tests for identifying subjects with AACD were found. The BSRT identified 23.6% (89 of 377 subjects completing this test), the TMT-A 19.9% (79/396), the TMT-C 23.3% (87/376), the VFT 19.3% (76/393) and the CVRT 22.5% (89/396) of the subjects as having AACD. Of those who were classified into the AACD category, 60.7% (65/107) met the criteria due to one test only. Subsequently, 21.5% (23/107) were classified with two tests, 11.2% (12/107) with three tests, 5.6% (6/107) with four tests, and 0.9% (1/107) with all five tests as having AACD. For those who met the criteria of one test alone, this test was the BSRT in 26.2% (17/65), VFT in 21.5% (14/65), CVRT in 20.0% (13/65), TMT-C in 20.0% (13/65), and TMT-A in 12.3% (8/65) of the cases.

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6. DISCUSSION

In this study, we report a high prevalence rate for AAMI, 38.4%, in a random sample of an elderly population. For an alternative diagnosis, AACD, we found a lower prevalence rate, 26.6%. We found evidence for a distinct cognitive profile in the AAMI subjects when compared to age-matched controls with intact memory. The AAMI subjects had impairment not only in memory but also in tests assessing frontal lobe function. In the follow-up, we observed AAMI to be a relatively stable condition. The incidence of dementia in AAMI subjects appeared to be only slightly elevated when compared to incidence rates previously found in the general population. A battery of neuropsychological tests proved to be of value in predicting which AAMI subjects would develop dementia during the follow- up. Furthermore, we found that complaints of memory loss, a criterion for AAMI and AACD diagnosis, were associated more with personality traits than with actual memory performance. In the literature, the construct of AAMI has been supported by several authors, but serious criticism has also been raised. Our study enables the diagnostic methodology and epidemiological properties of AAMI and AACD to be considered from various perspectives. In the following discussion, the methodological aspects crucial for diagnosing and characterizing AAMI and AACD in this study are discussed first. Second, the broader significance of the present results for research into normal aging

and dementia are discussed.

6.1. METHODOLOGICAL CONSIDERATIONS OF THE STUDY

The sample sizes in the population-based phases of the present study (I, IV, V) were rather large, and the demographic characteristics were comparable to those of general population in this age group living in Kuopio (Koivisto 1995). The participation rates in all population-based study phases (from 70.4% to 80.3%) can be considered acceptable when compared to previous epidemiological studies of elderly subjects (Kay 1991). However, the participants of the prevalence studies (I, IV) may represent a somewhat selective group of subjects from the total random samples, as they tended to be younger than those who did not participate. The subjects for studies of frontal lobe functions (II) and memory complaints (III) were taken from the population-based samples, which makes these smaller populations more representative.

The methods used to categorize and diagnose age-related cognitive changes have been criticized in previous studies and reviews (e.g., Rosen 1990, Smith et al. 1991, Rosenman 1991, Nicholl 1995, Christensen et al. 1995). The suitability of proposed cutoff points and the reliability of neuropsychological tests included in the diagnostic criteria of AAMI and AACD also appeared to be problematic in the present series of studies.

6.1.1. Neuropsychological tests in diagnosing AAMI and AACD

Assessment of AAMI

The conceptualization of memory in AAMI criteria is a simple one. Recommended tests assess retrieval process in secondary episodic memory. No more multidimensional assessment of different processes (e.g., long-term storage, recognition) or systems (e.g., semantic memory) is involved. When proposing the criteria, the NIMH work group gave three tests with fixed cutoff points as examples of tests to be used, but it did not give restrictions for test selection (Crook et al. 1986). Other tests with normative data would be equally appropriate. La Rue and Blackford (1989) postulated that the cutoff points should vary according to the population studied. Later, however, the use of specified tests and score levels for AAMI assessment was suggested (Smith et al. 1991, Lezak 1995). We chose this latter approach and used two of the memory tests (BVRT, PAL) recommended by the NIMH work group with suggested cutoffs in all parts of the study.

The prevalence rates for AAMI can vary widely depending on which memory tests and cutoff points are used (Smith et al. 1991, Barker et al. 1995). The present results are in agreement with such findings. The Benton Visual Retention Test (BVRT) was the most inclusive measurement (78.4 % in Subpopulation 1, 67.4 % in Subpopulation 2, and 70.9 % in Subpopulation 3), whereas the Paired Associated Learning Test (PAL) was the least inclusive (43.6 % in Subpopulation 1, 31.9 % in Subpopulation 2, and 36.7 % in Subpopulation 3). This could be explained by the impairment of visual memory before verbal association learning memory in aging or, more likely (see Salthouse 1995), by unsuitability of the proposed cutoff points for diagnosing AAMI. Moreover, Barker et al. (1995) reported recently rather different inclusion rates for these same tests and cutoffs (BVRT: 57% and PAL: 61%). Educational level is a strong contributor to neuropsychological test performance (e.g., Koivisto et al. 1992, Wiederholt et al. 1993, Portin et al. 1995). The NIMH work group did not specify on which studies the recommended cutoff points were based (Crook et al. 1986), but those norms undoubtedly were not completely appropriate for our population with a rather low educational level (mean 7.3 years). Direct comparison with the study by Barker et al. (1995) cannot be conducted , because they did not report the educational level of the population studied. Cultural influences independent of educational level have also been observed in psychometric tests and scales (Salmon et al. 1989, Loewenstein et al. 1994), which further complicates the generalization of these specific tests and cutoffs in different populations.

