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AGE-ASSOCIATED MEMORY IMPAIRMENT, and APOLIPOPROTEIN E

A population-based clinical, neuropsychological, neurophysiological and neuroimaging study

Doctoral dissertation

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ABSTRACT

The purpose of the present study was to characterize Age-associated memory impairment (AAMI) using clinical, neuropsychological, neuroradiological and neurophysiological methods. A further aim was to evaluate the relationship between Apolipoprotein E (ApoE) ε4 allele and cognitive functions, structural and functional neuroimaging findings among elderly individuals without dementia. Diagnostic criteria of AAMI proposed by the National Institute of Mental Health were used.

The population based study comprised of 90 elderly individuals, 43 of whom were AAMI subjects and 47 were healthy controls. There were no significant differences between these two groups in volumes of the medial temporal lobe structures on magnetic resonance imaging (MRI) or regional cerebral metabolism on single photon emission tomography (SPECT). The AAMI neuropsychological and neurophysiological findings suggested impairments in attentional processes, dysfunction of the frontal, executive attention system, and the subsequent effect of this on the memory function may have contributed significantly to the memory deficis which are characteristic to AAMI. These findings are in agreement with previous reports which suggest that frontal lobe dysfunction plays an important role in the memory loss of elderly people. Thus, AAMI appears more likely to be a phenomenon of normal aging rather than a continuum from normal aging to a pathologic state such as Alzheimer's disease.

Out of the 90 subjects, 34 participated in a follow-up study 2.8 years later. Volumetric hippocampal atrophy occurred at a similar rate in both the AAMI and control groups. The subjects with AAMI had more pronounced episodic memory deterioration than the controls. Furthermore, they showed a higher frequency of the ε4 allele (0.47) compared to the control subjects (0.16). The follow-up of the AAMI subjects suggested that AAMI, in general, is nonprogressive but the criteria for AAMI might select more ε4 carriers than non-carriers among elderly individuals.

The study group was also divided into two groups according to each subject's ApoE ε4 status. In the ε4 carriers, the rate of memory decline was greater than in the non-carriers although hippocampal atrophy occurred at a similar rate.

The study demonstrated that the AAMI diagnosis appears to identify a very heterogeneous group of subjects and does not, of itself, predict the presence of incipient dementia. In contrast, the ApoE ε4 allele may be a marker for accelerated cognitive aging. Thus, the ε4 carriers form one risk group for progressive memory decline among the elderly. In addition to this genetic (ApoE) testing, the results underscore the need to develop new sensitive diagnostic tests to predict the presymptomatic and very mild stages of AD, where therapeutic intervention might be more effective.

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To Maria, Mikael and Tero

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Merja Hallikainen

ABBREVIATIONS

A	Amygdala
AACD	Aging-associated cognitive decline
Aβ	Amyloid β protein
AAMI	Age-associated memory impairment
AD	Alzheimer's disease
ANOVA	Analysis of variance
ApoE	Apolipoprotein E
ARCD	Age-related cognitive decline
BSRT	Buschke Selective Reminding Test
BVRT	Benton Visual Retention Test
CERAD	The Consortium to Establish a Registry for Alzheimer's Disease
CT	Computed tomography
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
DSp-WAIS	Digit Span subtest from the WAIS
DSy-WAIS	Digit Symbol subtest from the WAIS
EC	Entorhinal cortex
EEG	Electroencephalography
ERP	Event-related potential
GDS	Geriatric Depression Rating Scale
HC	Hippocampus
HM-PAO	Hexamethylpropyleneamine oxime
ICA	Sagittal intracranial area
ICD-10	International Classification of Diseases, 10th revision
IQ	Intelligence Quotient
ISI	Interstimulus interval
ITI	Intertrain interval
MAC-Q	Memory Complaint Questionnaire
MMN	Mismatch negativity
MANOVA	Multivariate analysis of variance
MMSE	Mini-Mental Status Examination
MRI	Magnetic resonance imaging
NFT	Neurofibrillary tangle
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
PCR	Polymerase chain reaction
PAL	Paired Associated Learning subtest from WMS
PET	Positron emission tomography
QEEG	Quantitative electroencephalography
rCBF	Regional cerebral blood flow
ROI	Region of interest
SD	Standard deviation
SP	Senile plaque
SPECT	Single photon emission 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 WAIS
WAIS	Wechsler Adult Intelligence Scale
WCST	Wisconsin Card Sorting
WMS	Wechsler Memory Scale

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1. INTRODUCTION

The continuing increase in the proportion of elderly people in the population has led to an increase in awareness and interest of diseases that affect cognitive function in the elderly. Alzheimer's disease (AD) accounts for 70% of all cases of late-onset dementia (after 65 years of age). Since the incidence of AD doubles every 5 years after 60 years of age (Terry and Katzman 1994, Tanzi et al 1996), the incidence of AD is expected to increase further as more people live to advanced ages. Characteristic neuropathological features of AD include neurofibrillary tangles (NFTs), and extracellular deposits of β-amyloid protein (Aβ) in senile plaques (SPs). However, AD seems to be etiologically as well as genetically heterogeneous, with probable interactions between genetic and nongenetic factors. Three "causative" genes, have been identified in early onset familial AD. There is one "susceptibility" gene, the Apolipoprotein E (ApoE) gene, which affects risk and age of the onset of AD. This was originally identified in late-onset familial AD. Accumulation of NFTs and Aβ is also much less extensive in individuals who reached advanced ages without clinical dementia (Terry et al 1987, Hansen et al 1988, Terry and Katzman 1994).

Throughout adult life, all physiological functions gradually decline (Rudman and Rao 1992). The amount of days with restricted activity and the number of admission to hospitals and nursing homes sharply increases after the age of 70 years (Kosorok et al 1992). Most elderly individuals will die from atherosclerosis, cancer, or dementia. Distinguishing AD from normal aging has been a recurring nosological and diagnostic problem (Drachman 1983, Berg et al 1988, Morris et al 1991). Considerable evidence indicates that the neurodegenerative process of AD commences long before dementia is apparent. The study of Ohm et al. (1995) suggests that Alzheimer-like neurofibrillary changes may begin 50 years before the onset of visible cognitive symptoms and that the process is influenced by ApoE genotype. Enviromental risk factors most likely interact with genetic risk factors to determine the age of onset (Finch and Tanzi 1997).

To respond to a growing interest in initiating drug trials to arrest or reverse aging related cognitive changes among the healthy elderly, in 1985 the National Institute of Mental Health (NIMH) convened a working group to develop research diagnostic criteria for identifying healthy older adults with memory impairment. These Age-Associated Memory Impairment (AAMI) (Crook et al 1986) criteria include the presence of complaints of gradual memory loss in everyday activities of daily life in persons older than the age of 50, objective evidence of impairment on a standardized memory test as compared with the mean established for young adults, evidence of adequate intellectual function, and absence of dementia or any medical condition that could contribute to cognitive deterioration. The AAMI criteria leave open the question of the progression in the condition: is AAMI a phenomenon of normal aging rather than a continuum from normal aging to a pathologic state such as AD.

In the future, the need for an early diagnosis of dementia will be of vital importance: treatment of this disease is expected to be more successful in the early stages before changes in the brain have become structural (Jolles et al 1995). In addition, it is of great importance to have diagnostic methods which accurately differentiate those patients with mild dementia from those with more benign forgetfulness, because of the public's growing awareness of dementia as a major health problem and the corresponding anxiety associated with this awareness (Commissaris et al 1993, 1994). As currently there are no objective in vivo markers for AD, then neuroimaging, for example with magnetic resonance imaging (MRI), electroencephalography (EEG), positron (PET) or single photon emission tomography (SPECT), of typical structural or functional changes that are able to support the very early diagnosis of AD would be of great importance. Previous reports have suggested that there are some neurophysiological, structural and

metabolical factors in the brain characteristic for AAMI subjects (Soininen et al 1994, 1995a, Parnetti et al 1996), but these findings are not yet firmly established.

The present study is part of a larger project to investigate the nature of cognitive decline in aging and the relationship between normal aging and dementia. The study is based on a series of 90 patients who were randomly selected from a population of 578 individuals who participated in the study of AAMI prevalence in the Kuopio city area.

2. REVIEW OF THE LITERATURE

2.1. Normal aging

I can live with my arthritis , My dentures fit me fine,
I can see with my bifocals, But I sure do miss my mind (Anonymous).

Aging is one of the absolute certainties of life. In many populations the proportion of elderly people is growing steadily, particularly the proportion of the more elderly. Aging is accompanied by a progressive but variable deterioration in health. The importance of aging is obvious in both the decline of cognitive function in the elderly and the vulnerability of the aging nervous system to degenerative diseases (Drachman 1997).

Investigators involved in aging studies have recognized the importance of separating pathologic changes from those that could be attributed to aging per se. Thus, for physiologic studies careful guidelines have been developed to exclude individuals whose age-determined responses and behaviors might be contaminated by specific disease processes (Rowe and Khan 1987). Results from the population remaining after such exclusions have then been interpreted as representing "normal" aging.

Throughout adult life, all physiological functions gradually decline. There is a diminished capacity for cellular protein synthesis, a decline in immune function, an increase in fat mass, a loss of muscle mass and strength, and a decrease in bone mineral density (Rudman et Rao 1992). Part of the aging process affecting body composition might be related to changes in the endocrine system (Korenman 1982, Rudman and Rao 1992, Lamberts et al 1997).

Within the category of normal aging, a distinction can be made between usual aging, in which extrinsic factors, such as diet, exercise, personal habits, and psychososial factors, heighten the effect of aging alone, and successful aging, in which extrinsic factors play a neutral or positive role. Genetic factors, life style, and community investments in a safe and healthy environment are important aspects of succesful aging. The people in the usual aging group would perform at a lower level than they did previously, and those in the successful aging group would be able to continue active and creative lives. Nontheless, the problem of normal / abnormal definition will recur (Rowe and Khan 1987).

Although age-based generalizations of declining cognitive functioning relating to younger subjects have dominated the literature, the heterogeneity of cognitive aging is beginning to attract serious attention. Increased variability in performance is reported among older subjects on a range of tests (Morse 1993, Christensen et al 1994), with significant numbers of older subjects performing within the range of younger subjects (Schaie 1988, Albert 1993, Daffner et al 1994).

2.2. Cognitive functions

Cognition (latin; *cognoscere* = to know) refers to "*all aspects of perceiving, thinking and remembering*" (Dorland's Illustrated Medical Dictionary, 1988). The main domains of cognition are memory, executive functions, abstraction, problem solving, visuospatial ability, and language.

Many different types of models and terms are used by different authors to describe memory functions. Squire and Zola-Morgan (1988) proposed a distinction between declarative and non-declarative memory. Declarative (explicit) memory refers to conscious recollections of facts and events and depends on the

integrity of the medial temporal lobe. In particular, the hippocampus, has an integrative and temporary role for encoding new memories and binding together the different memory stores of the neocortex. During information processing, structural or plastic changes occur in the synapses associated with learning, and more permanent memory develops (DeKosky and Scheff 1990). There is the unidirectional flow of information through the perforant pathway, which originates in layer II of the entorhinal cortex (EC) and terminates in the outer molecular layer of the dentate gyrus, thus providing the key interconnection between the neocortex and the hippocampus (Amaral and Witter 1989, Witter et al 1989). The EC is a region of extraordinary convergence of inputs from the association cortex, essentially funneling highly processed neocortical information into the dentate gyrus of the hippocampus and thereby playing a crucial role in memory (Squire and Zola-Morgan 1988). The memory stores of the neocortex are considered to become independent of the medial temporal lobe memory system and to represent a long-term memory (Squire and Zola-Morgan 1991). There are anatomical connections between the two medial temporal structures through both direct hippocampal commissural pathways and possible indirect pathways involving subcortical structures or the frontal lobe (Gloor et al 1993).

Non-declarative (implicit) memory comprises a heterogeneous collection of learning and memory abilities, all of which are nonconscious and expressed through performance. The formation of non-declarative memory is independent of the medial temporal lobe (Squire and Zola-Morgan 1991). Basal forebrain and lateral temporal cortex are regions likely to be involved in storing representations of acquired information (Squire and Zola-Morgan 1988).

Tulving (1989) suggested that there are three systems: procedural, semantic and episodic memory. Procedural memory refers to learned connections between stimuli and responses, which are not accessible to consciousness. Semantic memory refers to a general knowledge of the world which is not linked to particular temporal-spatial context; it permits the organism to construct mental models of the world. Episodic memory refers to conscious recollection of personally experienced events and their temporal relations. Procedural memory supports semantic memory and semantic memory supports episodic memory.

The serial path of information processing extends from the sensory modalities to the short-term and long-term memory stores. The flow of information through memory stores is assumed to be controlled by “Working memory”, a central attentional control system of short-term memory, which feeds forwards to the long-term memory (Baddeley 1988). The prefrontal cortex has been characterized as a central executive or working memory system that is responsible for coordinating the planning, elaborative, and organizational processes that facilitate encoding and retrieval functions supported by the hippocampal system (Moscovitch and Umilta 1990, Rezai et al 1993). The PET studies resulted in another important finding which Tulving et al. (1994) termed the ”hemispheric encoding, retrieval asymmetry”. They found that for encoding of episodic information, the left prefrontal cortex was differentially activated whereas, during retrieval, the right prefrontal cortex was activated. Patients with dorsolateral frontal lobe lesions often perform well on tests of memory but may fail on tasks where they must devise an internally generated strategy to guide memory performance, such as free recall (Jetter et al 1986, della-Rocchetta 1986, Janowsky et al 1989), recency or temporal order judgements (Milner 1971, Shimamura et al 1991), self-ordered-pointing (Petrides and Milner 1982), conditional associative learning (Petrides 1985), and recollection of the source of information (Janowsky et al 1989). Thus, these patients provide evidence for a dorsolateral prefrontal component of stategic memory system.

Attentional behaviors represent an interaction between divided and selective attention. Frontal lobes seem to be the one cortical area most intimately related to regulation of selective attention (Mesulam 1985).

Visuospatial ability refers to those abilities to produce and recognize two or three-dimensional figures and space. Disorders of spatial and constructional analysis are usually due to lesions of occipito-parietal regions of the brain (Mesulam 1985).

Language is the sequal system used by one individual to communicate with another. Disturbances in language are usually a consequence of left frontal or temporal lesions (Mesulam 1985).

The amygdala may be responsible for the affective association of events (Squire and Zola-Morgan 1988) and for the impairment of memory for emotional material (Markowitsch et al 1994, Bechara et al 1995, Clark 1995, LaBar et al 1995, Cahill et al 1995, 1996).

2.3. Cognitive functions in advanced aging

In the working memory model, attentional mechanisms are the principal tools for the retention of information (Baddeley 1988). The major distinction is usually made between divided and selective attention. Tests of divided attention assess the capacity to perform more than one task simultaneously whereas tests of selective attention measure resistance to some form of distraction (Robbins and Everitt 1987). In normal aging the capacity for attention declines after 60 years of age, as has been shown in particular with tests of divided attention (Albert 1988).

Studies of intact and impaired memory in age-related diseases suggest that normal aging has markedly different effects upon different memory systems. Aging may have little or no effect upon the neocortical memory system which mediates conceptual and perceptual priming. In contrast, aging has a continuous, life-long effect upon the frontal lobe system that mediates critical aspects of working and strategic memory. Salthouse (1990) proposed that the reduction in working memory processing which is dependent on the frontal lobes is a crucial factor for age-related changes in many cognitive functions including memory. Daigneault and Braun (1993) agreed with this view and suggested that the frontal lobe function is usually the first to decline in normal aging. Degeneration in this system may account for much of the age-related decline in declarative memory seen in healthy people in their 60s and 70s. Whether mild memory impairment can be included in the spectrum of normal aging or can be accounted for by the insidous, late onset of AD, is still debatable.

Language functions can be studied by evaluating speech, verbal fluency, naming ability, repetition, reading, writing and verbal comprehension. All of these functions are preserved during aging except naming ability, which slightly declines after age of 70 (Albert 1988, Bayles and Kazniak 1987).

Simple visuospatial functions are usually intact in healthy elderly persons. Simple visuospatial tasks are copying a complex design or judging the angular orientation of lines. More complex tasks are the Block Design, Object Assembly and Picture Completion subtest of the WAIS (Killian et al 1984). However, performance of complex spatial tasks is impaired after 60 years of age (Albert 1988).

Abilities such as abstract thinking, reasoning, understanding of logical relationships and many other cognitive functions are generally considered to be aspects of intelligence. A common cultural stereotype is that intelligence declines somewhat with normal aging. Early investigators concluded the same result in their studies (Miles and Miles 1932, Wechsler 1939). However, it has become increasingly clear that “general intelligence” cannot be said to deteriorate with age (Bayles and Kazniak 1987). A slowing of response and

processing speed has been shown to make a major contribution towards the changes in intelligence test performances seen with aging.

The most common intelligence test, the Wechsler Adult Intelligence Scale (WAIS) (Wechsler 1955), is composed of multiple subtests. Scores on these subtests are combined to provide a sum total, usually expressed as an intelligence quotient (IQ). The marked relationship between education and IQ is illustrated in the results of Green (1969). When Green separated the WAIS fullscale IQ into component verbal IQ and performance IQ scores, verbal IQ showed an increase with older age, among the educationally matched age groups, whereas performance IQ showed a slight decline. In the 21-year Seattle Longitudinal Study (Schaie 1983) for those measures concerned with the recall and use of previously acquired knowledge, little evidence of deterioration was apparent until after 70 years of age. For those tasks involving more active and novel problem-solving, a greater age-associated decline was observed.

Horn and his colleagues (Horn and Cattell 1967, Horn and Donaldson 1976) suggested that adult age relationships can be understood if two types of intelligence are distinguished. The first, fluid intelligence, is reflected in tests of memory span, figural relations, inductive reasoning, and most processes involved in acquiring new information. Fluid intelligence decreases with old age. The second type, crystallized intelligence, is the cumulative product of information previously acquired by the activity of fluid intelligence, and thus represents the store of culturally transmitted information. Crystallized intelligence is measured by tests like vocabulary definition, general information knowledge, comprehension, arithmetic ability, and reasoning with familiar material. Crystallized intelligence remains stable throughout most of the adult life.

2.4. Age- associated memory impairment

2.4.1 Concept of memory impairment in the elderly

As people age, they often complain of memory loss. Kral (1962) introduced the term "*benign senescent forgetfulness*" to describe mild memory losses associated with aging that do not progress to a dementing illness. He distinguished it from the "*malignant forgetfulness*" of the organic amnestic syndrome and dementia. Although the concept of benign senescent forgetfulness has received considerable attention in the clinical aging litterature, it has been criticized for being poorly operationalized and insufficiently validated (La Rue 1982, Crook et al 1986). More recently, a National Institute of Mental Health (NIMH) Work Group on Aging and Memory recommended abandoning the earlier term and proposed a set of criteria for diagnosing *age-associated memory impairment (AAMI)* to describe the subjectively and objectively evidenced memory loss that may occur in healthy, elderly individuals in the later decades of their life (Crook et al 1986).

