The Neuropsychology of the Development of Alzheimer’s Disease

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INTRODUCTION

Dementia, particularly Alzheimer’s disease (AD), was first emphasized as a major public health problem 30 years ago (Katzman 1976). This led to increased research efforts to understand the clinical presentation and diagnosis, the pathobiology and underlying cause, treatments for established disease, and, more recently, an emphasis on early diagnosis and treatment.

It is fortunate that there is considerable consensus with regard to the clinical phenotype of AD. This has led to the development of widely accepted clinical criteria for use in both clinical and research settings (American Psychiatric Association, 1994; McKhann, Drachman, Folstein, Katzman, Price, & Stadlan, 1984). Many subsequent studies have demonstrated that these criteria can be reliably applied across sites and that accuracy of diagnosis in comparison with pathological findings is high (e.g., Blacker, Albert, Bassett, Go, Harrell, & Folstein, 1994). Agreement about clinical criteria also permitted the conduct of a large number of clinical trials, ultimately leading to approval of five medications for AD, four cholinesterase inhibitors and Memantine (an NMDA antagonist, which reduces glutamate transmission). These medications offer symptomatic relief, but do not alter the rate at which patients decline over time.

This has increased the urgency of finding better treatments for AD, as the demographic shift in the population toward greater life expectancy suggests geometrically increasing numbers of AD patients in the coming
decades, unless more effective treatments can be developed. An improved understanding of the neurobiology of AD has led to optimism that disease-modifying treatments may be on the horizon (Selkoe, 2005). There is, however, concern that if disease is too far advanced, response to these treatments may be muted. This, in turn, has led to a focus on identifying patients as early as possible in the course of disease.

Since AD was first described, it has been clear that the symptoms develop gradually over many years (Alzheimer, 1907). Thus, it would seem that, by definition, there must be a prodromal phase of disease during which symptoms are evolving but the individual does not yet meet criteria for dementia. Various terms have been used to describe this prodromal phase, but the term Mild Cognitive Impairment (MCI) has gained the widest recognition (Flicker, Ferris, & Reisberg, 1991; Petersen, Smith, Waring, Ivnik, Tangalos, & Kokmen, 1999). There has been divergence, however, in how the criteria for MCI have been applied, leading to widely varying estimates of its prevalence in the population (e.g., Larrieu et al., 2002; Ritchie, Artero, & Touchon, 2001) and controversy regarding its utility as a clinical syndrome (Gautier & Touchon, 2005).

The current review will focus on the neuropsychology of AD and MCI, delineating the broad areas of consensus that exist and, where there is disagreement, outlining the primary issues to be resolved. Since the cognitive deficits in AD and MCI are the result of selective alterations in the brain, the relationship between neuropsychological deficits and neuropathological or brain imaging findings will also be discussed, where relevant. An increasing area of interest is the boundary between normal aging and MCI, as well as predictors of maintenance of cognitive function with age, thus, recent research findings in this area will also be discussed.

**ALZHEIMER’S DISEASE AND RELATED DISORDERS**

As noted above, the most common form of dementia is AD, accounting for approximately 70% of the cases of dementia (either alone or in combination with other pathologies). Other causes of dementia include: frontotemporal dementia (FTD), diffuse Lewy body dementia (DLBD), multi-infarct dementia (MID), the dementia of Parkinson’s disease (PD) and Creutzfeldt-Jakob disease (CJD). Each of these has a characteristic clinical presentation, caused by characteristic pathological changes in the brain. Most of these dementing disorders cannot currently be definitively diagnosed during life without highly invasive procedures, such as a brain biopsy (with the exception of CJD). The clinical diagnosis is therefore considered “probable.” The Appendix to this chapter provides
information about the clinical presentation of AD and the ways in which it differs from the less common forms of dementia noted above.

This chapter will focus on research in the area of AD for several reasons. First, the neuropsychological approaches to studying AD are similar to those employed in the study of the other dementing disorders. Second, the conceptual issues that are the primary focus of research today in AD are likely to represent the future direction of research that will be undertaken with regard to the other disorders.

The initial cognitive deficit in the majority of patients with AD is a gradually progressive difficulty with learning and retention of new information (generally referred to as a deficit in episodic memory). This is consistent with the fact that the earliest pathological changes of the disease are seen in medial temporal lobe regions essential for normal memory (e.g., the entorhinal cortex and hippocampus; Braak & Braak, 1998). Over time, pathological abnormalities (e.g., neurofibrillary tangles, neuritic plaques, synaptic and neuronal loss) impact more and more brain regions, until these abnormalities are seen throughout the temporal, parietal and frontal lobes. The range of neuropsychological deficits in the patients increases as a function of this expanding pathology. The Appendix contains a description of the evolution of disease in a typical case of AD. The average duration of disease, after diagnosis, is approximately 10 years. Some brain regions have minimal pathology, even in the end stages of disease (e.g., the primary motor and sensory cortices). The selective manner in which the disease begins and progresses over time is why AD is thought to represent the degeneration of a selective brain system, with multiple nodes (Braak, Del Tredici, Schultz, & Braak, 2000). Other neurodegenerative disorders share this characteristic; recent advances in the treatment for PD have capitalized on this fact (Vitek et al., 2003).

There is consensus regarding how AD is clinically diagnosed, as mentioned above. This fact, in combination with the selective system degeneration in the brain, is likely the reason why neuropsychological studies of established AD have produced generally consistent findings. These are described in detail below.

PRODROMAL AD

There is also considerable evidence to support the argument that there is a transitional phase between normal function and AD dementia. This is consistent with the fact that the pathological changes take many years to accumulate in the brain. The feasibility of studying this transitional phase is based on the fact that the clinical hallmark of AD is a progressive
DECLINE IN COGNITIVE FUNCTION. A NUMBER OF RESEARCH GROUPS HAVE THEREFORE RECRUITED NONDEMENTED INDIVIDUALS WITH MILD COGNITIVE IMPAIRMENTS AND FOLLOWED THEM OVER TIME, WITH THE GOAL OF EXAMINING THE NATURE OF THE COGNITIVE CHANGES THAT OCCURRED DURING THE TRANSITIONAL PHASE BETWEEN NORMALITY AND FRANK DEMENTIA. THESE STUDIES HAVE DEMONSTRATED THAT COGNITIVE IMPAIRMENTS ARE PRESENT 5–10 YEARS PRIOR TO DEMENTIA AND CAN BE USED TO PREDICT WITH SIGNIFICANT ACCURACY WHICH SPECIFIC INDIVIDUALS ARE DESTINED TO DEVELOP DEMENTIA MANY YEARS LATER (E.G., ALBERT, MOSS, TANZI & JONES, 2001; TIERNEY, YAO, KISS, & McDOWELL, 2005).

NEUROPSYCHOLOGICAL STUDIES OF INDIVIDUALS DEFINED AS NEITHER NORMAL NOR DEMENTED DEMONSTRATE PROGRESSIVE DECLINES IN COGNITION OVER TIME, WHICH ARE PARTICULARLY STRIKING IN THE AREA OF EPISODIC MEMORY, AS DISCUSSED FURTHER BELOW. OTHER DOMAINS APPEAR TO BE AFFECTED AS WELL, CONSISTENT WITH THE FACT THAT THE CLINICAL CRITERIA FOR DEMENTIA REQUIRE IMPAIRMENT IN TWO OR MORE COGNITIVE DOMAINS.

