The Neuropsychology of Dementia

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As an increasing number of people survive into older age, there is growing clinical and research interest in age-associated cognitive decline. This interest has focused to a large extent on the detection and characterization of cognitive deficits associated with age-related neurodegenerative diseases such as Alzheimer’s disease (AD), but also includes identification of relatively subtle cognitive changes that take place during the course of normal healthy aging (for reviews, see Hedden & Gabrieli, 2004; Park et al., 2003). Cognitive decline that occurs with healthy aging is particularly evident in information-processing abilities such as effortful encoding of new information, processing speed, inductive reasoning, and working memory. Other cognitive abilities, such as semantic knowledge and vocabulary, autobiographical remote memory, and automatic memory processes (e.g., priming), show little age-related decline. This pattern of decline has led to the development of several psychological and neurological models to account for these changes. One prominent psychological model (Salthouse, 1996) suggests that a general decline in processing speed underlies most of the cognitive decline that occurs with age. According to this model, an age-related decline in information-processing speed reduces the ability to efficiently integrate and organize information, and causes a decline in memory by reducing the efficiency of information encoding, rehearsal, and retrieval. Similar psychological models suggest that cognitive decline in the healthy elderly is caused by decline in a single factor such as working memory, inhibitory processes, or sensory function (Kramer et al., 2004; Park et al., 2003).

It has also been suggested that specific areas of the brain are particularly vulnerable to aging, and their deterioration leads to a decline in the cognitive abilities they mediate. For example, there is evidence that atrophy of prefrontal cortex and loss of frontal white matter integrity occurs as a normal consequence of aging (Greenwood, 2000; West, 1996). These changes result in age-related declines in so-called frontal functions such as working memory, cognitive flexibility, verbal fluency, directed and divided attention, and self-monitoring performance (Grady & Craik, 2000; Raz, 2005; West, 1996). Aging may also have a particularly adverse effect on white matter tracts that integrate brain regions (Bartzokis, 2004; O’Sullivan et al., 2001; Pfefferbaum et al., 2005; Raz, 2005), which leads to an age-related “disconnection” syndrome that causes cognitive changes beyond those that are usually considered frontal lobe functions (e.g., memory, visuospatial abilities). Other investigators propose that a staggered decline in multiple neurological processes may better explain cognitive changes associated with normal aging than any single neurobiological factor (Band et al., 2002; Buckner, 2004; Kramer et al., 2004).

As our knowledge of the cognitive changes that occur throughout the lifespan has grown, research efforts in the neuropsychology of aging and dementia have focused on differentiating these changes from the cognitive deficits
associated with neurodegenerative disorders such as AD. In the remainder of this chapter, we review research that has identified the particular neuropsychological deficits that occur in the earliest stages of AD and show how this knowledge has enhanced the ability to clinically differentiate the early stages of the disease from normal aging. We will also examine the impact of aging on the ability to detect AD, and identify cognitive changes that might foreshadow the development of dementia in those with "prodromal" AD (see Dubois et al., 2007, for discussion). Finally, we will compare and contrast the patterns of cognitive deficits associated with AD and other age-related neurodegenerative disorders, and show how this has improved differential clinical diagnosis and provided important information about the neurological basis of various cognitive abilities. Before embarking on this discussion, it is first important to define the dementia syndrome, identify its prevalence and associated risk factors, and describe the most common age-related neurodegenerative diseases that lead to its manifestation.

The Syndrome of Dementia: Description, Prevalence, and Risk Factors

Definition

Dementia refers to a syndrome of acquired cognitive impairment due to brain dysfunction that is of sufficient severity to interfere with usual social or occupational functioning. According to most definitional schemes (e.g., Diagnostic and Statistical Manual of Mental Disorders [DSM]—4th edition, American Psychiatric Association, 1994; Bayles & Kaszniak, 1987; Cummings & Benson, 1992; NINCDS-ADRDA criteria, McKhann et al., 1984), the syndrome of dementia involves deterioration in memory and one or more of the following domains: language, visuospatial skills, judgment or abstract thinking, or gnosis. These cognitive changes must represent a change from a previously higher level of performance and adversely affect functional abilities. Changes in emotion or personality are also common, but not a necessary component of the dementia syndrome. A Practice Parameter article on the diagnosis of dementia (Knopman et al., 2001) concludes that these original criteria adopted in the DSM and by McKhann et al. (1984) are sensitive and specific with respect to the diagnosis of the dementia of AD, but may be less than ideal for the detection of dementia associated with other neurodegenerative diseases. Knopman et al. (2001) suggest that consideration of a broader array of cognitive (and behavioral) domains with less emphasis on memory might allow earlier and more accurate detection of vascular dementia (VaD), dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD). As we will describe in subsequent sections, memory impairment is not necessarily a prominent part of the initial presentation of these non-AD dementias and should not be required in the definition of dementia.

Prevalence

Estimates of the prevalence of dementia vary widely due to differences in dementia definitions, sampling techniques, and sensitivity of instruments used to identify cases. In studies of dementia in various countries, prevalence rates have ranged from 2% to 25% for persons over the age of 65 (see Inechin, 1987; Wancata et al., 2007). Cummings and Benson (1992), calculating the average of prevalence estimates across studies, suggest that approximately 6% of persons over the age of 65 have severe dementia, with an additional 10–15% having mild to moderate dementia. The prevalence of the syndrome of dementia is age-related, doubling approximately every 5 years after age 65 (Jorm et al., 1987). Not surprisingly, the prevalence of dementia is higher among hospital and nursing home residents than among those living within the community (Kramer, 1986; Smyer, 1988).

Risk Factors

Significant advances in our understanding of the epidemiology of dementia have occurred in recent years. Kawas and Katzman (1999) summarize a number of clear-cut findings that have emerged. First, by all accounts, age is the single most important risk factor for dementia. Community (population) studies in many different countries have confirmed that
The prevalence of the most common causes of dementia, AD and vascular disease, rises in an approximately exponential fashion between the ages of 65 and 85. Importantly, however, data on individuals greater than age 85, who represent the fastest-growing segment of our population, generally show prevalence rates for dementia ranging between 40% and 60%, suggesting that they asymptote beyond age 85.

Second, gender may be a significant risk factor for dementia. A large-scale epidemiological survey in Shanghai identified female gender, along with age and education, as an independent predictor of dementia (Zhang et al., 1990). A number of other studies suggest that women have a slightly greater risk for AD than men (although men may be at somewhat greater risk for vascular dementia). The results of these studies must be considered carefully, however, because the increased prevalence of AD in women may be attributable to differential survival after the onset of dementia due to their longer life expectancy. Although a 2.8:1 (female/male) ratio of AD was observed in the Framingham prevalence study (Bachman et al., 1992), no gender difference in the incidence of either dementia or AD was found in this cohort (Bachman et al., 1993). However, results from the Cache County epidemiological study of dementia demonstrate that incidence rates among women increase after age 80 and exceed the risk among men by more than twofold in late old age (Miech et al., 2002; Zandi et al., 2002).

Third, low education and low occupational attainment are associated with an increased risk for dementia. An uneducated individual over age 75 has twice the risk for dementia as someone who has completed at least a grade school education (Katzman, 1993; Kawas & Katzman, 1999; Mortimer, 1988; Zhang et al., 1990). Stern and colleagues (1994) demonstrated a similar relationship between risk for dementia and lifetime occupational attainment, and showed that a combination of low education and low lifetime occupational attainment results in a greater relative risk (i.e., close to a threefold increase in risk) than either one alone.

Katzman (1993) and Stern et al. (1992, 1994) were among the first to suggest that the decrease in risk of dementia with increasing levels of educational or lifetime occupational attainment may occur because these factors are a surrogate for brain or cognitive reserve. Such a reserve would help to delay the onset of the usual clinical manifestations of the disease. Stern et al. (1992) reasoned that if advanced education imparts a reserve, then more severe pathological brain changes would be present in patients with high education than in those with low education at a time when the groups were matched for overall severity of dementia. Consistent with this prediction, they found a significantly greater deficit in parietotemporal blood flow in high-education probable AD patients than in equally demented low-education patients. The relationship between dementia and educational or occupational attainment is now supported by numerous epidemiological and biological studies that show high education, occupational work complexity, and a mentally and socially integrated lifestyle postpones the onset of clinical dementia and AD (for reviews, see Fratiglioni & Wang, 2007; Kawas & Katzman, 1999).

