CRITICAL REVIEW

Neuropsychological and neuroimaging changes in preclinical Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is a common, devastating form of dementia. With the advent of promising symptomatic treatment, the importance of recognizing AD at its very earliest stages has increased. We review the extant neuropsychological and neuroimaging literature on preclinical AD, focusing on longitudinal studies of initially nondemented individuals and cross-sectional investigations comparing at-risk with normal individuals. We systematically reviewed 91 studies of neuropsychological functioning, structural neuroimaging, or functional neuroimaging in preclinical AD. The neuropsychological studies indicated that preclinical AD might be characterized by subtle deficits in a broad range of neuropsychological domains, particularly in attention, learning and memory, executive functioning, processing speed, and language. Recent findings from neuroimaging research suggest that volume loss and cerebral blood flow or metabolic changes, particularly in the temporal lobe, may be detected before the onset of dementia. There exist several markers of a preclinical period of AD, in which specific cognitive and biochemical changes precede the clinical manifestations. The preclinical indicators of AD reflect early compromise of generalized brain integrity and temporal lobe functioning in particular. (*JINS*, 2006, *12*, 707–735.)

Keywords: Dementia, Neuropsychology, Magnetic resonance imaging, Positron emission tomography, Cognition disorders, Memory disorders

INTRODUCTION

The neuropathologic changes of Alzheimer's disease (AD) begin well before the disease becomes clinically apparent. The brain may compensate for such changes until cognitive decline becomes obvious and disrupts daily functioning, and the clinical diagnosis of AD can be made. However, cognitive signs and brain changes are subtly present prior to clinical diagnosis, thus denoting a "preclinical" stage of AD in which affected individuals exhibit only very mild changes in cognition despite an ongoing disease process. This stage gradually progresses to mild cognitive impairment (MCI; Petersen et al., 2001), characterized by mild but detectable cognitive impairment, and then to the more severe and clinically apparent stages of AD.

Much research into new AD treatments has focused on slowing or halting the disease process, rather than reversing its neuropathology. Many patients with MCI already exhibit substantial neuropathologic signs of AD (Price & Morris, 1999), illustrating the need to identify the preclinical stages of AD so that treatment can begin promptly. Identifying preclinical disease markers would improve characterization of predisposing factors for AD, promote our understanding of disease course, and improve our ability to assess treatment response without waiting for evidence of significant cognitive or functional declines.

Better recognition of preclinical markers of AD could have profound social and financial effects. Early detection could help reduce the cost of Alzheimer's care ($100 billion per year in the United States; DeKosky & Orgogozo, 2001); an intervention delaying AD onset by two years would result in nearly two million fewer cases 50 years from now (Brookmeyer et al., 1998). Additionally, early and accurate diagnosis will aid patients and families in healthcare decision-making.

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We reviewed the current literature on neuropsychological and neuroimaging changes that may reflect preclinical AD. In doing so, we distinguished between "preclinical AD" and "MCI," typically defined as mild memory impairment without other cognitive or functional deficits (Petersen et al., 2001). In contrast, preclinical AD is conceptualized as a stage featuring subtle cognitive declines (not necessarily impairments, however, and not necessarily in the domain of memory) and no perceptible declines in daily functioning. Another distinction exists on autopsy, at which those with MCI may exhibit substantial AD pathology, whereas preclinical AD patients may exhibit only minor changes (Price & Morris, 1999). Detecting AD in its preclinical stage, before the development of MCI, is crucial, particularly given that the conversion rate from MCI to AD within two years is up to 30% (Petersen et al., 2001). In a recent meta-analysis, Bäckman et al. (2005) found that neuropsychological tests of global cognition, delayed recall, perceptual speed, and executive functioning best discriminated subjects who developed AD from those who remained well. However, of the 47 studies included in their meta-analysis, 27 investigated cognition in MCI, cognitively impaired, or memory clinic samples, thereby making memory measures the most likely to emerge as predictors of future AD. The current review excluded studies of subjects with MCI or memory complaints in favor of a more pure focus on preclinical AD. We present a model of accelerated, nonlinear cognitive decline in the preclinical period and provide evidence that helps reconcile the heterogeneity in AD presentation.

As a backdrop to our focus on preclinical AD, we first review briefly the neuropathology of AD and the diagnostic criteria for the disease. Study designs and the rationale for using at-risk samples in this research are outlined. A comprehensive review of the current neuropsychological and neuroimaging research follows. Finally, the empirical evidence is put into a clinical context, gaps in our understanding are presented, and the potential impact of research on preclinical AD is discussed.

Neuropathologic and Diagnostic Criteria for AD

AD is a progressive degenerative disease characterized by neocortical atrophy, neuron and synapse loss, neuritic plaques, and neurofibrillary tangles (Alzheimer, 1907; Terry et al., 1991). These neuropathologic changes occur primarily in the hippocampus and entorhinal cortex, with later changes occurring in frontal, temporal, and parietal association cortices (Braak & Braak, 1991; Hyman et al., 1984). Eventually, the limbic regions and neocortex are affected (Bobinski et al., 1999; Xu et al., 2000). Additionally, subcortical neuron loss in the nucleus basalis of Meynert and locus coeruleus results in decreased levels of cholinergic and noradrenergic markers, respectively (Bondareff et al., 1982).

Clinically, AD is characterized by profound global dementia, with severe amnesia and additional deficits in other cognitive domains, such as language, executive functions, attention, and visuospatial/constructional abilities (American Psychiatric Association, 1994; Salmon & Bondi, 1999). The current DSM-IV criteria (American Psychiatric Association, 1994) include: (a) Memory impairment and at least one additional cognitive impairment; (b) Impaired functioning and functional decline; (c) Gradual onset and continuing cognitive decline; (d) Cognitive deficits not due to other causes. The criteria for AD suggest that cognitive deficits, structural volume loss, or functional brain changes appear gradually and thus might be identified before the neural degeneration produces clinically diagnosable dementia.

Study Designs

The prototypic longitudinal case-control research design used to identify potential preclinical markers of AD involves a baseline assessment of a large cohort of normal older adults and periodic follow-up evaluations (Collie & Maruff, 2000). Then, individuals who later develop AD are compared with those who remain nondemented on the presence and magnitude of cognitive declines, structural changes, and/or functional imaging changes. Retrospective studies of nondemented individuals who came to autopsy have also been published, comparing neuropsychological profiles of individuals with and without AD pathology.

Studying individuals at high risk for AD has been a common approach to research on preclinical indicators of the disease. Early studies recruited individuals at risk for AD due to family history (e.g., Hom et al., 1994), whereas more recent studies have focused on older adults with genetic susceptibilities such as the presence of an apolipoprotein E (APOE) ϵ4 allele (Corder et al., 1993). Such studies have used both cross-sectional designs and longitudinal evaluations to examine cognitive decline or neuroimaging changes. To provide a backdrop for our review of longitudinal and cross-sectional studies of preclinical AD, we briefly discuss the established risk factors for AD next.

Risk Factors for AD

Advancing age is the single most important risk factor for AD (Kawas & Katzman, 1999), with exponential increases in AD prevalence in individuals between 65 and 85. Epidemiologic studies of people over age 85, the fastest growing segment of our population (U.S. Census Bureau, 2004), show that the incidence of AD does not plateau, as was previously speculated, but continues to rise in this advanced age group, with 25–50% of this cohort developing the disease (Kawas & Katzman, 1999; Rocca et al., 1998).

In addition to age, certain genetic mutations have been implicated in the pathogenesis of AD. Early-onset AD is associated with defects on chromosome 21, particularly a mutation of the amyloid precursor protein (APP) gene, chromosome 1, and chromosome 14, both due to mutations in the presenilin-2 and presenilin-1 genes (Kawas & Katzman, 1999). Together, these known genetic mutations account

for only about 2% of all cases of early-onset AD (Pericak-Vance et al., 2000).

The vast majority of people who develop AD do so after age 65, and the APOE gene on chromosome 19 has been identified as a susceptibility gene for both familial and sporadic late-onset AD (Corder et al., 1993). APOE is a protein influencing cholesterol transport in the blood and appears to be related to the deposition of amyloid and/or the formation of neurofibrillary tangles in the brain. The three different alleles (ϵ2, ϵ3, and ϵ4) yield different disease risks, with the ϵ4 allele conferring the greatest risk. APOE ϵ4 is present in up to 50% to 60% of AD patients, compared to only 16% of nondemented individuals. The risk of developing AD is three to four times higher for individuals with one copy of the ϵ4 allele, and approximately ten-fold in those with two copies of ϵ4 (Corder et al., 1993). Although APOE genotyping cannot be used alone as a diagnostic test for AD, it significantly improves diagnostic specificity when used in combination with clinical criteria (Mayeux et al., 1998). In a recent meta-analysis, Small et al. (2004) found significant differences between nondemented APOE ϵ4 carriers and noncarriers in global cognition, episodic memory, and executive functioning.

Numerous environmental, medical, and social factors have also been suggested as putative risk factors for AD, including head injury, hypertension, hypotension, toxin exposure, and low education. Some of these risk factors may interact with each other, and some may contribute to an individual's "cognitive reserve" or brain reserve capacity that buffers one against the cognitive effects of neurodegeneration (Kawas & Katzman, 1999).

METHOD

The literature providing a basis for this review was obtained by searching the Medline and PsycInfo databases for English-language articles containing the key terms "preclinical" and "Alzheimer." Other terms entered into the search included "neuropsychologic," "neuropsychological," and "neuroimaging." All articles up to April 2005 were included. Relevant papers from the reference lists of identified articles were also reviewed. Only studies that promoted knowledge on how to screen and diagnose AD using noninvasive, *in vivo* methods were included. Given our focus on *ante mortem* indicators, we excluded retrospective autopsy studies aimed at identifying biomarkers of AD after death. Family pedigree studies were only included if subjects were compared to normal control groups or genetically unaffected relatives. Given our specific focus on identifying AD before the manifestation of any clinical symptoms, we included only cross-sectional or prospective studies of nondemented, cognitively normal individuals; whereas studies of age-associated memory impairment (AAMI), MCI, questionable AD, or memory clinic populations were excluded. We also excluded investigations that focused solely on evoked potentials, event-related potentials, or olfactory testing, due to the relative paucity of research in these areas. Seventy-three neuropsychological studies, eleven structural neuro-imaging studies, and seven functional neuroimaging studies were included in the present review. Comprehensive tables of relevant research were constructed (see the Appendices). When articles presented both neuropsychological and neuroimaging results, they were listed in both tables; cross-sectional and longitudinal results from the same study were listed in those respective sections of the tables. We then summarized the results across studies in Table 1.