PATHOLOGICAL FINDINGS IN NONDEMENTED COGNITIVELY IMPAIRED INDIVIDUALS ARE PARTICULARLY IMPORTANT IN THIS CONTEXT, SINCE IT IS ESSENTIAL TO DEMONSTRATE THAT AT LEAST SOME OF THESE NONDEMENTED INDIVIDUALS HAVE THE PATHOLOGICAL FEATURES OF AD. GIVEN THE DIFFICULTY OF OBTAINING BRAIN TISSUE AT A TIME WHEN INDIVIDUALS ARE NOT DEMENTED, IT IS NOT SURPRISING THAT FEW PUBLISHED RESULTS ARE AVAILABLE. THE LARGEST SAMPLE COMES FROM THE RELIGIOUS ORDER STUDY AND INCLUDED 37 INDIVIDUALS WITH A CLINICAL DIAGNOSIS OF MCI, 60 NORMAL CONTROLS, AND 83 CASES OF AD (BENNETT ET AL., 2005A). OF THE 37 MCI CASES, 40% HAD A LOW LIKELIHOOD OF AD BASED ON THE NEUROPATHOLOGICAL CRITERIA FOR AD (KNOWN AS THE NIA-REAGAN, NIA-R, CRITERIA), WITH 60% DEMONSTRATING AN INTERMEDIATE OR HIGH LIKELIHOOD OF AD. THIS WAS IN CONTRAST TO THE NORMALS, WHERE THESE PROPORTIONS WERE REVERSED (60% VS. 40%, RESPECTIVELY). ONLY 10% OF THE CASES WITH CLINICALLY DIAGNOSED AD HAD A LOW LIKELIHOOD OF AD BASED ON PATHOLOGICAL CRITERIA.

A REPORT FROM THE MAYO CLINIC INCLUDED 15 INDIVIDUALS WHO DIED WITH A CLINICAL DIAGNOSIS OF MCI, 28 NORMAL CONTROLS AND 23 CASES OF AD (PETERSEN ET AL., 2006). MOST PATIENTS WITH MCI DID NOT MEET NEUROPATHOLOGIC CRITERIA FOR AD; THE AUTHORS ARGUED THAT THE PATHOLOGICAL FEATURES REPRESENTED A TRANSITIONAL STATE OF EVOLVING AD. THESE REPORTS CONTRAST WITH THE FINDINGS FROM WASHINGTON UNIVERSITY WHERE ALMOST ALL OF THE CASES MET PATHOLOGICAL CRITERIA FOR AD (MORRIS ET AL., 2001). THIS SUGGESTS THAT THERE IS LIKELY VARIATION IN THE CLINICAL CRITERIA USED TO DEFINE THE CASES DURING LIFE.

IT IS EVIDENT THAT IN SOME SETS OF COGNITIVELY IMPAIRED NONDEMENTED CASES, THE PROPORTION OF THOSE WITH A HIGH LIKELIHOOD OF AD BASED ON PATHOLOGICAL CRITERIA IS MUCH LESS THAN AMONG INDIVIDUALS WHO MEET CLINICAL CRITERIA FOR AD. HOWEVER, A SUBSTANTIAL NUMBER OF NONDEMENTED COGNITIVELY IMPAIRED INDIVIDUALS DO MEET PATHOLOGICAL CRITERIA FOR AD. IT IS ALSO IMPORTANT TO NOTE THAT MANY OF THE CASES, REGARDLESS OF CLINICAL DIAGNOSIS,
had evidence of vascular disease (Bennett et al., 2005a; Petersen et al., 2006).

Taken together, these findings indicate that it is possible to identify individuals in a transitional state between normal function and AD dementia, and that such individuals have cognitive and brain changes that are consistent with a transitional phase of disease. For research purposes, it seems important to retain the distinctiveness of this phase of disease so that the characteristics of this phase and the effectiveness of interventions can be carefully studied. In clinical settings, distinguishing a transitional phase of disease also seems very important in order to provide appropriate feedback to patients. Recent research studies indicate that there is considerable variation in the clinical outcome of individuals who are said to be cognitively impaired but nondemented by whatever criteria. As prediction of outcome remains challenging, even in research settings, it seems important to communicate this lack of certainty when providing a clinical diagnosis to individual patients.

HETEROGENEITY OF MCI

A review of the literature suggests that much of the controversy surrounding the term MCI derives largely from the fact that the criteria have been implemented in a variety of ways in research settings, while at the same time the syndrome is more heterogeneous than originally suggested. The clinical criteria have changed over time in recognition of this heterogeneity. However, a number of important issues remain to be clarified.

The MCI criteria elucidated by Petersen and colleagues in 1999 implied that cases of MCI represented a fairly uniform group of individuals (Petersen, Smith, Waring, Ivnik, Tangalos, & Kokmen, 1999). These criteria were as follows:

- memory complaint, corroborated by an informant if possible
- objective memory impairment for age
- relatively preserved general cognition for age
- intact basic activities of daily living
- not demented.

Following studies demonstrating that MCI cases defined in this manner had a more variable outcome than had been previously suggested, the criteria were modified to permit clinical subtypes with variable outcomes, based on the presumed etiology underlying the disorder. Two primary subtypes were delineated, based on whether a predominant memory disorder was present or absent, called amnestic and nonamnestic MCI.
(Petersen, 2004). The revised criteria also acknowledged the possibility that more than one cognitive domain might be impaired within each of these subtypes (e.g., amnestic MCI, single or multiple domain impaired). These revised criteria are conceptually similar to the term Cognitive Impairment No Dementia (CIND) introduced by the Canadian Study of Health and Aging (Davis & Rockwood, 2004) in that they encompass a broad range of cognitive deficits caused by multiple etiologies.

In this context, the original clinical criteria for MCI were clearly focused on amnestic MCI, and Petersen and colleagues were attempting to focus on individuals likely to be in the prodromal phase of AD. Their work and that of numerous other groups has since demonstrated that amnestic MCI subjects (single or multiple domain impaired) are at increased risk of progressing to a diagnosis of AD over time.

What was also unrecognized in the original reports was the importance of the source of subjects as a factor in both the severity and the nature of the population under study. In retrospect it now seems clear that the broader one casts the net of inclusion in a study, the more likely one is to include individuals with less severe underlying disease. It is therefore not surprising that studies emerging from memory clinics in tertiary care settings report the highest proportion of individuals who progress to meet criteria for AD over time (e.g., Rubin, Morris, Grant, & Vendegna, 1989); whereas studies that recruit broadly from the community (e.g., via the media) are likely to have much lower rates of “conversion” to AD on follow-up (e.g., Daly, Zaitchik, Copeland, Schmahmann, Gunther, & Albert, 2000). This does not necessarily mean that the underlying disease process is different, but rather that the investigators have captured a different range of disease severity within their study population.

An additional source of variation is introduced when studies are conducted in epidemiological settings as opposed to clinical settings. In epidemiological settings it is virtually impossible to require that each subject should have an informant (as is usually the case in clinic-based studies), as epidemiological studies seek to represent the entire range of individuals in the population. Therefore it is necessary to rely more heavily on neuropsychological testing as the marker of cognitive decline. This increases the importance of the particular cognitive tests that have been selected. The reliability and validity of each of the tests are critical, as well as the range of cognitive domains included in the test battery. For example, if tests are selected that have a ceiling effect, it is likely that fewer individuals with impairments will be found. Likewise, if a particular cognitive domain is not included in a test battery (e.g., executive function), it is not possible to determine whether the subjects would have been impaired in that domain. In order to maximize enrollment and follow-up it is also necessary to reduce the length of the evaluation in an
epidemiological setting, as opposed to a clinical setting, resulting in less detailed information than is optimal. These restrictions, if applied equally to all participants, most likely influence the absolute numbers of individuals identified in a particular category (as sensitivity will vary depending on the procedures employed), but they should not alter the relative proportion of individuals meeting criteria for various diagnostic categories, or the proportion of individuals who change status over time.