The follow-up population in our study also included a subgroup with "normal memory", i.e., those whose memory test performance in the AAMI criterion tests was better at follow-up than at baseline. However, this increase of scores in the "normal memory group" was significant only in the Benton Visual Retention Test, not in the Paired Associate Learning Test. The explanation for this "recovering" subgroup might be due to the practice effect, which has been shown to appear with the repeated administration of neuropsychological tests (Mitrushina and Satz 1991). This finding is in agreement with previous criticism against the reliability of the methods used for memory testing in AAMI diagnosis (Blackford and LaRue 1989, Smith et al. 1991). The reliability might easily be enhanced by the use of additional scores in the BVRT. The scoring system crediting only totally correct responses is vulnerable to chance. The same total score can be achieved with quite different levels of performance in the most difficult items of the test involving multiple figures to be reproduced from memory. Thus, including the error score (the number of different types of errors in each figure) (Lezak 1995) in the assessment might enhance the differentiative value of the BVRT.

The diagnosis of AAMI also depends on intellectual capacity. A score of 9 or higher (raw score of 32 or higher) in the Vocabulary subtest of the WAIS was suggested to be evidence of "adequate intellectual function". We applied this criterion only in Subpopulation 3. However, we used the Mini- Mental State Examination (MMSE) score to exclude possibly demented subjects. Both MMSE and Vocabulary scores have been shown to correlate with education (Alekoumbides et al.. 1987, O'Connor et al. 1989). According to previous studies, many subjects with little education (but who are not demented) score low in the MMSE (Koivisto et al. 1992, Ylikoski et al. 1992) and are, therefore, excluded from AAMI diagnosis. If the MMSE could thus be considered as an approximate measure of intelligence, the group of subjects classified as having AAMI without adequate intellectual function might not be large enough to distort the results. Moreover, using the Vocabulary score with a fixed cutoff point as a part of the AAMI diagnosis has been criticized for skewing the subject population (Blackford and La Rue 1989, Rosen 1990). A cutoff score of at least 9 has been estimated to exclude 37 % of the lower end of the population continuum (Blackford and La Rue 1989). Our results (Study 3 in Publication I) agree with this suggestion. Using the same cutoff score in our population would have resulted in the exclusion of as many as 42.3% of our subjects from AAMI diagnosis because of inadequate intellectual function.

Assessment of AACD

Each one of the neuropsychological tests in the "AACD battery" assigned a rather similar proportion of subjects (19.3% to 23.6%) to the AACD category. The BSRT, a memory test employing the selective reminding method, was the most inclusive test and the VFT, a test of verbal fluency, the least inclusive in classifying subjects as having AACD. Of those who were classified as having AACD, about 60% met this classification on the basis of one test only. This suggests that the number of tests in the battery is critical for the identification of AACD. We may speculate that if the number of tests were increased, the incidence of AACD cases would also be elevated.

The selection of tests for neuropsychological evaluation undoubtedly influences the prevalence of AACD. In the present study, we employed one test for each cognitive domain. Each test employed can cover only one part of the wide spectrum of cognitive abilities. Although the VFT has been frequently cited as a test of verbal function (e.g., Almkvist 1996) the most crucial aspect in it is the executive control of performance. In our test battery, however, the category fluency test was best for the assessment of verbal abilities, as it can also be considered to reflect basic naming skills. The copying portion of the VRT is a test of visuoconstructive function, but does not include spatial components. In addition to attention, the TMT-A involves motor function, which may obscure the results especially in elderly subjects. The TMT-C assesses effortful processing and problem-solving in a stressing situation, but like the TMT-A, it is also dependent on attention and motor performance. Some other test which had no time-limiting or motor components would be better than the TMT-C for assessing "pure" problem-solving. The BSRT has been considered as a quite accurate measure of memory. The major advantage of our test battery was that all the tests are well-known and widely used, both in research and clinical settings.

In accordance with previous studies (e.g., Koivisto et al. 1992, Wiederholt et al. 1993, Portin et al. 1995), we observed the effect of education on test performance. The education-specific cutoff score for every neuropsychological test was highest in the best-educated subjects. This relationship between education and performance in neuropsychological tests is especially problematic for AAMI assessment. The use of education-specific norms in the AACD criteria provides at least an approximate estimate of a person's former level of functioning, which the test criteria for AAMI diagnosis completely fail to take into account. However, psychometric criteria for both AAMI and AACD are theoretically unjustified because they employ cross-sectional measures for change over time.

Prediction of dementia in AAMI

A substantial number of neuropsychological tests has been investigated for use in the early detection of dementia (e.g., Christensen et al. 1991). We selected widely used and well studied traditional tests for our test battery. However, the test battery which we used (in addition to assessment of AAMI) in the baseline of the follow-up study (IV) covered only a limited number of aspects crucial for the early detection or prediction of dementia. For example, we did not include tests for recognition memory or cued recall, which have been shown to be relatively well preserved in normal aging but impaired in early dementia (Kazniak et al. 1986, Grober and Buschke 1988). Testing also these aspects of memory might have revealed a different pattern in the predictive value of the test battery.