Fourth, a growing literature suggests that environmental influences such as physical activity and maintaining involvement in cognitively stimulating mental activity buttress cognitive functioning as we age (Hultsch et al., 1999; Kramer et al., 2004; Wilson et al., 2002). Furthermore, there is some evidence that physical and mental activity may result in structural brain changes in animals and humans (Churchill et al., 2002; van Praag et al., 2005), although studies directly investigating the impact of physical and/or mental activity on brain structure in humans have been extremely limited. Long-term benefits of exercise and cardiorespiratory fitness on cognition have been established, and clinical trials have shown that a fitness training intervention has a positive impact on cognitive functioning (particularly executive functions; Barnes et al., 2003). Physical activity has been shown to reduce risk for dementia and improve cognition in both cognitively normal and cognitively impaired older adults (see Fratiglioni et al., 2007; Kramer & Erickson, 2007, for reviews).

Fifth, the risk of developing dementia is increased approximately fourfold by a family history of AD in a first-degree relative (i.e., mother, father, brother, or sister; van Duijn et al., 1991). Given the findings of specific point mutations
on the amyloid precursor protein gene of chromosome 21 and presenilin gene mutations on chromosomes 1 and 14, there is now little question that this familial association is genetically based and expressed in an autosomal dominant fashion, although a number of newer candidate genes for AD also relate to oxidative stress and inflammatory response (Serretti et al., 2007). Furthermore, the ε4 allele of the apolipoprotein E (APOE) gene located on chromosome 19 has been identified as the single most important susceptibility gene for dementia and AD (Corder et al., 1993; Saunders et al., 1993; Strittmatter et al., 1993) because of its overrepresentation in AD relative to healthy elderly.

Finally, head injury has been identified as a risk factor for the development of dementia (Jellinger, 2004; Mortimer et al., 1991). Dementia pugilistica may occur in individuals who have suffered repeated blows to the head while boxing (Corsellis et al., 1973), and retired professional football players with histories of recurrent concussions also show increased cognitive impairments in late life compared to retired players without concussive histories (Guskiewicz et al., 2005). The risk of developing AD is doubled for individuals with a history of a single head injury that led to loss of consciousness or hospitalization (Mortimer et al., 1991), and this relationship may be modulated by a gene–environment interaction as Mayeux and colleagues (1995) found a tenfold increase in the risk of AD in people with both the APOE ε4 allele and head injury risk factors. Jordan et al. (1997) also found that possession of an APOE ε4 allele was associated with increased severity of chronic neurologic deficits in high-exposure boxers.

The epidemiological evidence to date suggests that, as the population ages, dementia will increasingly become the dominant disorder in late life. In the short term, advances in identifying risk factors may improve our ability to detect dementia in its earliest stages when palliative treatments may be most effective and, in the long term, may lead to the discovery of specific biological mechanisms that cause the disease. Knowledge of the risk factors for dementia, and particularly AD, is growing rapidly, and now includes not only those imparted in late life but also those that arise across the lifespan. Early-life factors such as perinatal conditions, brain development, body growth, socioeconomic conditions, environmental enrichment, and cognitive reserve can influence the ultimate development of dementia and AD (see Borenstein et al., 2006). Even the major susceptibility gene for AD, the APOE ε4 allele, may have divergent effects on cognition across the lifespan. For example, studies suggest that the presence of the APOE ε4 allele may have a beneficial effect on cognition early in the lifespan (Bloss et al., 2008; Alexander et al., 2007; Han et al., 2007; Hubacek et al., 2001; Keltikangas-Jarvinen et al., 1993; Mondadori et al., 2007; Wright et al., 1993), in contrast to its well-known deleterious effects in late life. These seemingly discrepant effects of the APOE ε4 allele across the lifespan are consistent with the theory of antagonistic pleiotropy (Albin, 1993; Williams, 1957), a concept from evolutionary biology that posits that individual alleles can have different effects on fitness at different ages (see Han & Bondi, 2008; Alexander et al., 2007, for discussion). Regardless, the literature on risk factors for dementia suggests that risk is likely not determined at any single point in time, but results from a complex interplay between genetic and environmental exposures throughout one's life (Bornstein et al., 2006).

**Specific Dementing Disorders:**

**Clinical and Neuropathologic Features**

Dementia is associated with more than 70 different causes. As mentioned earlier, AD is the most common cause of dementia, accounting for roughly half of all cases (for review, see Cummings & Benson, 1992; Kawas & Katzman, 1999). Vascular dementia (VaD) is usually regarded as the second most common cause, although in some community surveys (particularly, but not exclusively, those in Japan and China), VaD has been found to be as prevalent as AD (Dong et al., 2007). It is not clear whether such differences in relative prevalence estimates reflect actual regional disparities, or rather, methodological variation across studies. Other, less prevalent degenerative neurologic diseases (e.g., Huntington's disease [HD], Parkinson's disease [PD], dementia with Lewy bodies [DLB],...
Alzheimer's Disease

AD is a progressive degenerative brain disorder characterized by neuronal atrophy, synapse loss, and the abnormal accumulation of diffuse neuritic plaques and neurofibrillary tangles (Alzheimer, 1907; see Figure 8–1; see also the color figure in the color insert section). These pathologic changes begin primarily in medial temporal lobe limbic structures (e.g., entorhinal cortex, hippocampus) and then progress to the association cortices of the frontal, temporal, and parietal lobes (Braak & Braak, 1991). Primary motor and sensory cortices and most subcortical structures are relatively spared. Degeneration in the basal forebrain (e.g., the nucleus basalis of Meynert) results in a major decrement in neocortical and hippocampal levels of the neurotransmitter acetylcholine (Whitehouse et al., 1982). Consistent with these widespread neuropathologic changes, the primary clinical manifestation of AD is a progressive global dementia syndrome that usually begins in later life. The dementia syndrome of AD is usually characterized by prominent amnesia with additional deficits in language and semantic knowledge (i.e., aphasia and agnosia), abstract reasoning, “executive” functions, attention, and constructional (i.e., apraxia) and visuospatial abilities (Salmon & Bondi, 1999). These cognitive deficits and the decline in everyday function they produce are the core features of the AD dementia syndrome.

Vascular Dementia

VaD refers to a cumulative decline in cognitive functioning secondary to multiple or strategically placed infarctions, ischemic injury, or hemorrhagic lesions. The clinical and neuropathologic presentation of VaD is quite heterogeneous, and a variety of conditions fall under the general rubric of VaD (see the chapter by

Figure 8–1. The neuropathology of Alzheimer’s disease. Grossly apparent cortical atrophy in Alzheimer’s disease (Figure 1A) compared to normal aging (Figure 1B), and neocortical amyloid plaques (Figure 2), neurofibrillary tangles (Figure 3), and cerebrovascular amyloid angiopathy (Figure 4). (Images courtesy of Drs. Eliezer Masliah, Robert Terry, and Larry Hansen).
Brown in this volume). According to Hodges and Graham (2001), these conditions generally fall into three large categories: multi-infarct dementia (MID) associated with multiple large cortical infarctions (usually affecting 10 cc or more of brain tissue), dementia due to strategically placed infarction (e.g., left angular gyrus damage related to infarction of the posterior branch of the medial cerebral artery), and subcortical ischemic vascular dementia due to subcortical small vessel disease that results in multiple lacunar strokes, leukoaraiosis (Binswanger’s disease) or diffuse white matter pathology.

Specific research criteria for the diagnosis of VaD have been proposed (e.g., Chui et al., 1992, 2000; Roman et al., 1993). In general, these guidelines require that multiple cognitive deficits (i.e., dementia) occur in the presence of focal neurological signs and symptoms and/or laboratory (e.g., CT or MRI scan) evidence of cerebrovascular disease that are thought to cause the cognitive impairment (for review, see Chui, 2007). A relationship between dementia and cerebrovascular disease is often indicated if the onset of dementia occurs within several months of a recognized stroke, there is an abrupt deterioration in cognitive functioning, or the course of cognitive deterioration is fluctuating or stepwise. In one set of diagnostic criteria (Roman et al., 1993), VaD can be subcategorized on the basis of the suspected type of vascular pathology (as determined by clinical, radiologic, and neuropathologic features), and possible or probable VaD can be assigned depending on the certainty of the contribution of cerebrovascular disease to the dementia syndrome. Definite VaD is diagnosed only on the basis of histopathologic evidence of cerebrovascular disease that occurs in the absence of neurofibrillary tangles and neuritic plaques exceeding those expected for age and without clinical evidence of any other disorder capable of producing dementia (e.g., Pick’s disease, diffuse Lewy body disease).