2.4.2. Diagnostic Criteria for Age-associated memory impairment

AAMI is characterized by complaints of memory impairment in tasks of daily life, substantiated by evidence of such impairment on psychological performance tests with adequate normative data. The tests employed should assess recent memory for verbal and nonverbal material. The AAMI is applied to people over 50 years of age, although this does not imply that such impairment is qualitatively different than in younger adults, although being less frequently seen. The term is also a nonspecific relative to etiology and does not necessarily imply that disorder is nonprogressive (Crook et al 1986). Proposed research diagnostic criteria are seen in *Table 2*.

A comparable term, *age-associated cognitive decline (AACD),* was introduced by a working group of the International Psychogeriatric Association (Levy 1994) to describe a similar population. The AACD criteria allow a decline in any principal domain of cognition, not only in memory. In addition to AACD, *ARCD (age-related cognitive decline)* is included in the DSM-IV. The diagnostic criteria of ARCD are not detailed nor used in studies. ARCD is an objectively identified decline in cognitive functioning consequent to the aging process that is within normal limits given the person's age.

Table 2. Proposed research diagnostic criteria of AAMI (Crook et al 1986)

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 are equally appropriate.

Test	*Cutoff Score*
Benton Visual Retention Test	6 or less
Logical Memory subtest of 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, neuroradiological examination. 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 Ischemia Score of 4 or more, or by neuroradiologic examination.

e. History of repeated minor head injury (e.g., in boxing) or single injury resulting in a period of unconsciousness for 1 hour or more.

f. Current psychiatric diagnosis according to DSM-III criteria of depression, mania, or any major psychiatric disorder.

g. Current diagnosis or history of alcoholism or drug dependence.

h. Evidence of depression as determined by a Hamilton Depression Rating Scale score of 13 or more.

i. Any medical disorder that could produce cognitive deterioration including renal, respiratory, cardiac, and hepatic disease; diabetes mellitus unless well controlled by diet or oral hypoglycemics; endocrine, metabolic, or hematologic disturbances; and malignancy not in remission for more than 2 years. Determination should be based on complete medical history, clinical examination (including electrocardiogram), and appropriate laboratory tests.

j. Use of any psychotropic drug or any other drug that may significantly affect cognitive function during the month prior to psychometric testing.

2.4.3 Prevalence of Age-associated memory impairment

The prevalence of AAMI has not been clearly defined. Depending on the methodology and ages of the samples studied, the reported prevalence ranges from 4.6-34.9% (Coria et al 1993, Koivisto et al 1995).

The concept of AAMI has been widely criticized. The criteria for measuring objective memory impairment are postulated to lack of reliability (Rosen 1990, Smith et al 1991), and AAMI is said to be too broad an entity (O'Brien and Levy 1992, Caine 1993). Previous reports on the epidemiology of AAMI have not employed the specific diagnostic criteria for AAMI and have utilized varying methodology (Lane and Snowdon 1989, Coria et al 1993) or have been based on archival data reported for age-associated normative data on standard memory tests (Larrabee and Crook 1994). Koivisto et al. (1995) were the first to apply the specific AAMI criteria in a random, large-scale epidemiologic study, and they reported a prevalence rate for AAMI of 38.4%, based on 1,049 subjects aged from 60 to 78 years. Interestingly, prevalence rates of AAMI differed in different age groups, and instead of increasing with age, as would be expected, the prevalence rate declined in the oldest age groups, whereas objective memory decline increased. Soon after Koivisto's report, Barker et al. (1995) published a prevalence study of AAMI using the original criteria. They found a 24.1% prevalence of AAMI in 65- to 79-year-old subjects and a lower prevalence (11.8%) of AAMI in 80- to 94-year old subjects thus confirming the findings of Koivisto et al. (1995). The low rates 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. They also found, as in previous studies (Kahn et al 1975, Zonderman et al 1989, DerouŽsne 1990, Hänninen et al 1994), that complaint of memory decline is more strongly correlated with measures of affect and personality than with measures of current memory test performance or estimates of memory decline. However, many studies have shown a significant correlation between memory complaints and memory performance assessed with memory tests (Zelinski et al 1980, Riege 1982, Dixon and Hultsch 1983, Larrabee et al 1991). Some investigators have suggested that the criterion based on subjective memory loss should be abolished from the AAMI diagnosis (Smith et al 1991, Caine et al 1993) but some propose that memory complaints could be an early sign of dementia (O'Brien et al 1992a, Grut et al 1993).

Koivisto et al. (1995) share the concerns of other investigators regarding the overinclusive nature of AAMI (Smith et al 1991, O'Brien and Levy 1992, Caine 1993). On the other hand, medical exclusion criteria of AAMI may be too restrictive and thus exclude persons whose medical conditions do not affect their memory performance (Blackford and La Rue 1989, Koivisto et al 1995). In spite of mostly promising results of pharmacological treatment studies with AAMI, many researchers have criticized those studies as being premature in the current state of knowledge of this entity (O'Brien and Levy 1992, Barker and Jones 1993, O'Brien 1994).

Despite considerable research on memory and aging in persons without dementia, data is limited on the borders between AAMI and dementing ilnesses such as AD. A few longitudinal studies have been performed. Reisberg and his collegues (1986) evaluated elderly community-dwelling persons with mild cognitive decline corresponding to Global Deterioration Scale (GDS) stages 2 to 3 (Reisberg et al 1982). After a mean follow-up interval of 3.6 years, they found that such persons were less likely to show continued decline than those with moderate or severe impairment (GDS stages 4 to 6). Hänninen and co-workers (1995) found that 9.1 % of the AAMI population developed dementia in the 3.6-year follow-up period. Results of O´Brien et al. (1992a) are comparable (incidence of dementia 8.8 % in 3 years). These studies suggest that AAMI is generally nonprogressive but it also include subjects with early dementia.

2.5. Diagnosis of Alzheimer's disease

Dementia is an acquired syndrome of decline in memory and other cognitive functions sufficient to affect daily life in an alert patient (American Psychiatric Association 1995). Alzheimer's disease (AD) is the most common cause of dementia and increases exponentially with age. On average, two out of three patients displaying symptoms of dementia are diagnosed as having AD in Europe and North America (Hofman et al 1991, Rocca et al 1991). AD is a progressive neurodegenerative disorder associated with a sequential decline in cognition, behavior and multiple performance. These characteristics make AD a severely debilitating disease, not only for the patient, but for their caregivers as well. AD has a heterogeneous aetiology and over the past 20 years has been associated with a large number of putative environmental causative factors as well as more recently genetic mutations on chromosomes 1, 14 and 21, which cause rare, early onset familial forms (Goate et al 1991, Levy-Lahad et al 1995, Sherrington et al 1995). The Apo E ε4 allele on chromosome 19 is associated with an increased risk for the common late onset AD (Corder et al 1993).

In recent years, standardised diagnostic criteria for AD have been developed (Table 1), together with guidelines for their use, greatly improving the reliability of clinical diagnosis of AD. The diagnosis of AD has been divided into possible, probable and definite according to NINCDS-ADRDA criteria. The criteria for probable AD have been shown to have good correspondance to the pathological diagnosis of AD (Klatka et al 1996) and largely overlap with the more recent DSM-IV and ICD-10 criteria for AD. In the NINCDS-ADRDA criteria, the clinical diagnosis is considered as either possible or probable and the pathological diagnosis as defining.

Table 1. Standardised clinical diagnostic criteria for Alzheimer's disease

Abbreviation	*Title*	*Source*
NINCDS/ ADRDA	National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria	McKhann et al., 1984
ICD- 10	International Classification of Mental and Behavioural Disorders, In: International Statistical Classification of Diseases and Related Health Problems, 10th edition	World Health Organization, Geneve, 1993
DSM- IV	Diagnostic and Statistical Manual for Mental Disorders, 4th Edition	American Psychiatric Association, 1995

All three diagnostic frameworks share the essential positive requirement of progressive decline in memory and impairment in at least one non-cognitive intellectual function. Diagnosis of AD must be primarily one of inclusion, not exclusion, as is often supposed. In approximately 90 % of cases, the diagnosis can be made on the basis of a general medical and psychiatric evaluation (Rasmusson et al 1996, Larson et al 1996).

2.6. Changes in cognitive functions in Alzheimer's disease

Neuropsychology is a cornerstone in the assessment of early dementia (Cipolotti and Warrington 1995). In spite of some preliminary suggestions of qualitative differences between normal aging and AD, the evidence is not compelling (Nebes 1992). On the contrary, it seems likely that the alterations in memory

associated with early AD are substantially different from those associated with age-related changes in memory.

The clinical course of AD typically involves a gradual onset and slow progression. AD is characterized by impairment in a wide range of cognitive functions. Memory dysfunction is often the initial manifestation of AD. Investigators using the CERAD database, demonstrated that delayed recall or forgetting was sensitive in identifying patients with AD, and that this variable may be the first sign of a decline in cognitive function (Welsh et al 1991, Morris et al 1993). In the study by Petersen et al. (1994) a measure of learning with facilitation of performance using cues appears to be the best discriminator for detecting mild AD. Recently, Albert's (1996) findings indicated that tests of immediate and delayed recall, administered over brief delays, can be used to differentiate AD patients from controls, and from patients with a wide variety of dementing disorders.

In AD, both short-term and long-term memory are progressively impaired. Long-term episodic memory is affected early in the disease process (vanHoesen 1990), whereas semantic memory is usually affected later (Nebes et al 1984). Confabulation is a common feature and its specificity in AD patient with mild cognitive impairment may be related not to language deficiency, but to semantic memory disturbance (Finali et al 1993). Procedural memory is relatively well preserved (Mahler and Cummings 1990).

A disturbance in attentional performance is always present in the different dementias, and is usually greater in subcortical than in cortical dementias (Baddeley et al 1988). Reduced brain metabolism in mild AD is associated with a slowing of reaction time specifically in tests of divided attention (Nestor et al 1991).

The rate of decline in language functions is faster in a disease process with a greater involvement of the left hemisphere (Mortimer et al 1992). An early finding is impairment of verbal fluency for categories, for instance names of animals or words beginning with a particular letter. As dementia progresses, many patients become dysphasic. At a later stage, language is obviously nonfluent and repetition impaired; terminally speech deteriorates into total aphasia (Faber-Langendoen et al 1988).

Visuospatial impairment is seen already with mild AD when a disease process with greater involvement of the right hemisphere (Bayles and Kazniak 1987, Mortimer et al 1992). Visuospatial deficit results in symptoms such as misplacing objects or getting lost, and difficulty with tasks such as drawing complex figures. Difficulty with calculation, including skills such as handling money, apraxia, and agnosia are further problems that develop in AD.

Judgement, abstraction and executive functions are often impaired in mild AD, and deterioration occurs in both types of intellectual ability (Larrabee et al 1985), although Performance IQ is almost always lower than Verbal IQ (Miller 1977). While AD has its greatest effect upon WAIS performance subtest scores, all subtests reveal further deterioration as the disease progresses. AD patients with severe dementia are typically too impaired to be formally testable on measures such as the WAIS (Bayles and Kazniak 1987). Impairment of executive functions is common already in mild AD (Reid et al 1996).

Behavioral or psychiatric symptoms are a major source of stress for the dementia patient and their caregiver. Depressive symptoms occur in about 25 % of patients, although severe depression is uncommon (Cummings et al 1995). Delusions, usually simple persecutory delusions, are common, although they are rarely systematized, as in schizophrenia. The occurrence of affective and psychotic symptoms may exacerbate disability and lead to early institutionalization. The spectrum of behavioral abnormalities is broad

(wandering, agitation, aggression, insomnia, poor self-care, and so on) and often widens further as the disease progresses.

2.7. Neuropathological changes in normal aging with the reference to Alzheimer's disease

Systematic examination of changes in the human brain concerned with aging have taken place only relatively recently. A decrease in brain weight, ventricular dilatation, gyral atrophy, and selective loss of neurons within different brain regions are changes that occur in the brain during aging (Kemper 1994).

The extracellular senile plaques of β-amyloid protein (SPs), and the intracellular deposits of hyperphosphorylated tau, neurofibrillary tangles (NFTs), are the classical pathological hallmarks of AD seen at postmortem and are considered as a prerequisite for the neuropathologic diagnosis of AD and reflective of degeneration (Tomlinson and Corsellis 1984, Mirra et al 1991, 1997). SPs and NFTs are also found to a lesser extent in normal aging and are morphologically identical to those seen in patients with AD, although they are not found in normal young and middle-aged people (Tomlinson et al 1968). The number of NFTs has been correlated with the degree of dementia (Wilcock and Esiri 1982, Mountjoy et al 1983, Arriagada et al 1992, Berg et al 1993, Bierer et al 1995, Hyman et al 1995). In AD, the NFTs are first observed in medial temporal lobe structures, expecially in the EC and in the hippocampus. With the progression of AD, these regions become more severely affected (Braak and Braak 1991, Hyman et al 1990,1995, Ball et al 1988) and also NFTs and SPs are more widespread in all cortical areas. The crucial difference between the brains of normal elderly people and those with AD lies in the much larger numbers of SPs and, particularly, NFTs found in AD. It seems, therefore, that the numbers of SPs and NFTs in AD and normal aging do not form a continuum, but show a bimodal distribution (Tomlinson 1982, Mountjoy 1988, Köster et al 1989, Hubbart et al 1990).

Loss of neurons, when present, is generally slight in its extent during normal aging. The greatest loss of neurons and reduction in brain volume during aging is seen in the frontal lobes (Haugh et al 1983, Coffey et al 1992, Cowell et al 1994). Nerve cell loss is recognized to be an important component of AD, some studies finding higher correlations of mental impairment with cortical nerve cell loss than with SPs and NFTs (Neary et al 1986, Hubbard et al 1990). The temporal cortex generally shows more severe neuron loss than the frontal cortex. Gomez-Isla et al. (1996) reported a very severe neuronal loss in the EC even in the mildest stages of dementia in AD. The fact that neuronal loss does not occur in this region during the normal aging process (Gomez-Isla et al 1996) is consistent with the hypothesis that AD and aging are not part of a continuous spectrum and suggests that normal aging and AD can be differentiated both anatomically and clinically.

Many studies show a 15-20% reduction in synapses in frontal cortex during aging (Hutterlocher 1979, Gibson 1983, Masliah et al 1993). In AD, the degree of synaptic loss in the frontal cortex exceeds that amount found in normal aging and shows a strong correlation with the cognitive deficit (DeKosky and Scheff 1990, Terry et al 1991). Thus, the changes seen in AD are qualitatively similar but quantitatively greater than those seen in normal aging.

2.8. Apolipoprotein E

Apolipoprotein E (ApoE) is a plasma protein involved in the metabolism of cholesterol and triglycerides. Three alleles ε2, ε3, and ε4 exist for the ApoE gene, encoded on chromosome 19. The Apo E ε4 allele has firmly established itself among the major risk factors for late-onset familial AD (Corder et al 1993, Strittmatter et al 1993) and sporadic AD (Saunders et al 1993, Kuusisto et al 1994, Lehtimäki et al 1995,

Lehtovirta et al 1995, Polvikoski et al 1995), in addition to age, minimal cognitive impairment, family history, education, gender and head trauma. The number of ApoE ε4 allele copies correlates not only an increased risk of developing AD (Corder et al 1993, Rebeck et al 1993, Strittmatter et al 1993, Lehtovirta et al 1995) but also with an earlier age of onset (Corder et al 1993, Frisoni 1995, Lehtovirta et al 1995) and an increased density of SPs (Rebeck et al 1993, Schmechel et al 1993, Polvikoski et al 1995). The ApoE ε4 allele is associated with severe hippocampal damage and memory impairment in AD (Lehtovirta et al 1995). Soininen and her co-workers (1995b) found also minor hippocampal changes in healthy elderly people, particularly those with the ε4/ ε4 genotype.

The mechanism of action of ApoE in AD is still unknown. The ApoE4 isoform has a higher binding affinity in vitro for Aβ4 than E3 or E2 (Strittmatter et al 1994). It is therefore clear that ApoE and Aβ interact in vitro, but whether such an interaction occurs in vivo, and whether it is relevant to AD is currently unknown (Roses 1994). In vitro, ApoE also binds to tau, with ApoE3 binding more avidly than ApoE4, and this has been hypothesized to prevent tau phosphorylation, a prerequisite step in NFT formation (Strittmatter et al 1994). In brains displaying signs of AD, however, the ApoE genotype correlates with Aβ load rather than with NFT density (Gometz-Isla et al 1996). Moreover, ApoE is involved in regeneration and synaptogenesis following injury. Recently, Arend et al. (1997) showed also impaired regenerative capacity in AD patients carrying the ε4 allele compared to ε4 noncarriers. In AD, brain degeneration of the cholinergic neurones in the nucleus basalis of Meynert and a decreased level of choline aceteltransferase activity are the most consistent neurochemical abnormalities (Perry 1986, Rossor et al 1993). Poirier and his co-workers (1994, 1995) found a relationship between ApoE ε4 allele and cholinergic cortical and subcortical function. This finding is undercined by the fact that ApoE may be of particular importance for the cholinergic system, because acetylcholine can be derived from a lipid source. This relationship may explain the decreased responsiveness of patients with the ApoE ε4 allele to cholinesterase inhibitors as suggested by Poirier et al. (1995).

The work of Blacker et al. (1997) demonstrates that the ApoE ε4 allele exerts its maximal effect before age 70. On the other hand, the ApoE ε2 allele may play a protective role in AD both by decreasing the risk and by increasing the age of onset of the disease (Talbot et al 1994). A 3- year follow-up study showed also that subjects not displaying signs of dementia with ApoE phenotypes E2/2 or E2/3 were able to maintain their verbal learning performance, while subjects with other ApoE phenotypes did not (Helkala et al 1996).

Petersen et al. (1996) have shown that the presence of the ε4 allele is the strongest predictor of future dementia in a group of elderly people with mild cognitive impairment. A recent Dutch study showed that the ApoE ε4 allele predisposed to cognitive decline in a general population of elderly men (Feskens et al 1994). Blesa et al. (1996) determined the ApoE allele frequencies in patients with memory complaints but without dementia. They found a high ApoE ε4 allele frequency (0.315) in subjects with memory impairment, which agrees with the previous results (Petersen et al 1995, Small et al 1995, Reed et al 1994). Thus, they suggested that the ApoE ε4 allele could be a marker for the prediction of AD in subjects with memory impairment but without dementia.

Reiman et al. (1996) found an interesting relationship between the ApoE ε4 allele status and brain glucose hypometabolism in cognitively normal subjects having a family history of AD. These metabolic changes occurred in the same regions as in patients with probable AD.

2.9. Structural and functional neuroimaging

2.9.1. Magnetic resonance imaging

In normal aging, the volume of the hippocampus remains rather constant (Jack et al 1989, Bhatia et al 1993, DeCarli et al 1994, Zipursky et al 1994, Sullivan et al 1995). Atrophy in anterior and medial temporal lobes, especially in the hippocampus, is typical for AD. This is seen as a widening of the temporal horns of the lateral ventricles, the anterior portions of the Sylvian fissure and a widening of the third ventricle (de Leon et al 1980, Jacoby and Levy 1980, Creasey et al 1986). However, in spite of the overall consistency of these findings, there remains the conundrum that a large number of patients with dementia have normal cortical and ventricular size and, conversely, many healthy elderly subjects show atrophy.