RESULTS

Neuropsychological Changes in Preclinical AD

Compared with older adults who remain nondemented, those who later develop AD perform more poorly across a broad range of neuropsychological measures. Appendix 1, presents summaries of 73 studies of neuropsychological changes in the preclinical period. There were 30 longitudinal case-control studies (Appendix 1, part A); 16 longitudinal studies examining decline in APOE ϵ4+ and ϵ4− subjects (Appendix 1, part B); 26 cross-sectional studies comparing neuropsychological performance in subjects with and without the APOE ϵ4 allele (Appendix 1, part C); 3 retrospective studies using autopsy data (Appendix 1, part D); and 4 studies comparing neuropsychological performance in subjects with and without a family history of AD (Appendix 1, part E).

The domains most consistently associated with preclinical AD were attention (71% of studies in which it was assessed), verbal learning and memory (57% and 50%, respectively), executive functioning (44%), processing speed (43%), and language (33%), with studies showing either early declines in these abilities or significant differences between at-risk subjects and control subjects (see Table 1). Global measures of cognition (e.g., the Mini-Mental State Examination) were less consistently associated with preclinical AD (38% of studies). Although not the focus of the current review, there was one study (Schiffman et al., 2002) that included olfactory processing as part of a comprehensive neuropsychological battery; this and other studies (e.g., Murphy et al., 1998) have shown that olfactory impairment may be an important preclinical indicator.

The current review revealed that attention, although not as commonly assessed as learning and memory in studies of preclinical AD, is even more consistently associated with the later development of AD. Only 10% of the longitudinal case-control studies measured attention, but of those, 100% found that attention performance discriminated cases from controls. Furthermore, verbal learning was a somewhat more consistent indicator of preclinical AD than was verbal delayed recall; these findings suggest that the deficits in verbal delayed recall in preclinical AD may partly reflect poor attention and encoding.

Episodic memory decline is one of the earliest and most prominent features of preclinical AD (Bondi et al., 1995,

Table 1. Summary of neuropsychological and neuroimaging results across studies

(A) Neuropsychological studies

	All comparisons (n = 79)	Longitudinal AD+/AD− (n = 30)		Longitudinal decline ε4+/ε4− (n = 16)		Neuropsychological ε4+/ε4− (n = 26)		Autopsy AD+/AD− (n = 3)		Neuropsychological FH+/FH− (n = 4)	
	Percent of studies significant	Number of studies assessing	Number of studies significant	Number of studies assessing	Number of studies significant	Number of studies assessing	Number of studies significant	Number of studies assessing	Number of studies significant	Number of studies assessing	Number of studies significant
General cognitive	38%	23	14 (61%)	12	5 (42%)	19	3 (16%)	3	0 (0%)	4	1 (25%)
Attention	71%	3	3 (100%)	0	0 (0%)	3	1 (33%)	0	0 (0%)	1	1 (100%)
Processing speed	43%	8	6 (75%)	4	2 (50%)	11	3 (27%)	3	0 (0%)	2	1 (50%)
Verbal learning	57%	21	19 (90%)	10	4 (40%)	18	5 (28%)	3	1 (33%)	4	3 (75%)
Verbal memory	50%	15	13 (87%)	11	5 (45%)	17	5 (29%)	3	1 (33%)	4	1 (25%)
Visual learning	29%	13	8 (62%)	4	0 (0%)	11	2 (18%)	3	0 (0%)	3	0 (0%)
Visual memory	28%	6	1 (17%)	6	3 (50%)	11	3 (27%)	0	0 (0%)	2	0 (0%)
Working memory	12%	9	0 (0%)	3	1 (33%)	11	2 (18%)	1	0 (0%)	2	0 (0%)
Language	33%	16	13 (81%)	9	2 (22%)	13	0 (0%)	3	0 (0%)	4	0 (0%)
Motor speed	17%	3	0 (0%)	0	0 (0%)	2	1 (50%)	0	0 (0%)	1	0 (0%)
Executive functioning	44%	13	9 (69%)	7	3 (43%)	11	4 (36%)	2	0 (0%)	3	0 (0%)
Visuospatial	26%	12	5 (42%)	7	2 (29%)	8	1 (13%)	2	0 (0%)	2	0 (0%)
Praxis	17%	3	1 (33%)	1	0 (0%)	1	0 (0%)	1	0 (0%)	0	0 (0%)
Olfactory	100%	0	0 (0%)	0	0 (0%)	0	0 (0%)	0	0 (0%)	1	1 (100%)

(B) Neuroimaging studies

	All comparisons (n = 18)	Longitudinal MRI AD+/AD− (n = 3)		Longitudinal MRI E4+/E4− (n = 1)		Longitudinal PET E4+/E4− (n = 1)		Cross-sectional MRI E4+/E4− (n = 7)		Cross-sectional fMRI/PET E4+/E4− or FH+/FH− (n = 6)	
	Percent of studies significant	Number of studies assessing	Number of studies significant	Number of studies assessing	Number of studies significant	Number of studies assessing	Number of studies significant	Number of studies assessing	Number of studies significant	Number of studies assessing	Number of studies significant
Whole brain	27%	2	1 (50%)	0	0 (0%)	1	0 (0%)	2	1 (50%)	6	1 (17%)
Frontal lobe	40%	1	0 (0%)	0	0 (0%)	1	1 (100%)	2	0 (0%)	6	3 (50%)
Temporal lobe	64%	2	2 (100%)	0	0 (0%)	1	1 (100%)	2	0 (0%)	6	4 (67%)
Parietal lobe	45%	2	1 (50%)	0	0 (0%)	1	0 (0%)	2	0 (0%)	6	4 (67%)
Hippocampus	39%	3	2 (67%)	1	1 (100%)	1	0 (0%)	7	3 (43%)	6	1 (17%)
Amygdala	9%	1	0 (0%)	0	0 (0%)	1	0 (0%)	3	1 (33%)	6	0 (0%)
Parahippocampal g.	9%	2	0 (0%)	0	0 (0%)	1	1 (100%)	2	0 (0%)	6	0 (0%)
Posterior cingulate	36%	2	1 (50%)	0	0 (0%)	1	1 (100%)	2	0 (0%)	6	2 (33%)
Thalamus	0%	1	0 (0%)	0	0 (0%)	1	0 (0%)	2	0 (0%)	6	0 (0%)
Basal forebrain	10%	1	0 (0%)	0	0 (0%)	1	1 (100%)	2	0 (0%)	6	0 (0%)

1999; Linn et al., 1995). Subtle declines in episodic memory often occur several years before the emergence of the obvious cognitive and behavioral changes required for a clinical diagnosis of AD (Albert et al., 2001; Bäckman et al., 2001; Bondi et al., 1994, 1999; Chen et al., 2000, 2001; Fox et al., 1998; Grober & Kawas, 1997; Howieson et al., 1997; Jacobs et al., 1995; Lange et al., 2002; Masur et al., 1994). It is thought that episodic memory tasks are strong predictors of future AD, because the brain structures subserving episodic memory, such as the medial temporal lobes and the hippocampal formation (Squire, 1992), are among the first affected.

Some studies suggest that, compared to those who remain nondemented, individuals who later develop AD exhibit lower baseline levels of cognitive functioning. Fox and colleagues (1998), for example, tested asymptomatic at-risk members of early-onset familial AD pedigrees over a six-year period. Those who developed AD had demonstrated normal, but significantly lower verbal memory and performance IQ scores at their initial assessment (when they were ostensibly unaffected) compared to the group that remained nondemented. Similarly, Elias and colleagues (2000), in a 22-year prospective study of the Framingham cohort, found that only abstract reasoning (Similarities) and verbal retention performance predicted AD in subjects who were dementia-free for at least ten years after baseline neuropsychological assessment.

Lower baseline functioning among APOE $\epsilon 4$ carriers could represent either a preclinical stage of AD or simply a genetic phenotype for poorer cognition. One study suggested that the $\epsilon 4$ allele is associated with low normal cognitive performance (Berr et al., 1996). However, a later study found that $\epsilon 4$ and non-$\epsilon 4$ subjects' CVLT profiles did not differ once incident AD cases were excluded from the analyses (Bondi et al., 1999). Thus, it seems unlikely that allelic group differences represent evidence for a cognitive phenotype of the APOE gene (Reed et al., 1994). Instead, it appears that more $\epsilon 4$ individuals were demonstrating subtle memory decrements indicative of preclinical AD (see also Small et al., 1998 and Smith et al., 1998).

Although few studies have systematically examined the course of episodic memory changes during the preclinical phase (Bäckman et al., 2001; Chen et al., 2001; Lange et al., 2002; Rubin et al., 1998), summarizing and combining their findings may have important implications for detecting AD preclinically and projecting the course of decline. In two studies that have examined memory changes over time, Small et al. (2000a) and Bäckman et al. (2001) measured changes in episodic memory in individuals who eventually developed probable AD. Both studies found that the subjects who had mild episodic memory declines six years prior to diagnosis showed little memory change in the following three years, but exhibited precipitous declines just prior to the development of AD. Similarly, Chen et al. (2001) found a significant decline in episodic memory and executive functioning in individuals with preclinical AD during the 3.5 to 1.5 years before diagnosis, and Lange et al. (2002) found abrupt declines in episodic memory one to two years before AD onset.

The APOE $\epsilon 4$ genotype may hasten the decline in episodic memory that occurs prior to the emergence of diagnosable AD (Bondi et al., 1995, 1999; Reed et al., 1994). In the studies we reviewed, those comparing APOE genotype groups found that the $\epsilon 4$ allele is associated with both verbal and visual learning and memory. Caselli and colleagues (1999) compared performances of $\epsilon 4$ homozygotes, $\epsilon 4$ heterozygotes (all $\epsilon 3/\epsilon 4$), and non-$\epsilon 4$ carriers on various neuropsychological measures and found that older subjects in the $\epsilon 4$ homozygote group performed worse on immediate and delayed recall tasks. Baxter et al. (2003) also found that verbal learning ability declined over two years in a group of cognitively normal individuals who had the $\epsilon 4$ allele, but only in those who were 60 years of age or older. Thus, age-related memory decline seems to occur earlier in cognitively normal $\epsilon 4$ homozygotes than in $\epsilon 4$ heterozygotes and noncarriers, and precedes clinically detectable AD.