As studies of nondemented cognitively impaired individuals expanded to broader settings, it also became clear that there were substantial numbers of individuals whose memory impairment was the predominant but not sole cognitive problem that could be seen. Many individuals with prodromal AD were slightly impaired in other domains (e.g., language or executive function) in addition to memory. Likewise, individuals were seen whose primary cognitive impairment was in domains other than memory (e.g., attention or spatial skill). The recent revision of the MCI criteria (Petersen, 2004) recognizes these findings and appropriately acknowledges that multiple clinical syndromes must, by definition, have a transitional phase during which cognitive impairments are in evolution. The revised criteria now describe criteria for amnestic MCI (single and multiple domains impaired), which is thought to represent the majority of individuals who will progress to a diagnosis of AD over time. Those with nonamnestic MCI (single and multiple domains impaired) are thought to pertain to the transitional phase of other dementias (e.g., FTD, MID, DLBD) as well as psychiatric disorders (e.g., depression), though in practice these distinctions can be blurred (e.g., Fisk, Merry, & Rockwood, 2003). (See Petersen & Morris, 2005 and DeCarli, 2003 for a further discussion of these issues.)

It is therefore necessary to evaluate an MCI case who comes for clinical evaluation with the same rigor one would bring to the diagnosis of a patient with dementia. That is, to consider all potential medical, psychiatric or neurologic causes of cognitive impairment before making a diagnosis. The number of nonamnestic MCI cases that have been followed to a diagnosis of dementia is limited (e.g., Yaffe, Petersen, Linquist, Kramer, & Miller, 2006). It is therefore difficult to provide much information about which specific MCI criteria they fit the best, and the numbers of subjects with various non-AD dementias or psychiatric disorders one is likely to see within a group of MCI cases, defined broadly. There is, however, sufficient evidence to indicate that cases of depression will be included in this group. Moreover, cases of amnestic MCI who progress to AD are also likely to have neuropsychiatric symptoms (particularly dysphoria and irritability), thus making the diagnostic process challenging (Copeland, Daly, Hines, Mastromauro, Zaitchik, Gunther, & Albert, 2003; Hwang, Masterman, Ortiz, Fairbanks, & Cummings, 2004).
NEUROPSYCHOLOGICAL TESTING IN AD AND MCI

Episodic Memory

Difficulty with the acquisition of new information is generally the first and most salient symptom to emerge in patients with AD, as noted above. When clinical neuropsychological tests are used to evaluate memory in AD patients, it is clear that recall and recognition performance are impaired in both the verbal and nonverbal domain (Storandt & Hill, 1989; Wilson, Bacon, Fox, & Kaszniak, 1983).

Experimental studies have examined AD patients to determine whether the manner in which information is lost over brief delays is unique in any way to this patient group. A comparison of AD patients to amnestic patients with Korsakoff’s syndrome (KS) and demented patients with Huntington’s disease (HD) demonstrated that AD patients recalled significantly fewer words over a 2-minute delay than either of the other two patient groups (Moss, Albert, Butters, & Payne, 1986). Whereas the KS, HD, and normal control subjects lost an average of 10% to 15% of the verbal information between the 15-second and 2-minute delay intervals, patients with AD lost an average of 75% of the material.

Numerous studies have compared AD patients to controls and confirmed that the patients consistently showed a rapid loss of information over brief delays (e.g., Butters, Salmon, Heindel, & Granholm, 1988; Hart, Kwentus, Harkins, & Taylor, 1988). A comparison of AD patients and patients with FTD (Moss & Albert, 1988) and with progressive supranuclear palsy (PSP) (Milberg & Albert, 1989) demonstrated the severe recall deficits of the AD patients in comparison to patients with FTD and PSP. Consistent with the findings above, a comparison of a range of memory measures in a national study involving mildly impaired AD patients and controls (the CERAD study) concluded that measures of delayed recall (in the form of a saving score where measures are adjusted for the information originally acquired) are best at discriminating AD patients from controls (Welsh, Butters, Hughes, Mohs, & Heyman, 1991, 1992).

Measures of episodic memory are, however, not particularly useful in staging AD patients across levels of severity, primarily because memory is so impaired early in the course of disease. An analysis of the CERAD study data found that a combination of measures that included fluency, visuospatial ability, and recognition memory best differentiated mildly impaired patients from those with either moderate or severe levels of impairment (Welsh et al., 1992). These findings support the conclusion that in most patients with AD memory impairments precede impairments in language and spatial function.

As noted above, recently numerous research groups have recruited
nondemented individuals with MCI and followed them over time to determine the nature of the cognitive changes that occurred during prodromal AD. Among these studies there is considerable consensus that tests of memory are significantly different among nondemented individuals with mild memory deficits who receive a diagnosis of AD on follow-up, as compared with those who also have memory problems but do not progress to AD within a few years’ time (Albert et al., 2001; Bondi et al., 1994; Chen, Ratcliff, Belle, Cauley, DeKosky, & Ganguli, 2000; Howieson et al., 2003; Jacobs, Sano, Dooneief, Marder, Bell, & Stern, 1995; Kluger, Ferris, Golomb, Mittelman, & Reisberg, 1999; Newmann, Warrington, Kennedy, & Rossor, 1994; Petersen, Smith, Ivnik, Kokmen, & Tangalos, 1994; Rubin, Morris, Grant, & Vendegna, 1989; Small, LaRue, Komo, Kaplan, & Mandelkern, 1995; Tierney et al., 1996; Tuokko, Vernon-Wilkinson, Weir, & Beattie, 1991).

There is also widespread agreement concerning the underlying cause of these memory changes in AD. Synaptic dysfunction, neuronal loss, and AD pathology first occur in medial temporal lobe regions (Hyman, VanHoesen, Damasio, & Barnes, 1984; Selkoe, 2005). This is particularly evident in the entorhinal cortex and CA1 region of the hippocampus (Gomez-Isla et al., 1996), brain regions critical for normal memory (Squire & Zola, 1996). This conclusion is supported by in vivo neuroimaging studies showing significant atrophy of these brain regions in MCI cases (for reviews see Atiya, Hyman, Albert, & Killiany, 2003; Kantarci & Jack, 2003).

Executive Function

In addition to memory problems, mildly impaired AD patients are substantially impaired in a set of abilities collectively referred to as “executive functions.” These include: the concurrent manipulation of information, cue-directed attention, and concept formation.

An alteration in executive function ability among AD patients was not recognized initially, as early studies did not include sensitive tests of executive function. Once investigators began to evaluate mildly impaired AD patients with sensitive tests of executive function, these impairments became apparent. For example, mildly impaired patients were shown to be impaired on a task that involved coordinating two concurrent tasks (Baddeley, Logie, Bressi, Della Sala, & Spinnler, 1986) as well as tasks requiring shifting between stimulus dimensions (Filoteo, Delis, Massman, Demadura, Butters, & Salmon, 1992; Sahakian et al., 1990). Mild-to-moderately impaired patients also demonstrate executive function deficits (Becker, 1988; Bondi et al., 2002; Lafleche, Stuss, Nelson, & Picton, 1990; Morris & Baddeley, 1988; Nestor, Parasuraman, & Haxby, 1991).