Seab et al. (1988) used coronal sections to make volumetric measurements of the hippocampus. The hippocampal volume (normalized relative to the size of the lenticular nucleus) was reduced by 40% in the AD patients compared to the controls, and there was no overlap between the two groups. Hippocampal atrophy did not correlate with either overall brain atrophy or dementia severity. Later on, several studies have reported pronounced hippocampal atrophy in the early stage of the disease, detected using MRI (Kesslack et al 1991, Jack et al 1992, Ikeda et al 1994, Laakso et al 1995). The decreased hippocampal volume also correlates with declarative memory performance in AD patients (Scheltens et al 1992, Laakso et al 1995, Riekkinen et al 1995). Some authors have found atrophy of the amygdala to be a sensitive indicator of AD (Pearlson et al 1992, CuŽnod et al 1993, LehŽricy et al 1994), others in turn have not been able to confirm this proposal (Killiany et al 1993, Lehtovirta et al 1995).

DeCarli et al. (1994) have shown that temporal lobe volume does not decline in normal aging, whereas the posterior frontal lobe volume declines approximately by 1% per decade. Chertkow et al. (1995) reported decreased hippocampal volumes in 25% of subjects with questionable dementia / age-associated cognitive decline.

2.9.2. Single photon emission tomography

One of main indications for SPECT and visualization or calculation of regional cerebral blood flow (rCBF) of the brain is processes leading to dementia. Of more practical clinical importance is the differentiation between AD and other forms of dementia (Launes et al 1991). The most popular radiotracer for this purpose is Technetium-99 (99mTc) HM-PAO (Hexamethylpropyleneamine oxime).

The typical findings of advanced AD are a marked bilateral decrease of rCBF in the temporal, parietal and frontal cortex as well as in occipital areas, while the motor and the visual cortices as well as the subcortical structures are relatively well perfused (Gemmell et al 1987, Jagust et al 1987, Smith et al 1988, Liu et al 1992, O'Brien et al 1992b). These findings in the temporal and parietal cortices are already seen in mild AD and the severity of hypoperfusion correlates with the disease progression (Johnson et al 1988, Launes et al 1991). An interesting study was performed by Stern et al. (1995) to analyze the effect of occupation before the development of AD. This study demonsdrated that individuals with occupations requiring higher interpersonal and cognitive skills, independent of previous education, had less perfusion in the parietal region compared with individuals with less demanding jobs. This finding is similar to that demonstrating poorer parietal perfusion in AD patients with higher educational levels when matched for severity of disease (Stern et al 1992). Although these studies were performed on individuals with dementia,

it appears that individuals with higher levels of social and educational functioning tolerate a more significant decline in cerebral metabolism before demonstrating the same degree of dementia.

2.9.3. Electroencephalography

Previous studies have noted several types of changes in the EEG of elderly subjects. Intermittent focal slowing, usually temporal and greater on the left side, occurred in 17% to 59% of healthy elderly subjects (Hughes and Cayaffa 1977, Torres et al 1983, Katz and Horowitz 1982, Soininen et al 1982, Arenas et al 1986, Visser et al 1987, Polich 1997). On the other hand, in some studies the parameters of EEG in healthy elderly people are well preserved (Duffy et al 1984, Penttilä et al 1985, Hartikainen et al 1992, Könönen et Partanen 1993). Neurodegenerative disorders like AD or Parkinson's disease are usually characterized by slowing of the EEG (Coben et al 1983, Penttilä et al 1985, Soikkeli et al 1991, Soininen et al 1991). However, in mild AD even 50% of the patients may have normal EEG (Soininen et al 1989).

Modern computer techniques have formed the basis for quantitative EEG (QEEG). Routine frequency bands alpha (8-13 Hz), beta (13-30 Hz), delta (0.5-4 Hz) and theta (4-7 Hz) can be measured in terms of average amount of activity in microvolts (μV) in QEEG. Furthermore, using the computer based QEEG ratios between different frequency bands, e.g., the alpha-theta and the alpha-delta, ratios can be calculated and the mean and peak frequencies within a particular band can also be calculated.

Little or no changes in conventional and quantitative EEG have been found in comparisons between normal elderly and young subjects (Katz and Horowitz 1982, Duffy et al 1984, Dustman et al 1985, Penttilä et al 1985, Breslau et al 1989, Williamson et al 1990, Oken et al 1992).

2.9.4. Event-related potentials

Event-related potentials (ERPs) time-locked to cognitive decisions are utilized as an objective measure of mental activity. These brain potentials have not yet been widely utilized in the assessment of the aging population.

The first prominent negative-going deflection in auditory ERPs, N100, reflects detection of an auditory stimulus. Both electrical and neuromagnetic recordings imply that its main generators are in the auditory cortices (Vaughan and Ritter 1969, Hari et al 1980), and possibly within the frontal cortical areas (Näätänen and Picton 1987). Several ERP components overlap with N100, when the individual pays attention to the tones (processing negativity at 60—150 ms) (Hillyard et al 1973), and even when a deviant tone is not perceived (mismatch negativity at 100–200 ms) (Näätänen et al 1978, Kujala et 1995). Conscious efforts to attend to stimuli in any sensory modality elicit later ERP components, N2 (or N2b at about 200 ms) and P3 or P300 (about 300 ms after the stimulus onset), which presumably represents endogenous processing of external stimuli (Ritter et al 1968, Picton 1992). Goodin et al. (1978a) found that the latency of auditory P300 increased significantly with increasing age. They also reported that P300 was delayed in latency and decreased in amplitude in dementia (Goodin et al 1978b). Later studies have shown consistently a considerable overlap between normal elderly individuals and patients with dementia, which limits the clinical usefulness of the P300 (Picton 1992). In addition, there are several brain regions contributing to the generation of P300. Mesial temporal areas, parieto-occipital cortex, frontal lobes, and dorsal thalamic nuclei have all been studied as possible generators of P300 (Pineda and Westerfield 1993). Since there are also multiple cognitive processes occurring at this latency range after stimulation, the interpretation of observed changes in P300 has been controversial (Picton 1992). These brain potential

measures have not been sufficiently detailed to indicate how various cognition attributes change with age and there are only a few previous neurophysiological studies on AAMI subjects (Saletu et al 1990).

3. AIMS OF THE STUDY

There were two general aims of this study. *Firstly,* to more coherently characterize the entity called Age-associated memory impairment. *Secondly,* to investigate the relationship between the ApoE ε4 allele and cognitive functions, structural and functional neuroimaging findings among the elderly people without dementia.

The specific targets of the study were:

1. To characterize the cognitive functions in AAMI .

2. To examine the structural and functional changes in brain structures in AAMI subjects as compared to elderly subjects with intact memory.

3. To evaluate the relationship between the ApoE ε4 allele and cognitive functions and neuroimaging findings in AAMI and control group.

4. To evaluate the changes on cognitive functions and on the measurements of the MRI volumetry among AAMI subjects and cognitive healthy elderly subjects during a follow-up period of 2.8- years with special reference to the ε4 allele.

4. SUBJECTS AND METHODS

4.1. Subjects

The study was conducted in the Memory Research Clinic of Department of Neurology in the University of Kuopio between August 1992 and April 1995. The subjects in a cross-sectional sudy and a follow-up study were drawn randomly from the subpopulations 1 and 2 (Koivisto et al 1992).

Population 1: A random sample of 592 persons born from 1912 to 1921 was drawn from the Kuopio population register including all 5286 inhabitants of Kuopio in this age group on January 1, 1986. Of the 592 persons randomly selected, 402 (80.3%) participated. The examinations were carried out from January to August 1989.

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

Cross-sectional study. First we examined 18 AAMI-subjects, using the original diagnostic criteria for AAMI (Crook et al 1986), and 18 age-matched controls in our pilot study. Then we recruited more individuals so that the population totaled 43 AAMI subjects and 47 controls. The controls were cognitively healthy subjects, i.e. they reached test scores comparable to those of the young people. The demographic data for the subjects in the cross-sectional study are presented in Table 3.

Follow-up study. The 36 subjects (18 AAMI and 18 control subjects) of our pilot study were asked to participate in a follow-up study.

4.2. Study design

All respondents underwent a structured interview including demographic information, medical history and current medication. The NIMH criteria with suggested cutoff points for 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 over was considered to indicate subjective memory impairment (Crook et al 1992). Objective memory function was assessed with Benton's Visual Retention Test, form C, administration A (BVRT) and with Paired Associated Learning subtest of Wechsler Memory Scale (PAL). The cutoff scores for AAMI in these tests were 6 or less in BVRT and 13 or less in PAL. A score below cutoff in either one was considered as evidence of objective memory impairment. To examine the mental performance and to rule out the presence of dementia, the subjects were tested with the MMSE in which a score less than 24 was used to exclude possibly demented subjects.

All subjects were examined according to the following protocol: medical history, general physical and clinical neurological examination, extensive neuropsychological testing, QEEG, ERPs, SPECT and MRI. In the follow-up study QEEG, ERPs and SPECT were not done. The psychologist performed neuropsychological evaluations. The same exclusion criteria were used both for the AAMI and the control group.

In the cross-sectional study, to evaluate the influence of the ApoE ε4 allele on cognitive functions and neuroimaging findings, the subjects in the AAMI and control groups were subcategorised according to

their ApoE ε4 genotype in two groups: subjects homozygous or heterozygous for ε4 and subjects without the ε4 allele (*Table 16*). Furthermore *in the follow-up study* the data was analyzed for the AAMI and the control groups. Then, due to the small number of the study subjects in the follow-up, the AAMI and the control subjects could not be divided into two groups according to their ApoE genotype. For this reason subjects were subcategorised according to their ApoE ε4 genotype into two groups: subjects homozygous or heterozygous for ε4 and subjects without the ε4 allele (*Table 25*).

4.3. Neuropsychological assessment

The following neuropsychological tests were used in the study:

AAMI-tests:

In the *Benton Visual Retention Test* (BVRT) (Benton 1974), the subject is required to copy from memory ten different figures after a presention 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) 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 WMS manual.

The *Mini-Mental Status 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 score of all items.

In the *Vocabulary* subtest from *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.

Subjective complaints of memory loss were recorded by the *Memory Complaint Questionnaire* (MAC-Q) (Crook et al 1992). It includes six questions of one's ability to remember everyday matters (e.g., names of other people or phone numbers) as compared to 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) (Yeasavage 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 answers indicating symptoms or feelings of depression were used.

Episodic Memory:

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 reminds only those words which the subjects have not recalled and the subjects are asked to try to recall all ten words again. This precedure 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 reminding them).

In the Russell's adaptation of the *Visual Reproduction Test* (VRT) (Russell 1975) subjects have to reproduce geometrical figures from memory immediately after seeing them for ten seconds (VRI). To measure long-term retention, the subject is asked to reproduce the figures again after 30 minutes of unrelated testing (VRD).

Semantic Memory:

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 names as possible of animals in 60 seconds. The performance was scored by counting the total number of correct words produced for each letter or category.

Visuoconstructive Functions:

In the Russell's adaptation of the *Visual Reproduction Test* (VRT) (Russell 1975) subjects have to reproduce geometrical figures and the same figures were also used as a visuo-constructive task by asking the subjects to copy them after the delayed recall task (VRC).

The *Digit Symbol* (DSy-WAIS), a subtest from WAIS (Wechsler 1955), requires perceptual organization, sustained attention and visuo-motor coordination.

Executive Functions:

In Part A of the *Trail Making Test* (TMT-A) (Reitan 1958), the subjects have 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 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 response strategy according to feedback from the examiner. The scores recorded were the total number of correct responses and the number of perseveration errors.

In the *Stroop Test* (ST) (Golden 1978), two naming trials were used. The first trial requires the naming of color dots on a sheet of paper, and the second requires the naming of color when color names were 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 this time used to complete each naming trial and the difference between the interference condition and simple naming of color dots (interference effect).

The *Digit Span* (DSp-WAIS), a subtest from WAIS (Wechsler 1955), requires attention and primary memory.

4.4. Determination of Apolipoprotein E genotype

Samples of 10 ml venous blood were collected in EDTA tubes, and DNA was extracted by a standard phenol-chloroform extraction. ApoE genotypes were analyzed using a polymerase chain reaction (PCR) (Hixon and Vernier 1990, Tsukamoto et al 1993) with slight modifications. PCR products were digested with Hhal (New England Biolabs, Beverly, MA) and digested DNA fragments were analyzed with polyacrylamide gel electrophoresis. Separated fragments of DNA were visualized using ethidium bromide staining.

4.5. Magnetic resonance imaging

The subjects were scanned with a 1.5 T Magnetom (Siemens, Erlangen) using a standard head coil and a tilted coronal 3D gradient echo sequence (MP-RAGE: TR 10 msec, TE 4 msec, TI 250 msec, flip angle 12°, FOV 250 mm, matrix 256x192, one acquisition). This resulted in 128 contiguous T1-weighted partitions with a slice thickness of 1.5 to 1.8 mm oriented perpendicularly to the long axis of the hippocampus. The data was analyzed by a single rater who was not aware of the clinical data of the study subjects. Re-test validity based on 5 cases was assessted after half a year.

Determination of the volumes of hippocampus and amygdala. Standard anatomical atlases of the human brain (Duvernoy 1988, De Armond et al 1989) were used as guidelines with some adjustment from previous literature (Watson et al 1992), to determine the boundaries of the amygdala and the hippocampus on oblique coronal MRI sections. The boundaries of the region of interest were outlined by a trackball driven cursor proceeding from anterior to posterior in a sequential fashion. The number of voxels within the region were integrated using a program developed in-house for standard work console.

In this study, the outlines of the amygdala were considered to include the deep, the superficial, and the remaining nuclei of the amygdala (Soininen et al 1994). The hippocampus included the dentate gyrus, the hippocampus proper, and the subicular complex. The caudal end of the hippocampus was determined as the last section in which the fornices were still detectable in their full length.

Normalization of volumes. In order to exclude the effect of individual head and brain sizes, the normalization was done by dividing the volumes of the hippocampus and amygdala by the sagittal intracranial area (ICA). To get reasonable numbers for the statistical analysis, the normalized values were multiplied by 1000.

4.6. Single photon emission tomography

A dose of 370 to 555 Mbq of 99mTc-HMPAO (Amersham International, London, UK) was intravenously injected into a subject's vein in a dark and quiet room. The SPECT scan was carried out with a three-head Siemens MultiSPECT 3 gamma camera equipped with high resolution collimators (Kuikka et al 1993). Ten minutes after injection of the tracer, the radioactivity distribution of the brain was acquired in a 128x128 matrix mode. Data sets were acuired at 3° intervals for 35 s each, with a total of 40 sets (120° per camera head). Three and a half millimetre thick transaxial, sagittal, and coronal slices were reconstructed using a Butterworth filter (a cut-off frequency of 0.5 cm^{-1}) and a uniform attenuation correction of 0.12 cm^{-1}. The imaging resolution was 8-9 mm (Kuikka et al 1993). Two consecutive slices were summed in order to obtain a slice thickness of 7 mm and visually surveyed on a TV screen. Regional count densities were calculated for frontal, temporal, parietal, and occipital cortices. The regional counts

were related to the cerebellar count and rCBF is expressed as the ratio for each region. The rater was not aware of the clinical data on the subjects.

4.7. Electroencephalography

The subjects were lying awake during the recording of a conventional paper EEG with a 16 channel recorder (10-20 system, time constant 0.3 s, low-pass filter 70 Hz). EEG was recorded with the subject's eyes closed. A trained technician chose four artefact-free epochs (8.19 s). Eye movements were monitored on-line. The QEEG records were obtained from six bipolar derivations: T6-O2, T5-O1, C4-P4, C3-P3, F4-C4, and F3-C3. The samples were digitized at a 125-Hz sampling frequency, stored and analyzed off-line with a Hewlett Packard 310 computer. Every epoch was divided into three half-overlapping 4 second periods. Amplitude spectra were calculated for every 4 second period using Fast Fourier Transformation. The final spectra was calculated by averaging these 12 spectra. The absolute and relative (percentage of total) amplitude of delta (1.46-3.91 Hz), theta (4.15-7.32 Hz), alpha (7.57-13.92 Hz), beta (14.16-20.02 Hz) and fast beta (20.0-30.0 Hz) as well as peak frequency (4.15-13.92 Hz), mean frequency (1.46-20.02 Hz), and combined alpha and theta frequency (4.15-13.92 Hz) were calculated (Penttilä et al 1985). The amplitude parameters were transformed to natural-logarithm values prior to statistical analysis (Gasser et al 1982). The neurophysiologist was not aware of the subjects clinical data.

4.8. Event-related potentials

Habituation of auditory N100 was evaluated by delivering 50 trains of tones to the right ear at 60 dB above the hearing level. Each train consisted of four identical tones (800 Hz, duration 85ms) with an interstimulus interval (ISI) of 1 s. The intertrain interval (ITI), i.e., the time from the offset of the last tone in a train to the onset of the first tone in the following train was 12 s.

Auditory P3 and mismatch negativity (MMN) were measured in separate sessions using an auditory oddball paradigm with 85% of standard (800 Hz, duration 85 ms) and 15% of target (560 Hz, duration 85 ms) tones delivered randomly with an ISI of 1 s to the right ear at 60 dB above the hearing level. In the visual oddball paradigm, the stimuli were presented on a computer screen. The standard stimuli (85%, duration 100 ms) were white luminous squares and the target (15%, duration 100 ms) stimuli were slightly larger squares with a thin-line circle drawn inside the square. The total number of stimuli in both paradigms was 600.

During the sessions for habituation and MMN, the subject was instructed not to pay attention to the tones but instead to read a self-selected text. During the sessions for auditory and visual P3, the subjects were asked to respond to each target stimulus by pressing a button.

The ERPs were recorded using Ag/AgCl electrodes placed on the scalp according to the International 10-20 System. Both vertical and horizontal eye movements were monitored. All electrodes were referred to the right mastoid. EEG and eye movement signals were filtered with a bandpass of 0.5-100 Hz, and digitized continuously at 256 Hz. The continuous data were transformed off-line to epochs of -100 to 900 ms relative to the onset of each stimulus. Epochs containing eye movement artefacts were rejected using both automatic and manual checking of data. The epoched data were averaged and filtered digitally with a low pass cut-off frequency at 20 Hz (3 dB point of 24 dB/octave roll-off).

ERP amplitudes were measured relative to the 100-ms pre-stimulus baseline except for auditory N100 which was measured from the preceding positive deflection at about 50 ms. MMN was measured as the

mean amplitude of the deviant-standard difference curve over the 100-270 ms range (Pekkonen et al 1994). The neurophysiologist was not aware of the subjects clinical data or diagnosis.

4.9. Statistical analysis

The data were analyzed by using the SPSS-PC 4.0 software. The results for continuous variables are given as a mean ± SD. The level of significance was set at $p < 0.05$. Chi-square test was used for testing the differences in categorial data and to determine differences between the genotype frequencies across the study groups, and z-statistics for ε4 allele frequencies. Chi-square goodness-of-fit-test was used for testing the differences of the ε4 frequency between each of the study groups in a cross-sectional study and in a follow-up study. The differences between groups were assessed by univariate (ANOVA) or multivariate analysis of variance (MANOVA) in both studies. The Duncan method was applied in post hoc analysis to detect which groups differed significantly. If the data did not meet the assumption of parametric methods, we used Kruskall-Wallis analysis of variance over the subgroups, and the Mann-Whitney U-test to detemine which groups differed from each other.