Neuroimaging Changes in Preclinical AD

Although no routine diagnostic test confirms the presence of AD, imaging techniques are an adjunctive screening measure for undetected pathology (Knopman et al., 2001) and represent an important expanding field in biological neuropsychiatry. Structural imaging techniques can detect early volumetric changes predictive of dementia, and functional imaging can detect preclinical changes in cerebral blood flow, metabolic activity, and neurotransmitter and receptor function. Appendix 2 presents summaries of 18 studies of neuroimaging changes in the preclinical period. There were three longitudinal case-control studies (Appendix 2, part A); one longitudinal magnetic resonance imaging (MRI) study that examined decline in APOE $\epsilon 4+$ and $\epsilon 4-$ subjects (Appendix 2, part B); one longitudinal PET study that examined decline in APOE $\epsilon 4+$ and $\epsilon 4-$ subjects (Appendix 2, part C); seven cross-sectional studies comparing structural MRI data in subjects with and without the APOE $\epsilon 4$ allele (Appendix 2, part D); and six studies comparing functional imaging data in at-risk versus not-at-risk subjects (Appendix 2, part E).

Of the eleven structural imaging studies and seven functional imaging studies we reviewed (see Appendix 2), most hypothesized that, given the histopathology of AD and the cognitive hallmark of AD (rapid forgetting), changes in temporal and hippocampal functioning would be among the earliest indicators of AD. Indeed, temporal lobe changes were the most common finding in preclinical AD, with 64% of studies measuring temporal lobe changes finding significant differences; changes in the parietal lobe (45% of studies), frontal lobe (40% of studies), hippocampus (39% of studies), and posterior cingulate (36% of studies) were also identified (see Table 1). Global brain changes were not as consistently associated with preclinical AD (27% of studies). We review these studies further in the two following sections on structural and functional brain imaging.

Structural Brain Imaging

Autopsy studies reveal that neurofibrillary changes in incident AD cases occur initially in the transentorhinal and entorhinal cortex, then in the hippocampal formation, and later in the neocortical structures (Braak & Braak, 1995). Amyloid plaque deposition may occur early in other cortical structures (e.g., anterior cortical regions; Morris et al., 1996). MRI can measure volumes of specific brain structures and can thereby distinguish normally aging subjects from potential AD patients even in the earliest stages of the disease. MRI studies reveal that portions of the medial temporal lobe (MTL), particularly the entorhinal cortex and hippocampus, are initially affected in AD.

Studies of the relationship between morphological and cognitive measures of AD have demonstrated that atrophy of the MTL region, especially the hippocampus, correlates with episodic memory impairment in AD (de Leon et al., 1997). Other cognitive abilities are affected as the neuropathologic changes of AD spread from limbic structures to neocortical association areas (Braak et al., 1998). The longitudinal MRI studies reviewed in Appendix 2, part A, uniformly found that MTL volume loss was detectable in preclinical AD cases and that the rate of volume loss also predicted future AD. A similar pattern implicating hippocampal volume loss emerged when APOE status was investigated longitudinally (Cohen et al., 2001).

Controversy exists as to whether greater MTL volume reduction among APOE ϵ4 carriers reflects preclinical AD or a structural phenotype. Some studies have shown an ϵ4 effect on MTL volumes (den Heijer et al., 2002; Plassman et al., 1997; Tohgi et al., 1997), but others have not (Jernigan et al., 2001; Schmidt et al., 1996). Cohen et al. (2001), however, showed that ϵ4 carriers demonstrated greater hippocampal volume loss over time than did noncarriers, suggesting that the cross-sectional differences between groups may reflect a preclinical AD state.

Functional Brain Imaging

Positron emission tomography

Positron emission tomography (PET) studies of AD patients reveal hypometabolism in the neocortical structures, mainly the parietal, frontal, and posterior temporal association cortices, the same areas where neuronal and synaptic degeneration appear most severe in post-mortem AD brains. Later, more advanced stages of AD are denoted by functional brain changes across the neocortex, with relative preservation of the sensorimotor and visual cortices.

Many of the PET studies in this area have compared APOE ϵ4 carriers with noncarriers. In the first PET study of this kind, Kennedy and colleagues (1995) found that ϵ4 carriers had lower global and temporoparietal glucose metabolism than did noncarriers. Reiman and colleagues (1996), who compared cognitively normal, middle-aged ϵ4 homozygotes and matched non-ϵ4 control participants, found that

the ϵ4 homozygotes had reduced glucose metabolism in the posterior cingulate, parietal, temporal, and prefrontal regions, all of which were regions demonstrating specific metabolic reductions in mild AD. In a later study, Reiman et al. (2004) found that these same abnormalities existed in even younger (20–39 years old) ϵ4 carriers.

Functional magnetic resonance imaging

Functional MRI (fMRI) studies have generally shown decreased hippocampal activation in elderly subjects with memory decline relative to normal control groups. In one of the first studies to use fMRI to explore preclinical brain changes, Smith and colleagues (1999) examined cortical activation in two groups of cognitively normal middle-aged women who differed only in terms of their AD risk (i.e., family history of AD and APOE status). The groups performed equally well on visual naming and letter fluency tasks during scanning, but their activation patterns during both tasks differed, with the high-risk group demonstrating lower activations in the bilateral mid- and posterior inferotemporal regions.

Other researchers, however, have found increased activation associated with incipient AD. Bookheimer and colleagues (2000) found that during a word recall task, nondemented ϵ4 carriers had greater activation than did noncarriers in the left prefrontal region and bilateral orbitofrontal, superior temporal, and inferior and superior parietal regions. These abnormal patterns of activation may represent a compensatory functional response, that is, the use of additional brain resources to perform the task. The increased activations in the ϵ4 carriers were specific to episodic encoding, and were not seen in attentional tasks studied by the same group (Burggren et al., 2002).

Such studies suggest that compensatory mechanisms in brain activity exist in preclinical AD, before the manifestation of frank cognitive and functional impairments (Becker et al., 1996). Several functional neuroimaging studies have shown that the brain activity associated with performance on memory tasks is more diffuse in patients with early AD than in normal older individuals, probably because of the need to recruit additional brain resources to maintain performance. It may be that after an initial decline in memory following damage to MTL structures, patients in the preclinical stage of AD are able to recruit enough compensatory brain resources to slow further memory decline for a period of time. As the disease progresses, however, these additional resources become compromised and rapid episodic memory decline ensues (Lange et al., 2002).

It could be argued that functional neuroimaging methods will be more sensitive to early MTL dysfunction than will structural MRI (Haxby et al., 1986). However, PET studies of at-risk older adults or patients with early AD have not typically demonstrated MTL metabolic changes (Reiman et al., 1996; Small et al., 1995), findings that differ from those derived from structural neuroimaging and neuropathologic studies that demonstrate that the earliest changes in

AD occur in MTL regions (Braak & Braak, 1991). Furthermore, studies of brain changes using PET have not unequivocally demonstrated the characteristic temporal-parietal hypoperfusion or hypometabolism in all cases of early AD (Azari et al., 1993).

DISCUSSION

This literature review reveals that a preclinical phase of detectable cognitive decline and structural and functional brain changes precedes the clinical diagnosis of AD by several years or more. Declines in attention, episodic memory, atrophy in medial temporal lobe structures, and/or hypoperfusion in temporoparietal areas appear to be the most common markers of preclinical AD. In contrast to other reviews focusing solely or partially on MCI subjects (Bäckman et al., 2005; Wolf et al., 2003), we found relatively greater evidence for deficits in attention and more evidence for early differences in parietal and posterior cingulate volumes. Bäckman and colleagues' (2005) review found the largest effect for global cognitive measures [e.g., the Mini-Mental State Examination (MMSE) or the Dementia Rating Scale (DRS)], also reported that the effect size confidence intervals overlapped for the domains of episodic memory, executive functioning, and perceptual speed, and found moderate effect sizes for attention tests. Also consistent with our review, Greenwood et al. (2005a, 2005b) demonstrated deleterious effects of the APOE $\epsilon4$ allele on experimental tests of visuospatial attention, and Jacobson and colleagues (2005a) have shown that performance discrepancies *between* auditory and spatial attention are associated with presence of the APOE $\epsilon4$ allele in older adults. Together with this emerging literature, our review suggests that episodic memory is certainly not the only marker of preclinical AD. Using novel measures from cognitive neuroscience or comparing standardized neuropsychological measures in novel ways (e.g., cognitive asymmetry calculations) will be important new directions (Houston et al., 2005; Jacobson et al., 2005b).

Neuroimaging studies have predominantly focused on the temporal lobe, but newer methods examining, for example, the whole brain (e.g., voxel-based morphometry), amyloid imaging (Wu et al., 2005), or diffusion imaging (Medina et al., 2005), are suggesting other areas of interest in preclinical AD. Although neurofibrillary tangle pathology spreads from medial temporal to association cortices (Braak & Braak, 1991), the amyloid plaque burden is more widely dispersed (Arnold et al., 1991), variable in progression, and may also mediate the association of genetic risk to cognition (Bennett et al., 2005). Consistent with this early heterogeneity, AD may initially present with cognitive (Jacobson et al., 2002) or metabolic (Haxby et al., 1985) asymmetries. Recent MR morphometric studies also show that changes sensitive to progression to AD appear asynchronous across brain regions and are more pronounced with global indices, such as whole brain atrophy and ventricular enlargement rates, than with MTL structures (Gunter et al., 2003; Jack et al., 2005; Kaye et al., 2005). Thus, it may be that many

possible brain regions are susceptible, and earlier than previously thought, in preclinical AD. The neuropsychological and neuroimaging studies to date argue for comprehensive measurement of cognitive domains and brain regions in future studies.

The cognitive and neuroimaging changes of incipient AD appear to remain relatively stable until a few years before clinical diagnosis, when there is a more notable decline. The mild course of decline in the early preclinical period may reflect the initial invocation of compensatory brain mechanisms, whereas the more rapid decline of the clinical period may reflect the inability of these brain resources to overcome the accrual of plaques, tangles, and neuron and synapse losses. A growing body of fMRI evidence among at-risk persons supports this notion (Bookheimer et al., 2000; Bondi et al., 2005; Dickerson et al., 2005; Han et al., 2006; Johnson et al., 2004), and a similar compensatory response in brain-derived neurotrophic factors (Durany et al., 2000; Egan et al., 2003) or cholinergic activity (DeKosky et al., 2002) may also occur. Given these converging lines of evidence for brain compensation, we propose a nonlinear model of episodic memory decline and neuroimaging changes to characterize this preclinical period of accruing AD pathology (see Figure 1). Consistent with this model, Martins et al. (2005) have demonstrated that APOE $\epsilon4$ possession is associated with earlier and faster cognitive decline in patients with AD, whereas the $\epsilon2$ allele is related to slower decline, and that a nonlinear model best predicts these differential rates of decline.