An obvious weakness of the longitudinal study (IV) was that we followed only those subjects who had been previously identified as having AAMI. Because we did not know the incidence of dementia in the non-AAMI group of the present study, conclusions can be drawn only from comparison to the previous studies of dementia incidence in the general population. However, those AAMI subjects who did not participate in the follow-up had lower scores on a visual memory test (the VRT1 and VRT2 scores) in the baseline evaluation than those who participated. We may assume that this nonparticipant group would have had an incidence of cognitive decline and dementia at least as high as the subjects actually investigated in the follow-up. Furthermore, the number of demented subjects was remarkably small in the two youngest age groups (60 to 64 years and 65 to 69 years of age). The small number of demented subjects (12) in the discriminant analysis also weakened the conclusions concerning the value of neuropsychological tests in predicting the development of dementia.

The low educational level of the study population (mean 6.6 years in the follow-up study) might also have confounded the results concerning the incidence of dementia in AAMI. The low educational level in our population might have elevated the incidence rates, because low education has been suggested as a risk factor for dementia (Katzman 1993, Orrel and Sahakian 1995), although all studies have not found this association (Cobb et al. 1995). However, the educational level of our sample is representative for this age-group in Finland (Aromaa et al. 1989). Moreover, many subjects have had high-level occupations in spite of low levels of formal education. This might have counterbalanced the possible confounding effect of low education in our sample, because occupational experience, independent of education, may delay the manifestation of AD, as was recently demonstrated (Stern et al. 1995).

6.1.2. Memory complaints in diagnosing AAMI and AACD

Subjective complaints were proposed as part of both AAMI and AACD diagnosis, but this has remained a controversial issue in the literature (e.g., Nicholl 1995). Almost 80% of our subjects (Subpopulation 1 in I, V) reported a deterioration when assessed with the Memory Complaint Questionnaire (MAC-Q). The optional reports of decline from informants were not available for the AACD diagnosis. For studying AACD, it could be confounding that the MAC-Q is restricted only to memory. However, as the IPA working party pointed out, memory may be the cognitive domain about which elderly subjects most frequently complain (Levy 1994). Another characteristic of the MAC-Q which undoubtedly increases the number of subjects identified is that it asks the subjects to compare their present memory with their own memory when they were young, instead of some other set point, e.g., people of their own age. Thus, the frequency of complaints of cognitive decline for AACD assessment is more likely to be exaggerated than understated, although complaints in cognitive domains other than memory were not surveyed. This fact that the MAC-Q employs a comparison between present memory and own memory performance in youth has also been debated in the AAMI literature (Derouésne 1990, Parker and Jones 1993). In future studies, the particular methods used for assessing subjective reports of cognitive decline as part of diagnostic criteria still need a critical evaluation.

Subjective memory complaints were assessed twice during Study III: first, during the screening phase with the memory tests, and second, in conjunction with the personality questionnaire. The fact that the subjects' ratings on these two occasions were rather inconsistent (12 of 32 subjects classified differently, see Subjects and Methods, Chapter 4.1.) emphasizes the need for carefully studied instruments (see, e.g., Gilewski and Zelinski 1986) in the assessment of memory complaints as part of AAMI diagnosis. Moreover, in the follow-up evaluation (IV), almost 10% of the subjects no longer complained of a memory loss sufficiently severe (i.e., MAC-Q score below 25) for AAMI diagnosis (half of them also met some other AAMI exclusion criterion, e.g., dementia). Although the MAC-Q questionnaire has been demonstrated to have good test-retest reliability (Crook et al. 1992), a short questionnaire may be insufficient for the evaluation of memory complaints as part of diagnostic criteria.

An obvious limitation of the substudy concerning the background factors of memory complaints (III) was the small sample size in the final analysis. However, the groups studied were well-matched. Moreover, the comparison of these study groups with the larger sample (from which they were selected) and with the even smaller groups (the excluded subjects who could not be taken to the follow-up analysis) showed no major differences. This suggests that these groups were indeed representative of this larger sample.

6.1.3. Exclusion criteria in diagnosing AAMI and AACD

Absence of dementia is essential for the diagnosis of AAMI and AACD. By itself, the MMSE cutoff score less than 24 proposed in the AAMI criteria is an inadequate method for the assessment of dementia. Because MMSE scores correlate positively with education and inversely with age, this cutoff score will overestimate the prevalence of dementia in less-educated, normal older adults and underestimate the prevalence in younger, more educated subjects (O'Connor et al. 1989, Koivisto et al. 1992, Ylikoski et al. 1993). Indeed, Folstein et al. (1985) found a false-positive ratio as high as one-fourth by using a cutoff point of 23 in comprehensively examined subjects. Compared with the MMSE alone, a more accurate method for assessing dementia is the use of widely-accepted criteria for dementia, such as the DSM-IV (American Psychiatric Association 1994) or NINCDS-ADRDA (McKhann et al. 1984) criteria.

Blackford and LaRue (1989) suggested that the medical exclusion criteria for AAMI may be too restrictive, and may thus exclude persons whose medical conditions do not affect memory performance. In the present study, identical medical exclusions were applied when evaluating both AAMI and AACD. Smith et al. (1991) reported exclusion rates ranging from 7.5 % to 19.2 % when they applied the medical exclusion criteria to two samples of community-dwelling elderly persons. We found that 13.9 % (63/402 in Subpopulation 1) to 15.9 % (75/471 in Subpopulation 3) were excluded because of medical conditions. The number of excluded subjects would probably have been higher if we had used methods stricter than the medical history alone to detect diseases that can cause a decline in cognition.