Student's t-test for independent samples were used to compare ERP and QEEG data between groups, and the amplitude parameters of the QEEG were transformed to natural logarithm values prior to statistical analysis in the cross-sectional study. In both studies the volumes, measured by MRI, were normalized for the sagittal intracranial area as described in the methods.

4.10. Approval of Ethics Committee

The present study was approved by the Ethics Committee of Kuopio University and University Hospital. The subjects provided written consent for participation in the study.

5. RESULTS

5.1. Cross-sectional study

5.1.1. Clinical characteristics of the study subjects

Table 3 shows the demographic data of the AAMI subjects and the controls. The AAMI subjects and the controls did not differ significantly in age, but the controls were better educated than the AAMI subjects. There were also significantly (p= 0.002) more office workers and subjects with higher education in the control group. In the AAMI group, women were overrepresented.

In accordance with the criteria for AAMI, the AAMI subjects had lower scores in memory tests (BVRT, PAL) and also in the MAC-Q, assessing subjective memory impairment. The AAMI subjects had lower scores compared to controls in the Wechsler Adult Intelligence Scale (WAIS) Vocabulary subtest, however their intellectual function was adequate (raw score of at least 32). The study subjects had no clinical signs of dementia or depression (GDS below 15 in the both groups) although the AAMI subjects had lower GDS scores than controls (p = 0.02) (*Table 4*).

The study groups did not differ in alcohol consumption (> 4 cl/ day) but there were significantly more smokers among the control subjects. The AAMI and control subjects did not differ in the presence of concomitant diseases or in the use of estrogen during menopause, use of anti-inflammatory agents (*Table 5)* or any other drugs that might affect cognitive function. All participants were independent in their activities of daily living.

Table 3. Demographic data of the subjects with AAMI and the controls at the baseline

	AAMI	*CONTROLS*
N	43	47
Women/Men	31/12	24/23*
Age, years	69.9 ± 5.4	71.1 ± 4.0
Education, years	8.2 ± 3.2	9.9 ± 3.7*
Profession (%)*		
Office worker	13 (30%)	20 (43%)
Advanced education	3 (7%)	12 (25%)
No special education	20 (47%)	15 (32%)
Farmer	7 (16%)	0
Marital state		
Married	21 (49%)	30 (64%)
Single	3 (7%)	7 (15%)
Divorced	3 (7%)	1 (2%)
Widow	16 (37%)	9 (19%)

Student's t-test was used for comparison for age and education and presented as mean ± SD, χ^2 - test for other variables; * $p < 0.05$

Table 4. Performance in AAMI-tests in the AAMI subjects and the control subjects at the baseline

	AAMI	*CONTROLS*	*F/ Effect of group*	*p*
V-WAIS	42.2 ± 7.5	50.4 ± 6.9	21.2	0.001
MAC-Q	28.8 ± 3.1	26.6 ± 3.0	9.5	0.003
BVRT	5.2 ± 1.0	7.7 ± 0.8	156.1	0.001
PAL	14.1 ± 1.8	17.8 ± 2.0	68.2	0.001
GDS	6.7 ± 4.2	4.6 ± 3.3	6.8	0.011
MMSE	27.6 ± 1.6	28.3 ± 1.3	6.0	0.016

Values expressed as mean ± SD; ANOVA (df = 1, 85), adjusted for age and education; n.s., not significant; V-WAIS, Vocabulary subtest of the Wechsler Memory Scale; MAC-Q, Memory Complaint Questionnaire; BVRT, Benton Visual Retention Test; PAL, Paired Association Learning test; GDS, Geriatric Depression Scale; MMSE, Mini-Mental Status Examination

Table 5. Concomitant diseases, use of estrogen, anti-inflammatory drugs, alcohol consumption and smoking in the AAMI subjects and the control subjects at the baseline

	AAMI	*CONTROLS*
Disease:		
Cardiac insufficiency	1	2
Atrial fibrillation	0	1
Coronary heart disease	6	5
Myocardial infarction	0	0
Hypertension	7	11
Intermittent claudication	2	1
TIA	0	1
Stroke	0	0
Diabetes	0	2 (diet)
Psychiatric disorders	0	0
Other chronic disease	0	0
Medication:		
Estrogen	2	2
Anti-inflammatory drugs	2	3
Alcohol users	7	7
Current smokers	1	6*

χ^2 - test was used for comparisons, * $p < 0.05$

5.1.2. Cognitive functions in subjects with Age-associated memory impairment and control subjects

The AAMI subjects showed a significantly inferior performance as compared with controls in visual memory tests both in immediate and delayed versions, VRI and VRD, and in a verbal memory test, BSRT, sensitive to episodic memory function, and also in the VRC and DSy-WAIS sensitive to visuo-constructive abilities *(Table 6)*.

Compared to the controls, the AAMI subjects showed impaired performance in tests assessing executive functions. In the ST, speed for color naming did not differ but the performance was worse when there was interference in the AAMI subjects. In the TMT, inferior performance was found in the AAMI subjects with two speed variables, reflecting impairment both in psychomotor speed and in more complex executive processing. In the WCST, the AAMI group made fewer correct choices and more errors of all types than the control group. In the DSp-WAIS which requires attention and primary memory, performance did not differ between the study groups (*Table 6*). We used cluster-analysis based on tests to assess visuospatial abilities, to observe if there is a subclass with signs of posterior cortical involvement in the AAMI group. However, no such subclass could be characterized in the AAMI group (not presented in tables) .

Table 6. Memory, visuoconstructive and executive functions in the subjects with AAMI and the control subjects at the baseline.

	AAMI	*CONTROLS*	*F / Effect of Group*	*p*
Episodic Memory				
VRI	10.3 ± 2.7	12.8 ± 3.0	12.3	0.001
VRD	7.5 ± 3.8	10.7 ± 3.5	13.3	0.0001
BSRT	36.7 ± 8.6	40.9 ± 7.4	3.8	0.05
Semantic Memory				
VFT-L	40.2 ± 14.8	47.8 ± 14.8	3.6	n.s.
VFT-C	19.6 ± 5.6	21.9 ± 4.9	3.5	n.s.
Visuoconstructive Functions				
VRC	15.6 ± 1.0	16.3 ± 1.5	5.6	0.02
DSy-WAIS	28.1 ± 8.8	36.7 ± 8.8	22.3	0.001
Executive Functions				
TMTA	54.0 ± 18.0	44.4 ± 18.0	4.2	0.04.
TMTB	184.2 ± 76.4	117.5 ± 48.1	13.1	0.001
WCST,				
perseverative errors	4.9 ± 5.3	1.8 ± 2.8	Z=3.7#	0.001
correct resp.	25.2 ± 9.1	32.6 ± 10.5	6.8	0.011
ST				
colors,time (s)	40.6 ± 11.2	36.6 ± 10.0	2.4	n.s.
text, time (s)	87.0 ± 39.1	71.0 ± 15.4	6.1	0.016
DSp-WAIS				
forward	5.5 ± 1.0	5.7 ± 1.0	0.2	n.s.
backward	4.0 ± 1.1	4.5 ± 1.1	2.4	n.s.

Results are mean ± SD; ANOVA (df = 1, 85), adjusted for age and education; n.s., not significant; #Mann-Whitney U-test; VRI, Visual Reproduction, immediate recall; VRD, Visual Reproduction, delayed recall; BSRT, Buschke Selective Reminding Test, total recall; VRC, Visual Reproduction, copying the figures; VFT-L, Verbal Fluency Test using letters P, A and S; VFT-C, Verbal Fluency Test using animal category; DSy-WAIS, Digit Symbol; TMTA, Trail Making Test A ; TMTB, Trail Making Test B; WCST, Modified Wisconsin Card Sorting Test; ST, Stroop Test; DSp-WAIS, Digit Span

5.1.3. Magnetic resonance imaging findings

The normalized volumes of the right and left hippocampus of the AAMI subjects did not differ from those of the controls. In both groups, the mean volume of the right hippocampus was larger than the left. Although the volume difference of the hippocampus (volume of the right hippocampus minus volume of the left hippocampus) tended to be larger in the AAMI subjects than in the controls (8.6% / 7.8% , AAMI / controls) it was statistically nonsignificant *(Table 7)*.

The normalized right and left amygdaloid volumes, and the volumetric difference between the left and right amygdala in the AAMI subjects did not differ from those in the controls. In the controls and in the AAMI subjects, the left amygdala was larger than the right *(Table 7)*.

Table 7. Normalized volumes of the hippocampus (HC) and the amygdala (A) for the subjects with AAMI and the control subjects at the baseline

	AAMI	*CONTROLS*	*p*
HC_R	174.5 ± 26.1	169.9 ± 24.5	n.s.
HC_L	159.4 ± 22.8	156.6 ± 21.6	n.s.
HC_{R-L}	15.1 ± 17.8	13.3 ± 19.0	n.s.
A_R	108.4 ± 24.3	100.1 ± 12.8	n.s.
A_L	115.6 ± 310	109.0 ± 15.4	n.s.
A_{L-R}	7.4 ± 21.5	8.9 ± 15.9	n.s.

Values are mean ± SD; ANOVA (df = 1,79); n.s., not significant; HC_R = right HC; HC_L= left HC; HC_{R-L}= right-left HC; A_R= right A; A_L= left A; A_{L-R}= left-right A

5.1.4. Single photon emission tomography findings

Mean activity of frontal, temporal, parietal and occipital regions of interest (ROI) did not differ between the AAMI and the control groups (*Table 8*). Since absolute quantification with SPECT is not possible, relative tracer activity was calculated as the ratio of mean (right and left) cortical ROI activity to mean (right and left) cerebellar activity. Cerebellar activity was chosen because the cerebellum is not involved clinically in the early stage of AD (Ishii et al 1997).

Table 8. Regional cerebral blood flow presented as ratios of regions of interest activity to cerebellar activity in the AAMI subjects and the control subjects at the baseline

	AAMI	*CONTROLS*	*p*
Right prefrontal	1.01 ± 0.06	1.08 ± 0.04	n.s.
Left prefrontal	1.04 ± 0.06	1.06 ± 0.04	n.s.
Right frontal	1.01 ± 0.07	0.99 ± 0.11	n.s.
Left frontal	0.99 ± 0.06	0.97 ± 0.11	n.s.
Right temporal	1.04 ± 0.09	1.00 ± 0.10	n.s.
Left temporal	1.01 ± 0.09	0.98 ± 0.11	n.s.
Right parietal	1.00 ± 0.08	0.95 ± 0.12	n.s.
Left parietal	0.95 ± 0.07	0.92 ± 0.12	n.s.
Right occipital	1.11 ± 0.09	1.10 ± 0.11	n.s.
Left occipital	1.08 ± 0.08	1.08 ± 0.10	n.s.

Values are mean ± SD; ANOVA (df = 1,49); n.s., not significant

5.1.5. Electroencephalographic changes

In the AAMI subjects the overall EEG amplitude was enhanced.

The means of absolute and relative spectral EEG parameters in the subjects with AAMI and the control subjects are presented in Tables 10- 15. The absolute amplitude of fast beta (20.0-30.0 Hz) was significantly increased in the right and left frontal areas (F4-C4 and F3-C3, respectively, *Table 9*) and in the right and left centro-parietal areas (C4-P4 and C3-P3, respectively, *Table 10*) in the subjects with AAMI when compared with the controls. The absolute amplitude of beta was also significantly increased in the left frontal lead (F3-C3, *Table 9*) and in the left temporo-occipital lead (T5-O1, *Table 11*). The AAMI group had also significantly higher alpha amplitude in the right frontal lead (F4-C4, *Table 9*) than the control group. Moreover, in the right frontal lead (F4-C4, *Table 9*), the subjects with AAMI had significantly higher delta and theta amplitudes than the controls. The peak frequency was also significantly higher in the left temporo-occipital lead (T5-O1, *Table 11*) in the AAMI group than in the control group. The values of relative amplitudes did not differ between the groups (not presented in tables).

Table 9. Absolute delta, theta, alpha, beta and fast beta amplitudes (μV), peak and mean frequency, and mean frequency of combined alpha and theta bands (Hz) with eyes closed in the left (F3-C3) and right frontal (F4-C4) leads of EEG spectra in the subjects with AAMI and the control subjects

EEG paremeters	*AAMI*	*CONTROLS*
F3 - C3 lead (left)		
Absolute amplitude (μV)		
Delta	3.66 ± 0.92	3.30 ± 0.88
Theta	3.54 ± 1.50	3.13 ± 1.36
Alpha	8.55 ± 4.56	6.97 ± 4.11*
Beta	6.16 ± 2.34	5.22 ± 3.00*
Fast beta	6.86 ± 2.47	5.65 ± 2.63*
Frequency (Hz)		
peak	8.74 ± 2.20	8.83 ± 2.17
mean	9.06 ± 0.38	8.89 ± 0.35
mean (alpha + theta)	10.19 ± 0.75	9.88 ± 0.73
F4 - C4 lead (right)		
Absolute amplitude		
Delta	4.00 ± 0.99	3.46 ± 0.91*
Theta	3.78 ± 1.61	3.21 ± 1.49*
Alpha	9.19 ± 4.57	7.42 ± 4.00
Beta	6.62 ± 2.82	5.4 ± 2.61
Fast beta	6.97 ± 2.28	5.86 ± 2.26*
Frequency (Hz)		
peak	8.79 ± 2.10	8.31 ± 2.48
mean	9.03 ± 0.41	8.92 ± 0.37
mean (alpha + theta)	10.09 ± 0.87	9.94 ± 0.80

Values are mean ± SD; The log (x) for absolute values was used for statistical calculations; Student t-test, * $p < 0.05$.

Table 10. Absolute delta, theta, alpha, beta and fast beta amplitudes (μV), peak and mean frequency, and mean frequency of combined alpha and theta bands (Hz) with eyes closed in the left (C3-P3) and right centroparietal (C4-P4) leads of EEG spectra in the subjects with AAMI and the control subjects

EEG paremeters	*AAMI*	*CONTROLS*
C3 - P3 lead (left)		
Absolute amplitude (μV)		
Delta	3.48 (1.12)	3.31 (1.03)
Theta	3.96 (1.70)	3.60 (1.67)
Alpha	11.21 (5.79)	10.51 (6.67)
Beta	6.92 (2.71)	6.20 (2.82)
Fast beta	7.00 (2.43)	5.94 (2.43)*
Frequency (Hz)		
peak	9.48 (1.88)	9.40 (2.24)
mean	9.14 (0.42)	9.03 (0.36)
mean (alpha + theta)	10.38 (0.65)	10.15 (0.79)
C4- P4 lead (right)		
Absolute amplitude		
Delta	3.69 (1.22)	3.45 (1.09)
Theta	3.93 (1.71)	3.58 (1.64)
Alpha	11.86 (5.64)	10.83 (7.00)
Beta	7.16 (2.80)	6.22 (2.89)
Fast beta	7.23 (2.66)	6.12 (2.24)*
Frequency (Hz)		
peak	9.36 (2.28)	9.00 (2.12)
mean	9.20 (0.44)	9.07 (0.36)
mean (alpha + theta)	10.38 (0.66)	10.14 (0.78)

Values are mean ± SD; The log (x) for absolute values was used for statistical calculations; Student t-test, * $p < 0.05$.

Table 11. Absolute delta, theta, alpha, beta and fast beta amplitudes (μV), peak and mean frequency, and mean frequency of combined alpha and theta bands (Hz) with eyes closed in the left (T5-O1) and right temporo-occipital (T6-O2) leads of EEG spectra in the subjects with AAMI and the control subjects

EEG paremeters	*AAMI*	*CONTROLS*
T5 - O1 lead (left)		
Absolute amplitude (μV)		
Delta	3.87 (1.41)	3.53 (1.22)
Theta	4.08 (1.85)	3.82 (2.01)
Alpha	13.93 (6.52)	12.37 (8.06)
Beta	6.59 ± 2.34	5.64 ± 2.36*
Fast beta	5.76 ± 2.27	5.06 ± 2.4
Frequency (Hz)		
peak	9.96 ± 1.48	9.21 ± 1.79*
mean	9.32 (0.42)	9.17 (0.34)
mean (alpha + theta)	10.16 (0.62)	9.97 (0.58)
T6 - O2 lead (right)		
Absolute amplitude		
Delta	3.87 (1.32)	3.80 (1.42)
Theta	4.20 (2.09)	4.13 (2,29)
Alpha	14.02 (7.01)	12.94 (8.07)
Beta	6.49 (2.21)	5.95 (2.25)
Fast beta	5.84 (2.14)	5.43 (2.73)
Frequency (Hz)		
peak	9.63 (1.23)	9.17 (1.76)
mean	9.28 (0.14)	9.16 (0.34)
mean (alpha + theta)	10.14 (0.52)	9.96 (0.61)

Values are mean ± SD; The log (x) for absolute values was used for statistical calculations; Student t-test, * $p < 0.05$.

5.1.6. Event-related potential changes

In the AAMI group there were increased amplitudes and shortened latencies in the auditory ERP components and also the amplitudes of visual P1-N1 following attended visual stimuli were increased

The amplitudes of auditory N100 to the first and second tone were significantly increased in the AAMI subjects, and the latencies were decreased (*Table 12).* The mismatch negativity (MMN) area (mean 100-270ms), reflecting brain activation caused by automatic deviance detection in the auditory system (Kujala et al 1995), did not differ significantly between the AAMI subjects and the controls.

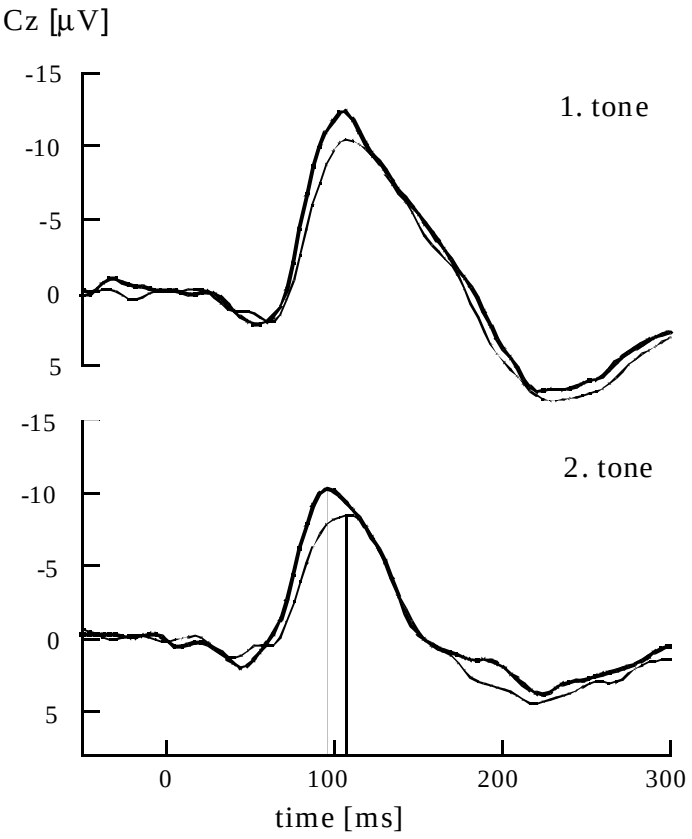
Figure 1 shows the grand average wave forms for the first and second tones in a tone train which was used to study the habituation of auditory N100 over central brain areas (Cz) for the AAMI subjects and controls.