We believe this review contributes to the field in four major ways. First, it provides the only comprehensive review of both neuropsychological and neuroimaging indicators of preclinical AD. Second, it addresses a significant flaw of previous studies or review articles by excluding studies of subjects with MCI, AAMI, or memory complaints. In doing so, it concludes that if one is looking for preclinical AD, one needs to look beyond memory and the temporal lobe. Third, from the extant literature we present a model of cognitive decline showing that there appears to be an accelerated and nonlinear decline in the period immediately preceding AD diagnosis. Fourth, we provide both evidence for the often conflicting presentation of AD changes in brain and cognition during the preclinical period, as well as possible explanations for these wide-ranging findings across the literature.

Our methodology for the present review has limitations. Although memory deficits are the hallmark of AD, we did not assume that memory declines would be the foremost marker of preclinical AD, and wanted to avoid "stacking the deck" in favor of memory. Thus, we excluded articles on MCI, AAMI, and memory clinic populations to focus specifically on normal older adults or younger people at risk for AD. However, some studies recruited participants via advertisements rather than population sampling, and some of the participants in the studies we reviewed may have met criteria for MCI or AAMI or may have had memory complaints. A second and related limitation is that by
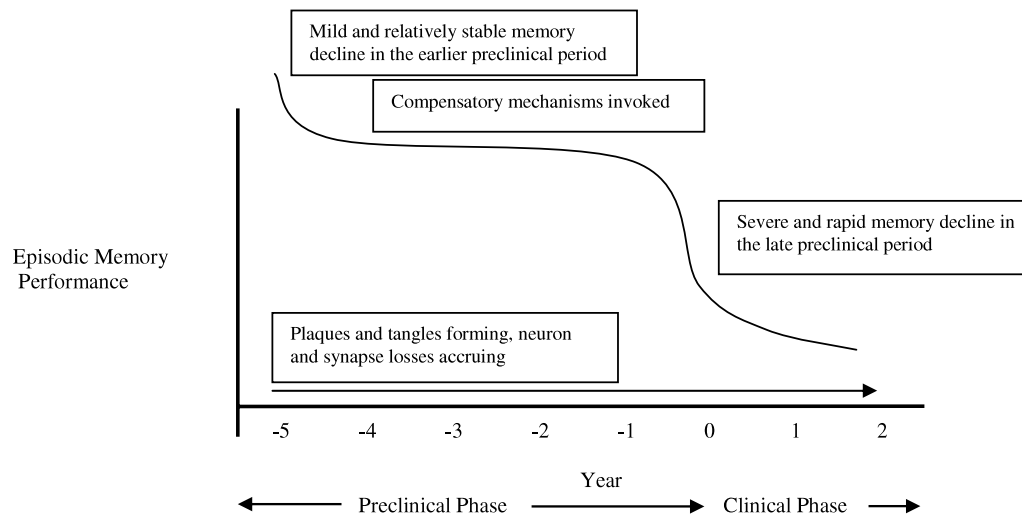
Fig. 1. Proposed model of nonlinear pattern of episodic memory decline during the preclinical period of Alzheimer's disease (based on data of Bäckman et al., 2001; Bunce et al., 2004; Chen et al., 2001; Lange et al., 2002).

excluding research on memory-impaired populations, the present review may over-represent certain groups (e.g., APOE ϵ4 carriers) whose cognitive profiles may not characterize those of the general population. For this reason, we separated the APOE studies from the others in our review. We focused on neuropsychological and neuroimaging tests, excluding other potentially promising methodologies without substantial published literature (e.g., olfactory testing, Murphy et al., 1998). Finally, although a formal meta-analysis that would have weighted each study based on the number of participants, we chose to use a "box score" approach to examining the findings of the included studies, due to considerable heterogeneity in study methodologies and measures.

Although there have been many exciting developments in this growing area of research, conclusions about the nature and course of preclinical AD remain limited by contradictory findings in at-risk groups and/or studies that rely on retrospective or cross-sectional designs or small datasets. To improve detection of preclinical markers, the neuropsychological functioning, brain structure, and brain functioning of at-risk individuals who develop AD should ultimately be tested against that of persons who remain dementia-free over the same follow-up period. Furthermore, they might be compared to individuals with other conditions (e.g., depression, other dementias) and validated by autopsy-confirmed diagnosis.

In addition to documenting the cognitive deficits in preclinical AD, the longitudinal course of these deficits is also important. There has been a lack of consensus regarding when the preclinical period begins and how early preclinical changes may be detected. Most investigations have used relatively short test-retest intervals (e.g., two to three years after initial assessment), but other studies have used longer intervals (decades or more). With longer test-retest intervals, cognitive changes are more likely to be detected, but it is more difficult to determine when decline began. With

some groups finding differences between AD cases and controls five to six decades before the onset of AD (see Snowdon et al., 1996 and Whalley et al., 2000), future research should address the question of the age range in which it is possible to detect a preclinical AD state and whether such states can be distinguished from lower levels of cognitive reserve.

With respect to fMRI studies of at-risk groups, contradictory findings across studies [e.g., decreased *vs.* increased blood oxygen level dependent (BOLD) responses] may reflect different mechanisms linking the hemodynamic response to its underlying neuroanatomy and neurophysiology. One concern is that differences in the "resting state" will influence the amplitude of the BOLD response (Cohen et al., 2002). If the AD brain is in a lower resting state, as suggested by Reiman et al. (1996), it should show an increased hemodynamic response compared with a non-AD brain in the context of equal stimulation. The BOLD signal must be calibrated to the resting state to prevent over-interpretation of greater BOLD responses as signifying heightened compensatory responses. Recent research using APP23 transgenic mice has demonstrated that amyloid plaques have a direct effect on the hemodynamic response, due partly to compromised cerebrovascular reactivity (Mueggler et al., 2002). Human studies also demonstrate that the hemodynamic response itself changes with age (D'Esposito et al., 1999). Thus, future efforts should incorporate other MR-based techniques such as perfusion imaging and structural morphometry to help delineate the contributions of the neuroanatomic and neurophysiologic underpinnings of the BOLD signal.

It remains that there is still no single marker of AD. Combined cognitive, imaging, and genetic assessments may ultimately be needed to achieve accurate and reliable identification of preclinical AD (Albert, 1996; Small et al., 1996). Detecting preclinical AD will probably be best accomplished by examining decline longitudinally with sensitive

cognitive tests and structural or functional markers of brain integrity. Early detection may be enhanced if risk factors such as advancing age or the presence of the APOE ϵ4 allele (Mayeux et al., 1998) are also considered.

The ability to detect AD in its earliest, preclinical phase will continue to be an important topic of neuropsychological and neuroimaging research. The rapid development of neuroprotective agents designed to impede the progression of the disease is a testament to the recognized importance of early identification and treatment of AD (DeLaGarza, 2003). Moreover, preserving cognitive status and functional independence with more effective interventions will have far-reaching implications for maintaining patients' quality of life and decreasing caregivers' financial and emotional burden (Brookmeyer et al., 1998).

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APPENDIX 1

Neuropsychological Studies

Part A. Prospective longitudinal studies of initially nondemented subjects, comparing cases (subjects who developed AD) and controls (subjects who remained nondemented)

Authors	Number and Type of Subjects; Methodological Comments	Age (A = mean years unless otherwise indicated) Gender (G = percent male) Education Level (E = mean years)	Tests Used	Results
Bäckman and Small (1998)	24 cases 134 controls 3-year study	Cases A = 84 G = 4% male E = 8 Controls A = 83 G = 18% male E = 9	MMSE Immediate memory tasks involving: 1. Free recall of slowly and rapidly presented unrelated words 2. Free and cued recall of related words	At baseline, cases performed worse on: MMSE Free and cued recall (regardless of speed of presentation or relatedness of words)
Bäckman et al. (2001)	15 cases 105 controls 6-year study	Cases A = 84 G = 7% male E = 9 Controls A = 82 G = 20% male E = 10	MMSE Free recall and recognition of slowly presented unrelated words WAIS-R Digit Span	At baseline and 3-year follow-up, cases performed worse on: MMSE Free recall and recognition These results held after controlling for age, education, and gender Cases and controls had similar slopes of decline

Bondi et al. (1994)	5 cases 51 controls 28/56 subjects were FH+ 3-year study Subjects also were compared to 25 patients with probable AD at baseline Cross-sectional results from baseline testing reported below	FH+: A = 70 G = 36% male E = 16 FH−: A = 71 G = 36% male E = 15 AD at follow-up: A = 74 G = 40% male E = 15 AD at baseline: A = 71 G = 56% male E = 14	CVLT MMSE DRS Number Information Test (general knowledge) Letter and category fluency BNT WAIS-R (Digit Span, Vocabulary, Arithmetic, Similarities, Digit Symbol) WISC-R Block Design Trail Making Test, Parts A and B Clock Drawing Test Clock Setting Test Grooved Pegboard Test Modified WCST WMS-R (Visual Memory Span, Logical Memory) SRT	Cases performed worse than controls but better than AD patients on: CVLT learning and delayed recall measures MMSE DRS Total Category Fluency WAIS-R Digit Symbol Logical Memory I SRT Total Cases performed worse than controls and comparably to AD patients on: CVLT learning and delayed recall measures DRS Conceptualization Letter Fluency WAIS-R Similarities Logical Memory II SRT Recall
Bondi et al. (1999)	7 cases 79 controls 23 ε4+ 63 ε4− Mean length of follow-up wa 3 years Sample included 52 subjects from Bondi et al. (1995) Cross-sectional results from baseline testing reported below	ε4+ A = 68 G = 47% male E = 15 ε4− A = 70 G = 43% male E = 15	MMSE DRS CVLT WMS Visual Reproduction WAIS-R (Digit Span, Digit Symbol, Vocabulary) WISC Block Design BNT Letter fluency Trail Making Test, Parts A and B Modified WCST	Cases performed worse on: CVLT List A Total Analyses controlled for age and education
Bunce et al. (2004)	162 cases 373 controls 161 ε4+ 374 ε4− 6-year study	ε4+ A = 80 G = 16% male E = 8 ε4− A = 80 G = 25% male E = 9	MMSE	Cases at 3-year follow-up and at 6-year follow-up exhibited greater declines on MMSE Decline was most marked in the 3 years prior to diagnosis E4 status did not predict rate of decline or AD diagnosis over time
Chen et al. (2000)	120 cases 483 controls 10-year study	Cases A = 78 G = 43% male E = 50% less than high school Controls A = 75 G = 38% male E = 32% less than high school	CERAD word list learning and memory test WMS Logical Memory Trail Making Test, Parts A and B Letter and category fluency CERAD version of BNT CERAD Praxis Clock Drawing MMSE	Cases performed worse on: Word List Delayed Recall Word List learning measures Trail Making Test, Part B MMSE
Chen et al. (2001)	68 cases 483 controls 10-year study Same sample as above, examined change between assessments 3.5 and 1.5 years before AD diagnosis	Cases A = 77 G = 43% male E = 47% less than high school Controls A = 73 G = 38% male E = 32% less than high school	CERAD word list learning and memory test WMS Logical Memory Trail Making Test, Parts A and B Letter and category fluency CERAD version of BNT CERAD Praxis Clock Drawing MMSE Orientation	Cases declined most on: Trail Making Test, Part A Trail Making Test, Part B Word List Delayed Recall and Recognition measures Word List learning measures CERAD Praxis Clock Drawing CERAD Boston Naming Test MMSE Orientation