6.1.4. Self-rating scales of personality and affective state

The use of the MMPI scales to assess personality traits might pose problems for the interpretation of our results. Two recent studies evaluated the use of

the MMPI in geriatric populations. The hypothesis that the Hs scale score is elevated in the elderly as a result of normally increased physical problems was supported in the study of Taylor et al. (1989), but Koeppl et al. (1989) did not detect age-related differences in either the Hs- or Pt scales. In the present study, it was not possible to compare the study groups to the general norms of the MMPI, because that would have required the score of one more scale (the so-called K-correction) which was not included in our questionnaire.

Lawton (1986) pointed out that cognition should not be considered apart from other domains of well- being (as is done in the AAMI and AACD criteria), as older people with well-preserved cognition are likely to be "living the good life" in many other ways. The Geriatric Depression Rating Scale (GDS) was used for the assessment of depressive symptoms in the studies of memory complaints (III) and frontal lobe functions in AAMI (II). It was developed to be especially appropriate for elderly populations (Yesavage et al. 1983). The GDS has been found to be not only a reliable measure of depression, but also an adequate measure of high levels of well-being (Coleman et al. 1995). Thus, the difference in GDS scores between AAMI subjects and controls in the study of frontal lobe functions (II) might reflect this because, although AAMI subjects scored higher, they scored well below the levels found in clinically mildly depressed subjects (Yesavage et al. 1983). Furthermore, the GDS might also be applicable to the assessment of the well-being of AAMI and AACD subjects when used more extensively than in our study.

6.1.5. Tests of frontal lobe functions

The test battery used in Study II (in addition to the "AAMI tests") has been considered to reflect frontal lobe functions in humans. Verbal fluency (VFT) deteriorates in a variety of disorders with prefrontal pathology, such as closed head injury (Crowe 1992), AD (Bayles et al. 1989, Monsch et al. 1992), Korsakoff syndrome (Kopelman 1991), and schizophrenia (Crawford et al. 1993). The card sorting of the WCST involves concept formation processes and inhibition of inappropriate responses, being therefore sensitive to frontal lobe disorders (Nelson 1974, Arnett et al. 1994). Eslinger and Grattan (1994) found that WCST performance was impaired when lesions affected the interconnections between the frontal lobe and basal ganglia, whereas the VFT seemed to require direct cortico-cortical interconnections with the frontal lobe. The Stroop Test also challenges executive functions and representational memory, and is a sensitive indicator of frontal lobe damage (Goldman-Rakic 1987, Van der Linden et al. 1993). The Trail Making Test is an attentional task with an interference component, involving visual scanning skills, set shifting ability, and complex conceptual tracking. Studies involving patients with focal frontal lesions have suggested that this test is also sensitive to deficits associated with damage in the frontal regions (Picton et al. 1986).

However, the "regional specificity" of these tests - their relationship to the function of a certain region of the prefrontal cortex - is not fully understood, and several studies have also suggested associations with other brain regions for the WCST (Anderson et al. 1991, Corcoran and Upton 1993, Strauss et al. 1993), the TMT (Reitan and Wolfson 1995) and the VFT (Vilkki and Holst 1994). Controversial results have emerged regarding whether the ST is associated with the left (Van der Linden et al. 1993) or the right (Vendrell et al. 1995) prefrontal cortex. Studies using controlled psychometric settings combined with cerebral blood flow measurements might provide more direct evidence about the localization of test performance than do studies with brain lesion patients. In a SPECT-study (Rezai et al. 1993), the WCST was associated with activation of the left dorsolateral prefrontal cortex. However, Cantor-Graae et al. (1993) did not agree with this, but rather found this region to be involved in VFT performance. In PET studies, WCST performance has also been associated with dorsolateral prefrontal cortex (Berman et al. 1996) and ST performance, specifically with the right anterior cingulate cortex (Pardo et al. 1990, Bench et al. 1993).

Our test battery did not include measures of memory which have been specifically associated with frontal lobe functions, such as memory for temporal order or source memory (Milner et al. 1985, Shimamura et al. 1991). Testing these functions might have elucidated the quality of memory impairment in the AAMI subjects.

6.2. MEMORY COMPLAINTS IN AAMI (III)

The use of memory complaints in the diagnosis of AAMI has been criticized (Caine 1993, Rosen 1990) and even ignored in some AAMI studies (Smith et al. 1991). In the present study, memory complaints were frequent: 76.3% of subjects in the total population (I). In the screening phase, the neuropsychological memory tests did not correlate with the degree of complaints in the MAC-Q. When assessed later by a questionnaire, those subjects who had complained strongly of memory deficits but who had had normal memory performance in the neuropsychological tests, scored higher on the Hs- and Pt scales of the MMPI than did subjects with normal memory but no complaints of memory deficits. Moreover, the MMPI subscale scores correlated positively with scores in the MAC-Q. The high scores on these MMPI scales indicate stronger tendencies towards somatic complaining, anxiety about physical health, inferior feelings about personal competence and capabilities, and also tendencies towards phobic, obsessive and compulsive reactions. The results suggesting that memory complaints are associated with these measures of personality traits agree with previous studies (Broadbent et al. 1982, Zonderman et al. 1989, Poitrenaud et al. 1989, O'Connor et al. 1990). The depressive mood measured by the Geriatric Depression Rating Scale did not seem to explain the differences in memory complaints; this differs from the results of many other studies (Kahn et al. 1975, Plotkin et al. 1985, Bolla et al. 1991). One possible explanation for this discrepancy could be that there were no seriously depressed persons in our sample. Also, the method used to detect depression was different.