Huntington’s Disease

Huntington’s disease (HD) is an inherited autosomal dominant disease that results in the mid-life (e.g., ages 30–40) development of movement disorder (e.g., chorea, dysarthria, gait disturbance, oculomotor dysfunction), behavioral changes (e.g., depression, irritability, and anxiety), and dementia. These deficits arise primarily from a progressive deterioration of the neostriatum (caudate nucleus and putamen) (Vonsattel & DiFiglia, 1998) that disrupts “fronto-striatal loops” that consist of projections from the frontal neocortex to the striatum, striatum to the globus pallidus, globus pallidus to thalamus, and thalamus back to specific neocortical regions of the frontal lobes (e.g., dorsolateral prefrontal, orbitofrontal, and anterior cingulate cortex) (Alexander et al., 1986). These circuits are believed to have a subcortical influence on both motor control and higher cognitive functions (Alexander et al., 1986). The cognitive and behavioral deficits associated with HD have been described as a “subcortical dementia” syndrome that is broadly characterized by slowness of thought, impaired attention, executive dysfunction, poor learning, visuoperceptual and constructional deficits, and personality changes such as apathy and depression (Albert et al., 1974; McHugh & Folstein, 1975; also see Chapter 10).

Dementia with Lewy Bodies

Dementia with Lewy bodies (DLB) is a clinicopathologic condition characterized by a dementia syndrome that occurs:

- in the presence of cell loss and the deposition of Lewy bodies (abnormal intracytoplasmic eosinophilic neuronal inclusion bodies) in a subcortical pattern similar to that of PD (e.g., in brain stem nuclei including the substantia nigra, locus ceruleus, dorsal motor nucleus of the vagus, and substantia innominata);
- in the presence of Lewy bodies diffusely distributed throughout the limbic system (e.g., cingulate, insula, amygdala, hippocampus, entorhinal cortex, and transentorhinal cortex) and neocortex (e.g., temporal, parietal, and frontal lobes), and in many cases AD pathology (i.e., neuritic plaques, neurofibrillary tangles) that occurs in the same general distribution throughout the brain as in "pure" AD (Gomez-Tortosa et al., 2000; Hansen et al., 1990; Ince et al., 1998; Kosaka et al., 1984; Perry et al., 1990)
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Figure 8-2. Histopathologic abnormalities in the limbic system and neocortex in Dementia with Lewy Bodies (DLB). The typical appearance of vacuolization in the entorhinal cortex, cortical Lewy bodies in the temporal lobe neocortex, and Lewy neurites (i.e., neurons containing abnormal alpha-synuclein filaments) in the CA3 region of the hippocampus. (Images courtesy of Dr. Eliezer Masliah).

(see Figure 8-2; see also color figure in the color insert section).

DLB is associated with widespread depletion of cortical choline acetyltransferase (ChAT) in the neocortex and striatum (e.g., Tiraboschi et al., 2002), and a disruption of dopaminergic input to the striatum due to the loss of pigmented substantia nigra neurons (Ince et al., 1998). Dementia with Lewy bodies is not rare and may occur in approximately 25% of all elderly demented patients.

Frontotemporal Dementia

FTD is a clinicopathologic condition characterized by deterioration of personality and cognition associated with prominent frontal and temporal lobar atrophy (Brun et al., 1994). A number of disorders fall under the rubric of FTD, including Pick’s disease (Kertesz et al., 1999; Pick, 1892), familial chromosome 17-linked frontal lobe dementia (Wilhelmsen et al., 1994), dementia lacking distinctive histopathology (DLDH; Knoopman et al., 1990), semantic dementia (Snowden et al., 1989), and primary progressive aphasia (Kertesz et al., 1994; Mesulam, 1982). Although each of these disorders has a somewhat unique clinical manifestation, FTD usually begins insidiously with personality and behavioral changes (e.g., inappropriate social conduct, inertia and apathy, disinhibition, perseverative behavior, loss of insight, hyperorality, and decreased speech output). These behavioral changes are accompanied (or soon followed) by cognitive deficits that include alterations in executive functions and/or aphasia, often with relative sparing of visuospatial abilities and memory (see Weder et al., 2007, for review). Various forms of FTD are thought to account for approximately 3–20% of all cases of dementia (Andreasen et al., 1999; Brun, 1987; Neary, 1999).

Neuropsychological Detection of Alzheimer’s Disease

A wealth of neuropsychological research over the past two decades has identified the particular neuropsychological deficits that occur in the earliest stages of AD and enhanced the ability to clinically differentiate the disease from normal aging. Given that the hippocampus and entorhinal cortex are affected in the earliest stages of AD (Braak & Braak, 1991), it is not surprising that measures of the ability to learn and retain new information are among the most effective in differentiating between mildly demented AD patients and normal older adults (e.g., Bayles et al., 1989; Delis et al., 1991; Eslinger et al., 1985; Huff et al., 1987; Kaszniak et al., 1986; Storandt et al., 1984). Patients with early AD are particularly impaired on measures of delayed recall, a characteristic that has important clinical utility for the detection and differential diagnosis of the disease (e.g., Butters et al., 1988; Locascio et al., 1995; Welsh et al., 1991). Several studies have shown that rapid forgetting expressed as absolute delayed recall scores or “savings” scores (i.e., amount recalled after the delay divided by the amount recalled on the immediate learning trial) can differentiate mildly demented...
AD patients from healthy elderly with 85-90% accuracy (Butters et al., 1988; Ficker et al., 1991; Knopman & Ryberg, 1989; Morris et al., 1991; Tröster et al., 1993; Welsh et al., 1991).

The abnormally rapid forgetting shown by patients with AD suggests that their memory disorder may be due to ineffective consolidation of information. This possibility is supported by studies that have shown to-be-remembered information is not accessible after a delay even if retrieval demands are reduced by the use of recognition testing (e.g., Delis et al., 1991), and by studies that demonstrate an abnormal serial position effect in the episodic memory performance of patients with AD (Bayley et al., 2000; Capitani et al., 1992; Carlesimo et al., 1995; Greene et al., 1996; Massman et al., 1993; Wilson et al., 1983). In these latter studies, patients with early AD consistently show a reduction of the primacy effect (i.e., recall of words from the beginning of a list), suggesting that they cannot effectively transfer information from primary memory (i.e., a passive, time-dependent, limited capacity store that allows the most recent items to be better recalled than other items) to secondary memory (an actively accessed, long-lasting store that allows early list items that received the greatest amount of processing to be better recalled than other items), or that they cannot maintain information in secondary memory after its successful transfer. This deficit has led to the development of several effective clinical tests for early AD that distinguish between primary (or short-term) and secondary (or long-term) memory (e.g., California Verbal Learning Test–2nd edition [CVLT-II]; Delis et al., 2000; Buschke selective reminding procedure; Buschke, 1973).

Impaired encoding ability may also adversely affect AD patients’ performance on episodic memory tests (Martin et al., 1985). Semantic encoding procedures (Goldblum et al., 1998) or the use of materials that allow the use of semantic encoding strategies (for review, see Backman & Small, 1998) are less effective in improving episodic memory performance in patients with AD than in normal elderly individuals. This semantic encoding deficit is targeted by several clinical memory tests that effectively differentiate between mildly demented AD patients and normal elderly individuals (e.g., Buschke et al., 1997; Knopman & Ryberg, 1989).

A prominent qualitative feature of the memory deficit of patients with AD is an enhanced tendency to produce intrusion errors (Butters et al., 1987; Fuld et al., 1982; Jacobs et al., 1990). That is, patients will incorrectly produce old, previously learned information during the attempt to recall new material. The abnormal production of intrusion errors has been interpreted as increased sensitivity to interference or deficient inhibitory processes in patients with AD. Although intrusion errors are not a pathognomonic sign of AD (Jacobs et al., 1990), their occurrence can be a useful adjunct to other memory measures (e.g., total recall, recognition memory, rate of forgetting) in developing clinical algorithms for detecting early AD and differentiating it from other types of dementia (Delis et al., 1991).