Dartigues et al. (1997)	59 cases 2667 controls 3-year study	A = 75 G = 40% male E = mostly grade school	MMSE BVRT Isaaks Set Test (category fluency)	Cases performed worse on: MMSE BVRT Isaaks Set Test All three tests were independent predictors of conversion to AD even after adjusting for age and education
Elias et al. (2000)	109 cases 967 controls 22-year study controlling for age, education, occupation level, and gender	Cases G = 21% male Controls G = 39% male A: 65–94 E: Majority of subjects had ≥HS	WMS (Logical Memory, Paired Associate Learning, Visual Reproduction) COWAT WAIS (Similarities, Digit Span) MMSE	Cases performed worse on: Logical Memory (% retained) Similarities Paired Associate Learning WMS Learning and Immediate Recall Among an older (age 75–94), but not a younger (age 65–74) cohort, lower COWAT scores were associated with later AD diagnosis
Fabrigoule et al. (1998)	16 cases 1143 controls 2-year study	A = 73 G = 44% male E = 56% grade school educated, remainder secondary or university education	MMSE BVRT WMS Paired Associates Test Isaacs Set Test (category fluency) Zazzo's Cancellation Task (processing speed) WAIS (Digit Symbol, Similarities)	Cases performed worse on: BVRT WAIS Digit Symbol Isaacs Set Test Zazzo's Cancellation Task Wechsler Paired Associates Test WAIS Similarities MMSE
Fox et al. (1998)	10 cases 53 controls All subjects at risk for autosomal dominant familial AD 6-year study	A = 45 G = 42% male E = NR	MMSE WAIS-R (Vocabulary, Arithmetic, Digit Span, Similarities, Block Design, Picture Completion, Picture Arrangement) Recognition Memory Test (words and faces) Graded Naming Test Visual Object and Spatial Perception Test Psychomotor Speed Tests Graded Difficulty Arithmetic Test Graded Difficulty Spelling Test NART	Cases performed worse on: Recognition Memory Test (words) WAIS-R Block Design, Picture Completion, and Picture Arrangement
Grober and Kawas (1997)	20 cases 60 controls 3-year study	Cases A = 79 G = 45% male E = 17 Controls A = 79 G = 48% male E = 17	SRT	Cases performed worse on: SRT learning measures
Hall et al. (2000)	35 cases 293 controls 15-year study	Cases A = 80 G = NR E = NR Controls A = 80 G = NR E = NR	SRT learning	Cases performed worse on: SRT learning
Howieson et al. (1997)	16 cases 31 controls Mean length of follow-up was 2.8 years	Cases A = 90 G = 44% male E = 15 Controls A = 85 G = 42% male E = 14	CERAD version of BNT WAIS-R (Vocabulary, Picture Completion, Block Design) CERAD Word List Memory Test WMS-R Logical Memory and Visual Reproduction	Cases performed worse on: Boston Naming Test Logical Memory I and II Block Design CERAD Word List Delayed Recall Picture Completion Visual Reproduction I

Jacobs et al. (1995)	41 cases 402 controls 4-year study	Cases A = 79 G = 22% male E = 8 Controls A = 73 G = 27% male E = 11	SRT BVRT MMSE Orientation items WAIS-R Similarities subtest DRS Identities and Oddities BNT (15 item version) Letter and category fluency BDAE Complex Ideational Material Rosen Drawing Test (visuoconstruction) Visual matching test (visuoperception)	Cases performed worse on: Boston Naming Test SRT Immediate Recall WAIS-R Similarities Analyses controlled for age, education, sex, and language of test administration
Katzman et al. (1989)	32 cases 402 controls 5-year study	Cases A = 81 G = 16% male E = modal 7–9 Entire sample A = 79 G = 36% male E = modal 7–9	Blessed Information-Memory-Concentration Test	Cases performed worse on: Blessed Information-Memory-Concentration Test Those with 0–2 errors developed AD at a rate less than 0.6% per year, whereas those with 5–8 errors developed AD at a rate of over 12% per year
Klages et al. (2003)	27 cases 182 controls 5-year study	A = 77 G = 38% male E = 10	SRT	Cases performed worse on: SRT (delayed free recall)
Laukka et al. (2004)	43 cases 149 controls 6-year study	A = 84 G = 16% male E = 9	WAIS-R Digit Span Episodic Memory (Random Recall, Organized Recall, Word Recognition, Face Recognition) Visuospatial Ability (WAIS-R Block Design, Clock Reading, Clock Setting) Letter and category fluency	Cases performed worse on: All episodic memory measures Fluency measures WAIS-R Block Design Clock Setting
Lindeboom et al. (2002)	24 cases 204 controls 3-year study	Cases A = 79 G = 25% male E = completed primary education Controls A = 73 G = 45% male E = completed primary education	MMSE	Cases performed worse on: MMSE
Lindsay et al. (2002)	194 cases 3894 controls 5-year study	Cases A = 81 G = 32% male E = 10 Controls A = 73 G = 42% male E = 11	3MS Examination	Cases performed worse on: 3MS
Linn et al. (1995)	55 cases 990 controls 13-year study	Cases A = 76 G = 29% male Controls A = 72 G = 38% male E = Majority of subjects had ≥HS	WMS (Logical Memory, Visual Reproduction, Paired Associate Learning, Digit Span) COWAT WAIS Similarities	Cases performed worse on: Logical Memory I and II and percent retained Visual Reproduction I Paired Associate Learning Controlled Oral Word Association Similarities Analyses controlled for age and education

Masur et al. (1994)	64 cases 253 controls Minimum length of follow-up was 4 years	Cases A = 80 G = 41% male E = modal 7–9 Controls A = 79 G = 39% male E = modal 7–9	WAIS (Information, Vocabulary, Similarities, Digit Span, Block Design, Object Assembly, Digit Symbol) Fuld Object Memory Evaluation SRT Category fluency Raven's Colored Matrices Purdue Pegboard Test	Cases performed worse on: SRT delayed recall Fuld Object Memory recall Category Fluency WAIS Digit Symbol
Nielsen et al. (1999)	102 cases 2350 controls 2-year study	A = 65–84 G = NR E = NR	CAMCOG: Orientation Comprehension Naming Category fluency Definitions Memory Recognized pictures General knowledge Attention Copying Ideomotor praxis Abstraction Visual perception	Cases performed worse on: Category fluency Memory General knowledge Attention
Rapp and Reischies (2005)	15 cases 172 controls 4-year study	A = 80 G = 50% male E = 11	MMSE Trail Making Test, Part B Digit Letter Test (processing speed) WAIS Digit Symbol WMS Paired Associate Learning Identical Pictures (attention) Memory for Text (learning) Activity Recall (recall of tests given)	Cases performed worse on: Trail Making Test, Part B Digit Letter Test Digit Symbol Substitution Test Identical Pictures Paired Associates Test Memory for Text Activity Recall After controlling for age differences between groups, cases performed worse on: Identical Pictures Trail Making Test, Part B
Saxton et al. (2004)	72 cases 621 controls Study combined data from 3 separate prospective studies with 8 years of follow-up	A = 73 G = 44% male E = 13	WMS-R Orientation WMS-R Immediate Memory (Verbal, Visual, General) WMS-R Delayed Memory Speed/Attention (WMS-R Attention/ Concentration, WAIS-R Digit Symbol, Trail Making Test, Parts A and B) Verbal Productivity/Vocabulary (WAIS-R Vocabulary, Letter and category fluency) BNT WAIS-R Block Design	For 1.5–3.4 year follow-up, cases performed worse on: WMS-R Verbal WMS-R Visual WMS-R General WMS-R Delayed WMS-R Attention/Concentration Trail Making Test, Parts A and B Category Fluency Boston Naming Test For 3.5–5 year follow-up, cases performed worse on: WMS-R General WMS-R Delayed Trail Making Test, Part B Category Fluency For 5.1–8 year follow-up, cases performed worse on: WMS-R Verbal WMS-R Delayed
Small et al. (1997b)	32 cases 189 controls 3-year study	A = 84 G = 19% male E = 9	MMSE	Cases performed worse on: MMSE (particularly delayed recall and orientation to time)

Small et al. (1997a)	26 cases 179 controls 3-year study	Cases A = 85 G = 12% male E = 9 Controls A = 83 G = 21% male E = 9	MMSE Face Recognition Task Free Recall and Recognition of Random and Organizable Words Letter and category fluency Poppelreuter's Figures (visual perception) Clock Test WAIS-R (Block Design, Digit Span)	Cases performed worse on: MMSE Face Recognition Task Free Recall and Recognition of Random and Organizable Words Letter and Category Fluency Poppelreuter's Figures Clock Test WAIS-R Block Design
Small et al. (2000a)	73 cases 459 controls 6-year study Cases were those diagnosed with AD at 6-year, but not 3-year, follow-up	Cases A = 82 G = 21% male E = 8 Controls A = 79 G = 23% male E = 9	MMSE	Cases performed worse on: MMSE delayed memory item
Yoshitake et al. (1995)	42 cases 784 controls 7-year study	A = 74 G = 40% male E = 26% had ε6	Hasegawa Dementia Scale (11-item mental status exam including orientation, memory, common knowledge, and calculation)	Cases performed worse on: Hasegawa Dementia Scale
Zonderman et al. (1995)	7 cases 364 controls Longitudinal study since 1960 with testing every 6–8 years	A = 72 G = 68% male E = mostly HS or college educated	BVRT	Cases performed worse on: BVRT learning Cases declined more rapidly on the BVRT in the 6 years before diagnosis of AD

Part B. Prospective longitudinal studies examining differential cognitive decline in ε4+ and ε4− subjects