As the subjective estimation of memory loss by the MAC-Q can be affected by other factors in addition to actual memory deficit, a more detailed questionnaire or a questionnaire also addressed to a close relative might be better able to differentiate subjects with age-related memory disturbances from those with no memory impairment. Indeed, relatives' ratings of a subject's memory have been shown to correlate better with objective memory scores than the subject's own assessment of memory problems (McGlone et al. 1990). Interestingly, two recent reports from a Dutch population-based study showed that subjects with memory complaints as evaluated by questions from the CAMDEX protocol performed more poorly in memory tests (Jonker et al. 1996), and that such complaints were of value in predicting dementia in a three-year follow-up (Schmand et al. 1996). In these studies, the frequency of complaints by the CAMDEX was clearly lower, 34.3%, than in the present study using the MAC-Q. Thus, the association between memory complaints and performance may depend on how the memory complaints are evaluated.

Patients with AD often have poor insight into their condition already in the early stages of the disease (Feher et al. 1994). Thus, subjects with low scores on complaint questionnaires might actually be underreporting due to an underlying memory deficit and impaired insight into their own cognitive function. The MAC-Q scores in the baseline evaluations of the present study may, therefore, have caused some subjects in the very early preclinical stages of dementia to be excluded from the follow- up. In the follow-up, however, the MAC-Q scores did not have any effect on the incidence rates of dementia, because the exclusion for absence of memory complaints was not accomplished until all other exclusion criteria (e.g., dementia) had been checked.

The criterion of the presence of memory complaints has been criticized, and some investigators have recommended that it should abolished from the criteria (Smith et al. 1991, Caine 1993). However, this criterion is the only one directly involved with change. The psychometric criteria include a certain number of subjects from the lower end of statistical variance in test performance without any regard to whether they have experienced changes during aging or not.

6.3. DECLINE OF FRONTAL LOBE FUNCTIONS IN AAMI (II)

We found that, compared to controls, AAMI subjects were impaired in tests assessing frontal lobe functions: the WCST, ST, and TMT, but not in the

VFT (II). These results agree with previous studies suggesting that frontal dysfunction has an important role in age-related memory loss (Craik et al. 1990, Parkin and Walter 1992, Parkin and Lawrence 1994). In an earlier study, the attentional aspects of executive function (the TMT) were associated with learning and working memory (California Verbal Learning Test), whereas more complex aspects such as abstraction, problem-solving, and planning (the WCST) were not associated with memory (Vanderploeg et al. 1994). In the present study, AAMI subjects were impaired for both kind of tasks. This discrepancy might be explained by the different age range of our subjects. Vanderploeg et al. did not consider the possible effects of aging.

Evidence is accumulating that age-related changes in brain structure are associated with cognitive changes. Previous studies have suggested that the medial temporal lobe (Launer et al. 1995) and specifically hippocampal (Golomb et al. 1993) atrophy is associated with mild memory impairment in normal aging. Furthermore, a previous study suggested that compared to controls, AAMI subjects have minor changes in medial temporal lobe structures, and these changes also correlate with tests of visual memory (Soininen et al. 1994). However, a more pronounced hippocampal atrophy is present in AD (Laakso et al. 1995), and it is associated with memory performance (Riekkinen et al. 1995). Structural changes in the frontal lobes have also been thought to contribute to age-related changes in cognition (Mittenberg et al. 1989, Dempster 1992). The inferior performance of the AAMI subjects of the present study in a frontal lobe test battery might reflect the existence of mild frontal lobe pathology. However, neither MRI volumetric analysis nor visual analysis of MRIs revealed any major structural abnormalities in the frontal lobes of our AAMI subjects. Only a few significant correlations between psychometric and MRI volumetric measures were found. This may be because we analyzed volumes of the frontal lobe as a whole and not more specifically; for example, volumes of the lateral convexity of the frontal lobe. However, the present neuropsychological results agree with previous results suggesting frontal involvement in AAMI on the basis of neurophysiological findings (Soininen et al. 1995). A recent PET study also suggested frontal lobe dysfunction in a subgroup of AAMI subjects (Small et al. 1994).

Although not universally demonstrated, frontal lobe dysfunction also appears to be common in the early phases of AD (Patterson et al. 1996). The possible relationship between slightly impaired frontal lobe functions and incipient dementia in AAMI subjects remains to be investigated in the future. However, an explanation for the inferior performance in frontal lobe functions in the AAMI subjects may be that it only reflects the presence of normal changes observed in "usual" aging, whereas the controls might, at least in this respect, constitute a group of "successfully" aged individuals.