Table 12. Auditory N100 habituation for non-attended stimuli at the vertex electrode (Cz), and MMN at the frontal electrode (Fz) for the AAMI subjects and the control subjects at the baseline

Auditory parameters at Cz	*AAMI*	*CONTROLS*	*p*
1st N100 amplitude (μV)	-16.1 ± 4.8	-13.9 ± 4.4	0.03
2nd N100 amplitude (μV)	-13.2 ± 3.4	-11.1 ± 3.4	0.003
Ratio of 1st and 2nd N100	1.2 ± 0.3	1.3 ± 0.4	n.s.
1st N100 latency (ms)	106.4 ± 8.1	112.2 ± 9.8	0.002
2nd N100 latency (ms)	101.0 ± 8.6	107.9 ± 8.9	0.0008
Mismatch negativity at Fz			
MMN amplitude (μV)	-1.8 ± 1.3	-1.6 ± 1.0	n.s.

Values are mean ± SD, Students t-test; n.s., not significant

Figure 1. The grand average event-related responses at the vertex electrode (Cz) to the first (upper panel) and second (lower panel) tone of a train of four tones for the AAMI subjects (thick lines) and the controls (thin line). In the lower panel, two extra dashed lines have been drawn to emphasize the latency difference.



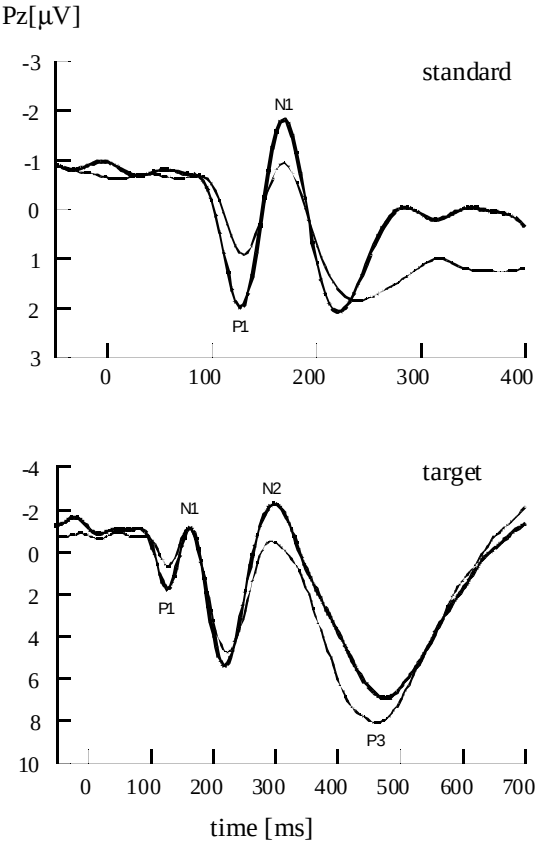
The only significant difference in the latencies of attended ERPs emerged in the auditory oddball paradigm for auditory N100 which showed a similar shortening of latency as in the habituation paradigm. Amplitudes of first cortical deflections, visual P1, N2 and especially P1-N1 (peak-to-peak) were increased at the parieto-occipital electrodes in the AAMI subjects (*Table 13*). There were no significant differences between the two groups in any of the visual P3 parameters. *Figure 2* shows the grand average waveforms elicited by standard and target visual stimuli in the attended condition over parietal brain areas (Pz).

Table 13. Mean auditory N100 and N200 parameters at the vertex electrode (Cz), and visual parameters at the parietal electrode (Pz) for the AAMI subjects and the control subjects in the attended condition at the baseline

Auditory stimuli at Cz	*AAMI*	*CONTROLS*	*p*
N100 amplitude (μV)	-7.5 ± 2.4	-6.6 ± 2.9	n.s.
N100 latency (ms)	104.0 ± 7.8	107.2 ± 7.1	0.04
N200 amplitude (μV)	-5.3 ± 5.6	-4.3 ± 6.2	n.s.
N200 latency (ms)	249.5 ± 23.1	254.2 ± 22.4	n.s.
Visual stimuli at Pz			
P1 amplitude (μV)	2.8 ± 2.6	1.7 ± 1.7	0.03
P1 latency (ms)	123.2 ± 15.7	126.1 ± 20.3	n.s.
P1-N1 amplitude (μV)	5.5 ± 2.8	3.8 ± 2.6	0.004
N2 amplitude (μV)	-3.7 ± 4.7	-1.7 ± 3.7	0.02
N2 latency (ms)	312.6 ± 29.3	319.5 ± 31.5	n.s.

Values are mean ± SD, Students t-test; n.s., not significant

Figure 2. The grand-average waveforms in the parietal midline electrode (Pz) following standard (upper panel) and target (lower panel) stimuli in a visual oddball task for the AAMI subjects (thick lines) and for the controls (thin lines)



5.1.7. Frequency of different Apolipoprotein E alleles

The AAMI subjects had a higher frequency of the ApoE ε4 allele than the control subjects, but this difference was not statistically significant. The ε4 frequency for the AAMI subjects was 0.24 compared to 0.15 for the controls (*Table 14*).

Table 14. Apolipoprotein E genotypes and allele frequencies in the AAMI subjects and the controls at the baseline

Genotype	*AAMI n=42*	*CONTROLS n=47*
2/3	1	6
2/4	1	1
3/3	24	30
3/4	13	7
4/4	3	3
Allele frequency		
ε2 + ε3	0.76	0.85
ε4	0.24	0.15

χ^2 -test, not significant; Z-statistics for ε4 allele frequencies

5.2. The influence of Apolipoprotein E genotype in Age-associated memory impairment subjects and control subjects

The AAMI and the control subjects were divided into two groups according to their ApoE genotype: *a group with one or two e4 alleles (e4+)* and *a group without any e4 alleles (e4-).* Age did not differ between groups. The AAMI subjects were less educated overall than the control subjects but this finding was independent of the ApoE genotype as were also the scores of AAMI tests. There was also no significant interaction between ApoE and group (*Table15).* There were more women in the AAMI ε4 + group (77%) than in the control ε4 + group (24%)(χ^2, p = 0.003).

Table 15. Clinical characteristics and performance in AAMI tests in the AAMI subjects and in the control subjects with one or two ε4 alleles (ε4+) or without the ε4 allele (ε4-).

	AAMI		*CONTROLS*		*F*	
	ε4+	ε4-	ε4+	ε4-		*p**
N	17	25	11	36		
Women/men	13/4	18/7	4/7	20/16		
Age, year	68.5 ± 6.2	70.7 ± 4.7	72.1 ± 3.6	70.7 ± 4.1		n.s.
Education, y	7.7 ± 2.9	8.3 ± 3.4	11.1 ± 4.2	9.4 ± 3.4	7.69	a) 0.007
MMS	27.6 ± 1.7	27.5 ± 1.5	28.7 ± 0.9	28.1 ± 1.4	6.18	a) 0.015
BVRT	5.3 ± 1.1	5.1 ± 0.9	7.7 ± 0.8	7.7 ± 0.8	135.24	a) 0.0001
PAL	14.1 ± 1.7	14.0 ± 1.9	17.0 ± 1.6	18.0 ± 2.0	51.33	a) 0.0001
MACQ	29.3 ± 3.6	28.5 ± 2.6	25.9 ± 3.5	26.7 ± 2.8	13.34	a) 0.0001
GDS	6.9 ± 4.1	6.9 ± 4.3	3.6 ± 2.5	4.9 ± 3.5	8.93	a) 0.004

Values are mean ± SD; ANOVA (df = 1,85); * effect of group; n.s., not significant MMS, Mini-Mental Status Examination; BVRT, Benton Visual Retention Test; PAL, Paired Association Learning test; MACQ, Memory Complaint Questionaire; GDS, Geriatric Depression Scale.

5.2.1. Memory, visuoconstructive and executive functions

The changes in cognitive functioning, excluding DSy-WAIS, was independent of the effect of ApoE genotype in the study groups (*Table 16)*. In the DSy-WAIS, there was a main effect of group and an interaction effect between group and ApoE: the AAMI group was inferior to control group. Post hoc test showed that the ε4 carriers were more impaired than the non-carriers only in the control group ($F [1, 40] = 4.7$, $p < 0.05$).

Table 16. Memory, visuoconstructive and executive functions in the AAMI subjects and the control subjects with one or two ApoE ε4 alleles (ε4+) or without the ε4 allele (ε4-) at the baseline

	AAMI		*CONTROLS*		*F*	
	e4+	*e4-*	*e4+*	*e4-*		*p*
Episodic Memory						
VRI	10.2 ± 3.1	10.4 ± 2.5	13.4 ± 2.7	12.5 ± 2.9	15.17	a) 0.000
VRD	7.5 ± 4.7	7.5 ± 3.0	10.8 ± 4.0	10.6 ± 3.3	12.65	a) 0.001
BSRT	35.9 ± 9.2	37.2 ± 8.4	37.7 ± 9.4	41.7 ± 6.6		n.s.
Semantic Memory						
VFT-L	41.8 ± 13.6	36.1 ± 13.7	49.7 ± 10.7	45.2 ± 15.7	5.88	a) 0.017
VFT-C	19.0 ± 5.7	19.9 ± 5.7	20.2 ± 4.9	22.5 ± 4.8		n.s.
Visuoconstructive Functions						
VRC	16.0 ± 1.0	15.3 ± 0.94	16.3 ± 0.74	16.3 ± 1.5	4.45	a) 0.038
DSy-WAIS	31.2 ± 8.2	26.1 ± 8.7	32.0 ± 7.0	38.0 ± 8.9	9.5	a) 0.003
					7.30	c) 0.008
Executive Functions						
TMTA	50.8 ± 15.3	56.1 ± 19.8	50.2 ± 20.6	42.8 ± 16.0		n.s.
TMTB	146.2 ± 72.9	149.1 ± 79.6	131.2 ± 60.1	113.1 ± 45.0	3.96	a) 0.053
WCST,						
perseverative errors	5.2 ± 5.9	4.6 ± 4.8	0.7 ± 2.0	2.2 ± 2.9	8.6	a) 0.004
correct resp.	24.6 ± 8.7	25.7 ± 9.4	30.6 ± 12.2	33.1 ± 10.0	7.41	a) 0.008
ST						
colors, time (s)	42.0 ± 15.2	38.9 ± 7.2	37.4 ± 5.4	36.3 ± 10.7		n.s.
text, time (s)	82.7 ± 29.7	83.9 ± 35.7	73.0 ± 12.4	70.5 ± 16.1		n.s.
DSp- WAIS						
forward	5.3 ± 0.6	5.6 ± 1.0	6.0 ± 1.3	5.6 ± 0.9		n.s.
backfard	4.0 ± 1.0	4.1 ± 1.2	4.8 ± 0.9	4.5 ± 1.2		n.s.

Values are mean ± SD; ANOVA (df = 1, 85), a) effect of group; b) effect of ApoE; c) interaction effect of group and ApoE; n.s., not significant; VRI, Visual Reproduction, immediate recall; VRD, Visual Reproduction, delayed recall; BSRT, Buschke Selective Reminding Test, total recall; VRC, Visual Reproduction, copying the figures; VFT-L, Verbal Fluency Test using letters P, A and S; VFT-C, Verbal Fluency Test using animal category; DSy-WAIS, Digit Symbol; TMTA, Trail Making Test A ; TMTB, Trail Making Test B; WCST, Modified Wisconsin Card Sorting Test; ST, Stroop Test; DSp-WAIS, Digit Span

5.2.2. Magnetic resonance imaging

There was no main effect of group or ApoE nor any interaction effect between group and ApoE on the MRI volumetry in the study groups (*Table 17).*

Table 17. Normalized volumes of the hippocampus (HC) and the amygdala (A) in the AAMI subjects and the control subjects with one or two ApoE ε4 alleles (ε4+) or without the ε4 allele (ε4-)

	AAMI		*CONTROLS*		
	e4+	*e4-*	*e4+*	*e4-*	*p*
HC_R	173.6 ± 27.9	174.6 ± 26.3	171.6 ± 17.5	169.4 ± 26.3	n.s.
HC_L	156.6 ± 28.7	161.1 ± 19.2	157.9 ± 24.4	156.2 ± 21.2	n.s.
HC_{R-L}	17.0 ± 16.6	13.5± 18.8	13.8 ± 16.8	13.2 ± 20.1	n.s.
A_R	104.8 ± 18.4	110.7 ± 27.8	104.4 ± 9.7	98.8 ± 13.5	n.s.
A_L	114.5 ± 36.1	116.6 ± 28.8	103.7 ± 12.9	110.5 ± 15.9	n.s.
A_{L-R}	9.7 ± 32.8	5.9 ± 11.1	–07 ± 12.7	11.7 ± 15.8	n.s.

Values expressed as mean ± SD; ANOVA (df = 1,76); n.s., not significant; HC_R = right HC; HC_L= left HC; HC_{R-L}= right-left HC; A_R= right A; A_L= left A; A_{L-R}= left-right A

5.2.3. Single photon emission tomography

Mean activity of the right (F [1,46] = 6.35, p= 0.015) and left (F [1,46]= 5.60, p= 0.022) prefrontal ROIs (referred to the cerebellar activity) were slightly lower in the control subjects with one or two ε4 alleles compared with the controls without the ε4 allele. In the AAMI subjects, the effect of the ε4 allele was opposite *(Table 18).* The post hoc test showed that the ε4 carriers differed from the non-carriers in the control group (for right prefrontal activity F [1,20] = 14.5, $p < 0.001$, and for left F [1,20] = 11.7, $p < 0.003$).

Table 18. 99mTc-HMPAO SPECT results both in the AAMI subjects and in the control subjects with one or two ApoE ε4 alleles (ε4+) or those without the ε4 allele (ε4-). Values expressed as mean ± SD; ANOVA (df = 1,46); n.s., not significant, * interaction effect of group and ApoE.

	AAMI		*CONTROLS*		
	e4+	*e4-*	*e4+*	*e4-*	*p**
Right prefrontal	1.07 ± 0.05	1.05 ± 0.06	1.03 ± 0.03	1.09 ± 0.03	0.015
Left prefrontal	1.06 ± 0.05	1.03 ± 0.06	1.01 ± 0.04	1.07 ± 0.03	0.022
Right frontal	1.00 ± 0.10	1.02 ± 0.06	1.02 ± 0.04	0.99 ± 0.12	n.s.
Left frontal	0.97 ± 0.08	1.00 ± 0.06	1.00 ± 0.05	0.97 ± 0.12	n.s.
Right temporal	1.02 ± 0.13	1.04 ± 0.07	1.05 ± 0.02	0.99 ± 0.11	n.s.
Left temporal	1.00 ± 0.11	1.01 ± 0.09	1.02 ± 0.03	0.97 ± 0.12	n.s.
Right parietal	0.97 ± 0.12	1.00 ± 0.06	1.01 ± 0.05	0.94 ± 0.13	n.s.
Left parietal	0.94 ± 0.10	0.96 ± 0.06	0.96 ± 0.06	0.91 ± 0.13	n.s.
Right occipital	1.10 ± 0.12	1.11 ± 0.08	1.15 ± 0.06	1.08 ± 0.11	n.s.
Left occipital	1.08 ± 0.11	1.08 ± 0.07	1.11 ± 0.04	1.08 ± 0.11	n.s.

5.2.4. Electroencephalography

Minor changes were observed in the EEG parameters. Unexpectedly, the mean frequency was higher and the EEG slow wave activity decreased in the ε4 carriers compared with the non-carriers in the AAMI group and the control group.

The mean frequency of the alpha and theta range was higher in the ε4 carriers in the left frontal (F3-C3, F[1,70]=5.4, p=0.023; *Table 19*) and in the right and the left temporo-occipital leads (T6-O2, F[1,79]=12.1, p=0.001 and T5-O1, F[1,79]=8.1, p=0.006, *Table 20*). The mean frequency was higher in the ε4 carriers in the left frontal (F3-F4, F [1,70]=4.9, p=0.03, *Table 19*) and in the right temporo-occipital lead (T6-O2, F[1,78]=4.3, p=0.04, *Table 20*).

The relative theta amplitude was significantly decreased in the left frontal lead (F3-C3, F[1,70]=7.2, p=0.009, *Table 21)* and also the relative delta amplitude was decreased in the left frontal lead (F3-C3,F[1,70]=4.1,p=0.046, *Table 24)* and the right and left temporo-occipital leads (T6-O2, F [1,78]=4.0, p=0.05 and T5-O1, F[1,79]=4.4, p=0.039, *Table 25*) for the ε4 carriers compared with the non-carriers in both groups.

The relative value of the beta amplitude was significantly higher in the right temporo-occipital lead (T6-O2, F [1,78]=4.4, p=0.039, *Table 22*) for the ε4 carriers than the non-carriers in the study groups.

No main effect of group or the interaction effect between ApoE and group were seen in QEEG parameters in the study groups.

Table 19. Absolute delta, theta, alpha, beta and fast beta amplitudes (μV), peak and mean frequency, and mean frequency of combined alpha and theta bands (Hz) with eyes closed in the left (F3-C3) and right frontal (F4-C4) leads of EEG spectra in the subjects with AAMI and the control subjects with the ε4 allele (ε4+) or without the ε4 allele (ε4-)

EEG parameters	*AAMI*		*CONTROLS*		
	e4+	*e4-*	*e4+*	*e4-*	*p**
F3- C3 lead (left)					
Absolute amplitude (μV)					
Delta	3.34 ± 0.91	3.92 ± 0.87	3.52 ± 1.39	3.24 ± 0.69	n.s.
Theta	3.01 ± 0.71	3.96 ± 1.83	3.31 ± 1.20	3.08 ± 1.41	n.s.
Alpha	7.83 ± 3.18	9.10 ± 5.42	8.39 ± 4.02	6.59 ± 4.10	n.s.
Beta	6.21 ± 2.33	6.12 ± 2.41	5.69 ±2.22	5.08 ± 3.19	n.s.
Fast beta	7.36 ± 2.74	6.47 ± 2.25	6.63 ± 3.07	5.38 ± 2.48	n.s.
Frequency (Hz)					
peak	9.26 ± 1.98	8.33 ± 2.33	8.82 ± 2.04	8.83 ± 2.23	n.s.
mean	9.22 ± 0.32	8.93 ± 0.38	8.98 ± 0.39	8.86 ± 0.35	0.030
mean (alpha + theta)	10.51 ± 0.62	9.94 ± 0.77	10.10 ± 0.62	9.82 ± 0.76	0.023
F4- C4 lead (right)					
Absolute amplitude					
Delta	3.90 ± 1.20	4.06 ± 0.86	3.42 ± 1.07	3.47 ±0.88	n.s.
Theta	3.40 ± 1.02	4.01 ± 1.88	3.27 ± 0.99	3.19 ± 1.61	n.s.
Alpha	8.60 ± 3.60	9.56 ± 5.16	9.38 ± 3.87	6.90 ± 3.93	n.s.
Beta	6.57 ± 3.15	6.67 ± 2.68	6.13 ± 2.70	5.21 ± 2.60	n.s.
Fast beta	6.97 ± 2.37	6.96 ± 2.28	6.52 ± 2.39	5.68 ± 2.24	n.s.
Frequency (Hz)					
peak	8.95 ± 2.06	8.69 ± 2.17	8.94 ± 1.95	8.15 ± 2.60	n.s.
mean	9.14 ± 0.35	8.96 ± 0.44	9.08 ± 0.41	8.88 ± 0.35	n.s.
mean (alpha + theta)	10.23 ± 0.79	10.01 ± 0.93	10.19 ± 0.69	9.87 ± 0.82	n.s

Values are mean ± SD; The log (x) for absolute values was used for statistical calculations, ANOVA (df = 1,78); * effect of ApoE; n.s., not significant

Table 20. Absolute delta, theta, alpha, beta and fast beta amplitudes (μV), peak and mean frequency, and mean frequency of combined alpha and theta bands (Hz) with eyes closed in the left (T5-O1) and right temporo-occipital (T6-O2) leads of EEG spectra in the subjects with AAMI and the control subjects with the ε4 allele (ε4+) or without the ε4 allele (ε4-).