Patients with AD often exhibit a severe deficit in the ability to remember past events that were successfully remembered prior to the onset of the disease (i.e., retrograde amnesia). The retrograde amnesia of AD is temporarily graded with memories from the distant past better retained than memories from the more recent past (Beatty et al., 1988; Hodges et al., 1993; Kopelman, 1989; Sagar et al., 1988; Wilson et al., 1981). This pattern of loss is similar to that of patients with circumscribed amnesia (Albert et al., 1979; Squire et al., 1989) and has been attributed to the interruption of a long-term consolidation process (e.g., shifting memory from an episodic to a semantic form) that is critically dependent upon the hippocampal-diencephalic memory system (Cermak, 1984; Squire, 1987; Zola-Morgan & Squire, 1990; but see Nadel & Moscovitch, 1997). However, AD patients are often impaired even for the most remote time periods, which may result from a combination of the episodic and semantic memory deficits that they suffer (for review, see Salmon, 2000).

Although the episodic memory impairment described above is usually the earliest and most prominent feature of the dementia of AD, a number of higher-order cognitive processes become affected as the neuropathology spreads beyond medial temporal lobe structures to the association cortices of the temporal, frontal, and parietal lobes (Braak & Braak, 1991). For example, semantic memory that underlies general knowledge and language is often disturbed relatively early in the course of AD (for reviews, see
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Hodges & Patterson, 1995; Nebes, 1989; Salmon et al., 1999). This disturbance is evident in AD patients' reduced ability to recall overlearned facts (e.g., the number of days in a year; Norton et al., 1997), and in their impairment on tests of confrontation naming (Bayles & Tomoeda, 1983; Bowles et al., 1987; Hodges et al., 1991; Huff et al., 1986; Martin & Fedio, 1983), verbal fluency (Butters et al., 1987; Martin & Fedio, 1983; Monsch et al., 1994), and semantic categorization (Aronoff et al., 2006; Chan et al., 1998). In addition, the spontaneous speech of patients with AD is frequently vague, empty of content words, and filled with indefinite phrases and circumlocutions (Nicolas et al., 1985).

The semantic memory deficit exhibited by patients with AD may reflect the loss of semantic knowledge for particular items or concepts during the course of the disease. Studies that have probed for knowledge of particular concepts across different modes of access and output (e.g., fluency, confrontation naming, sorting, word-to-picture matching, definition generation) showed that patients with AD were significantly impaired on all measures of semantic memory, and when a particular stimulus item was missed (or correctly identified) in one task, it was likely to be missed (or correctly identified) in other tasks that accessed the same information in a different way (Chertkow & Bub, 1990; Hodges et al., 1992). A true loss of semantic knowledge (rather than deficient retrieval) in mildly demented patients with AD was also implicated in a longitudinal study by Norton and colleagues (1997) that showed year-to-year consistency in the items missed during progressive decline on a test of general knowledge (i.e., the Number Information Test) that had minimal language demands (also see Salmon et al., 1999).

In addition to memory and language deficits, patients with early AD often exhibit deficits in "executive functions" responsible for concurrent mental manipulation of information, concept formation, problem solving, and cue-directed behavior (Perry & Hodges, 1999). A study by Lefèche and Albert (1995) demonstrated that the ability to perform concurrent manipulation of information appears to be particularly vulnerable in early AD. In this study, very mildly demented patients with AD were significantly impaired relative to elderly normal control subjects on tests that required set-shifting, self-monitoring, or sequencing, but not on tests that required cue-directed attention or verbal problem solving. The executive function deficits associated with AD are also evident on difficult problem-solving tests such as the Tower of London puzzle (Lange et al., 1995) and the modified Wisconsin Card Sorting Task (Bondi et al., 1993), on tests of relational integration (Waltz et al., 2004), and on various other clinical neuropsychological tests such as the Porteus Maze Task, Part B of the Trail-Making Test, and the Raven Progressive Matrices Task (Grady et al., 1988; for review, see Duke & Kasznia, 2000).

Some aspects of attention are often impaired relatively early in the course of AD. Attention deficits in mildly demented AD patients have been shown by using dual-processing tasks, tasks that require the disengagement and shifting of attention, and working memory tasks that are dependent upon the control of attentional resources (for reviews, see Duke & Kasznia, 2000; Parasuraman & Haxby, 1993; Perry & Hodges, 1999). The ability to focus and sustain attention is usually only affected in later stages of the disease, as was shown by the essentially normal performance of mildly demented AD patients on the Attention/Concentration Index of the Wechsler Memory Scale-Revised (WMS-R), a measure derived from performance on tests of digit span (forward and backward), visual memory span (forward and backward), and mental control (Butters et al., 1988).

Patients with AD often exhibit deficits in visuospatial abilities that are apparent on visuoconstructional tasks such as the Block Design Test (Mohr et al., 1990; Pandovani et al., 1995; Villardita, 1993), the Clock Drawing Test (for review, see Freedman et al., 1994), or copying a complex figure (Locascio et al., 1995; Mohr et al., 1990; Pandovani et al., 1995; Villardita, 1993). Deficits are also often apparent on tasks that require visuoception and visual orientation, such as the Judgment of Line Orientation test (Ska et al., 1990), the Money Road Map Test (Locascio et al., 1995), and the Hooper Visual Orientation Test (Paxton et al., 2007). These visuospatial deficits are usually not apparent in the very earliest stages of AD and may have little to contribute to the differentiation of early dementia from normal aging (e.g., Locascio et al.,...
1995; Storandt et al., 1984). However, visuospatial abilities decline over time in AD and may be useful for tracking the progression of the disease (see Paxton et al., 2007).

Taken together, the neuropsychological research findings reviewed above suggest that AD usually results in a specific pattern of cognitive deficits that can help differentiate the disease from normal aging. Prominent deficits in episodic memory (e.g., rapid forgetting), certain executive functions (e.g., cognitive set-shifting), and semantic knowledge characterize the disease early on, and are thought to have clinical utility for early detection of AD. This was confirmed in a study that directly compared the ability of a number of sensitive measures of learning and memory, executive abilities, language, and visuospatial abilities to differentiate between 98 patients with mild AD (i.e., scored ≥ 24 on the Mini-Mental State Exam) and 98 gender-, age-, and education-matched normal control subjects (Salmon et al., 2002). The diagnosis of AD was verified in each of the AD patients by subsequent autopsy or longitudinal clinical evaluations that showed a typical course for the disease. Receiver Operating Characteristic (ROC) curve analyses showed excellent sensitivity and specificity for the detection of very mild AD for learning and delayed recall measures from the California Verbal Learning Test (CVLT) (sensitivity: 95–98%, specificity: 88–89%), the category fluency test (sensitivity: 96%, specificity: 88%), and Part B of the Trail-Making Test (sensitivity: 85%, specificity: 83%). A diagnostic model obtained using a nonparametric recursive partitioning procedure (Classification Tree Analysis) showed that a combination of performance on the category fluency test (a measure of semantic memory and executive function) and the delayed recall measure of the Visual Reproduction Test accurately classified 96% of the patients with AD and 93% of the elderly normal control subjects, a level of accuracy higher than achieved with any individual cognitive measure; similar correct classification rates were seen when the Dementia Rating Scale was allowed in the analysis (see Figure 8–3). These findings substantiate the typical pattern of deficits usually observed

![Decision Tree for AD Diagnosis](image)

**Figure 8–3.** Two classification and regression tree models that were maximally effective in differentiating patients with mild Alzheimer’s disease from healthy older adults. The variables retained in the models included a measure of category fluency (i.e., sum of animals, fruits, and vegetables) and either global cognition (i.e., DRS total score) or delayed recall (i.e., Visual Reproduction Test raw score). (Adapted from Salmon et al., 2002).
in AD and attest to the clinical utility of a thorough neuropsychological evaluation for early diagnosis.