Authors	Number and Type of Subjects; Methodological Comments	Age (A = mean years unless otherwise indicated) Gender (G = percent male) Education Level (E = mean years)	Tests Used	Results
Baxter et al. (2003)	54 ε4+ 59 ε4− 2-year study	ε4+ A = 58 G = 33% male E = 16 ε4− A = 59 G = 37% male E = 16	RAVLT COWAT	ε4+ subjects over age 60 declined in their novel word learning ability
Bretsky et al. (2003)	227 ε4+ 738 ε4− 7-year study	A = 74 G = 44% male E = NR	Overall cognitive performance: 4 items from WAIS-R Similarities Delayed spatial recognition BNT (18-item version) Spatial ability Memory: Delayed verbal and visual memory Story recall	At 3-year follow-up, ε4+ subjects declined in naming and spatial ability At 7-year follow-up, ε4+ subjects declined in overall cognitive performance, naming, spatial ability, abstraction, and verbal and visual memory
Cohen et al. (2001)	16 ε4+ 9 ε4− 2-year study Groups also compared on structural MRI (see findings reported below)	ε4+ A = 55 G = 0% male E = NR ε4− A = 61 G = 0% male E = NR	SRT free recall Letter and category fluency Rey CFT WMS-R WAIS-R Block Design	No significant group differences

Dik et al. (2000)	213 ϵ4+ 653 ϵ4− Mean length of follow-up was 3.1 years	A = 72 G = 51% male E = 9	MMSE (baseline only) Alternate forms of an abbreviated (3-trial) RAVLT	At baseline, ϵ4+ and ϵ4− subjects did not differ on the MMSE At follow-up, ϵ4+ subjects over 75 performed better on RAVLT immediate recall
Ercoli et al. (2003)	23 ϵ4+ 31 ϵ4− 2-year study	ϵ4+ A = 65 G = 39% male E = 15 ϵ4− A = 66 G = 42% male E = 15	MMSE MMSE subset items (delayed 3-item recall; serial 7s; intersecting pentagons; time and place orientation)	No significant group differences For ϵ4+ subjects, lower baseline scores on the MMSE subset items predicted decline in visual construction and naming
Helkala et al. (1996)	192 ϵ4+ (including ϵ2/ϵ4) 378 ϵ3/ϵ3 62 ϵ2+ 3-year study	A = 73 G = 35% male E = 7	MMSE SRT (total score) Visual Reproduction test (immediate, delay, copy) Letter and category fluency Trail Making Test, Parts A and B	At follow-up, ϵ2+ subjects performed better than ϵ4+ and ϵ3/ϵ3 subjects on: SRT Letter fluency
Hofer et al. (2002)	94 ϵ4+ 340 ϵ4− 7-year study	A = 76 G = 49% male E = 12	Verbal ability (Vocabulary, Similarities, NART items) Memory (word recognition test, 3 word recall with 2 minute delay, address recall with 2 minute delay) Speed (symbol-letter modalities test)	ϵ4+ subjects declined on: Memory
Jonker et al. (1998)	25 ϵ4+ 292 ϵ4− 3-year study	A = 75 G = 43% male E = 8	CAMCOG (total score, memory and nonmemory subscales)	ϵ4+ subjects declined on: CAMCOG total score memory subscale nonmemory subscale
Mayeux et al. (2001)	80 ϵ4+ 483 ϵ4− 7-year study	A = 76 G = 31% male E = 10	Visuospatial/Cognitive factor (Rosen Drawing Test, BVRT, DRS Identities and Oddities) Language factor (BNT, COWAT, WAIS-R Similarities) Memory factor (seven subtests of the SRT)	ϵ4+ subjects declined faster on: Memory
Pendleton et al. (2002)	201 ϵ4+ 566 ϵ4− 15-year study	A = modal 60–69 G = 30% male E = NR	Heim AH4 part 1 (fluid general intelligence)	No significant group differences
Reiman et al. (2001)	10 ϵ4+ 15 ϵ4− All subjects had a family history of AD 2-year study Groups also compared on PET (see findings reported below)	ϵ4+ A = 56 G = 30% male E = 15 ϵ4− A = 57 G = 33% male E = 16	MMSE RAVLT CFT BNT WAIS-R (Information, Digit Span, Block Design, Arithmetic, Similarities) COWAT	No significant group differences
Riley et al. (2000)	34 ϵ4+ 207 ϵ4− All subjects were nuns 4-year study	A = 81 G = 0% male E = 17	CERAD: MMSE Delayed word recall Verbal fluency BNT Constructional praxis	ϵ4+ subjects declined on: MMSE Delayed word recall

Small et al. (1998)	20 $\epsilon 4+$ 54 $\epsilon 4-$ 3-year study Cross-sectional results from baseline testing reported below	$\epsilon 4+$ A = 80 G = 25% male E = 10 E4− A = 82 G = 30% male E = 10	MMSE Face Recognition Task Free Recall and Recognition of Random and Organizable Words Letter and category fluency Poppelreuter's Figures Clock Test WAIS-R (Block Design, Digit Span)	$\epsilon 4+$ subjects declined on: Recognition memory for faces and words
Wilson et al. (2002)	161 $\epsilon 4+$ 450 $\epsilon 4-$ 6-year follow-up Cross-sectional results from baseline testing reported below	A = 76 G = 38% male E = 18	Episodic memory (CERAD Word List Memory, Recall, and Recognition, Immediate and Delayed Story Memory, WMS-R Logical Memory Story A) Semantic memory (BNT, Verbal Fluency, Extended Range Vocabulary, NART) Working memory (WMS-R Digit Span, Digit Ordering, Alpha Span) Perceptual speed (Symbol Digit Modalities Test, Number Comparison) Visuospatial ability (Judgment of Line Orientation, Raven's Standard Progressive Matrices)	$\epsilon 4+$ subjects declined on all cognitive domains, with the most decline on episodic memory
Winnock et al. (2002)	130 $\epsilon 4+$ 470 $\epsilon 4-$ 7-year study Cross-sectional results from baseline testing reported below	A = 74 G = 76% male E = mostly primary education or above	MMSE	No significant group differences in decline
Yaffe et al. (before 1997)	271 $\epsilon 4+$ 1479 $\epsilon 4-$ 6-year study Cross-sectional results from baseline testing reported below	A = 71 G = 0% male E = 12	MMSE Trail Making Test, Part B WAIS-R Digit Symbol	$\epsilon 4+$ subjects declined on all cognitive tests

Part C. Cross-sectional studies comparing neuropsychological profiles of healthy, nondemented $\epsilon 4+$ and $\epsilon 4-$ subjects

Authors	Number and Type of Subjects; Methodological Comments	Age (A = mean years unless otherwise indicated) Gender (G = percent male) Education Level (E = mean years)	Tests Used	Results
Albert et al. (1995)	60 $\epsilon 4+$ 158 $\epsilon 4-$	A = 74 G = 26% male E = 8	SRT (total recall and delayed recall)	No significant group differences
Berr et al. (1996)	270 $\epsilon 4+$ 904 $\epsilon 4-$	A = 65 G = 42% male E = 11	MMSE Trail Making Test, Part B RAVLT Benton Face Recognition Test WAIS-R Digit Symbol Finger Tapping Test BVRT Raven's Progressive Matrices PASAT Word Fluency Test	After adjusting for age, education, and gender, the number of $\epsilon 4$ alleles was associated with worse performance on: MMSE Trail Making Test, Part B Finger Tapping Test

Bondi et al. (1999)	43 ϵ4+ 90 ϵ4− Sample included 52 subjects from Bondi et al. (1995) Longitudinal results reported above	ϵ4+ A = 68 G = 47% male E = 15 ϵ4− A = 70 G = 43% male E = 15	MMSE DRS CVLT WMS Visual Reproduction WAIS-R (Digit Span, Digit Symbol, Vocabulary) WISC Block Design BNT Letter fluency Trail Making Test, Parts A and B Modified WCST	ϵ4+ subjects performed worse on: WCST nonperseverative errors CVLT learning and memory measures
Caselli et al. (1999)	25 ϵ4/ϵ4 25 ϵ4 heterozygotes 50 ϵ4− All subjects were first-degree relatives of AD patients	ϵ4/ϵ4 A = 56 G = 28% male E = 16 ϵ4 heterozygotes A = 56 G = 28% male E = 15 ϵ4− A = 57 G = 28% male E = 15	COWAT WAIS-R (Arithmetic, Digit Span, Similarities, Block Design, Information) WMS-R Orientation RAVLT BNT CFT BVRT	No significant group differences, whether all three groups were compared or whether ϵ4+ subjects were compared with ϵ4− subjects
Caselli et al. (2001)	20 ϵ4/ϵ4 20 ϵ4 heterozygotes 40 ϵ4− All subjects were first-degree relatives of AD patients	ϵ4/ϵ4 A = 57 G = 40% male E = 16 ϵ4 heterozygotes A = 56 G = 40% male E = 16 ϵ4− A = 56 G = 40% male E = 16	COWAT WAIS-R (Arithmetic, Digit Span, Similarities, Block Design, Information) WMS-R Orientation RAVLT BNT CFT BVRT	ϵ4 heterozygotes performed worse than did ϵ4− subjects on: Complex Figure Test Recall
Caselli et al. (2002)	42 ϵ4/ϵ4 38 ϵ4− ϵ4/ϵ4 subjects were matched to ϵ4− subjects on age, gender, education, family history of dementia	A = 55 G = 31% male E = 16	MMSE RAVLT BVRT Rey-Osterrieth CFT WAIS-R (Information, Digit Span, Arithmetic, Similarities, Block Design) Letter fluency BNT	ϵ4/ϵ4 subjects performed worse than did ϵ4− subjects on: RAVLT learning Similarities
Chen et al. (2002)	72 ϵ4+ 81 ϵ4−	A = 67 G = 50% male E = 16	MMSE CVLT	No significant group differences
Deary et al. (2004)	120 ϵ4+ 342 ϵ4− All subjects born in 1921	A = 79 G = 41% male E = NR	MMSE WMS-R Logical Memory Raven's Progressive Matrices Letter fluency	ϵ4+ subjects performed worse on: Logical Memory I and II
Fillenbaum et al. (2001)	548 ϵ4+ 1343 ϵ4− Longitudinal study with applicable cross-sectional data at baseline	A = 77 G = 33% male E = 10	Short Portable Mental Status Questionnaire	ϵ4+ subjects performed worse on: Short Portable Mental Status Questionnaire