EEG parameters	*AAMI*		*CONTROLS*		
	e4+	*e4-*	*e4+*	*e4-*	*p**
T5- O1 lead (left)					
Absolute amplitude (μV)					
Delta	3.44 ± 0.76	4.18 ± 1.70	3.58 ± 1.21	3.52 ± 1.24	n.s.
Theta	3.70 ± 1.31	4.35 ± 2.15	3.97 ± 1.65	3.77 ± 2.12	n.s.
Alpha	13.22 ± 5.52	14.45 ± 7.24	13.80 ± 6.65	11.96 ± 8.46	n.s.
Beta	6.62 ± 2.35	6.58 ± 2.39	6.77 ± 2.29	5.32 ± 2.32	n.s.
Fast beta	6.17 ± 2.51	5.47 ± 2.09	6.41 ± 2.97	4.67 ± 2.11	n.s.
Frequency (Hz)					
peak	9.96 ± 1.65	8.99 ± 1.79	10.33 ± 1.38	9.70 ± 1.51	n.s.
mean	9.46 ± 0.50	9.22 ± 0.34	9.30 ± 0.34	9.13 ± 0.33	n.s.
mean (alpha + theta)	10.36 ± 0.59	10.01 ± 0.61	10.32 ± 0.51	9.87 ± 0.56	0.006
T6- 02 lead (right)					
Absolute amplitude					
Delta	3.44 ± 0.91	4.19 ± 1.50	3.82 ± 2.03	3.79 ± 1.22	n.s.
Theta	3.61 ± 1.37	4.63 ± 2.44	4.20 ± 1.90	4.10 ± 2.42	n.s.
Alpha	12.85 ± 5.89	14.87 ± 7.74	14.58 ± 7.70	12.46 ± 8.22	n.s.
Beta	6.50 ± 1.86	6.49 ± 2.47	7.11 ± 2.30	5.61 ± 2.16	n.s.
Fast beta	6.25 ± 2.06	5.54 ± 2.20	7.37 ± 4.67	4.86 ± 1.51	n.s.
Frequency (Hz)					
peak	10.06 ± 1.37	9.32 ± 1.03	8.79 ± 1.42	9.28 ± 1.85	n.s.
mean	9.42 ± 0.47	9.18 ± 0.34	9.25 ± 0.37	9.14 ± 0.33	0.042
mean (alpha + theta)	10.39 ± 0.46	9.95 ± 0.49	10.32 ± 0.46	9.85 ± 0.61	0.001

Values are mean ± SD; The log (x) for absolute values was used for statistical calculations, ANOVA (df = 1,78); * effect of ApoE; n.s., not significant

Table 21. Relative delta, theta, alpha, and beta amplitudes (%) with eyes closed in the left frontal (F3-C3), the right frontal (F4-C4), the left (T5-O1) and right temporo-occipital (T6- O2) leads of EEG spectra in the subjects with AAMI and the control subjects with the ε4 allele (ε4+) or without the ε4 allele (ε4-)

Relative amplitude (%)	*AAMI*		*CONTROLS*		
	e4+	*e4-*	*e4+*	*e4-*	*p**
F3 - C3 lead (left)					
Delta	16.9 ±4.0	19.1 ± 5.2	17.1 ± 3.4	20.2 ± 5.6	0.046
Theta	15.1 ± 1.8	18.1 ± 5.0	16.0 ± 2.2	17.6 ± 3.1	0.009
Alpha	37.7 ± 5.1	40.1 ± 1.5	39.4 ± 7.2	35.1 ± 6.6	n.s.
Beta	30.4 ± 4.7	28.0 ± 6.0	27.5 ± 6.2	27.1 ± 4.6	n.s.
F4 - C4 lead (right)					
Delta	18.2 ± 5.4	18.3 ± 6.1	16.0 ± 3.3	20.0 ± 5.3	n.s.
Theta	15.6 ± 2.3	16.6 ± 3.3	15.2 ± 2.7	17.1 ± 3.0	n.s.
Alpha	37.7 ± 6.6	37.7 ± 8.0	41.8 ± 6.6	35.3 ± 6.3	n.s.
Beta	28.6 ± 5.7	27.4 ± 6.4	27.0 ± 5.9	27.5± 5.3	n.s.
T5- O1 lead (left)					
Delta	13.4 ± 3.4	15.1 ± 4.5	13.3 ± 2.7	16.0 ± 4.7	0.039
Theta	14.1 ± 3.5	14.5 ± 2.4	14.2 ± 2.2	15.6 ± 2.7	n.s.
Alpha	47.8 ± 8.0	46.9 ± 8.0	47.4 ± 8.1	45.4 ± 8.8	n.s.
Beta	23.5 ± 5.4	23.5 ± 5.4	25.2 ± 6.4	23.0 ± 5.0	n.s.
T6- O2 lead (right)					
Delta	13.7 ± 3.2	15.0 ± 4.1	13.1 ± 2.9	16.2 ± 5.3	0.05
Theta	13.9 ± 2.7	15.1 ± 2.8	14.3 ± 2.3	15.8 ± 3.0	n.s.
Alpha	47.1± 8.8	47.2 ± 8.0	47.4 ±7.8	45.1 ± 8.6	n.s.
Beta	25.3 ± 5.1	22.7 ± 4.9	25.3 ± 5.0	22.9 ± 4.8	0.039

Values are mean ± SD; The log (x/(1-x)) for relative values was used for statistical calculations. ANOVA (df=1,65); * effect of ApoE ; n.s., not significant

5.2.5. Event- related potentials

Auditory N100 habituation was significantly impaired in the AAMI subjects especially in the ε4 carriers compared the control groups in the non-attended condition at the vertex electrode (Cz, *Table 22*): The mean ratio of 1st and 2nd N100 amplitude was shorter in the ε4 carriers than noncarriers in the AAMI group whereas it was the opposite in the control group ($F[1,45]=4.3$, $p=0.05$). The post hoc test showed that the ε4 carriers differed from the non-carriers in the AAMI group ($F[1,22] = 5.4$, $p< 0.05$).

Table 22. Auditory N100 habituation for non-attended stimuli at the vertex electrode (Cz) both for the AAMI and control subjects with at least one ε4 allele (ε4+) or those without the ε4 allele (ε4-)

Auditory parameters at Cz	*AAMI*		*CONTROLS*		
	e4+	*e4-*	*e4+*	*e4-*	*p*
1st N100 latency (ms)	109.0 ± 9.5	105.0 ± 7.6	108.1 ± 15.2	113.5 ± 7.4	a) 0.020
1st N100 amplitude (μV)	-14.6 ± 4.8	-16.6 ± 5.0	-12.3 ± 2.2	-14.4 ± 4.8	n.s.
2nd N100 latency (ms)	101.2 ± 8.1	100.6 ± 9.1	104.4 ± 11.1	109.0 ± 8.0	a) 0.006
2nd N100 amplitude (μV)	-14.1 ± 4.2	-12.9 ± 3.4	-9.5 ± 3.0	-11.6 ± 3.4	a) 0.03
Ratio of 1st and 2nd N100 amplitude (μV)	1.04 ± 0.2	1.29 ± 0.2	1.45 ± 0.7	1.25 ± 0.3	c) 0.05

Values are mean ± SD, ANOVA (df = 1,45); a) effect of group, b) effect of ApoE, c) interaction effect of group and ApoE; n.s., not significant

A minor differences were seen in auditory ERP parameters in the attended condition at the vertex electrode (Cz, *Table 23*). The mean latency of auditory N100 was shorter in the AAMI group than in the control group. Furthermore there was no difference between the groups on the mean latency or amplitude of P300 (not presented in tables). The mean latency of visual N2 was shorter in the ε4 carriers than in the noncarriers in both of the groups ($F[1,73]=4.4$, $p=0.04$) in the attended condition at the parietal electrode (Pz, *Table 23*).

Table 23. Mean auditory parameters at the vertex electrode (Cz) and visual parameters at the parietal electrode (Pz) in the attended condition both for the AAMI and control subjects with at least one ε4 allele (ε4+) or those without the ε4 allele (ε4-). Values are mean ± SD, ANOVA (df = 1,77); a) effect of group, b) effect of ApoE, c) interaction effect of group and ApoE; n.s., not significant

Auditory stimuli at Cz	*AAMI*		*CONTROLS*		
	e4+	*e4-*	*e4+*	*e4-*	*p*
N100 latency (ms)	107.3 ± 4.9	101.4 ± 8.9	103.3 ± 7.1	108.3 ± 6.8	a) 0.03
N100 amplitude (μV)	-8.2 ± 2.1	-7.1 ± 2.5	-6.0 ± 3.4	-6.8 ± 2.8	n.s.
N200-P300 amplitude (μV)	15.4 ± 6.9	12.4 ± 6.9	9.3 ± 5.1	14.9 ± 8.6	n.s.
Visual stimuli at Pz					
N1 latency (ms)	169.3 ± 10.7	172.4 ± 17.4	171.6 ± 23.7	176.4 ± 24.7	n.s.
N1 amplitude (μV)	-2.4 ± 2.7	-3.80± 2.1	-1.8 ± 3.2	-2.1 ± 1.7	n.s.
P1-N1 amplitude (μV)	5.3 ± 3.1	5.7 ± 2.6	3.8 ± 3.2	3.8 ± 2.4	a) 0.004
N2 latency (ms)	302.4 ± 27.6	320.7 ± 28.7	310.3 ± 34.6	322.5 ± 30.4	b) 0.04
N2 amplitude (μV)	-4.0 ± 5.3	-3.5 ± 4.3	-0.6 ± 3.9	-2.1 ± 3.6	a) 0.04

5.3. Follow-up study

5.3.1. Subjects

The 36 subjects of 90 subjects who participated in the cross-sectional study, as pilot subjects, were asked to participate in the follow-up study 2.8 years later. Out of those 36 subjects, two had moved away from the region and were unable to be relocated for re-evaluation and another subject was unwilling to participate further. *Firstly,* we analyzed the data for the AAMI and the control groups (Study 1). *Secondly,* due to the small number of the study subjects in the follow-up, the AAMI and the control subjects could not be divided into two groups according their ApoE genotype. For this reason, the data was analyzed for two groups: homozygous or heterozygous for ε4 (ε4+), and subjects without the ε4 allele (ε4 -) (Study 2). *Table 24* lists the clinical characteristics of the subjects in Study 1 and Study 2.

Table 24. Clinical characteristics of the subjects in Study 1 and Study 2

	STUDY 1			***STUDY 2***		
	AAMI	*CONTROLS*	*p*	*e4+*	*e4-*	*p*
N	15	18	n.s.	16	17	n.s.
Women/men	11/ 4	7/ 11	0.05*	8/8	10/7	n.s.*
Age at baseline	67.2 ± 6.9	68.7 ± 3.9	n.s	67.6 ± 6.0	68.5± 5.1	n.s.
Education, y	8.0 ± 3.3	11.7 ± 3.6	0.005	10.0 ± 4.4	10.0 ± 3.5	n.s.

Values expressed as mean ± SD; P-value obtained by Student's t-test, except *χ^2; n.s., not significant

5.3.2 A follow-up of subjects with Age-associated memory impairment and control subjects (Study 1)

5.3.2.1. Memory, visuoconstructive and executive functions

The AAMI subjects differed from the controls in AAMI-tests at the baseline but their performance in those tests had not deteriorated during the 2.8 year follow-up period. The control subjects maintained their superior performance in AAMI tests but they did show a significant decline in their scores in the BVRT ($F[1,30]=4.91$, $p=0.03$, *Table 25*).

Table 25. Performance in AAMI-tests in the subjects with AAMI and the control subjects at the baseline and after the 2.8 year-follow-up (Study 1)

	AAMI	*CONTROLS*	*Effect of time, p*	*F / Effect of time and group*	*p*
V-WAIS, Baseline	42.8 ± 7.9	50.4 ± 7.8	n.s.		n.s.
Follow-up	43.7 ± 8.3	50.5 ± 7.7			
MMSE, Baseline	27.8 ± 1.7	28.5 ± 1.1	n.s.		n.s.
Follow-up	27.2 ± 2.2	28.1 ± 1.6			
MAC-Q, Baseline	30.6 ± 3.3	26.0 ± 3.1	n.s.		n.s.
Follow-up	31.2 ± 2.2	26.5 ± 4.0			
BVRT, Baseline	5.3 ± 1.2	8.0 ± 0.7	n.s.	4.91	0.03
Follow-up	5.3 ± 1.5	7.0 ± 1.3			
PAL, Baseline	13.5 ± 1.5	18.0 ± 2.0	n.s.		n.s.
Follow-up	14.6 ± 3.6	16.8 ± 2.1			
GDS, Baseline	7.9 ± 4.4	3.5 ± 3.5	n.s.		n.s.
Follow-up	8.7 ± 7.1	4.0 ± 3.4			

Values expressed as mean ± SD; MANOVA (df=1,30) adjusted for education; n.s., not significant; 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

The subjects with AAMI showed a significant decline in scores in the BSRT sensitive to episodic memory function whereas the control subjects did not show any significant deterioration. Multivariate analysis of variance for repeated tests showed a significant effect of time ($F[1,29]=8.22$, $p=0.008$) and an interaction between time and group (AAMI / controls) ($F[1,29]=4.58$, $p=0.04$) in BSRT during the follow-up time of 2.8 years. Post hoc analysis showed that the AAMI subjects also recalled fewer words in the BSRT after the delay ($F[1, 29] = 10.17$, $p= 0.003$) in the follow-up examination (*Table 26*).

The AAMI subjects performed better in the WCST ($F[1,25]=5.34$, $p= 0.03$) as well as in the ST after the 2.8 year follow-up than at the baseline visit. The control subjects also performed better in the ST at the follow-up examination than at the baseline. There was a significant effect of time ($F[1,30]=6.32$, $p=0.02$) and an interaction between time and group ($F[1,30]=7,72$, $p=0.009$) on VFT-C during the follow-up period of 2.8 years. The control subjects showed a significant decline in scores in the VFT-C sensitive to semantic memory and language function (*Table 26*).

Table 26. Memory, visuoconstructive and executive functions in the subjects with AAMI and the control subjects at the baseline and after the 2.8-year follow-up (Study 1)

	AAMI	*CONTROLS*	*F / Effect of time*	*p*	*F/ Effect of time and group*	*p*
Episodic Memory						
VRI, Baseline	10.3 ± 3.4	13.0 ± 2.9		n.s.		n.s.
Follow-up	10.7 ± 4.0	12.6 ± 2.5				
VRD, Baseline	8.4 ± 4.4	10.9 ± 3.6		n.s.		n.s.
Follow-up	8.0 ± 5.0	11.1 ± 3.6				
BSRT, Baseline	37.5 ± 7.6	42.6 ± 5.7	8.22	0.008	4.58	0.04
Follow-up	32.8 ± 7.3	41.9 ± 6.1				
Semantic Memory						
VFT-L, Baseline	37.5 ± 12.0	46.5 ± 13.3		n.s.		n.s.
Follow-up	42.4 ± 14.7	46.1 ± 16.0				
VFT-C, Baseline	20.1 ± 5.9	22.8 ± 4.6	6.32	0.02	7.72	0.009
Follow-up	19.1 ± 5.0	19.6 ± 5.1				
Visuoconstructive Functions						
VRC, Baseline	15.9 ± 0.9	16.5 ± 1.3		n.s.		n.s.
Follow-up	15.9 ± 1.2	15.8 ± 1.2				
DSy-WAIS, Baseline	30.5 ± 10.3	39.2 ± 10.7		n.s.		n.s.
Follow-up	31.2 ± 12.0	41.7 ± 11.3				
Executive Functions						
TMTA, Baseline	50.9 ± 17.0	44.0 ± 17.0		n.s.		n.s.
Follow-up	57.21 ± 26.4	40.6 ± 12.5				
WCST						
perseverative errors,						
Baseline	5.1 ± 6.7	0.9 ± 1.8		n.s.		n.s.
Follow-up	2.6 ± 4.1	3.9 ± 10.1				
correct resp.,Baseline	24.3 ± 9.4	37.5 ± 7.8		n.s.	5.34	0.03
Follow-up	31.6 ± 9.8	34.9 ± 13.8				
ST						
colors,time (s), Baseline	44.6 ± 16.3	39.2 ± 14.3	9.6	0.004		n.s.
Follow-up	37.9 ± 11.7	33.4 ± 7.1				
text, time (s), Baseline	81.2 ± 34.5	71.6 ± 18.0		n.s.		n.s.
Follow-up	78.9 ± 32.8	69.6 ± 16.4				
DSp-WAIS						
forward, Baseline	5.5 ± 0.8	5.8 ± 0.8		n.s.		n.s.
Follow-up	5.6 ± 0.9	5.7 ± 0.9				
backward, Baseline	4.3 ± 1.3	4.8 ± 1.3		n.s.		n.s.
Follow-up	4.2 ± 0.9	4.5 ± 0.9				

Results are mean ± SD; MANOVA (df = 1, 29), adjusted for education; n.s., not significant; [#]Mann-Whitney U-test; VRI, Visual Reproduction, immediate recall; VRD, Visual Reproduction, delayed recall; BSRT, Buschke Selective Reminding Test, total recall; VRC, Visual Reproduction, copying the figures; VFT-L, Verbal Fluency Test using letters P, A and S; VFT-C, Verbal Fluency Test using animal category; DSy-WAIS, Digit Symbol; TMTA, Trail Making Test A ; TMTB, Trail Making Test B; WCST, Modified Wisconsin Card Sorting Test; ST, Stroop Test; DSp-WAIS, Digit Span

5.3.2.2. Magnetic resonance imaging

Hippocampal volumes significantly decreased in both of the groups during the follow-up period (*Table 27*). There was no significant interaction effect between time and group (AAMI / controls). The annual decline in the right hippocampus was 5.0% / 4.2% and 4.1% / 4.0% in the left hippocampus for the AAMI/ control subjects. The decline in the right hippocampal volume of the AAMI subjects tended to be greater than in the control subjects.