In order to determine whether an impairment in executive function
precedes or coexists with significant deficits in spatial and language function, a number of studies have compared very mildly impaired AD patients to controls on tasks assessing a range of cognitive domains. Grady et al. (1988) reported that deficits on tasks of memory and executive function preceded impairments in language. Lafleche and Albert (1995) attempted to characterize the specific aspect of executive function that was impaired in very mildly impaired AD patients. They assessed a broad range of executive abilities, including: set shifting and self-monitoring (i.e., the concurrent manipulation of information), cue-directed attention (e.g., the ability to use cues to direct attention), and concept formation (e.g., abstraction). Most of the tasks that revealed a significant deficit were those that required set shifting and self-monitoring. By contrast, performance on tasks that assessed cue-directed attention and verbal concept formation were not significantly impaired in the patients. Likewise, performance on the tests of confrontation naming, figure copying, and sustained attention were not impaired. Taken together, these findings suggest that selected aspects of executive function, particularly those involving set shifting and self-monitoring, are affected very early in the course of the disease.

There is, however, a lack of consensus regarding whether executive function deficits are prominent during prodromal AD. The discrepancies among studies are due, at least in part, to the fact that few studies have examined a wide variety of cognitive domains, thus limiting the types of associations that can be found.

A number of studies have reported that executive function abnormalities are evident in the prodromal stage of AD (Albert et al., 2001; Albert, Blacker, Moss, Tanzi, & McArdle, in press; Chen et al., 2000; Chen, Ratcliff, Belle, Cauley, DeKosky, & Ganguli, 2001; Grady et al., 1988; Sahakian et al., 1990, Tierney et al., 1996). Others have reported that declines in confrontation naming are more likely to be impaired among those destined to develop AD (e.g., Saxton et al., 2004). The reasons for these discrepancies remain to be resolved.

The brain abnormalities responsible for the executive function deficits seen among individuals destined to develop AD are also unclear. At least two potential neurobiological explanations have been suggested. Findings from functional imaging indicate that during prodromal AD there is dysfunction within a brain network that involves the dorsolateral prefrontal cortex and the anterior cingulate (Milham et al., 2002). Alterations in these brain regions have been associated with impairments in executive function (Bush et al., 2002). An alternative possibility is that the disruption of the cortico-cortical connections that are seen in AD, and are not specific to the frontal lobes (Morrison & Hof, 2002), may be responsible for executive dysfunction during prodromal AD.
Language

Mild-to-moderately impaired AD patients have impairments in confrontation naming and verbal fluency. Some investigators have argued that these deficits are the result of a broader impairment in semantic memory, defined as “that system which processes, stores and retrieves information about the meaning of words, concepts and facts” (Warrington, 1975).

Semantic memory abnormalities in patients with AD have been documented using a range of tasks that include category fluency (Chan, Butters, Paulsen, Salmon, Swenson, & Maloney, 1993; Hodges, Salmon, & Butters, 1992; Martin & Fedio, 1983; Troster, Salmon, McCullough, & Butters, 1989), category membership (Grossman, Robinson, Biassou, White-Devine, & D’Esposito, 1998), confrontation naming (Grossman et al., 1998; Hodges et al., 1992; Martin & Fedio, 1983), and similarity judgments (Chan et al., 1993, 1995, 1997). In addition, several studies of word priming (Glosser, Grugan, Friedman, Lee, & Grossman, 1998; Milberg, McGlinchey-Berroth, Duncan, & Higgs, 1999; Salmon, Shimamura, Butters, & Smith, 1988) have reported significant deficits in AD patients, though other studies failed to find this effect (Nebes & Brady, 1988).

Studies of semantic memory in AD patients suggest that some conceptual domains may be more impaired than others, in particular, that patients with AD have a specific impairment in the conceptual domain of “living things.” For example, in studies assessing confrontation naming (Grossman et al., 1998; Silveri, Daniele, Giustolisi, & Gainotti, 1991) and picture recognition (Silveri et al., 1991), mild to moderate AD patients performed significantly worse on living things than nonliving things. Other studies have, however, failed to reveal such category-specific differences, using a variety of tasks including recognition naming (Tippett, Grossman, & Farah, 1996), category-naming fluency and drawing fluency (Mickanin, Grossman, Onishi, Auriacombe, & Clark, 1994), and category membership judgments (Grossman et al., 1998). It has been suggested that discrepant findings regarding category-specific semantic loss in AD patients relate to the fact that some brain regions are more critical for category-specific judgments than others, and the appearance of a deficit depends on the anatomic distribution of disease in the specific patients examined (Grossman et al., 1998). These issues remain unresolved.

Visuospatial Function

Visuospatial function is impaired in the course of AD. On simple copying tasks, such as drawing a clock or a triangle, mild AD patients do not differ from normal controls (Kararasch, Sinerva, Granholm, Rinne, & Laine, 2005; Rouleau, Salmon, Butters, Kennedy, & McGuire, 1992). However,
visuospatial impairments are common among mild-to-moderately impaired patients (Kurylo, Corkin, & Growdon, 1994; Rouleau, Salmon, & Butters, 1996).

When subjects are asked to draw a figure to command, such as a clock, impairments are evident among mildly impaired AD patients. However, these appear to be the result of conceptual errors, rather than visuospatial errors. Mildly impaired AD patients tend to make perseverative errors and “stimulus-bound responses” but graphic difficulties are extremely uncommon at this stage of disease (Rouleau et al., 1992). Evaluations of patients at differing levels of severity (Heinik, Solomesh, Shein, & Becker, 2002) as well as longitudinal data collected from the same individuals (Rouleau et al., 1996) indicate that performance on clock drawing to command gets progressively worse over time, and that conceptual errors are particularly sensitive to overall change in dementia severity.

The sensitivity of clock drawing to command in mild AD patients led investigators to determine whether this task might be sensitive to individuals in the prodromal phase of AD. However, a number of studies indicate that clock drawing to command is not useful for the identification of MCI cases (Powlishta et al., 2002; Siegerschmidt, Mosch, Siemen, Forstl, & Bickel, 2002).

It should be noted that some aspects of spatial skill are very well retained early in the course of AD. Mirror-tracing skill, which involves tracing a pattern (e.g., a 4- or 6-pointed star seen only in a mirror-reversed view), has been the best studied. While mild-to-moderately AD patients have poor recall or recognition of their mirror-tracing experience, they acquire and retain mirror-tracing skill and generalize it to another object as well as normal subjects (Gabrieli, Corkin, Mickel, & Growdon, 1993; Rouleau et al., 2002). This is comparable to the findings reported in the amnestic patient H.M. (Gabrieli et al., 1993).

Attention

Mild AD patients do not have impairments on a simple test of sustained attention that makes few demands on memory, such as digit span forward. However, mildly impaired patients demonstrate selective impairments on attentional tasks that are more complex. Tests of choice reaction time and cued choice reaction time are impaired in mild AD (Levinoiff, Saumier, & Chertkow, 2005). Dual task performance is also impaired in mild AD patients, particularly when one or both of the tasks are not relatively automatized (Crossley, Hiscock, & Foreman, 2004; Fernandez-Duque & Black, 2006).
ADDITIONAL APPROACHES

Inference of Emotion and Beliefs

Successful social interaction depends at least in part on the ability to make inferences about the emotions and beliefs of others (Fodor, 1987). The ability to infer what another person is feeling has been studied for many years in patients with acute brain damage, such as a stroke. The data suggest that impairments in emotion perception are related to difficulty with social interactions. The ability to infer what another person believes to be true (often known as the individual’s “theory of mind”) has also been studied for many years, initially in children with developmental disabilities. These data also suggest that impairments in inference of belief are related to difficulty with social interaction.

Studies investigating emotion processing in patients with AD have focused primarily on the ability to identify emotions (either perceptually or by inference). Results of these studies suggest that AD patients are not impaired in processing emotional information conveyed in facial expression, vocal intonation, or gesture, but that they are impaired on tasks that require interpretation of situational information portrayed in scenes and stories (Albert, Cohen, & Koff, 1991; Allender & Kaszniak, 1989; Cadieux & Greve, 1997; Koff, Zaitchik, Montepare, & Albert, 1999).