Flory et al. (2000)	61 ε4+ 159 ε4−	A = 46 G = 51% male E = 16	Verbal associative learning Verbal associative learning delayed recall Verbal associative learning recognition CFT delayed recall WAIS-R (Digit Symbol immediate recall, Digit Span)	ε4+ subjects performed worse on: CFT delayed recall Verbal associative learning
Greenwood et al., (2000)	38 ε4+ 48 ε3/ε3 11 ε2+	A = 59 G = 39% male E = 17	Cued letter discrimination task Cued visual search task Vigilance task	No significant group differences in accuracy or reaction time on any task ε4+ subjects had slower reaction times to invalid cues than did other groups on the cued letter discrimination task and had reduced spatial scaling of attention on the cued visual search task
Greenwood et al. (2005)	64 ε4+ 113 ε4− Cross-sectional study examining ε4 "dose"	A = 59 G = 42% male E = 17	Spatial cued letter discrimination task Spatial working memory task	ε4 dose was associated with impairment in: Redirecting visuospatial attention to unexpected locations Retaining locations in working memory Using attentional scaling to enhance spatial working memory
Kim et al. (2002)	74 ε4+ 392 ε4−	A = 70 G = 27% E = 6	Korean version of CERAD: MMSE Verbal fluency test Modified BNT Word list memory test Word list recall test Word list recognition test Constructional praxis test Constructional recall test	No significant group differences
Levy et al. (2004)	61 ε4+ 115 ε4−	A = 59 G = 36% male E = 17	Prose Recall (WMS-R Logical Memory I and II, percent retained) Word Recall (SRT, WMS-R Verbal Paired Associates I and II) Design Recall (WMS-R Visual Reproduction I and II, percent retained, CFT 3 minute recall) Visuospatial Ability (CFT copy, WAIS-R Block Design, Digit Symbol) Language (Letter and category fluency, BNT)	ε4+ subjects performed worse on: Logical Memory II Logical Memory percent retained
Reed et al. (1994)	40 dizygotic twins (20 pairs) discordant for presence of the ε4 allele Cross-sectional study comparing education-adjusted scores on neuropsychological tests in twins discordant for ε4	A = 63 G = 100% male E = NR	BVRT COWAT MMSE WAIS-R Digit Symbol Modified version of the Telephone Interview for Cognitive Status	ε4+ twins performed worse than their ε4− co-twins on: BVRT
Rosen et al. (2002)	21 ε4+ 21 ε4−	A = 62 G = 43% male E = 17	Operation Span Task (working memory) SRT	ε4+ subjects performed worse on: Operation Span Task
Salo et al. (2001)	12 ε4+ 34 ε4−	A = 89 G = 48% male E = 4	MMSE Fuld Object Memory Evaluation Letter and category fluency WAIS-R Similarities	No significant group differences

Schmidt et al. (1996)	39 ε4+ 175 ε4− Groups also compared on structural MRI (see findings reported below)	ε4+ A = 59 G = about 50% male E = 11 ε4− A = 61 G = about 50% male E = 12	German verbal and visual learning and memory test German cancellation (attention and speed) test German complex reaction time test WCST Trail Making Test, Part B WAIS-R Digit Span Purdue Pegboard Test	ε4+ subjects performed worse on: Verbal and visual memory
Small et al. (1998)	20 ε4+ 54 ε4− Longitudinal results reported above	ε4+ A = 80 G = 25% male E = 10 ε4− A = 82 G = 30% male E = 10	MMSE Face Recognition Task Free Recall and Recognition of Random and Organizable Words Letter and category fluency Poppelreuter's Figures Clock Test WAIS-R (Block Design, Digit Span)	No significant group differences
Small et al. (2000b)	91 ε4+ 322 ε4−	A = 73 G = 49% male E = 14	3MS Spot-the-Word (premorbid IQ test) Hopkins Verbal Learning Test Word stem Completion Task (implicit memory) Trail Making Test, Parts A and B Stroop Test	No significant group differences
Smith et al. (1998)	90 ε4+ 251 ε4−	ε4+ A = 80 G = 30% male E = 14 ε4− A = 80 G = 31% male E = 13	Verbal Comprehension (WAIS-R Vocabulary, Information) Perceptual Organization (WAIS-R Block Design, Picture Arrangement, Picture Completion; WMS-R Visual Reproduction I) Attention/Concentration (WMS-R Digit Span, Mental Control; WAIS-R Arithmetic) Learning (RAVLT acquisition; WMS-R Verbal and Visual Paired Associates I) Retention (percent retention for RAVLT, WMS-R Logical Memory, and WMS-R Visual Reproduction) BNT RAVLT delayed recall	No significant group differences
Staehelin et al (1999)	72 ε4+ 198 ε3/ε3 62 ε2+ (including 11 ε2/ε4)	A = 76 G = 68% male E = NR	Reaction Time Delayed free recall WAIS-R Vocabulary (German version)	ε3/ε3 and ε4+ subjects performed worse than did ε2 subjects on: Reaction Time ε4+ subjects performed worse than did ε3/ε3 on: WAIS-R Vocabulary
Tohgi et al. (1997)	14 ε4+ 40 ε4− Groups also compared on structural MRI (see findings reported below)	A = 59 G = 52% male E = 12	MMSE	No significant group differences
Wilson et al. (2002)	161 ε4+ 450 ε4− Longitudinal results reported above	A = 76 G = 38% male E = 18	Episodic memory (CERAD Word List Memory, Recall, and Recognition, Immediate and Delayed Story Memory, WMS-R Logical Memory Story A) Semantic memory (BNT, Verbal Fluency, Extended Range Vocabulary, NART) Working memory (WMS-R Digit Span, Digit Ordering, Alpha Span) Perceptual speed (Symbol Digit Modalities Test, Number Comparison) Visuospatial ability (Judgment of Line Orientation, Raven's Standard Progressive Matrices)	ε4+ subjects performed worse on: Episodic memory Visuospatial ability

Winnock et al. (2002)	130 $\epsilon4+$ 470 $\epsilon4-$ Longitudinal results reported above	A = 74 G = 76% male E = mostly primary education or above	MMSE	$\epsilon4+$ subjects performed worse on: MMSE (but not after controlling for education)
Yaffe et al. (1997)	271 $\epsilon4+$ 1479 $\epsilon4-$ Longitudinal results reported above	A = 71 G = 0% male E = 12	MMSE Trail Making Test, Part B WAIS-R Digit Symbol	$\epsilon4/\epsilon4$ subjects performed worse on: Trail Making Test, Part B

Part D. Cross-sectional studies comparing neuropsychological profiles of nondemented subjects with AD-like and normal brains at autopsy

Authors	Number and Type of Subjects; Methodological Comments	Age (A = mean years unless otherwise indicated) Gender (G = percent male) Education Level (E = mean years)	Tests Used	Results
Goldman et al. (2001)	5 preclinical AD brains with neuritic and diffuse plaques 11 normal brains	Preclinical AD brain A = 80 G = 40% male E = 14 Normal brain A = 83 G = 78% male E = 14	WMS (Mental Control, Logical Memory, Digit Span, Paired Associate Learning) BVRT WAIS (Information, Block Design, Digit Symbol) Trail Making Test, Part A Crossing-off (processing speed) BNT Letter fluency	No significant group differences
Hulette et al. (1998)	4 "possible AD" brains per CERAD autopsy criteria 8 normal brains	Possible AD brain A = 83 G = 50% male E = 15 Normal brain A = 82 G = 50% male E = 17	MMSE Letter and category fluency Naming test Constructional Praxis Symbol-Digit Modalities Test Trail Making Test, Parts A and B CERAD Word List Memory WMS Logical Memory BVRT	Subjects with possible AD at autopsy performed worse on: Memory percent retained Trail Making Test, Parts A and B Category fluency (trends only; sample size too small to permit inferential tests)
Schmitt et al. (2000)	7 AD-like brains 52 normal brains	A = 84 G = 46% male E = 16	MMSE Blessed Information-Memory-Concentration Test Temporal Orientation Test WMS (Mental Control, Logical Memory) BVRT Alzheimer's Disease Assessment Scale (word list learning/recognition and design reproduction) COWAT Animal naming BNT WAIS-R (Vocabulary, Digit Symbol) Trail Making Test, Parts A and B	Subjects with AD-like brains performed worse at the evaluation before death on: Logical Memory I Word list delayed recall

Part E. Cross-sectional studies comparing neuropsychological profiles of healthy, nondemented, FH+ and FH− subjects

Authors	Number and Type of Subjects; Methodological Comments	Age (A = mean years unless otherwise indicated) Gender (G = percent male) Education Level (E = mean years)	Tests Used	Results
Bondi et al. (1994)	5 cases 51 controls 28/56 subjects were FH+	FH+: A = 70 G = 36% male E = 16	CVLT MMSE DRS Number Information Test (general knowledge)	FH+ subjects performed worse on: CVLT learning and delayed recall measures

	Longitudinal results reported above	FH−: A = 71 G = 36% male E = 15	Letter and category fluency BNT WAIS-R (Digit Span, Vocabulary, Arithmetic, Similarities, Digit Symbol) WISC-R Block Design Trail Making Test, Parts A and B Clock Drawing Test Clock Setting Test Grooved Pegboard Test Modified WCST WMS-R (Visual Memory Span, Logical Memory) SRT	
Diaz-Olavarrieta et al. (1997)	14 FH+ (from FAD families) 14 FH− Cognitive test scores were averaged over two evaluations in a one-year period	FH+ A = 39 G = 30% male E = 11 FH− A = 38 G = 71% male E = 11	MMSE Digit Span Corsi cubes WMS (Orientation, Mental Control) Immediate verbal memory Paired word association Verbal learning curve Rey-Osterreith CFT (immediate and delayed recall) Block Design BNT Letter and category fluency	No significant group differences
Hom et al. (1994)	20 FH+ (first-degree relatives of AD probands) 20 FH−	FH+ A = 55 G = 15% male E = 14 FH− A = 56 G = 15% male E = 12	WAIS WMS-R (Logical Memory, Visual Reproduction) Halstead Category Test Tactual Performance Test Seashore Rhythm Test Speech-Sounds Perception Test Reitan-Indiana Aphasia Screening Examination	FH+ subjects performed worse on: WAIS Verbal IQ Seashore Rhythm Test Logical Memory I WAIS Information Halstead Impairment Index
Schiffman et al. (2002)	33 FH+ 32 FH−	A = 61 G = 54% male E = 15	MMSE CERAD battery WMS-R Logical Memory BVRT COWAT Trail Making Test, Parts A and B Symbol Digit Modalities Test Taste Detection Threshold, Memory, Recognition, Identification Smell Detection Threshold, Memory, Recognition, Identification	FH+ subjects performed worse on: Logical Memory I Trail Making Test Part A Smell Detection Threshold Smell Memory Taste Memory