Table 27. Normalized volumes of the hippocampus (HC) in the subjects with AAMI and the control subjects at the baseline and after the 2.8-year follow-up (Study 1)

	AAMI	*CONTROLS*	*F/ Effect of time*	*p*	*Effect of time and group, p*
HC_R					
Baseline	176.9 ± 31.4	174.7 ± 19.9	69.16	0.0001	n.s.
Follow-up	148.1 ± 33.9	153.6 ± 14.8			
Decline %/ year	5.0 ± 1.8	4.2 ± 2.9			
HC_L					
Baseline	161.9 ± 30.6	152.7 ± 17.6	49.10	0.0001	n.s.
Follow-up	138.9 ± 21.9	133.1 ± 15.9			
Decline %/ year	4.1 ± 2.8	4.0 ± 2.6			
HC_{R-L}					
Baseline	15.6 ± 16.9	21.9 ± 11.6		n.s	n.s.
Follow-up	9.2 ± 17.6	20.5 ± 11.5			

Values expressed as mean ± SD; MANOVA (df = 1,23); n.s., not significant; HC_R = right HC; HC_L= left HC; HC_{R-L}= right-left HC;

5.3.2.3. Frequency of different Apolipoprotein E alleles

The AAMI subjects had a higher frequency of the ε4 allele than the control subjects, but this difference was not statistically significant. The ε4 frequency for the AAMI subjects was 0.47 compared to 0.16 for the controls (*Table 28*). However, there was a significant difference in the ε4 frequency between the AAMI subjects in the cross-sectional study and in the follow-up study, chi-square goodness-of-fit-test (χ^2 = 9.0, df= 2, p= 0.011). This difference was not seen between the control subjects in these two studies.

Table 28. Apolipoprotein E genotypes and allele frequencies in the AAMI subjects and the controls in a follow-up study (Study 1)

Genotype	*AAMI n=15*	*CONTROLS n=18*
2/3	1	1
2/4	0	0
3/3	3	12
3/4	8	4
4/4	3	1
Allele frequency		
ε2 + ε3	0.53	0.84
ε4	0.47	0.16

χ^2-test; z-statistics for ε4 allele frequency; not significant

5.3.3. The influence of Apolipoprotein E genotype in the follow-up study (Study 2)

We analyzed the data for two groups: subjects homozygous or heterozygous for ε4 (ε4+), and subjects without the ε4 allele (ε4 -) *(Table 24).* The study subjects displayed no signs of depression (Geriatric Depression Rating Scale, values below 15 for both groups).

5.3.3.1. Memory, visuoconstructive and executive functions

AAMI tests: Scores in BVRT ($F[1,30]=5.42$, $p=0.03$) significantly decreased in both of the groups during the follow-up period *(Table 29).* There was no interaction between time and group in AAMI tests.

Table 29. Performance in AAMI tests in the ε4 carriers (ε4+) and the noncarriers (ε4-) at the baseline and after the 2.8-year follow-up period (Study 2)

	e4+	*e4-*	*F / Effect of time*	*p*	*Effect of time and group, p*
V-WAIS, Baseline	46.5 ± 9.7	46.7 ± 7.6		n.s.	n.s.
Follow-up	48.6 ± 9.8	45.4 ± 7.0			
MMSE, Baseline	28.1 ± 1.6	28.3 ± 1.4		n.s.	n.s.
Follow-up	27.6 ± 2.0	27.9 ± 1.9			
MAC-Q, Baseline	28.3 ± 4.8	27.9 ± 3.1		n.s.	n.s.
Follow-up	29.4 ± 3.8	28.0 ± 4.3			
BVRT, Baseline	6.1 ± 1.8	7.4 ± 1.2	5.42	0.03	n.s.
Follow-up	6.0 ± 1.9	6.6 ± 1.3			
PAL, Baseline	15.3 ± 2.5	17.3 ± 2.9		n.s.	n.s.
Follow-up	15.1 ± 3.6	16.8 ± 2.3			
GDS, Baseline	5.9 ± 4.6	5.3 ± 4.6		n.s.	n.s.
Follow-up	7.0 ± 6.7	5.4 ± 5.1			

Values expressed as mean ± SD; MANOVA (df= 1,30) adjusted for education; n.s., not significant; BVRT, Benton Visual Retention Test; PAL, Paired Associated Learning Test; MMSE, Mini-Mental State Examination; MAC-Q, Memory Complaint Questionnaire; V-WAIS, Vocabulary subtest of the Wechsler Memory Scale; GDS, Geriatric Depression Scale.

The subjects with one or two ApoE ε4 alleles showed a significant decline in scores in the BSRT which is sensitive to episodic memory function whereas the ε4 noncarriers did not show any significant deterioration. Multivariate analysis of variance for repeated tests showed a significant effect of time ($F[1,29]=8.24$, $p=0.007$) and an interaction between time and group (ε4+ / ε4-) ($F[1,29]=5.29$, $p=0.003$) on BSRT during the follow-up time of 2.8 years. Post hoc analysis showed that the ε4 carriers also recalled fewer words in the BSRT after the delay ($F[1,29]=13.11$, $p < 0.001$) in the follow-up examination. In the ST, which is sensitive to executive functions, both of the groups performed better at the follow-up examination than they had at the baseline (*Table 30)*.

Table 30. Memory, visuoconstructive and executive functions in the subjects with one or two ε4 alleles (ε4+) and those without the ε4 allele (ε4-) at the baseline and after the 2.8-year follow-up (Study 2)

	e4+	*e4-*	*F / Effect of time*	*p*	*F/ Effect of time and group*	*p*
Episodic Memory						
VRI, Baseline	11.5 ± 3.7	12.0 ± 3.1		n.s.		n.s.
Follow-up	11.7 ± 3.5	11.7 ± 3.4				
VRD, Baseline	9.6 ± 4.8	9.8 ± 3.6		n.s.		n.s.
Follow-up	9.2 ± 4.8	10.0 ±4.3				
BSRT, Baseline	39.0 ± 8.9	41.2 ± 4.7	8.42	0.007	5.29	0.003
Follow-up	34.1 ± 8.4	40.6 ± 6.5				
Semantic Memory						
VFT-L, Baseline	42.7 ± 11.8	41.9 ± 14.8		n.s.		n.s.
Follow-up	46.6 ± 15.9	43.5 ± 15.5				
VFT-C, Baseline	20.8 ± 6.4	21.1 ± 5.1		n.s.		n.s.
Follow-up	19.3 ± 5.1	18.8 ± 4.9				
Visuoconstructive Functions						
VRC, Baseline	16.1 ± 0.9	16.2 ± 1.3		n.s.		n.s.
Follow-up	16.4 ± 1.0	15.4 ± 1.1				
DSy-WAIS, Baseline	31.6 ± 8.7	39.7 ± 11.0		n.s.		n.s.
Follow-up	31.5 ± 11.5	42.0 ± 11.9				
Executive Functions						
TMTA, Baseline	52.2 ± 15.5	42.3 ± 17.4		n.s.		n.s.
Follow-up	51.8 ± 19.1	44.6 ± 23.3				
WCST						
perseverative errors,						
Baseline	4.3 ± 6.5	1.2 ± 2.0		n.s.		n.s.
Follow-up	2.1 ± 3.8	4.7 ± 11.0				
correct resp., Baseline	27.9 ± 10.5	35.6 ± 9.7		n.s.		n.s.
Follow-up	33.3 ± 10.5	33.6 ± 14.0				
ST						
colors, time (s), Baseline	44.0 ± 15.5	38.6 ± 15.2	9.64	0.004		n.s.
Follow-up	38.4 ± 11.0	32.3 ± 6.8				
text, time (s), Baseline	75.5 ± 26.6	76.4 ± 27.6		n.s.		n.s.
Follow-up	78.1 ± 29.4	78.6 ± 17.3				
DSp-WAIS						
forward, Baseline	5.6 ± 0.7	5.8 ± 1.0		n.s.		n.s.
Follow-up	5.6 ± 0.9	5.8 ± 1.0				
backward, Baseline	4.2 ± 1.2	4.8 ± 1.3		n.s.		n.s.
Follow-up	4.2 ± 1.0	4.6 ± 0.9				

Results are mean ± SD; MANOVA (df = 1, 29), adjusted for education; n.s., not significant; #Mann-Whitney U-test; VRI, Visual Reproduction, immediate recall; VRD, Visual Reproduction, delayed recall; BSRT, Buschke Selective Reminding Test, total recall; VRC, Visual Reproduction, copying the figures; VFT-L, Verbal Fluency Test using letters P, A and S; VFT-C, Verbal Fluency Test using animal category; DSy-WAIS, Digit Symbol; TMTA, Trail Making Test A ; TMTB, Trail Making Test B; WCST, Modified Wisconsin Card Sorting Test; ST, Stroop Test; DSp-WAIS, Digit Span

5.3.3.2. Magnetic resonance imaging

The results showed that the right (F[1,23]=66.7, p= 0.001) and the left hippocampal volume (F[1.23]=48.9, p= 0.001) significantly decreased in both ε4 carriers and noncarriers during the follow-up period *(Figure 3 and Table 31)*. There was no significant interaction between time and group (ε4+ / ε4-). An almost significant effect of side and group (p = 0.058) was found for hippocampal volumes. The annual decline was 4.7% / 4.3% in the right hippocampus and 4.3% / 3.9% in the left hippocampus for the ε4+ / ε4- subjects. It is noteworthy that the right hippocampal volumes were smaller and the left ones were greater in the ε4+ subjects than in the ε4- subjects, and the decline in the right hippocampal volume of the ε4 carriers tended to be greater than in the ε4- subjects.

Figure 3. The decrease in the right hippocampal (HC_R) and the left hippocampal (HC_L) volumes in the ε4 carriers (ε4+) and the noncarriers (ε4-) which had taken place during the 2.8-year period (Study 2)

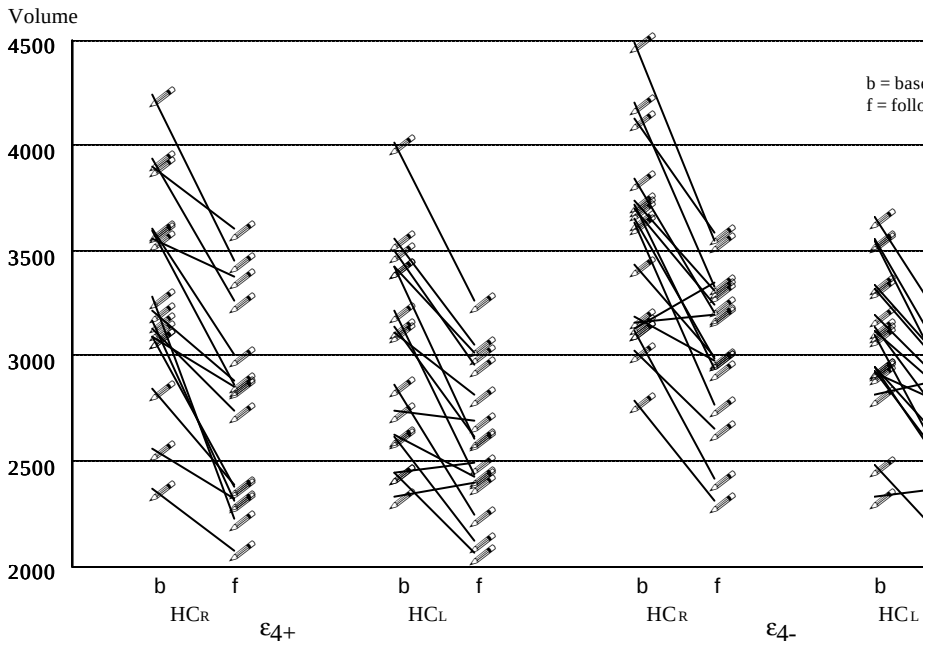


Table 31. Normalized volumes of the hippocampus (HC) in the subjects with one or two ε4 alleles (ε4+) and those without the ε4 allele (ε4-) at the baseline and after the 2.8-year follow-up (Study 2)

	e4+	*e4-*	*F / Effect of time*	*p*	*Effect of time and group, p*
HC_R					
Baseline	173.3 ± 23.7	178.5 ± 29.1	66.72	0.0001	n.s.
Follow-up	145.9 ± 27.3	156.1 ± 24.9			
Decline % / y	4.7 ± 2.0	4.3 ± 1.9			
HC_L					
Baseline	159.2 ± 28.4	155.6 ± 22.2	48.85	0.0001	n.s.
Follow-up	136.7 ± 19.9	135.5 ± 19.0			
Decline % / y	4.3 ± 2.6	3.9 ± 2.6			
HC_{R-L}					
Baseline	14.1 ± 14.8	22.9 ± 14.5		n.s	n.s.
Follow-up	9.1 ± 17.6	20.6 ± 11.5			

Values expressed as mean ± SD, MANOVA df (1,23); n.s., not significant; HC_R = right HC; HC_L= left HC; HC_{R-L}= right-left HC;

6. DISCUSSION

6.1. Cross-sectional study

6.1.1 Study design

The present study is based on data from a series of 90 subjects who were randomly selected from a population of 578 individuals who participated in the study of AAMI prevalence in the Kuopio city area. Out of those 90 subjects, 43 were AAMI subjects and 47 were controls. The distribution of age was equal in both groups but there were more women in the AAMI group than in the control group. Therefore, gender was taken in consideration in the statistical analysis. When proposing the criteria for evaluating AAMI, the NIMH work group suggested three tests, Benton Visual Retention Test, Logical Memory subtest of the WMS, and Associated Learning subtes of the WMS, with fixed cutoff points as examples for tests to be used, but it did not pose restrictions on test selection (Crook et al 1986). Later, the use of specified tests and score levels for AAMI assessment have been proposed (Smith et al 1991, Lezak 1995). In the present study, we used two of the memory tests (BVRT, PAL) recommended by the NIMH work group with the suggested cutoff levels.

The Geriatric Depression Rating Scale was used for the assessment of depressive symptoms in this study. It was developed to be appropriate especially for elderly populations (Yesavage et al 1983). The GDS has been found not only to be a reliable measure of depression but to provide an adequate measure for the high levels of well-being (Coleman et al 1995). Thus, the difference in GDS scores between the AAMI subjects and the controls in our study might reflect this because, although the AAMI subjects had higher scores, they were well below the levels which have been found in clinically mildly depressed subjects (Yesavage et al 1983). However, when depression was taken in consideration in the statistical analysis, it did not influence the results.

The neuropsychological, neuroimaging, and neurophysiological methods in our study are widely used and standardised. One rater, who was not aware of clinical data, performed volumetric measurements of baseline and follow-up scans on the same occasion. Furthermore, the determination of Apo E genotypes using the PRC technique is a reliable and widely accepted method.

The AAMI concept per se (Bamford and Caine 1988, O'Brien and Levy 1992, Caine 1993, Koivisto et al 1995) and all fundamental components of the proposed criteria (Blackford and LaRue 1989, DerouesnŽ 1990) have been criticized. The subjective estimation of memory loss can be affected by other factors in addition to actual memory deficit, such as the affective state and personality traits (Zonderman et al 1989, Derouesné 1990, Hänninen et al 1994). Indeed, relatives' ratings of 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). Blackford and LaRue (1989) suggested that the proposed V-WAIS cutoff score provides a potential skewing of the subject population. Koivisto et al. 1995 agreed with this: in the Finnish population, using the same cutoff score, 42.3% had intellectual functions inadequate for assessment for AAMI. In the present study, the same AAMI criteria were applied and so, our AAMI subjects might represent slightly low-spirited individuals with high intellectual capacity. Same medical exclusions were applied both in the AAMI subjects and the controls. Therefore, the control group may represent the successful aging group. The AAMI and the control subjects did not differ in the use of estrogen during the menopause, or use of anti-inflammatory agents and any other drugs that might have affected cognitive function.

6.1.2. Cognitive functions

Several factors may contribute to performance in neuropsychological tests. Age and occupation, as indicators of educational level, are strongly associated with cognitive function (Colsher and Wallace 1991, Koivisto et al 1992, Launer et al 1993, Wiederholt et al 1993, Portin et al 1995). The AAMI subjects and the controls did not differ significantly in age, but the controls were better educated than the AAMI subjects. However, the analysis of variance adjusted for age and education was used to compare the means of neuropsychological data.

In this study, the AAMI subjects had worse performance than controls not only in AAMI- memory tests but also in tests of episodic memory: BSRT, VRI, and VRD, and in a test battery designed to assess executive function: TMT, WCST and ST. 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). The inferior performance of the AAMI subjects as compared with the controls in episodic memory test is not unexpected because impairment is requirement imposed by the AAMI criteria.

It has been postulated that there is at least two distinct dementia syndromes: the dementias that present with (Type 1) and without posterior cortical features (Type 2) (Royall and Polk 1998). Both types can affect memory, language, and or constructional praxis. However, they differ in how these impairments become manifested. Both affect the frontal systems that are responsible for the control of complex behavior. Type 1 dementias also affect posterior cortical regions and can be discriminated from Type 2 dementias on this basis. AD is by far the most common cause of the Type 1 syndrome, and apathy and depression are the most common kinds of Type 2 disorders. Many authors have concluded that AAMI may include a group of patients with early AD. Therefore, we used cluster-analysis based on neuropsychological tests, to observe if there was a subclass with the dysfunction characteristics of posterior cortical involvement in the AAMI group. However, only frontal dysfunction was found in the AAMI group. This might reflect age-associated frontal system pathology. Therefore no different subtypes were found in our AAMI group. On the other hand, we did not use many tests to assess visuospatial abilities which might have altered our conclusion.

The greatest loss of neurons and the largest reduction in brain volume during aging is seen in the frontal lobes (Haugh et al 1983, Coffey et al 1992, Cowell et al 1994). The integration of neuroanatomical and neuropsychological evidence suggest that frontal regions are the last to develop during maturation and, in later life, the first to undergo involution: the ability to store and to reproduce new information generally follows a curvilinear trend with improvements in memory from childhood to early adulthood, and a decline from the twenties to old age (Dempster 1992). In subjects over 50 or 60 years of age, memory problems are frequently observed even in the absence of clinically significant neurodegenerative changes (Light 1991, Moscovitch and Winocur 1992, Burke and Mackay 1997). Such age-associated declarative memory changes have been discussed in relation to reduced attentional and processing resources in more advanced age and in relation to age-related changes in brain areas relevant for memory processing, such as the medial temporal and the frontal lobes (Parkin 1991). 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 the semantic memory.

Our results suggest that an impairment in executive function may influence the performance in declarative memory tasks in the AAMI subjects, and that AAMI simply reflects the variability in cognitive

performance of elderly individuals. On the other hand, the control group in our study was more likely to represent a successsful, rather than a usual aging group.

6.1.3. Magnetic resonence imaging

In this study, there was no hippocampal or amygdaloid damage in the AAMI subjects. In the normal population, the size of certain areas of the brain, such as the hippocampus, may vary considerably between individuals (Watson et al 1992). It is not known how the normal volumetric variation, or the magnitude of pathological damage, is reflected on the functioning of that particular structure. In the present study, when we analyzed the hippocampal and the amygdaloid volumes in the AAMI subjects and the controls, we found that neither the volumes of the right and the left hippocampus nor the volumes of the right and the left amygdala differed between groups. The right hippocampus was larger than the left and the left amygdala was larger than the right one in both study groups. These findings differ from those in the study of Parnetti et al. (1996): they reported that mean volumes of right and left hippocampus were significantly lower in AD and AAMI compared with controls. However, Parnetti et al. studied only six subjects in each of three groups and this should be taken into account in the interpretation of their findings.