The ability to infer beliefs in others has also been examined in several studies involving AD patients. One of these studies included both first-order tasks (where participants are asked to infer the beliefs of others) and second-order tasks (where participants are asked to infer someone’s belief about someone else’s belief). In this study, performance of AD patients on the first-order tasks was no different from that of healthy controls, but AD patients were impaired relative to controls on the second-order tasks (Gregory et al., 2002). One study examining only first-order tasks (Zaitchik, Koff, Brownell, Winner, & Albert, 2006) and another examining only second-order tasks (Garcia-Cuerva, Sabe, Kuzis, Tiberti, Dorrego, & Starkstein, 2001) reported similar findings.

A recent study has directly compared the ability to infer emotions with the ability to infer beliefs in patients with mild-to-moderate AD (Zaitchik et al., 2006). Parallel procedures were used to assess inference of beliefs and inference of emotion in both first-order and second-order tasks. Each task included a control condition to determine whether any impairments of the subjects are due to the mental state inference in particular (i.e., inference about an emotion or a belief), as compared with inferences about information unrelated to a mental state (e.g., inference about an object, such as a picture). Results showed that the ability to infer emotions and beliefs in first-order tasks remains largely intact in mild-to-moderate
AD patients. Patients were able to utilize mental states in the prediction, explanation, and moral evaluation of behavior. Impairment on second-order tasks involving inference of mental states was equivalent to impairment on control tasks, suggesting that patients’ difficulty is secondary to their cognitive impairments.

Screening Tests

The most widely used screening tests are the Mini Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975), the Blessed Dementia Scale (Blessed, Tomlinson, & Roth, 1968), the Short Portable Mental Status Questionnaire (Pfeiffer, 1975), the Clock Drawing Test (CDT; Watson, Arfken, & Birge, 1993) and the 7-Minute Screen (Solomon et al., 1998). These tests all take approximately 10 minutes to administer and have high test–retest reliability.

Of these, the MMSE has most commonly been used in clinical settings. Its strength is that it assesses a broad range of cognitive abilities (i.e., memory, language, spatial ability, set shifting) in a simple and straightforward manner. In addition, the wide use of the MMSE in epidemiologic studies has yielded cut-off scores that facilitate the identification of patients with cognitive dysfunction. The other screening tests have been used in a variety of experimental settings, but epidemiologic data are limited. Finally, the extensive use of the MMSE has produced widespread familiarity with its scoring system, facilitating communication among clinicians.

Each of these tests is imperfect as a screening tool, in that they are not sensitive to early stages of disease and are impacted by the age, education and racial background of the individual (Manly et al., 1999). As a result, there is a continuing debate about whether screening for dementia is beneficial, particularly in primary care settings. The most recent consensus statement from the US Preventive Services Task Force did not recommend screening for dementia (Boustani, Peterson, Hanson, Harris, & Lohr, 2003). They found good evidence that some screening tests have good sensitivity but only fair specificity in detecting cognitive impairment and dementia. In the absence of effective treatments for AD, they could not recommend screening, particularly because the feasibility of screening and treatment in routine clinical practice and the potential harms of screening (i.e., labeling the patient) are unknown. When disease-modifying agents for AD are available, the risk–benefit ratio for screening will change. The consensus recommendations may then change as well.
Neuropsychological Evaluation in Clinical Trials

All randomized controlled clinical trials in the US of medications aimed at treating patients with AD have used neuropsychological tests as one of the two primary markers of drug efficacy (the other measure is a global clinical rating). The most widely used test in these clinical trials is the Alzheimer’s Disease Assessment Scale–Cognitive Subscale (ADAS–Cog; see Mohs, 1996 for a review). The primary reason the ADAS–Cog has been so widely accepted is that it was shown to be not only a valid and reliable measure of cognition in AD patients, but to also change reliably with disease severity over time. Although the FDA has not mandated its use, the inclusion in early trials accepted by the FDA resulted in the concern that use of any other test would be problematic.

Several recent clinical trials have attempted to broaden the way in which cognition is evaluated in patients with AD and MCI. The Alzheimer’s Disease Cooperative Study group evaluated five types of tasks that might extend the cognitive domains assessed by the ADAS–Cog as well as the range of symptom severity covered. These tasks included: a word list learning test with delayed free recall; a recognition memory test for faces; a series of letter and digit cancellation tests; tests of praxis; and a series of maze completion tests. The test that proved to be sensitive to a broad range of dementia severity was the digit cancellation (Mohs et al., 1997). The word list learning test and a subset of maze tasks were impaired in very mild AD cases. These were therefore recommended for inclusion in future trials. An alternative approach is best represented by the test battery used by Elan in the trial of AN-1792 (the first immunotherapy trial for AD; Gilman et al., 2005). A broad neuropsychological battery was included as an adjunct to the ADAS–Cog and clinical global rating. No significant differences were found between the antibody responder and placebo groups for the ADAS–Cog or the clinical global rating of change. However, analyses of a composite score from the neuropsychological battery demonstrated improvement in the antibody responders. This finding was used to support the continuation of the development of an immunization approach to AD.

The Alzheimer’s Disease Neuroimaging Initiative (ADNI) a multicenter national effort, designed as a natural history clinical trial, is focused on developing imaging measures for inclusion in clinical trials of cases of AD and MCI (Mueller et al., 2005). However, a broad range of neuropsychological measures have been included in the study, and data will therefore be available on the relationship between the cognitive and imaging measures as markers of disease progression.

These, and other data, will therefore be available to determine improved ways of assessing cognition for use in future clinical trials. This
will be particularly important when trials are routinely extended to cases of MCI.

BOUNDARY BETWEEN AGING AND MCI

There is increasing evidence that the pathology of AD can take many years, if not decades, to evolve, as noted above. This suggests that some individuals who appear normal (i.e., functionally asymptomatic) have gradually accumulating pathology. Recent reports based on autopsies of well-characterized normal individuals corroborate this hypothesis (Bennett et al., 2005b; Hulette et al., 1998; Knopman et al., 2000). For example, in the Religious Order Study mentioned above, of 60 normal individuals who had come to autopsy, approximately 60% had a low “likelihood” of AD, based on the NIA-R criteria, while 40% had an intermediate or high “likelihood” of AD.

These findings suggest that it may be possible to identify characteristic changes among normal individuals with a high likelihood of substantial underlying AD pathology during life, using existing methodologies. One potential approach is to determine whether neuropsychological performance among normal individuals can predict the time to develop mild degrees of cognitive impairment, suggestive of the incipient stages of AD.

Few studies to date have addressed this issue. One previous report (Schmitt, Davis, Wekstein, Smith, Ashford, & Markesbery, 2000) concerned normal subjects who received detailed neuropathological examinations and died shortly thereafter (Schmitt et al., 2000). Not only did these individuals have test scores that fell within the normal range, but neither they nor a collateral source had observed any functional decline in daily life. Some normal individuals were found to have AD pathology on autopsy, and the investigators reported that episodic memory performance differed between subjects with and without pathological findings. Another recent study is consistent with this report (Blacker et al., 2007). These investigators found that the likelihood of progressing from normal to MCI was considerably greater among those with lower scores on measures of episodic memory. It is noteworthy that the episodic memory tests that were significant predictors of progression from normal to MCI measured verbal learning and recall in a setting where multiple learning trials are provided, and performance can be improved if the subject takes advantage of organizational clues that are provided either implicitly or explicitly (i.e., the California Verbal Learning Test, the Selective Reminding Test, respectively). This suggests that this type of episodic memory test may be particularly beneficial for revealing mild deficits in normal individuals likely to progress to MCI. These results are also consistent
with a previous report of an association between degree of AD pathology in cognitively normal individuals and performance on tests of episodic memory (Schmitt et al., 2000). They are also consistent with the known neurobiology of AD, which involves medial temporal lobe structures essential for normal memory, as noted above.