6.4. AAMI IN THE CONTINUUM FROM NORMAL AGING TO DEMENTIA? (I,IV,V)

Alzheimer's disease follows a gradually progressive course, starting with mild problems in cognitive performance and resulting in a complete loss of independence and finally in death (Katzman 1993). During the preclinical phase before the appearance of clinical manifestations of the disease, specific long-term changes have taken place in the patient's brain (Hardy and Allsop 1991). It has been debated whether AAMI could be viewed as an intermediary state in a continuum from normal aging to Alzheimer's disease, or whether it just reflects an increased variability of cognitive performance in the elderly population. Very mild stages of dementia seem to merge with AAMI whether assessed with memory tests (Youngjohn et al. 1992), or cognitive and behavioral scales (Brayne 1994). The present series of studies enables the continuum hypothesis to be examined from various perspectives.

6.4.1. Prevalence of AAMI

A possible connection between AAMI and AD can be evaluated by comparing the prevalence and incidence rates of these entities. The present results suggest that the epidemiology of AAMI is not similar to the epidemiology of AD. The overall pattern of age and sex differences in AD has been consistent in recent studies: the prevalence of AD increases exponentially with advancing age, and is higher in women than in men (Rocca et al. 1990, Fratiglioni et al. 1991). In contrast, the prevalence rate for AAMI was higher in men (42.5 %) than in women (35.7 %) and it declined with age in both sexes. Thus, AAMI appears not to be age-associated in this population aged 60 to 78 years. An explanation for this is the increase in the proportion of subjects meeting the exclusion criteria (MMSE score less than 24 or a disease) in the older samples. However, some kind of selective loss of participants might also contribute to these prevalence rates.The AAMI prevalence could be higher among older subjects who possibly more frequently could not participate in the study due to, e.g., rheumatic diseases.

The methodological differences in studies of the epidemiology of AAMI and related categories are numerous. In one longitudinal study, the prevalence rate for AAMI was 34.9 % and the annual incidence rate was 6.6 % in the age group of 65 years and older (Lane and Snowdon 1989). However, the study population in this door-to-door survey was small and highly select: only 146 subjects of 1000 dwellings completed their AAMI assessment. Crook et al.. (1994) reported an "upper-bound estimate" of the prevalence for AAMI. When applying only memory test cutoff scores without any exclusion criteria, they found the prevalence to range from 39% in the age group of 50 to 59 years to 85% in the age group of over 80 years.

Recently, Barker et al. (1995) reported a lower prevalence rate for AAMI (18.5% in a sample of 50- to 94-year-old subjects), than that suggested by previous studies and found in our study. The highest rate, 24.1%, found by Barker et al. was in the age group 65 to 79 years, which is most closely comparable with the age range in our study. Barker et al. carefully applied all the criteria proposed by the NIMH Work Group. The difference between the results of Barker et al. and ours might be explained by the differences in the population used in the study. Their total sample was rather small (125 subjects examined), and they did not specify how many subjects were included in the different age groups. Nor did they specify the educational level of their population. The distributions of some test scores in their study were notably different from the present results. The Vocabulary subtest from the WAIS excluded only 11% of their subjects whereas, if used in our study it would have excluded 42% of our subjects (in Population 3 in Publication I). Using the MAC-Q cutoff score of 25 or higher, only 48% of their subjects had significant memory complaints, whereas this cutoff included 73.9% to 79.8% of our subjects. These differences might reflect population differences, but maybe also the cultural variation which has been found in the neuropsychological tests (Loewenstein et al. 1994). The proportion of subjects excluded by medical exclusion criteria was almost identical in the present study (28.6%) and that of Barker et al. (29.0%).

In a Spanish community-based survey of the population aged 40 years and older, the prevalence rate for AAMI was very low: only 3.6 % in individuals 40 years and older, and 7.1 % in individuals 65 years and older (Coria et al. 1993). This study used a screening test which was primarily aimed at identifying potentially demented patients during the door-to-door phase. This screening identified only 52 of 476 subjects (10.9 %) interviewed for further examinations including the assessment for AAMI. Thus, Coria et al. defined AAMI as an "amnestic syndrome of unclear etiology, which is best categorized as AAMI". In a Canadian multicenter study, Ebly et al. (1995) also screened only cognitively impaired subjects for further assessments of AAMI and related categories. In this select population of subjects categorized as "cognitively impaired, not demented", the prevalence of AAMI varied from 16.9% to 31.4% depending on the study center, because no rigorously determined common criteria were applied at all study sites. In fact, both the Spanish and Canadian studies made their AAMI diagnoses within groups which probably would have been excluded from AAMI diagnosis because of low scores in the MMSE if the proper criteria by NIMH had been employed.

6.4.2. Incidence of dementia in AAMI

The incidence of dementia found in the AAMI population of the present study was somewhat high when compared to the level found in previous studies in the general population. The incidence of dementia has been shown to increase sharply with age (Nilsson 1984, Kay 1991). O'Brien et al. (1992) estimated the dementia incidence rates for different age groups on the basis of European studies which have reported relatively high rates. They proposed that the annual incidence rate would be 0.5% in the population 60-69 years of age, 1.5% in the population 70-74 years old, and 3.0% in the population 75- 79 years old. Our rates in the oldest group (Table 10) were close to those above, but in the younger groups, as well as in the total follow-

up sample, our rates were higher. Also, according to Kay's (1991) review of recent incidence studies, the rates found in our AAMI population appear to be elevated.