Abbreviations Used:

3MS = Modified Mini-Mental State Exam
AD = Alzheimer's disease
BDAE = Benton Diagnostic Aphasia Examination
BNT = Boston Naming Test
BVRT = Benton Visual Retention Test
CAMCOG = Cambridge Mental Disorders of the Elderly Examination—Cognitive Section
CERAD = Consortium to Establish a Registry for Alzheimer's Disease
CFT = Complex Figure Test
COWAT = Controlled Oral Word Association Test
CVLT = California Verbal Learning Test
DRS = Dementia Rating Scale
$\epsilon4$ = APOE $\epsilon4$ allele
$\epsilon3$ = APOE $\epsilon3$ allele
$\epsilon2$ = APOE $\epsilon2$ allele
FAD = Familial Alzheimer's disease

FH = Family history of AD
HS = High School
MMSE = Mini-Mental State Examination
MRI = Magnetic resonance imaging
NART = National Adult Reading Test
NR = Not reported
PASAT = Paced Auditory Serial Addition Test
PET = Positron emission tomography
RAVLT = Rey Auditory Verbal Learning Test
SRT = Selective Reminding Test
WAIS = Wechsler Adult Intelligence Scale
WAIS-R = Wechsler Adult Intelligence Scale-Revised
WCST = Wisconsin Card Sorting Test
WISC = Wechsler Intelligence Scale for Children
WISC-R = Wechsler Intelligence Scale for Children–Revised
WMS = Wechsler Memory Scale
WMS-R = Wechsler Memory Scale-Revised

APPENDIX 2

Neuroimaging Studies of Preclinical Alzheimer's Disease

Part A. Longitudinal structural MRI studies examining development of Alzheimer's disease

Authors	Number and Type of Subjects; Methodological Comments	Age (A = mean years unless otherwise indicated) Gender (G = percent male) Education Level (E = mean years)	Regions Examined	Results
Fox et al. (1996)	3 FH+ cases 4 FH+ controls (All 7 from a familial AD pedigree) 38 normal controls 3-year study	FH+ A = 45 G = 86% male E = NR Normal controls A = 48 G = 50% male E = NR	Hippocampal formation volume	In the 3 subjects who developed AD, significant, asymmetric hippocampal atrophy was detectable before the development of symptoms The 4 FH+ subjects who remained well did not differ from NCs on hippocampal volume
Fox et al. (2001)	4 FH+ cases (All 4 from a familial AD pedigree) 20 normal controls 8-year study	FH+ A = median 43 G = NR E = NR Normal controls A = median 51 G = NR E = NR	Whole brain	FH+ subjects had higher annual rates of global volume loss, particularly in the medial temporal lobe, inferolateral temporal lobe, parietal lobe, and posterior cingulate
Kaye et al. (1997)	12 cases 18 controls Mean length of follow-up was 3.5 years	Cases A = 90 G = 42% male E = 15 Controls A = 87 G = 44% male E = 14	Supratentorial intracranial cavity volume; Temporal lobe tissue volume; Parahippocampal gyrus volume; Hippocampal volume	Subjects who developed AD had smaller hippocampal and temporal lobe tissue volumes at baseline and showed greater temporal lobe atrophy over time. Hippocampal and temporal lobe tissue volumes at baseline and rate of temporal lobe volume loss were significant predictors of group status.

Part B. Longitudinal structural MRI study comparing nondemented $\epsilon4+$ and $\epsilon4-$ subjects

Authors	Number and Type of Subjects; Methodological Comments	Age etc.	Regions Examined	Results
Cohen et al. (2001)	16 $\epsilon4+$ 9 $\epsilon4-$ 2-year study Groups also compared on neuropsychological performance (see findings reported above)	$\epsilon4+$ A = 55 G = 0% male E = NR $\epsilon4-$ A = 61 G = 0% male E = NR	Hippocampal volume	Compared with $\epsilon4-$ subjects, $\epsilon4+$ subjects demonstrated greater hippocampal volume loss

Part C. Longitudinal functional imaging study comparing nondemand $\epsilon4+$ $\epsilon4-$ subjects

Authors	Number and Type of Subjects; Methodological Comments	Age (A = mean years unless otherwise indicated) Gender (G = percent male) Education Level (E = mean years)	Tasks Used	Results
Reiman et al. (2001)	10 $\epsilon4+$ 15 $\epsilon4-$ All subjects were FH+	$\epsilon4+$ A = 56 G = 30% male E = 15	Resting PET examining regional rates of glucose metabolism	$\epsilon4+$ subjects had significantly greater glucose metabolism declines over 2 years in temporal, posterior cingulate, prefrontal cortex, basal forebrain, parahippocampal gyrus, and thalamus

	2-year study	ε4−		
		A = 57		
	Groups also compared	G = 33% male		
	on neuropsychological	E = 16		
	performance (see find-			
	ings reported above)			

Part D. Cross-sectional structural MRI studies comparing nondemented ε4+ and ε4− subjects

Authors	Number and Type of Subjects; Methodological Comments	Age (A = mean years unless otherwise indicated) Gender (G = percent male) Education Level (E = mean years)	Regions Examined	Results
den Heijer et al. (2002)	117 ε4+ 259 ε3/ε3 52 ε2+	A = 72 G = 48% male E = NR	Hippocampal and amygdalar volume	ε4+ subjects had smaller hippocampal and amygdalar volumes bilaterally No significant differences between ε2+ subjects and ε3/ε3 subjects
Jack et al. (1998)	30 ε4+ 95 ε4−	ε4+ A = 80 E = 13 ε4− A = 79 E = 13 G = 26% male	Hippocampal volume	Trend toward smaller hippocampi in the ε4+ group
Jernigan et al. (2001)	21 ε4+ 22 ε4−	A = NR G = NR E = NR	Whole brain	ε4+ subjects had lower subcortical gray matter volumes than did ε4− subjects; the difference was due to lower lenticular nucleus volumes in the ε4+ subjects
Plassman et al. (1997)	3 ε4+ twin pairs 7 ε4− twin pairs	ε4+ A = 65 G = 33% male E = 15 ε4− A = 62 G = 29% male E = 13	Hippocampal volume	Controlling for education, the ε4+ group had smaller hippocampi than did the ε4− group; there were no group differences in hippocampal volume asymmetry.
Reiman et al. (1998)	11 ε4/ε4 22 ε4− All subjects were FH+	ε4+ A = 55 G = 27% male E = 17 ε4− A = 56 G = 27% male E = 16	Hippocampal volume	ε4 homozygotes had 8% smaller left and right hippocampal volumes, but the difference was not statistically significant
Schmidt et al. (1996)	39 ε4+ 175 ε4− Groups also compared on neuropsychological performance (see findings reported above)	ε4+ A = 59 G = about 50% male E = 11 ε4− A = 61 G = about 50% male E = 12	Whole brain	No differences in presence of infarcts, white matter hyperintensities, sulcal widening, ventricular enlargement, or hippocampal/ parahippocampal volumes
Tohgi et al. (1997)	14 ε4+ 40 ε4− Groups also compared on neuropsychological performance (see findings reported above)	A = 59 G = 52% male E = 12	Hippocampal volume	Compared to ε4− subjects, ε4+ subjects had smaller right hippocampal volumes

Part E. Cross-sectional functional imaging studies comparing at-risk subjects ($\epsilon4+$ or FH+) to non-at-risk subjects ($\epsilon4-$ or FH−)

Authors	Number and Type of Subjects; Methodological Comments	Age (A = mean years unless otherwise indicated) Gender (G = percent male) Education Level (E = mean years)	Tasks Used	Results
Bookheimer et al. (2000)	16 $\epsilon4+$ 14 $\epsilon4-$ fMRI	$\epsilon4+$ A = 63 G = 44% male E = 15 $\epsilon4-$ A = 62 G = 50% male E = 15	Word pair learning and recall task compared with resting condition	$\epsilon4+$ subjects exhibited greater magnitude and extent of activation in left hippocampal, parietal, and prefrontal regions than did $\epsilon4-$ subjects
Burggren et al. (2002)	13 $\epsilon4+$ 12 $\epsilon4-$ fMRI	$\epsilon4+$ A = 65 G = 38% male E = 16 $\epsilon4-$ A = 66 G = 42% male E = 16	Digit span forward task (1–8 digits)	No significant group differences in activation, even as task difficulty increased
Kennedy et al. (1995)	24 FH+ subjects from a familial AD pedigree 16 age-matched control subjects PET	FH+ A = 45 G = NR E = NR Controls: A = 50 G = NR E = NR	Resting PET examining global and regional rates of glucose metabolism	Compared to controls, the at-risk subjects had lower global and temporoparietal glucose metabolism
Reiman et al. (1996)	11 $\epsilon4/\epsilon4$ 22 $\epsilon4-$ All subjects were FH+ PET	$\epsilon4+$ A = 55 G = 27% male E = 17 $\epsilon4-$ A = 56 G = 27% male E = 16	Resting PET examining regional rates of glucose metabolism	$\epsilon4$ homozygotes had significantly lower glucose metabolism in posterior cingulate and bilateral parietal, temporal, and prefrontal regions
Reiman et al. (2004)	12 $\epsilon4+$ (all heterozygotes) 15 $\epsilon4-$ PET	$\epsilon4+$ A = 31 G = 25% male E = 16 $\epsilon4-$ A = 31 G = 20% male E = 16	Resting PET examining regional rates of glucose metabolism	$\epsilon4+$ subjects had significantly lower glucose metabolism bilaterally in posterior cingulate, parietal, temporal, and prefrontal regions
Smith et al. (1999)	14 $\epsilon4+$, FH+ 12 $\epsilon4-$, FH− fMRI	$\epsilon4+$, FH+ A = 52 G = 0% male E = 15 $\epsilon4-$, FH− A = 53 G = 0% male E = 15	Visual naming Letter fluency	$\epsilon4+$, FH+ subjects had lower activation in the bilateral mid- and posterior inferotemporal regions during both tasks

Abbreviations Used:
AD = Alzheimer's disease
$\epsilon4$ = APOE $\epsilon4$ allele
$\epsilon3$ = APOE $\epsilon3$ allele
$\epsilon2$ = APOE $\epsilon2$ allele
fMRI = Functional magnetic resonance imaging

FH = Family history of AD
MMSE = Mini-Mental State Examination
MRI = Magnetic resonance imaging
NC = Normal control
NR = Not reported
PET = Positron emission tomography