There is a growing body of experimental evidence to indicate that the cortical neuropathology of AD results in the loss of effective interaction between distinct and relatively intact cortical information-processing systems (e.g., Delacoste & White, 1993). Because the neurofibrillary tangle pathology of AD has a strong predilection for cortical layers (e.g., Layer-III and Layer-V) and cell types (e.g., mid-size pyramidal neurons) that support connections between functionally related cortical association areas, it effectively disconnects the hippocampus from neocortex (e.g., Hymn et al., 1984) and disrupts corticocortical pathways that connect cortical association areas (for review, see Hof & Morrison, 1999). This disconnection is evident in marked abnormalities in the interregional pattern of blood-flow activation elicited during the performance of cognitive tasks (e.g., Delbeuck et al., 2003; Grady et al., 2001; Haab et al., 1985), and reduced coherence (i.e., synchronization) between electroencephalography (EEG) signals measured at different scalp surface electrode sites that correspond to neocortical association areas that must work in concert during integrative cognitive tasks (e.g., cross-modal stimulus processing) (e.g., Dunkin et al., 1995; Hogan et al., 2003; Jelic et al., 1996; Knott et al., 2000; Stevens et al., 2001). Behaviorally, corticocortical disconnection in patients with AD is demonstrated by an impaired ability to “bind” distinct visual stimulus features that are effectively processed in different cortical streams (i.e., motion and color; Festa et al., 2005), to identify objects through the integration of perceptual, lexical, and semantic representations mediated by distinct cortical regions (Della Sala et al., 2000; Dobkins & Albright, 1998; Foster et al., 1999; Freedman & Oscar-Berman, 1997; Kurylo et al., 1996; Lakmache et al., 1998; Tales et al., 2002; Tippett et al., 2003), or to perform cross-hemispheric integration of information discretely processed in left- or right-hemisphere cortical regions (Golob et al., 2001). These results suggest that behavioral evidence of cortical disconnection may have potential as a cognitive marker for detecting and tracking progression of AD.

Impact of Aging on the Neuropsychological Detection of Alzheimer’s Disease

The boundaries between normal age-related cognitive change and early signs of AD are particularly difficult to delineate in very elderly individuals (e.g., over the age of 80). This is because many of the early structural and functional changes of AD overlap with changes that occur in normal aging. Normal aging is associated with mild brain atrophy on structural magnetic resonance imaging (MRI; Jack et al., 1998; Jernigan et al., 2001; Piefferbaum et al., 1994), decreased hemodynamic response on functional MR imaging (D’Esposito et al., 1999), reduced synaptic density (Masliah et al., 1993), and increased white matter abnormalities (Guttman et al., 1998; Jernigan et al., 2001; Salat et al., 1999). These brain changes are thought to mediate age-related decline in information-processing speed, executive functions, learning efficiency, and effortful retrieval (Corey-Bloom et al., 1996; Desgranges et al., 1998; Grady et al., 1995; Gunning-Dixon & Raz, 2000; Kaszaik & Newman, 2000; Schacter et al., 1996; Ylikoski et al., 1993). Because normal aging detrimentally affects many of the same cognitive abilities affected by AD (see the previous section), the prominence of specific deficits related to AD may be much less evident in the Very-Old than in the Young-Old, especially after performance is standardized to the age-appropriate normal cohort. This may result in a less distinct and somewhat atypical cognitive deficit profile associated with AD in the Very-Old compared to Young-Old.

This possibility was confirmed in a study that directly compared the neuropsychological test performance of AD patients who were over the age of 80 (Very-Old) or below the age of 70 (Young-Old) (Bondi et al., 2003). Despite achieving similar raw scores on all neuropsychological measures, the Young-Old and Very-Old AD patients differed in the severity and pattern of cognitive deficits they exhibited in relation to their age-appropriate control groups (see Figure 8-4). Analysis of composite age-appropriate z-scores in various cognitive domains showed that Young-Old AD patients were generally more impaired than Very-Old patients and
had a typical AD profile. That is, they exhibited deficits in executive functions and the retention of episodic memories (i.e., savings scores) that were greater than their deficits in other cognitive domains. By contrast, Very-Old AD patients exhibited a similar level of impairment across all cognitive domains so that their deficit profile lacked the disproportionate saliency of memory and executive function deficits typical of the disease.

It is interesting to note that the distinct cognitive profiles exhibited by Young-Old and Very-Old AD patients actually reflected differences in the respective age-matched normative cohorts. Although the raw scores of the younger and older AD patients were similar, the older control group performed significantly worse than the younger control group on nearly all cognitive tests, with the largest differences apparent on tests of memory, executive functions, and category fluency. Thus, the better z-scores of the Very-Old AD patients compared to the Young-Old AD patients are a function of lower mean performance in the older control group on tests of cognitive abilities that are vulnerable to normal age-related decline. Although increased variability in test performance related to normal aging could also impact the z-scores of the Very-Old AD patients, Bondi and colleagues (2003) showed that this was not the driving factor in their study because the variance associated with the various cognitive scores did not differ between the older and younger normal control groups.

These and similar results clearly indicate that normal aging can significantly impact the severity and pattern of neuropsychological deficits associated with early AD and reduce the saliency of the deficit profile as a diagnostic marker of the disease. This finding has important clinical implications because it identifies the significant risk of false-negative diagnostic errors in very elderly AD patients if the clinician expects to see the typical deficit pattern characteristic of younger AD patients.

**Neuropsychological Detection of “Prodromal” Alzheimer’s Disease**

It is now commonly accepted that the neurodegenerative changes of AD begin well before the clinical manifestations of the disease become apparent (e.g., Katzman, 1994). As the pathologic changes of AD gradually accumulate, a threshold for the initiation of the clinical symptoms of the disease is eventually reached. Once this threshold is crossed, cognitive deficits associated with AD become evident and
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Figure 8–5. Modification of the chronic disease model of Alzheimer’s disease first proposed by Katzman (1976). The solid line (—) represents a typical trajectory of cognitive decline for most individuals who do not carry risk factors for the disease. The dotted line (….) represents a trajectory of decline for individuals who have the same degree of neuropathologic changes and contributing causes as those depicted in the solid line but who have less brain reserve capacity perhaps from poorer neural development or interconnectivity. The dashed line (—-) represents individuals with the same relative brain reserve capacity as those depicted in the solid line but who have a genetic or environmental predisposition to AD.

Gradually worsen in parallel with continued neurodegeneration. When the cognitive deficits become global and severe enough to interfere with normal social and occupational functioning, established criteria for dementia and a clinical diagnosis of AD are met. It is clear from this sequence of events that subtle cognitive decline is likely to occur in a patient with AD well before the clinical diagnosis can be made with any certainty. Identification of the cognitive changes that occur during this “prodromal” phase of the disease might provide a way to reliably detect AD in its earliest stages, when potential disease-modifying treatments might be most effective (Thal, 1999). Because of the importance of this goal, the attempt to identify prodromal cognitive changes of AD is one of the most active areas of neuropsychological research (see Figure 8–5).

In light of neuropathological evidence that the earliest changes of AD usually occur in the medial temporal lobe structures that are known to be critical for episodic memory (Braak & Braak, 1991), it is not surprising that the search for prodromal cognitive markers of the disease has focused largely on this aspect of cognition. Indeed, a number of prospective longitudinal studies of cognitive function in nondemented older adults have shown that a subtle decline in episodic memory often occurs prior to the emergence of the obvious cognitive and behavioral changes required for a clinical diagnosis of AD (Bondi et al., 1994; Fuld et al., 1990; Grober & Kawas, 1997; Howieson et al., 1997; Jacobs et al., 1995; Tschanz et al., 2006). In some cases, decline in episodic memory becomes apparent many years prior to the onset of dementia (Backman et al., 2001; Bondi et al., 1999; Kawas et al., 2003; Linn et al., 1995; Schaie et al., 2005; Small et al., 2000). These and similar findings led to the development of formal criteria for Mild Cognitive Impairment (MCI; Peterson et al., 1995), a predementia condition in elderly individuals that is characterized by both subjective and objective memory impairment that occurs in the face of relatively preserved general cognition and functional abilities (for reviews, see Albert & Blacker, 2006; Collie & Maruff, 2000; Peterson et al., 2001).