Some previous studies have evaluated the clinical course of AAMI or closely related conditions. Most of them have found no evidence of accelerated cognitive deterioration associated with these conditions (Kral 1962, Flicker et al. 1993, Reisberg et al. 1988, Youngjohn and Crook 1993). For example, Reisberg et al. (1986) found that 95 % of the elderly community residents who were in the forgetfulness phase according to the Global Deterioration Scale remained clinically unchanged during the follow-up period of 3.6 years. However, Johansson et al. (1992) found that very old subjects (84 to 90 years of age) with mild cognitive impairment ("comparable with AAMI") had a higher risk of mortality. Moreover, 17 of 47 (36.2%) subjects acquired dementia during a two-year follow-up. O'Brien et al. (1992) classified a group of memory clinic patients with subjective memory complaints but without "objective evidence of significant memory problems in clinical testing" as having benign senescent forgetfulness, and found a slightly elevated incidence of dementia, 8.8% within three years. This population had a wider age range compared to our AAMI population, but otherwise O'Brien's results seem comparable to ours.

Both O'Neill et al. (1992) and Coria et al. (1992) diagnosed AAMI in subjects for whom clear evidence of cognitive decline was obtained but who did not meet dementia criteria. In these subjects, the incidence rate for dementia during follow-up was remarkably high. Six of eight cases (75.0%) progressed to dementia within six months in O'Neill's study, and eight of 22 cases (36.3%) developed AD within 12 to 24 months in Coria's study. These figures are not comparable to our results due to the different inclusion criteria.

The present study agrees with previous results suggesting that AAMI (or BSF) generally seems to be nonprogressive. However, our results emphasize the need for further attention directed to the subgroups within the AAMI category. A study by Paykel et al. (1994) agreed with this, as it showed a high incidence (10 of 22, 45.0%) of dementia in subjects (aged older than 75) diagnosed as having "minimal dementia" by the CAMDEX interview in a 2.4-year follow-up. This diagnostic category contains a greater degree of impairment than is present in AAMI which, however, does not reach clinical dementia threshold.

6.4.3. Prediction of dementia in AAMI

The subgroup that developed dementia during follow-up (IV) could be distinguished from the AAMI group at the screening phase with an accuracy of over 80% by neuropsychological testing. The variables most efficient in predicting dementia were the total recall from the Buschke Selective Reminding Test and the immediate recall from the Visual Reproduction Test. In these memory tests, we could observe the cutoff points which offered sufficient sensitivity and specificity. The Verbal Fluency Tests on category or letters and other memory tests, the Benton Visual Retention Test and the Paired Associate Learning Test, were somewhat less efficient. However, the most accurate prediction was reached when these tests were combined. Thus, those subjects having difficulties in the memory tests and scoring low on verbal fluency (though with normal MMSE scores and not demented) appeared to be at a higher risk for developing dementia.

Our results are consistent with those of previous studies suggesting that both verbal and visual memory tests are sensitive at differentiating demented from normal elderly subjects (Christensen et al. 1991, Chouinard and Braun 1993). Similarly, the tests of verbal fluency have been regarded as indicators of an age-associated decline in cognition (Daigneault et al. 1992) and as being sensitive in the detection of dementia (Stern et al. 1992, Monsch et al. 1992). Larrabee et al. (1986) also found that tests of selective reminding and associate learning were especially useful in differentiating BSF from AD. Our results further suggest that these tests, together with the tests of verbal fluency, are of predictive value as to whether an individual with AAMI will develop dementia or not.

Some longitudinal studies have used the baseline data of initially nondemented subjects to determine which factors might predict the development of dementia during the follow-up period. Two studies with follow-up periods of approximately two years demonstrated that tests of word finding, abstract reasoning and memory (Jacobs et al. 1995), and the list learning test with the selective reminding method (Flicker et al. 1991) are of value in predicting the development of dementia. Corresponding results were recently obtained in a study using a neuropathologically-confirmed diagnosis of dementia (Crystal et al. 1996).

Some studies with longer follow-up periods have also been conducted. Katzman et al. (1989) found the score of the Blessed Information-Memory-Concentration Test to be predictive for dementia in an 80- year-old cohort followed over a 5-year period. Masur et al. (1994) followed subjects for at least 4 years and showed that the baseline results from the selective reminding, object memory, verbal fluency and Digit Symbol tests were associated with incipient dementia. Linn et al. (1995) showed that neuropsychological impairment may precede AD by more than 7 years. They suggested that measures of secondary verbal memory are sensitive to the very early, preclinical stage of AD. Our finding that a list learning task with the selective reminding method (BSRT) was the most valuable in predicting dementia in AAMI agrees with these suggestions.

Recent evidence regarding the genetics of AD increases possibilities for the identification of at-risk individuals. Several studies have reported an increased frequency of the apolipoprotein E (ApoE) allele E4 in patients with AD (Saunders et al. 1993, Kuusisto et al. 1994). Petersen et al. (1995) classified elderly nondemented subjects according to memory test performance (cued recall) and ApoE genotype and found that a combination of mild cognitive impairment and the presence of the ApoE E4 allele predicted incipient dementia during a three- to four-and-a-half-year follow-up.