These results differ, however, from another study that also performed autopsies on a small number of normal subjects who had been carefully examined during life. These investigators (Goldman et al., 2001) reported that there was no decline in cognitive performance for normal individuals with pathology \((n = 3)\) on autopsy as compared with those lacking pathological findings \((n = 5)\), based on either individual test scores or a factor score derived from the test battery as a whole. The explanation for this discrepancy may relate to the impact of the small sample size (making it difficult to identify differences between groups), as well as the individual tests examined, and the fact that neuropsychological testing was administered annually.

This area of research is likely to be greatly expanded in the coming years in anticipation of the time when disease-modifying agents become available for AD. It will then be important to intervene as early as possible in the disease, and the ideal time to intervene would be when individuals are considered normal (i.e., asymptomatic). A thorough understanding of the difference between age-related changes in memory and those related to the earliest stage of AD will be essential for progress in this area.

**PREDICTORS OF MAINTENANCE OF COGNITIVE FUNCTION WITH AGE**

The ideal intervention would be to delay the development of AD pathology as long as possible, since delaying the disease by even 5 years is estimated to reduce the prevalence of disease by one-half (Brookmeyer, Gray, & Kawas, 1998). Thus, studies examining factors predictive of maintenance of cognitive function have increased greatly in recent years.

Most of the work in this area involves epidemiological studies of community-dwelling individuals. All of the studies have a common design, in that individuals are selected from a representative sample of the population who are high functioning, a wide variety of factors are assessed, above and beyond cognition, and the subjects are then re-evaluated after a number of years have elapsed. The analyses have then looked either at factors predicting maintenance of cognition over time or risk of dementia in general or AD in particular.

The first of these studies (Albert et al., 1995) examined individuals who were already elderly (i.e., ages 70–80). Many subsequent reports have,
however, been based on individuals who were assessed in middle age, and were then followed into old age (Karp, Paillard-Borg, Wang, Silverstein, Winblad, & Fratiglioni, 2006). This latter approach is preferable since it reduces the likelihood that the pathological processes responsible for the cognitive decline (e.g., AD) might have already accumulated at the time of the first evaluation and thereby influenced behavior in subtle ways, even though participants appeared to be asymptomatic. Moreover, the subjects who have been evaluated vary widely in ethnic and cultural background, and live in both urban and rural settings (e.g., Albert et al., 1995; Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001; Rovio et al., 2005; Scarmeas, Levy, Tang, Manly, & Stern, 2001; Schmand, Smit, Geerlings, & Lindeboom, 1997; Verghese et al., 2003; Weuve, Kang, Manson, Breteler, Ware, & Grodstein, 2004; Wilson et al., 2002; Wilson, Bennett, Bienias, Mendes, DeLeon, Morris, & Evans, 2003). This reduces the likelihood that factors unrelated to the variables of interest are responsible for the findings. It is also notable that these studies have used a wide range of cognitive measures as outcomes. Some have examined composite scores based on a comprehensive neuropsychological battery, while others have looked primarily at selected areas of cognition, such as memory. Thus, the results appear to be reasonably robust and to transcend one particular cognitive domain.

A panel of scientists, convened by three of the institutes at the National Institutes of Health (i.e., NIA, NINDS, NIMH), reviewed the existing literature and issued a White Paper on their findings (Hendrie et al., 2006). The review concluded that there were four independent factors (apart from genetics) that appear to be consistently predictive of maintenance of cognitive function:

- increased levels of physical activity
- increased levels of mental activity
- increased social engagement
- control of vascular risk factors.

Moreover, the data suggest that the benefit gained from each of these lifestyle interventions provides an added benefit, in that risk of cognitive decline is incrementally reduced with the addition of two or more of these factors (Karp et al., 2006).

Physical activity is generally assessed by evaluating a range of physical activities in which the participant might engage in daily life (e.g., walking, climbing stairs, etc.), and developing a measure of total kilocalories expended, adjusted for potentially confounding factors (e.g., comorbid conditions, physical limitations, smoking, etc.; Albert et al., 1995; Weuve et al., 2004). In earlier studies, mental activity was measured by
educational attainment, but in more recent studies it has been assessed by evaluating a range of mental activities in which the participant might engage (e.g., reading books, going to lectures, playing board games, etc.) and developing a measure of the total hours spent doing these activities, adjusted for potentially confounding factors (Wilson et al., 2002, 2003). Social engagement was measured by a variety of scales that assessed social factors, such as social networks, feelings of self-efficacy, feelings of self-worth, etc. (Albert et al., 1995; Karp et al., 2006). Vascular risk factors assessed include: blood pressure, cholesterol, diabetes, weight, and smoking (Elias et al., 2004).

The mechanisms by which these lifestyle factors may benefit brain function are an increasingly active area of research. These have been best studied by the use of animal models, since animal models can disentangle the issue of innate differences during life vs. differences based on experience and, at the same time, address the issue of the underlying brain mechanisms that may be involved. The study design most commonly employed has been to examine changes in brain function, as well as cognition, in groups of animals prior to and after exposure to an environmental manipulation, and compare these measures to those from animals with no environmental manipulation. The animal most commonly used in these studies has been the rodent (i.e., rats or mice), and cognitive performance has most often been assessed by measuring memory performance in the Morris Water Maze (Morris, 1984). Genetics can be controlled by dividing litter mates into experimental and control groups.

The best animal model developed to date pertains to physical activity, where a voluntary exercise paradigm has been employed. In this paradigm, a running wheel is made available to the animal for short (e.g., 4 weeks) or long periods of time (e.g., 5 months), with measurements of brain function and cognition conducted in those with exposure to the exercise paradigm vs. those without. Several consistent findings have emerged:

1. Exercise enhances learning in the water maze in both young animals (Berchtold, Kesslak, & Cotman, 2002) and old animals (van Praag, Kemperman, & Gage, 2000).
2. Exercise enhances mRNA expression of brain-derived neurotrophic factor (BDNF) in at least one subregion of the hippocampus (i.e., the dentate gyrus) (e.g., Berchtold et al., 2002; Farmer, Zhao, van Praag, Wodtke, Gage, & Christie, 2004).
3. Exercise enhances neurogenesis in the hippocampus (e.g., Brown et al., 2003).

It is noteworthy that, while neurogenesis has been reported in young and
old animals in both the hippocampus and the olfactory bulb, the increase in neurogenesis following exercise occurs only in the hippocampus. Increases in BDNF expression likely serve to increase synaptic plasticity in nerve cells, while neurogenesis provides an increased supply of nerve cells in a brain region essential for normal memory. Investigators are currently examining the effects of varying factors such as frequency, duration, and age of exposure to exercise in order to determine the specific parameters of physical activity that might be most beneficial, as well as to more convincingly demonstrate a causal relationship between physical activity and cognition, rather than just an association (for reviews of these issues see Cotman & Berchtold, 2003; Dishman et al., 2006). The impact of physical exercise on animal models of Alzheimer’s disease is described below.