The course of episodic memory change during the prodromal phase of AD has been the focus of a number of studies (Backman et al., 2001; Chen et al., 2001; Rubin et al., 1998; Small et al., 2000; Storandt et al., 2002). These studies suggest that memory performance may be poor but stable a number of years prior to the development of the dementia syndrome in those with AD, and then decline rapidly in the period immediately preceding the dementia diagnosis. Consistent with this plateau model of decline, Small et al. (2000) and Backman et al. (2001) found that episodic memory was mildly impaired 6 years prior to dementia onset, but changed little over the next 3 years. In contrast, Chen et al. (2001) and Lange et al. (2002) showed a significant and steady decline in episodic memory beginning about 3 years prior to the dementia diagnosis in individuals with prodromal AD. These results indicate that an abrupt decline in memory in an elderly individual might better predict the imminent onset of dementia than poor but stable memory ability. Such a plateau model (i.e., mild but stable episodic memory decline followed by more abrupt decline in the years proximal to diagnosis) was validated in a large-scale study by Smith et al.
(2007), who found that the plateau was evident on tests of episodic memory, but not on tests of other cognitive domains.

Although the search for cognitive changes in prodromal AD has largely focused on episodic memory (see also position paper by Dubois et al., 2007), several recent reviews and meta-analyses suggest that there is largely nonspecific cognitive decline in the 2 to 3 years preceding a dementia diagnosis. Although a decline in episodic memory is consistently found in these studies, they also often reveal additional deficits in executive functions, perceptual speed, verbal ability, visuospatial skill, and attention during the prodromal phase of AD (Backman et al., 2004, 2005; Storandt et al., 2006; Twamley et al., 2006). This widespread decline in cognitive abilities mirrors evidence that multiple brain regions (e.g., medial and lateral temporal lobes, frontal lobes, anterior cingulate cortex) are impaired in prodromal AD (Albert et al., 2001; Small et al., 2003) (see Table 8–1).

Several studies suggest that measures of semantic knowledge (i.e., vocabulary, naming, category fluency) decline during the prodromal period of AD, even though they are relatively independent of episodic memory impairment (Koenig et al., 2007) and not particularly susceptible to normal age-related decline (Mickes et al. 2007; see also Cueto et al., 2007; Powell et al., 2006). Thus, semantic memory impairment may be a promising cognitive marker for prodromal detection of AD in at-risk elderly individuals. This possibility is supported by the results of a recent neuropsychological study that showed that both semantic and episodic memory declined rapidly in a 3 year prodromal period progressing to AD, whereas decline in executive functions was not especially prominent (Mickes et al., 2007; see Figure 8–6). Based upon these findings, Mickes et al. suggested that cognitive functions subserved by the medial and lateral temporal lobes (episodic memory and semantic knowledge, respectively) are substantially more impaired than cognitive functions subserved by the frontal lobes (executive functioning) in early AD. In addition, these results are consistent with a report of decreased semantic access in nondemented older adults at risk for AD owing to the presence of the APOE e4 allele (Rosen et al., 2005), and with the results of a study that demonstrated that language tasks were predictive of AD pathology observed 6 years later (Powell et al., 2006).

A study by Jacobson and colleagues (2002) identified asymmetric cognitive profiles as a possible prodromal marker of AD in at-risk older adults. Based upon prior research showing lateralized cognitive deficits (e.g., greater verbal than visuospatial deficits, or vice versa) in subgroups of mildly demented patients with AD, these investigators suggested that inconsistent findings of cognitive markers in at-risk groups occur because subgroups of subjects have asymmetric deficits that cannot be appreciated with the use of a single test. To test this hypothesis, Jacobson and colleagues compared 20 cognitively normal elderly adults who were in a prodromal phase of AD (i.e., they were diagnosed with AD approximately 1 year later) and 20 age- and education-matched normal control subjects on a number of individual cognitive test scores and a derived score that reflected the absolute difference between verbal and visuospatial ability (i.e., a measure of cognitive asymmetry). Although the groups performed similarly on individual cognitive tests of memory, language, and visuospatial ability, the prodromal AD

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<th>Neuropsychological Domain</th>
<th>Percentage of Studies with Affected Domain</th>
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<tr>
<td>Attention</td>
<td>71</td>
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<tr>
<td>Verbal Learning</td>
<td>57</td>
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<tr>
<td>Verbal Memory</td>
<td>50</td>
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<td>Executive Functions</td>
<td>44</td>
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<td>Processing Speed</td>
<td>43</td>
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<tr>
<td>General Cognition</td>
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<td>Language</td>
<td>33</td>
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<td>Visual Learning</td>
<td>29</td>
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<td>Visual Memory</td>
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<td>Visuospatial Abilities</td>
<td>26</td>
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<td>Praxis</td>
<td>17</td>
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<td>Motor Speed</td>
<td>17</td>
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<td>Working Memory</td>
<td>12</td>
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Notes: The cognitive domains most consistently associated with prodromal AD were attention (e.g., 71% of studies in which it was assessed), verbal learning and memory, executive functions, processing speed, and language.

Source: Adapted from Twamley et al. (2006).
patients were more likely than normal control subjects to exhibit evidence of cognitive asymmetry in either the verbal or visuospatial direction. These results suggest that a subgroup of prodromal AD patients have asymmetric cognitive changes that are obscured when cognitive scores are averaged over the entire group. Additional evidence of cognitive asymmetry in prodromal AD or in elderly individuals at risk for AD has been shown in subsequent studies that compared auditory versus spatial attention (Jacobson et al., 2005a), verbal versus design fluency (Houston et al., 2005), global versus local item processing (Jacobson et al., 2005b), and response inhibition versus cognitive flexibility (Wetter et al., 2005). Consideration of these nonmemory changes in conjunction with subtle declines in episodic memory may improve the ability to detect AD in its earliest stages.

**Differentiating Alzheimer's Disease from Other Dementias**

Dementia can arise from a wide variety of etiologically and neuropathologically distinct disorders that give rise to somewhat different patterns of preserved and impaired cognitive abilities. Knowledge of these differences might lead to better understanding of the neurobiological basis of various cognitive disorders, have important implications for the neurobiological basis of normal cognition, and improve differential diagnosis of various neurodegenerative disorders. The remaining sections will review similarities and differences in the cognitive deficits of AD and those of other age-related causes of dementia including HD, DLB, FTD, and VaD.

**Alzheimer's Disease vs. Huntington's Disease**

Many aspects of cognition are affected in qualitatively distinct ways by AD and HD. One distinction is evident in the nature of the episodic memory deficits associated with the two disorders. As described in the section above, the dementia of AD is usually characterized by a severe deficit in episodic memory that has been attributed to ineffective consolidation (i.e., storage) of new information (Salmon, 2000). In contrast, the dementia of HD is usually...
characterized by mild to moderate memory impairment that appears to result from a general deficit in the ability to initiate and carry out the systematic retrieval of otherwise successfully stored information (Butters et al., 1985, 1986; Moss et al., 1986). These differences were demonstrated in a study by Delis and colleagues (1991) that directly compared AD and HD patients on a rigorous test of verbal learning and memory (i.e., the CVLT). Despite comparable immediate and delayed recall deficits (based on age-corrected normative data), patients with AD were just as impaired on the recognition trial as they were on the free recall trials, whereas patients with HD were less impaired on the recognition trial than on free recall trials. The benefit of recognition testing for the HD patients suggests that their memory impairment is attenuated when the need for effortful, strategic retrieval is reduced (Butters et al., 1985, 1986), a benefit not shared by patients with AD. In addition, patients with AD exhibited significantly faster forgetting over the 20-minute delay interval than did patients with HD (also see Butters et al., 1988; Troster et al., 1993). Patients with AD retained less than 20% of the initially acquired information, whereas those with HD retained a near-normal 70%. These distinct deficit patterns are consistent with the notion that information is not effectively consolidated by patients with AD because of early damage to medial temporal lobe structures (e.g., hippocampus, entorhinal cortex), whereas information can be successfully stored but not effectively retrieved by patients with HD, presumably owing to disruption of frontostriatal circuits (although some residual memory deficit is apparent even when retrieval demands are reduced; Brandt et al., 1992; for review, see Montoya et al., 2006).