A variation of the volume of the hippocampus and the amygdala in controls is considerable in the published studies (Watson et al 1992, Jack et al 1989, Cook et al 1992, Cendes et al 1993). The differences probably are related to slice thickness, slice orientation, software programs used for volumetric calculations, and determination of the boundaries of the structures of interest.

In the present study, the size of the right hippocampus was larger than that of the left hippocampus, which agrees with many (Jack et al 1988, 1989, Cascino et al 1991, Watson et al 1992) but not all earlier studies (Lencz et al 1990, Ashtari et al 1991, Cook et al 1992). In this study the left amygdala was larger than the right, which differs from Watson et al. (1992), who proposed that the right amygdala is larger than the left.

It is not known exactly to what extent neurons, glia, and the associated processes need to be destroyed in a certain structure to be detected by MRI. The volumes of temporal lobe cortical areas, such as the entorhinal, perirhinal, and parahippocampal cortices, might be even more relevant areas to study in AD, especially in the very early phase of the disease (Juottonen et al 1998). In particular, mild dementia and incipient AD has been shown to be associated with profound neuronal loss in the entorhinal cortex (Gometz-Isla et al 1996).

6.1.4. Single photon emission tomography

There were no differences in perfusion ratios between the AAMI and the control subjects. For studying patients with dementia, rCBF SPECT is a convenient method in clinical use, the only discomfort being the i.v. injection of the tracer. The most popular radiopharmaceutical used for this purpose is HM-PAO. Although regional cerebral metabolism and blood flow in AD have been studied extensively with PET and SPECT, few reports describe regional cerebral metabolism and blood flow in aging or AAMI. Holman et al. (1992) determined the predictive value of 99mTc-HM-PAO SPECT for presence of AD based on a prospective study of 132 consecutive patients coming to the nuclear medicine clinical unit for evaluation of their memory loss or cognitive abnormalities. During clinical follow-up averaging 10.1 months, a final diagnosis was established in 113 patients, 52 of whom would suffer AD. The probability was only 19 % that a patient with memory loss and normal perfusion had AD. For abnormal perfusion patterns, the probability of AD was 82% with bilateral temporoparietal defects, 77% with bilateral temporoparietal

defects with additional defects, 57% with unilateral temporoparietal defects, 43% with frontal defects only, 18% with other larger defects and 0% with multiple small cortical defects. They concluded that for SPECT the predictive value of bilateral temporoparietal defects for AD is high, while the perfusion patterns of unilateral temporoparietal perfusion defects or frontal defects alone, which occur in 20% of patients with AD, are not predictive of that disease. They also suggested that SPECT is useful in the diagnostic evaluation of patients with memory and cognitive abnormalities.

In the study of Parnetti and her co-workers (1996), 99m Tc HM-PAO SPECT was performed in healthy older subjects as well as subjects suffering from AAMI and AD. They did not observe any difference between the AAMI and the control group. In the AD group, a statistically significant association between hypoperfusion and degree of cognitive impairment was documented in the temporo-occipital regions. We found no differences in perfusion ratios between the AAMI and the control subjects which is in line with Parnetti's study. Normalization of regional metabolic data to cerebellar values has been considered as being reliable, because cerebellar glucose metabolism is not significantly reduced until AD is severe (Ishii et al 1997). However, it is possible that cerebral blood flow is decreased in all brain areas but regional cerebral metabolism does not change at all.

However, one limitation of PET and SPECT studies in healthy individuals could be intersubject variability on regional glucose metabolic values. A PET study of Wang et al. (1994) showed significant intersubject variability for regional brain metabolic values in normal controls and documented age-related decreases in frontal metabolism that occur even in relatively young adults (40 years of age).

6.1.5. Electroencephalography

In the present study, in the AAMI subjects, fast amplitudes (fast beta and beta) were significantly enhanced in all areas with eyes closed. Slow activity amplitudes (delta and theta) were significantly enhanced in the right frontal area (F4-C4) with eyes closed but the relative amplitudes of delta and theta band were not enhanced. Thus, the overall EEG amplitude in the AAMI subjects was also enhanced which is in line with some earlier studies of normal aging (Breslau et al 1989, Williamson et al 1990, Hartikainen et al 1992, Koyama et al 1997). Several previous studies have reported slight EEG alterations in normal aged individuals. The main changes that have been described are: slowing of the alpha rhythm, appearance of slow-wave activity, and focal theta activity in the left temporal region (Hartikainen et al 1992, Polich 1997). On the other hand, Koyama et al. (1997) found significantly higher relative beta power in elderly subjects compared with younger individuals.

The EEG findings are in agreement with our neuropsychological results suggesting a dysfunction of the frontal, anterior attention system in AAMI. This may reflect only the presence of normal changes of age, which may be more pronouceed in some individuals than others, because the anterior, executive attention system is more sensitive to the effects of increasing age than the posterior, visuospatial attention system (West and Bell 1997).

6.1.6. Event- related potentials

In the AAMI group we observed increased amplitudes and shortened latencies in the auditory ERP components which reflected a detection of a novel stimulus and simultaneous nonspecific, automatic arousal (Vaughan and Ritter 1969). Also, in AAMI the amplitudes of visual P1-N1 following attended visual stimuli were increased whether or not the eliciting stimuli were assigned as relevant.

Latency decreases of auditory N100 have not been previously reported in the elderly. In contrast, latency increases of ERPs have generally been described in conjunction with aging and degenerative disorders (Goodin et al 1978b). The observed latency changes in AAMI may be due to loss or diminishing of a nonspecific arousal component, which emerges slightly later than the modality-specific contribution from auditory cortices (Vaughan and Ritter 1969). On the other hand, attentional enhancement and latency changes of auditory N100 are well documented for tasks involving a conscious attentive effort during dichotic listening (processing negativity at 60—150 ms)(Hillyard et al 1973). In this case, the observed N100 enhancement and latency decrease would thus suggest tonically maintained attention to auditory stimuli and an inability to release underlying attentional processes. Both possible explanations would point to an impairment in the automatic ability to allocate attentional resources.

The behavior of auditory N100 response to novel auditory input reveals properties common to the orienting response (Hillyard et al 1973). The orienting response reflects general arousal, but it is also associated with lowering of the sensory thresholds, and thus it is linked specifically to an attention switch to a new stimulus. In a non-attentive situation, the "habituation" of N100 may thus reflect an arousal to the abrupt onset of a tone after a long silence, a subsequent redirection of attention, and learning (or recalling) of important stimulus features. Thus, the degree of habituation in an experimental set-up such as the present one may reflect a subject's overall state of arousal and the automatic function of distributed attentional networks (Mesulam 1990).

The enhancement of visual P1-N1 amplitude has typically been observed following attended stimuli in studies in which unilateral stimuli have been presented to attentive and unattentive locations in a random order (Eason et al 1969, Harter et al 1982, Mangun and Hillyard 1987, Rugg et al 1987, Luck et al 1990). There seems to be an intense attentional modulation of the visual P1-N1 amplitude with spatial attention enhancing the amplitude. Similar enhancement has been found for validly cued targets in an experiment in which the targets were preceded by a predictive or a non-predictive cue (Anllo-Vento 1995).

In this study, a visual P1-N1 amplitude was much larger among the AAMI subjects compared with the controls. This suggests that the AAMI subjects direct their spatial attention more intensely to the stimuli than the controls. One reason for this may be that they cannot control the sharing of attention resources appropriately, i.e., they allocate more spatial attention for the task than would be actually needed. This explanation is very tempting because it fits with the changes in auditory ERPs and suggests that symptoms in AAMI may reflect problems in the ability to divide attention between several simultaneous stimuli. The observed alterations in ERPs suggest a widespread inability to allocate attention resources effectively. Impairment of these attention mechanisms and the subsequent defective memory trace formation may contribute significantly to those deficits in memory tests which are characteristic to AAMI. On the other hand, there are several brain regions contributing to the generation of ERPs and further research of the basic mechanisms underlying ERP components will be needed.

6.1.7. Apolipoprotein E polymorphism

The ApoE ε4 allele represents a major risk factor for AD in all ethnic groups, across all ages between 40 and 90 years, and in both men and women (Farrer et al 1997), although little data is available on the ApoE ε4 frequencies of subjects with memory complaints. Blesa et al. (1996) determined the ApoE allele frequencies in patients with AD, subjects with memory complaints without dementia (age-related memory decline,ARMD) and controls. Self-appreciation of memory loss was considered as the main characteristic of the ARMD group. Thus, no cutoff of scores in neuropsychological testing was used but they used the

same medical exclusion criteria for ARMD as we did for AAMI. The average age and education was comparable in all their groups. The age was 70.1 years and a schooling of 7.6 years in their ARMD group, which is comparable in our AAMI group. They found an ApoE ε4 allele frequency of 0.315 in the ARMD group, similar to 0.293 in the AD group and in contrast to 0.057 in the control group. In our study the ε4 frequency for the AAMI subjects was 0.24, and 0.15 for controls. The frequency of the ε4 allele in previous studies from the same area as our study, was 0.36 and 0.43 for AD patients and 0.17 and 0.11 for controls (Kuusisto et al 1994, Lehtovirta et al 1995). Thus, the ε4 allele frequency for AAMI subjects was intermediate between those of AD and control subjects.

Petersen et al. (1995) demonstrated that many of the ε4 subjects who were in a memory impaired group of individuals went on to develop AD over a 54-month period. They concluded, that the detected ε4 high frequency in subjects with ARMD, together with the known strong correlation between the presence of ε4 allele in AD, suggest that ApoE could be a marker for the prediction of AD in subjects showing memory impairment but without dementia.

6.2. The influence of Apolipoprotein E genotype in Age-associated memory impairment subjects and control subjects in the cross-sectional study

In the present cross-sectional study, the ε4 carriers did not have impairments in neuropsychological testing or on the measurements of the MRI volumetry. These neuropsychological findings are in line with the study of Helkala and her co-workers (1996). She did not find any significant differences between ε4 carriers and non-carriers at a baseline examination when the mean age (72 years) and education of subjects were about the same as in our study. However, ε4 carriers deteriorated more rapidly compared with non-carriers during the 3-year follow-up.

In the present study, in the 99mTc-HM-PAO SPECT mean activity of the right and left prefrontal ROIs were significantly lower among ε4 carriers compared with non-carriers in the control group. So, the minor, perhaps not biologically significant, changes were seen in additional prefrontal regions, which may be preferentially affected during normal aging. Reiman et al. (1996) performed PET in 11 subjects homozygous for the ε4 and 22 controls without the ε4 allele. They all were cognitively normal for the 50-65 years of their age, also their level of education was the same and they reported a family history of AD. The ε4 homozygotes had significantly reduced rates of glucose metabolism in the posterior cingulate, parietal, temporal, and prefrontal regions as did their previously studied patients with probable AD. This is different from Higuchi et al. (1997), who demonstrated that the frontal glucose metabolism was significantly increased in patients with AD carrying the ApoE ε4 allele in a dose-dependent fashion. However, in the temporo-parietal regions, reduced rates of glucose metabolism were obtained as in Reiman's study.

In this study only minor electrophysiological changes were observed. The influence of the ApoE ε4 allele on neurophysiological parameters were similar as the influence of aging in some previous studies (Katz and Horowitz 1982, Duffy et al 1984, Breslau 1989, Hartikainen et al 1992). The relative delta amplitude was diminished in the ε4 carriers compared with non-carriers. This might be due to the fact that the mean frequency was higher in the same areas as well as the relative beta amplitude. Therefore, the overall EEG amplitude in the ε4 carriers with their eyes closed was enhanced. In ERP parameters, auditory N 100 habituation was impaired in the ε4 carriers in a similar way as in the whole AAMI group.It is still not known whether or not genetic heterogeneity of ApoE can influence the findings of some functional laboratory tests, such as QEEG or ERPs in patients with AD or normal elderly individuals. It has been reported that there was a tendency to more pronounced EEG slowing in AD patients carrying the ε4 allele

(Lehtovirta et al 1995). On the other hand, Jelic et al. (1997) concluded that the ApoE ε4 allele does not influence EEG slowing at all.

A role for genetic factors as modificators of cognition in aging has been suggested (Finkel and McGue 1993, Helkala et al 1996). AD patients carrying the ε4 allele differ from those AD patients without the allele in that, ε4 carriers have an earlier age of onset, a more pronounced cholinergic deficit, a more extensive hippocampal atrophy and a more severe impairment in tests assessing delayed recall (Soininen and Riekkinen 1996). Some of the changes may readily be encountered in elderly subjects carrying the ε4 allele. These include at least lower performance in some cognitive domains (Reed et al 1994, Helkala et al 1995, Soininen and Riekkinen 1996), abnormalities in glucose metabolism as seen by PET (Small et al 1995, Reiman et al 1996) and minor changes in the volumes of the hippocampus (Soininen et al 1995b, Plassman et al 1997).

A Dutch study showed that the ApoE ε4 allele is associated with cognitive decline in a general population (Feskens et al 1994). The report of Blesa et al. (1996) described an increased ε4 frequency in age-related memory decline (ARMD) subjects and they suggested that ApoE could be a marker for the prediction of AD in subjects with memory impairment but without dementia. ARMD share some of the AAMI criteria but there is no age restriction nor is there any cutoff score for neuropsychological testing used to exclude subjects from this group.

6.3. A Follow-up study

Study 1. In our follow-up study, none of the AAMI subjects showed signs of dementia at the follow-up examination. However, the AAMI subjects did show a decline of scores in the BSRT which is sensitive to episodic memory whereas the control subjects did not show any such deterioration, although hippocampal atrophy occurred in a similar rate.

Earlier studies have evaluated the clinical course of AAMI or other closely related conditions. Most of them have found no evidence of accelerated cognitive deterioration associated with these conditions (Kral 1962, Reisberg et al 1988, Flicker et al 1993, 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. In some studies the mild cognitive impairment determined by the clinical evaluation and neuropsychological tests seem to be useful in predicting dementia from two to three years before the condition became clinically manifest (Flicker et al 1991, Bickel and Cooper 1994).

In the follow-up study, the AAMI subjects had a significantly higher frequency of the ApoE ε4 allele than the AAMI subjects in the cross-sectional study. However, that was not the case in the control subjects. Therefore, this high ε4 allele frequency may contribute to the decline of scores in the test that is sensitive to episodic memory among the AAMI subjects.

Study 2. Due to a small number of the study subjects in the follow-up, the AAMI and the control subjects could not be divided into two groups according their ApoE genotype. For this reason, the whole study population was then divided into two groups according to the subjects' ApoE ε4 status. In the ε4 carriers the rate of memory decline was greater than in the non-carriers. In agreement with this data, Bondi and coworkers (1995) also showed that episodic memory changes were associated with the ApoE ε4 allele in older adults without dementia. In a population based study of elderly individuals without dementia, the only difference in cognitive functions was seen in those tests which assessed delayed recall; the ε4 allele had an

adverse effect on memory scores whereas ε2 carriers maintained their memory functions in a 3-year follow-up (Helkala et al 1996).

The hippocampal volumes significantly decreased in both groups. It is noteworthy that the right hippocampal volumes were smaller and the left hippocampi were greater in the ε4+ subjects than in the ε4- subjects. Accordingly, another study showed that in AD patients, the effect of the ApoE ε4 allele is stronger in the volume decline of the right hippocampus (Lehtovirta et al 1995). Interestingly, a 42-month study with annual MRI volumetry in 30 elderly subjects without dementia by Kaye and coworkers (1997) suggested that the hippocampal volumes declined both in those who remained nondemented and those who were in the preclinical stage of AD. On the other hand, there are several previous volumetric MRI studies that have reported that the size of the hippocampus may remain unaffected by normal aging (Bhatia et al 1993, DeCarli et al 1994, Sullivan et al 1995, Jack et al 1997)

The ApoE ε4 allele is a definite risk factor of AD, but its exact role in the development of AD remains to be resolved. With respect to memory functions, the associations between ApoE ε4 and impaired plastic response (Arend et al 1997) and severe cholinergic depletion (Kay 1991) are of major interest. So far, none of the subjects in our series have progressed to fulfill the criteria of dementia. Previous studies (Feskens et al 1994, Petersen et al 1995) have shown that the presence of the ε4 allele is a strong predictor of AD in subjects suffering from memory impairment. We found the rate of memory decline to be greater in the ε4 group when this was measured with a verbal memory test, BSRT, but not with a visual memory test, VRT. The selective reminding method used in the BSRT requires more elaborate processing of information than the more simple procedure used in the VRT. Therefore, the BSRT focusses more on the executive functions, which also have been shown to deteriorate early in the development of AD (Albert 1996, Patterson et al 1996). Accordingly, an inferior performance in the verbal list learning task has also been found to be one of the most sensitive predictors of dementia (Flicker et al 1991, 1993, Masur et al 1994, Jacobs et al 1995, Hänninen et al 1995). Therefore, the decline in the BSRT may precede the more profound cognitive decline in the subjects of ε4 group although they have not yetprogressed to dementia. In conclusion, in ApoE ε4 carriers episodic memory decline was greater than in non-carriers but hippocampal atrophy occurred in a similar rate.

6.4. AAMI in the continuum from normal aging to dementia

Our results suggest that AAMI subjects are for the most part reflecting the aging effects, whereas subjects with cognitive performance superior to AAMI might reflect “successful” aging. AAMI is a heterogeneous category that includes some subjects who indeed are at risk of developing dementia. To be more precise, it seems that the presence of the ApoE ε4 allele is more common in AAMI subjects in comparison with control subjects. Therefore, the criteria for AAMI might select more ε4 carriers than non-carriers among elderly individuals, which means that actually the presence of the ε4 allele is a risk factor for AD not AAMI itself. Furthermore, the use of a longer follow-up time than possible in the present study, especially for AAMI ε4 carriers, might cast further light on the matter. Consequently, the usefulness of the entire construct of AAMI remains more or less ambiguous, perhaps AAMI might not have any real value for detecting early preclinical dementia.

7. CONCLUSIONS

1. The AAMI neuropsychological and neurophysiological findings pointed to impairments in attentional processes, dysfunction of the frontal, executive attention system, and the subsequent effect of this on the memory function may have contributed significantly to the memory deficits which are characteristic to AAMI.

2. There were no significant differences between the AAMI and control groups in the volumes of hippocampus and amygdala, or regional cerebral metabolism as measured by SPECT.

3. The follow-up of the AAMI subjects suggested that AAMI, in general, is nonprogressive but the criteria for AAMI might select more ε4 carriers than non-carriers among elderly individuals.

4. In the ε4 carriers, the rate of memory decline was greater than in the non-carriers although hippocampal atrophy occurred at a similar rate.

In this study, the AAMI diagnosis appears to identify a very heterogeneous group of subjects and does not, by itself, predict the presence of incipient dementia. The ε4 carriers form one risk group for progressive memory decline among the elderly. In addition to the genetic (ApoE) testing, the results underscore the urgent need to develop new sensitive diagnostic tests which would be positive during the presymptomatic and very mild stages of AD.

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