The animal model most commonly used to mimic mental activity is the enriched environment (Hebb, 1947). In the current version of this paradigm, the enriched environment consists of an animal cage in which many objects have been placed that the animal can explore. Like the voluntary running wheel, duration of exposure can be varied, as can degree of stimulation (e.g., by changing the objects at varying frequencies and/or by altering the number of animals in the cage at the same time). Two consistent findings have emerged from this work as well: (a) an enriched environment enhances learning in the water maze (e.g., Kemperman, Kuhn, & Gage, 1997), and (b) an enriched environment enhances hippocampal neurogenesis, but not neurogenesis in the olfactory bulb (Brown et al., 2003). There are also reports of increased expression of growth factors, such as nerve growth factor (Pham et al., 1999), but these findings have been less widely replicated. The interpretation of the findings from these studies remains unclear, however, as investigators have not disentangled the overall effect of increased exercise in the enriched environment and mental enrichment. There have, in fact, been few direct comparisons of enrichment vs. exercise. One potential approach would be to determine if the benefits are additive, i.e., exposure to an enriched environment following exposure to exercise provides a greater change in the outcome measures than either intervention alone. It would also be helpful to find additional changes in the brain following both interventions than one alone (see van Praag et al., 2000 for a review of this issue). Difficulty with interpretation of the animal data increases the challenge of interpreting the human findings as well. It has been hypothesized that mentally stimulating activity may reduce risk of cognitive decline by strengthening processing skills such as working memory, permitting compensation for age-related declines, and thereby providing cognitive reserve. (The concept of cognitive reserve is discussed by Christensen and colleagues in chapter 4.) An alternative hypothesis is that mental activity
has a direct impact on AD pathology. This hypothesis has been tested in animal models and is discussed further below.

The animal models of social engagement have, to date, been limited and much less satisfactory. For example, restraining the movement of an animal for varying periods of time impairs memory performance (Conrad, Galea, Kuroda, & McEwen, 1996). It is hypothesized that this alteration is the result of increased glucocorticoid levels in the brain (glucocorticoids are adrenal steroid hormones secreted in response to stress). In addition, increasing glucocorticoid levels alters spatial memory, synaptic plasticity and hippocampal volume (e.g., Bodnoff, Humphreys, Lehman, Diamond, Rose, & Meaney, 1995). However, an animal model which establishes a firm connection between increased periods of stress, elevation of glucocorticoids, and damage to neuronal function has yet to be developed (for a review of these issues see Sapolsky, 2003).

Although there are animal models of individual vascular risk factors, such as increased blood pressure (Moore, Killianey, Rosene, Prusty, Hollander, & Moss, 2003), the association between increased vascular risks and cognitive decline has been best demonstrated through both epidemiological and clinical data in humans, rather than animal models. It has been demonstrated that older individuals with multiple vascular risks have poorer cognitive function than healthy controls (Selnes, Grega, Borowicz, Royall, McKhann, & Baumgartner, 2003), and that individuals with evidence of vascular risk factors are at greatest risk for cognitive decline (Elias et al., 2004; Grodstein, Chen, Wilson, & Manson, 2001; Pelia, White, Masaki, Petrovitch, & Launer, 2006; Qiu et al., 2006; Swan et al., 1998). Dietary patterns thought to alter vascular risks have also been associated with lowering risk for cognitive decline and dementia (Morris et al., 2003; Scarmeas, Stern, Tang, Mayeux, & Luchsinger, 2006). There is also evidence that the greater the number of vascular risks, the greater the likelihood of cognitive decline over time (Whitmer, Sidney, Selby, Johnston, & Yaffe, 2005).

Though the findings described above are quite consistent and have been replicated by numerous independent groups, the primary limitation in making specific recommendations to the general public is that the data in humans are primarily based on observational findings. There are some findings from controlled clinical trials, but these are limited. Small clinical trials have been conducted in the area of physical activity and these results have been encouraging. For example, it has been shown that exposing older individuals to a 6-month program of aerobic activity enhances performance on neuropsychological tasks (e.g., attention and executive functions), as well as increasing brain activation during a functional MRI task requiring complex attention (Erickson et al., 2006). Likewise, there have been a number of controlled clinical trials looking at
the effect of lowering blood pressure on cognitive decline, but the results have been mixed (McGuinness, Todd, Passmore, & Bullock, 2006), and no trials have examined more than one vascular risk factor at a time. Much more work needs to be done in this area before firm guidelines can be provided to the general public about the nature and type of lifestyle changes that are most likely to reduce the risk for cognitive decline.

A better understanding of the role of genetics would also be beneficial. As noted above, it is clear that genetic factors influence learning ability in general. For example, from studies of identical twins reared together vs. those reared apart, it appears that genetic factors account for approximately 50% of an older individual’s memory performance (Finkel & McGue, 1998; Johansson, Whitfield, Pedersen, Hofer, Ahern, & McClearn, 1999; McClearn et al., 1997) (see chapter 2 by McGue & Johnson on Genetics of Cognitive Aging for a review). Thus, it is important to know if lifestyle factors can modify genetic risk for cognitive decline. Animal models have again been used to help address this issue. Several relevant studies have been conducted using transgenic mice, containing genetic mutations that increase risk for AD. These mice produce plaques, similar to those seen in AD, which contain the amyloid beta (Aβ) protein. Moreover, as the animals age, they develop memory problems above and beyond those seen by their litter mates without the genetic mutations.

Several studies have now examined whether exposure to an enriched environment or voluntary exercise improves memory in these transgenic animals and alters amyloid load. Those studies that have examined cognition consistently find that memory performance is improved in the mice exposed to the environmental manipulation. However, studies differ with regard to whether amyloid burden also decreases; some report reduced levels of Aβ (Adlard, Perreau, Pop, & Cotman, 2005; Lazarov et al., 2005), some report that levels of Aβ are stable (Arendash, Garcia, Costa, Cracchiolo, Wefes, & Potter, 2004), and some report increased amounts of Aβ (Jankowsky et al., 2005). Much work remains to be done to identify the methodological differences that contribute to these varying results.

In addition, the relationship between lifestyle factors and severity of AD pathology has been examined in a small number of recent studies. The findings suggest that level of education modifies the association of amyloid load with cognitive performance (Bennett et al., 2005b); a similar finding has also been reported for social network size as a modifier of the association between AD pathology and cognition (Bennett, Schneider, Tang, Arnold, & Wilson, 2006). These findings also need to be expanded in order to be fully understood.
APPENDIX

Typical Clinical Presentation of AD

Clinical Vignette

A 75-year-old female, married for almost 50 years, began having evidence of gradual cognitive decline. She had increasing difficulty remembering recent events. For example, from one week to the next she might forget a conversation she had with her daughter over the phone, she was increasingly likely to forget appointments with friends, and might forget to buy some of the items at the store that she needed to get. Over time, the memory problems became more pronounced, so that she might forget conversations from one day to the next, rather than one week to the next, and began asking the same questions over and over within a short period of time. She could, however, still remember important personal and political events from the past. In addition, multistep tasks, such as cooking or balancing the checkbook, became problematic. For example, she had been an excellent cook, and on occasion would forget an essential ingredient in a recipe she knew well, or overcook one item in a meal, while another was underdone. In casual social situations she seemed unchanged, but she seemed less interested in spending time with family and friends, and when at community events was less likely to be actively engaged.

As these problems became gradually worse, her family realized that something was wrong and brought her for evaluation. Her neurological examination was unremarkable. She had a snout reflex and decreased ankle jerks, but no focal signs or symptoms. On mental status testing, she received a score of 25 on the Mini Mental State Examination (MMSE), losing 2 points on recall of the three items, losing 2 points on orientation, and 1 point on spelling WORLD backwards.

Formal neuropsychological testing showed impaired recall of a story after a delay, and impaired list learning and retention. She was impaired on Trails B of the Trail Making Test (which requires one to alternate connect numbers and letters in sequence); she took much longer than normal to complete the task, and made two errors. Her verbal fluency was decreased both for generation of words based on letters (e.g., F, A, S) and categories (e.g., animals). Her confrontation naming ability, as assessed by the Boston Naming Test, was slightly low. Trails A of the Trail Making Task (which only requires one to connect numbers in sequence) was, however, within normal limits, as was digit span forward (the ability to repeat a series of numbers in the order they were given).