The ineffective retrieval exhibited by patients with HD on tests of episodic memory is also evident in their performance on tests of remote memory. Whereas patients with AD show a severe and temporally graded retrograde amnesia, patients with HD exhibit a relatively mild retrograde amnesia that equally affects all time periods (Albert et al., 1981; Beatty et al., 1988; Sadek et al., 2004). Presumably, episodic memory that was acquired in the past is successfully stored and retained over time by these patients, but retrieval of this information is generally deficient, causing the remote memory deficit to be equally distributed across decades. This interpretation is bolstered by an analysis of cued retrieval in a remote memory task that indicated a preferential cueing benefit for patients with HD compared to patients with AD (Sadek et al., 2004).

A number of qualitative differences exist in the language and semantic knowledge deficits exhibited by patients with AD and HD. For example, patients with AD usually exhibit a significant confrontation naming deficit (e.g., Bayles & Tomoeda, 1983), and the greatest proportion of their naming errors are semantically based (e.g., superordinate errors such as calling a "camel" an "animal"). In contrast, patients with HD usually have little difficulty with confrontation naming (Hodges et al., 1999; Hodges et al., 1999), and the naming errors they make tend to be perceptually based (e.g., calling a "pretzel" a "snake", Hodges et al., 1999). Differences also exist in the pattern of verbal fluency deficits associated with the two disorders. Patients with HD are severely and equivalently impaired on both letter fluency (i.e., generate words that begin with the letters "F," "A," or "S") and category fluency (i.e., generate exemplars of animals, fruits, or vegetables) tasks, whereas patients with AD are more impaired on category fluency than on letter fluency tasks (Butters et al., 1987; Monsch et al., 1994; for reviews, see Henry et al., 2004, 2005). Studies of the temporal dynamics of retrieval from semantic memory during the letter and category fluency tasks provide some information about the nature of the loss that underlies these distinct deficit patterns (Rohrer et al., 1995, 1999). Patients with AD achieved a lower-than-normal mean latency consistent with the idea that they effectively draw exemplars from a semantic set that is abnormally small due to a loss of semantic knowledge. Patients with HD, in contrast, had a higher-than-normal mean response latency consistent with the notion that they have a normal semantic set size, but draw exemplars abnormally slowly due to ineffective retrieval.

The view that AD and HD differentially impact the integrity of the structure and organization of semantic memory was directly examined by Chan and colleagues using cluster analysis.
and multidimensional scaling techniques to statistically model a spatial representation of the degree of association between concepts in semantic memory (for review, see Chan et al., 1998). The degree of association between the various exemplars in the category “animals” was estimated from their proximate position when generated in a verbal fluency task, or from the frequency with which they were paired in a triadic comparison task. Modeling showed that the network of semantic associations for patients with HD was virtually identical to that of control subjects, whereas that of patients with AD was characterized by less consistency and weaker and more concrete associations (i.e., size was emphasized rather than domesticity). Thus, AD appears to be characterized by a decline in the structure and organization of semantic knowledge that does not occur in HD. Because the categorization task placed little demand on retrieval processes, the results also support the possibility that HD is characterized by a general retrieval deficit that is not influenced by the demands various tasks place on the structure of semantic memory.

Although memory is usually thought of as a conscious process in which an individual explicitly attempts to remember a specific bit of information, there are some forms of memory that occur without conscious awareness (i.e., implicit memory) and without dependence upon the medial temporal lobe structures important for explicit episodic memory (Schacter, 1987; Squire, 1987). Two forms of implicit memory include priming, a phenomenon in which the ability to identify or to generate a particular stimulus is enhanced simply through prior exposure to an identical or associated stimulus, and motor and cognitive skill learning that occurs with repeated practice. These forms of implicit memory are differentially impaired in AD and HD. Mildly demented patients with AD, but not those with HD, are impaired on various priming tasks including lexical (word stem completion) priming, semantic paired-associate priming, and priming to enhance the identification of fragmented pictures (see Fleischman & Gabrieli, 1998, for review), whereas motor learning is relatively spared (Eslinger & Damasio, 1986). In contrast, mildly demented patients with HD, but not those with AD, are impaired in the ability to learn and retain certain motor and cognitive skills such as pursuit rotor tracking, adaptation-mediated weight biasing, visual prism adaptation, serial reaction time sequences, reading mirror-reversed text, complex problem solving (e.g., Tower of Hanoi puzzle), and probabilistic classification learning (Gabrieli et al., 1997; Heindel et al., 1988; for review, see Heindel & Salmon, 2001). Taken together, these findings indicate that there is a dissociation in the neural substrates that support various forms of implicit memory. Priming appears to be mediated by the basal forebrain and association cortices damaged in AD, whereas motor and cognitive skill learning is largely mediated by the neostriatal structures (particularly the caudate nucleus) damaged in HD.

Distinct aspects of attention, working memory, and executive functions are differentially affected in AD and HD. In general, a deficit in attention is more salient in HD than in AD (e.g., Butters et al., 1988). The attention deficit in HD is characterized by difficulty in shifting or allocating attention (Hanes et al., 1995; Lange et al., 1995; Lawrence et al., 1996), particularly when attentional shifts must be internally regulated (Sprengelmeyer et al., 1995). Several studies have shown, for example, that the ability to effectively shift attention between stimulus dimensions (e.g., from color to shape) in a visual discrimination task is impaired in moderately to severely demented HD patients, but not in patients with AD or in mildly demented HD patients (Lange et al., 1995; Lawrence et al., 1996).

Alzheimer’s disease and HD differentially affect working memory (Baddeley, 1986). Early in the course of HD, working memory deficits are apparent in the ability to maintain information in temporary memory buffers (e.g., as evidenced by poor digit span performance), to inhibit irrelevant information, and to use strategic aspects of memory (e.g., planning, organization) to enhance free recall (Butters et al., 1978; Caine et al., 1977; Lange et al., 1995; Lawrence et al., 1996). Working memory deficits are relatively mild in early AD and are primarily characterized by a disruption of the central executive with sparing of the phonological loop and visuospatial scratchpad (Baddeley et al., 1991; Collette et al., 1999). It is only in the
later stages of AD that all aspects of working memory become compromised (Baddeley et al., 1991; Collette et al., 1999).

One of the most salient aspects of the dementia associated with HD is impairment of various “executive” functions involved in planning and problem solving. Patients with HD usually exhibit deficits in goal-directed behavior, the ability to generate multiple response alternatives, the capacity to resist distraction and maintain response set, and the cognitive flexibility needed to evaluate and modify behavior (for review, see Brandt & Bylsma, 1993). These deficits have been documented with a wide variety of tests that assess executive functions, including the Wisconsin Card Sorting Test (Paulsen et al., 1995; Peinemann et al., 2005; Pillon et al., 1991; Ward et al., 2006), the Stroop Test (Peinemann et al., 2005; Ward et al., 2006), the Tower of London Test (Lange et al., 1995), the Gambling Decision Making task (Stout et al., 2001), and tests of verbal concept formation (Hanes et al., 1995). Similar deficits in executive functions occur in AD (for reviews, see Duke & Kasznial, 2000; Perry & Hodges, 1999), but few studies have directly compared this aspect of cognition in the two disorders. Further research is needed to determine if specific aspects of executive dysfunction are more common in one dementia syndrome than the other, and to establish whether or not this facet of cognitive impairment can differentiate between AD and HD.

Visuospatial processing deficits occur in both AD (for review, see Cronin-Golomb & Amick, 2001) and HD (Brandt & Butters, 1986; Brouwers et al., 1984; Bylsma et al., 1992; Caine et al., 1986; Josiassen et al., 1983; Lawrence et al., 2000; Ward et al., 2006). In one of the few studies to directly compare visuospatial performance in the two disorders, Brouwers and colleagues (1984) showed that AD and HD had differential impacts on personal and extrapersonal orientation abilities. Patients with AD, but not those with HD, were impaired on tests of visuocconstructional ability that required extrapersonal orientation (e.g., copying a complex figure). Patients with HD, but not those with AD, were impaired on visuospatial tasks that required personal orientation (e.g., the Money Road Map Test). This dissociation was supported by the results of a more recent study that examined the ability of AD and HD patients to mentally rotate representations of objects (Lineweaver et al., 2005). Patients with HD were significantly slower than normal control subjects in performing mental rotation, but were as accurate as controls in making the rotation and reporting the correct side of the target. Patients with AD, in contrast, performed the mental rotation as quickly as controls, but were significantly impaired in making an accurate rotation and reporting the correct side of the target. These results were interpreted as showing that HD patients can effectively perform mental rotation of visual representations, but suffer a general bradyphrenia (i.e., slowed thinking) that parallels the bradykinesia that characterizes the disorder. Conversely, patients with AD are impaired in performing mental rotation, perhaps due to extrapersonal visual orientation deficits secondary to neocortical damage in regions involved in processing visual motion (e.g., the middle temporal gyrus).