6.4.4. Prevalence of AACD

The prevalence rate for AACD in subjects aged 68 to 78 years was 26.6% according to the criteria of IPA (V). Sex, age and education had some effect on the prevalence of AACD, but the differences between subgroups were not significant. The prevalence of AAMI in the present study was higher than the prevalence of AACD. Previously, AAMI has been suggested to be a rather stable condition (Youngjohn and Crook 1993), and in our follow-up study (IV) it was shown to identify a very heterogeneous subject group with an incidence of dementia that was only slightly elevated. The lower prevalence rate for AACD suggests that AACD might be better than AAMI for categorizing subjects who deviate from normal aging or who are near the critical end in the continuum from normal aging to dementia. This finding contradicts the apprehension that the broadening of the construct from mere memory impairment (AAMI) to a wider range of domains (AACD) might increase the proportion of subjects identified (Levy 1994), at least when age-specific cutoff points are used.

According to our results, the construct of AACD might better identify those who have a genuine cognitive decline and should therefore be observed in follow-up studies for the possible development of dementia. Also, pharmacological trials to develop means for early intervention for preclinical dementia might prove to be justified for these subjects. AACD might also turn out to be more clinically relevant than AAMI. This has to be confirmed by follow-up studies with AACD subjects. The follow- up of subjects with AAMI (IV) suggested that a more detailed neuropsychological test battery has predictive value for the development of dementia. In this battery, however, the best result was obtained when several tests were used in a combination. This may be a more reliable procedure than that used in current AAMI and AACD criteria, which are fulfilled if at least one test is below the cutoff point.

6.4.5. Continuum from normal aging to dementia?

Rosenman (1991) suggested that the methods used to diagnose mild dementia (e.g., the Clinical Dementia Rating Scale (Hughes et al. 1982) and the Global Deterioration Scale (Reisberg et al. 1982)) lack reliability. He found them poorly concordant, inadequately in agreement with a clinician's judgement or with cognitive scales, and unable to identify those subjects whose cognitive impairment will progress to dementia. According to Rosenman, the failure of the attempts to distinguish diseases of mild dementia provides evidence for the continuum hypothesis. He stated that "they are attempts to create a category where no natural category offers itself". Christensen et al. (1995) found a prevalence of 4% for mild cognitive disorder according to the ICD-10 criteria in a sample of elderly subjects. They questioned the validity of the diagnosis and suggested that a multidimensional approach should be employed, instead of "imposing a categorical system on what seems to be a continuous dimension". Our results agree with these speculations and suggest that AAMI subjects mostly reflect those aging effects which might be accounted for by "usual" aging, whereas subjects with cognitive performance superior to AAMI might reflect "successful" aging. However, a subgroup of AAMI subjects is evidently at risk for developing dementia, thus reflecting "pathological" aging.

The results of the present study suggest that the usefulness of the construct of AAMI is ambiguous. Although we obtained evidence for a distinct cognitive profile in AAMI (inferior performance also in tests assessing frontal lobe functions), AAMI does not appear to describe any homogeneous group of subjects. Thus, the use of the AAMI construct to characterize any group of elderly subjects might generate studies which are not easily comparable and might result in confusing conclusions. AAMI subjects also appear to be too heterogeneous a group to target for pharmacological treatment trials. More detailed neuropsychological methods must be used to distinguish meaningful groups of elderly subjects. AACD criteria might prove to be superior to AAMI in this respect, but this remains to be confirmed in further studies.

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7. CONCLUSIONS

1. The prevalence of AAMI, as defined by the diagnostic criteria of the NIMH work group, is high in the Finnish elderly population. AAMI seems likely to be a phenomenon of normal aging rather than a continuum from normal aging to a pathologic state such as Alzheimer's disease. As in many previous studies, the neuropsychological methods used for AAMI diagnosis appear ambiguous in this study also.

2. AAMI subjects appear to be impaired not only in tests assessing memory but also in tests of executive functions associated with frontal lobe function. This finding agrees with previous reports suggesting an important role for frontal dysfunction in the memory loss of elderly people.

3. Subjective feelings of memory impairment are more closely associated with personality traits than with actual memory performance in normal elderly people. This complicates the use of memory complaints in the inclusion criteria of AAMI diagnosis.

4. In the follow-up, a slightly elevated incidence of dementia was observed in AAMI subjects as compared to previous studies in the general population. This finding suggests that AAMI, in general, is nonprogressive, but that the AAMI population also includes subjects with very early dementia. However, these subjects can be identified by means of a more detailed neuropsychological evaluation.

5. The prevalence of AACD, as defined by the diagnostic criteria of the IPA work group, was found to be lower than that of AAMI. As AAMI tends to identify a very heterogeneous subject group, the AACD diagnosis might prove superior to AAMI in differentiating a meaningful subgroup from the elderly population both for research purposes and in clinical settings. This remains to be confirmed in follow- up studies.

In summary, the present study demonstrates that the validity of the AAMI construct is still dubious. Several aspects of the diagnostic criteria are disputable. The AAMI diagnosis appears to identify a very heterogeneous group of subjects of only vague clinical or theoretical significance. The relevance of the AACD diagnosis remains to be evaluated in further studies. Nevertheless, more reliable diagnostic approaches are needed in studies trying to identify risk factors for dementia or to find treatment for very early dementia.

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