A magnetic resonance imaging (MRI) scan showed atrophy, but no
evidence of strokes or other structural lesion. Laboratory tests performed to examine potential metabolic problems were within normal limits. She was taking medication for hypertension and hypercholesterolemia, both of which appeared to be well treated.

Over the course of the next 6 years, the cognitive problems became progressively worse. Her memory impairment was so severe that she no longer remembered getting married or recognized her children or grandchildren. She developed progressive difficulty with language; over time she had more and more difficulty finding words in conversation. She was able to read but comprehension was gradually impaired. Her social interaction was limited, as she was increasingly fearful outside the home and became agitated in group situations with a lot of activity.

On postmortem, she received a diagnosis of definite AD. She had widespread neuronal loss, and evidence of neuritic plaques and neurofibrillary tangles throughout the temporal, parietal and frontal lobes. She also had a couple of lacunar infarcts and other evidence of small vessel disease.

Clinical Issues

Cognitive Presentation

This clinical presentation typifies the vast majority of patients with AD. It is a disorder whose initial feature is gradually progressive difficulty with learning and retention of new information. This difficulty with episodic memory is evident in day-to-day activities where retention over a delay is needed (such as remembering conversations and appointments), and on memory tasks that require an individual to learn something new (e.g., a story or a word list) and then retain it over a delay (Welsh et al., 1991). Once the disease is well established, impairments are evident on episodic memory tasks that assess both verbal and nonverbal information (Storandt & Hill, 1989).

Problems with executive function are also common in most patients early in the course of disease. Multistep tasks that require switching from one aspect of a task to another, such as preparing a meal, are particularly prone to difficulty. Neuropsychological tasks that emphasize set formation and set switching are, likewise, most sensitive impairments in the early phase of disease. The Trail Making Test is a good example of this, particularly because it requires the individual to switch from one over-learned series to another (i.e., switching from numbers to letters, both of which must be connected in order).

The typical AD patient then develops problems with language. There are subtle problems with naming and verbal fluency early in disease. Some investigators have argued that this is because of an underlying
problem with semantic networks (Chan et al., 1993), an issue that is discussed further above. During the middle phase of disease, it is the language problems that become progressively worse. The patient has increasing difficulty finding the words to express themselves and understanding complex ideas or sentences. Interestingly, reading is generally preserved till late in the disease, but this is often accomplished with little understanding of what is being read.

Spatial abilities also experience the greatest decline in the middle stages of disease in patients with a typical presentation. As a consequence, tasks that involve copying two-dimensional figures are generally preserved in mildly impaired patients. It has been reported that tasks that involve a spatial component are impaired in mild AD, but this is usually because they make other types of cognitive demands as well. For example, clock copying is generally preserved in mildly impaired patients, whereas clock drawing to command, which requires planning and organization, as well as spatial ability, is not (Rouleau et al., 1996).

Sustained attention is well preserved in mild-to-moderately impaired AD patients. If a task is simple enough that the patient can keep the instructions in mind (e.g., as in digit span where one is asked to repeat a series of numbers in order), then it is generally performed within the normal range. This finding is so consistent, that impairments in attention in an otherwise mildly impaired patient are used as a marker that the patient has a disorder other than AD, such as dementia with Lewy bodies (McKeith, 2006) or delirium (Kramer & Reifler, 1992).

It should be noted that the symptoms of a small number of AD patients present and evolve in a different manner. In one group of patients onset is characterized by gradually progressive difficulty with spatial ability. Any task that requires spatial skill will be impaired. There is difficulty with episodic memory but in the early stage of disease there tends to be less loss of information over a delay than retention over a delay than is the case in the typical patient (Albert, Duffy, & McAnulty, 1990), leading to less memory impairment in daily life. For a second group of patients, the initial symptoms consist of gradually progressive difficulty with language ability, including problems with naming, comprehension, repetition, and reading. Both of these unusual presentations tend to occur in early onset cases and are, in fact, rare among patients over the age of 65.

Cognitive History

While cognitive testing is important in confirming the diagnosis of AD, a good cognitive history is essential. Since the patient’s self-report may be unreliable, it is important to obtain a cognitive history from one or more
family members (or equivalent caregivers). The history needs to elicit information about three issues:

- the initial symptoms
- the time of onset
- the nature of progression.

Determining the initial symptoms will provide essential information regarding the diagnosis. For example, an early symptom of frontotemporal dementia (FTD) is often a change in personality (e.g., inappropriate behavior), while the most common early symptom of Alzheimer’s disease is a gradually progressive decline in the ability to learn new information. Several years after the disease has begun, which is when most patients’ conditions are actually diagnosed, the cognitive symptoms of the two disorders may be very similar, so that information regarding the initial symptoms may be critical to accurate diagnosis.

Establishing the time of onset will provide important clues regarding the nature of the disorder, because some diseases are well known for their particularly rapid rate of decline (e.g., Creutzfeldt-Jakob disease). It will also enable the clinician to give the family some tentative feedback regarding the course of the illness. If the point at which the disorder began is known, the rate of decline can be determined by seeing how long it has taken the patient to reach the present level of function. While estimates of the rate of progression can be only roughly approximated, it is extremely helpful for the family to have an estimate in making plans for the future.

Determining whether the initial symptoms came on suddenly or gradually also aids in diagnosis. If the onset of illness is gradual and insidious, as in Alzheimer’s disease, it is often only in retrospect that the family realizes that a decline has occurred. In contrast, a series of small strokes, even if not evident on CT, generally produce a history of sudden onset and stepwise progression. There may, for example, be an incident (e.g., a fall or a period of confusion) that marks the beginning of the disorder. Delirium generally has an acute onset as well, although if they are the result of a condition such as drug toxicity, this may not be the case. The manner in which the symptoms have progressed over time also provides important diagnostic information. A stepwise deterioration, characterized by sudden exacerbations of symptoms, is most typical of multi-infarct dementia. However, a physical illness in a patient with Alzheimer’s disease (e.g., pneumonia, a hip fracture, etc.) can cause a rapid decline in cognitive function. The sudden worsening of symptoms in a psychiatric patient (e.g., depression) also can produce an abrupt decrease in mental status. Careful questioning is therefore necessary to determine the underlying cause of a stepwise decline in function.
Neurological Examination, Laboratory, and Imaging Findings

The neurological examination is generally unremarkable in the early stage of AD. Thus it is most useful for identifying whether signs and symptoms of disorders other than AD are present (e.g., Parkinson’s disease, Creutzfeldt-Jakob disease, Huntington’s disease, etc.). Laboratory findings are also used to identify causes of cognitive decline that are unrelated to a neurodegenerative process (e.g., thyroid, liver or kidney disease, B12 deficiency, etc.). Likewise, in the clinical setting, imaging findings are generally used to determine whether other diseases, beside AD, are the cause of the patient’s cognitive decline (e.g., strokes, tumors, etc.). In the United States, positron emission tomography (PET) is approved for reimbursement only for the differential diagnosis of AD vs. FTD. Thus, physicians are only supposed to request reimbursement from Medicare for a PET scan if FTD is suspected.

Diagnostic Criteria for AD

The clinical diagnostic criteria for AD encapsulate the description above. They require that the patient has a gradually progressive decline in two or more domains of cognition (with memory predominant), of sufficient severity to impair social and occupational function. As noted above, these criteria (American Psychiatric Association, 1994; McKhann et al., 1984) have been widely accepted for a number of decades. This uniformity of approach has greatly helped research into the underlying cause of the disease because it has meant that similar patient populations are likely to be included in studies regardless of their location around the world.

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