Another study that directly compared visuospatial abilities in patients with AD or HD examined their ability to draw and copy clocks (Rouleau et al., 1992). The two patient groups were impaired on both conditions of this task, but patients with AD were significantly worse in the draw-to-command condition than in the copy condition, whereas patients with HD were equally impaired in both conditions. A qualitative analysis of the types of errors produced showed that HD patients tended to make graphic, visuospatial, and planning errors in both the command and copy conditions consistent with planning and motor deficits mediated by frontal-subcortical dysfunction. In contrast, AD patients tended to make conceptual or semantically based errors (e.g., drawing a face without numbers, or hands) in the command condition but not the copy condition, consistent with a deficit in accessing knowledge of the attributes and meaning of a clock due to neocortical damage in regions supporting semantic knowledge.

Alzheimer's Disease vs. Dementia with Lewy Bodies (DLB)

The dementia syndromes associated with AD and DLB are quite similar and include insidious
onset of cognitive decline with early involvement of memory (Hansen et al., 1990; Hansen & Galasko, 1992; McKeith et al., 1996). Mild parkinsonism (e.g., bradykinesia, rigidity, masked facies), recurrent and well-formed visual hallucinations, and fluctuations in attention or alertness (Cercy & Bylsma, 1997; Galasko et al., 1996; Hansen et al., 1990; McKeith et al., 1996; Merdes et al., 2003) are more prevalent in DBL than in AD, and are the basis for consensus criteria designed to help clinically diagnose DBL and distinguish it from AD (McKeith et al., 1996, 2005). Unfortunately, these clinical features are not ubiquitous in DBL and occur with only about 50% frequency at any time during the course of the disorder (Merdes et al., 2003). Thus, patients found to have DBL at autopsy have often been clinically diagnosed as having probable or possible AD during life (e.g., Hansen et al., 1990; Merdes et al., 2003).

A number of studies have compared the neuropsychological deficits associated with DBL and AD. These studies have consistently shown that the most salient difference between the two disorders is disproportionately severe visuospatial and visuoconstructive deficits in DBL. This distinction has been shown using tests of visual perception (Calderon et al., 2001; Lambo Ralph et al., 2001; Mori et al., 2000), visual search (Cormak et al., 2004), drawing simple and complex two-dimensional figures (Aarsland et al., 2003; Connor et al., 1998; Galasko et al., 1996; Gnanalingham et al., 1996, 1997; Hansen et al., 1990; Noe et al., 2003; Salmon et al., 1996), and construction of three-dimensional objects (Hansen et al., 1990; Shimonura et al., 1998). Calderon and colleagues (2001), for example, found that DBL patients performed worse than AD patients on tests of fragmented letter identification, discrimination of "real" objects from nonobjects, and segregation of overlapping figures. These particularly severe deficits in visuospatial and visuo perceptual abilities were apparent even though the DBL patients performed significantly better than the patients with AD on a verbal memory test and at the same level on tests of semantic memory (also see Lambo Ralph et al., 2001). Similar results were obtained by Mori and colleagues (2000), who found that DBL patients performed significantly worse than equally demented AD patients on tests of visual attention, size and form discrimination, and visual figure-ground segregation. A study of visual search processes (Cormak et al., 2004) showed that DBL patients were more impaired than AD patients in the ability to perform serial search that required feature integration (i.e., detect a single red target circle within arrays of 2, 8, or 16 green circles and red squares distracters) and in "preattentive" parallel search processes that usually elicit the "popout" phenomenon (i.e., detecting a single red target circle within arrays of 2, 8, or 16 green distractor circles). Performance on the parallel search task provided relatively good sensitivity (85%) and specificity (87%) for distinguishing patients with DBL from those with AD.

The disproportionately severe visuospatial deficits exhibited by patients with DBL may be related to occipital cortex dysfunction, which does not usually occur in patients with AD. A number of studies have shown hypometabolism and decreased blood flow in primary visual and visual association cortex in DBL but not in AD (e.g., Minoshima et al., 2001). Neuropathologic studies have identified white matter spongiform change with coexisting gliosis in the occipital cortex of patients with DBL (Higuchi et al., 2000), and in some cases deposition of Lewy bodies is also observed (e.g., Gomez-Tortosa et al., 1999). In contrast, AD pathology in the occipital cortex is rare. The relationship between the structural and metabolic abnormalities in the occipital cortex of patients with DBL and their prominent visuospatial deficits remains unknown.

In addition to disproportionate visuospatial deficits, patients with DBL often have greater deficits in attention and executive functions than patients with AD. Studies have shown that DBL patients perform worse than equally demented AD patients on measures of attention such as the WAIS-R Digit Span subtest (Hansen et al., 1990), the Cancellation Test (Noe et al., 2004), and a computer-based visual search task that assesses the ability to focus attention (Sahgal et al., 1992b). Patients with DBL are also more impaired than AD patients on verbal fluency tests that require initiation and systematic retrieval from semantic memory (Aarsland et al., 2003; Ballard et al., 1996; Connor et al., 1998; Galasko et al., 1998; Hansen et al., 1990),
paired-associates learning tests (Galloway et al., 1992), delayed matching-to-sample tests (Sahgal et al., 1992a), and spatial working memory tasks that assess both spatial memory and the ability to use an efficient search strategy (Sahgal et al., 1995). Abstract reasoning abilities assessed by the Raven Colored Progressive Matrices (Shimomura et al., 1998) and the WAIS-R Similarities subtest (Galasko et al., 1998) are more impaired in patients with DLB than in those with AD.

The prominent attention and executive function deficits associated with DLB are similar to those that occur in patients with basal ganglia dysfunction that interrupts frontostriatal circuits (e.g., patients with HD). In DLB, these circuits may be disrupted by substantia nigra pathology that interrupts dopaminergic projections to the striatum, and by direct neocortical Lewy body pathology in the association areas of the frontal lobes. In addition, AD pathology may be superimposed upon the Lewy body pathology in the frontal cortex of patients with DLB. This combination of pathologic processes may induce the disproportionately severe executive function and attention deficits that characterize the disease.

Although deficits in visuospatial abilities, executive functions, and attention are usually greater in patients with DLB than in equally demented patients with AD, memory is often more impaired in patients with AD. Furthermore, qualitative differences in impaired memory processes are evident in the two disorders. These differences were highlighted in a study that directly compared the performances of patients with autopsy-confirmed DLB (all with concomitant AD pathology consistent with Lewy body variant of AD) and patients with autopsy-confirmed AD on the CVLT and the WMS-R Logical Memory Test (Hamilton et al., 2004). Despite equivalent deficits in their ability to learn new verbal information on these tests, the DLB patients exhibited better retention and better recognition memory than patients with AD (also see Ballard et al., 1996; Calderon et al., 2001; Connor et al., 1998; Heyman et al., 1999; Salmon et al., 1996; Shimomura et al., 1998; Walker et al., 1997). These differences are consistent with the particular pathological changes that occur in the two disorders. A number of studies using neuropathologic (Lippa et al., 1998) or magnetic resonance imaging (Barber et al., 2001; Hashimoto et al., 1998) procedures have shown that the medial temporal lobe structures important for memory (e.g., hippocampus, entorhinal cortex, parahippocampal gyrus) are more severely affected in AD than in DLB. This may account for the poorer retention (i.e., consolidation) exhibited by the AD patients. The greater recognition memory performance of the DLB patients compared to patients with AD suggests that they may have a particular deficit in the ability to initiate and carry out systematic retrieval of successfully stored information. This retrieval deficit may be mediated by the frontostriatal damage that occurs in DLB but not in AD.

The results of the studies reviewed above indicate that visuospatial, attention, and executive function deficits are more prominent in DLB than AD, whereas memory impairment is greater in AD than in DLB. These distinct deficit patterns have been confirmed in a number of recent studies that compared clinically diagnosed or autopsy-confirmed DLB and AD patient groups on relatively extensive batteries of neuropsychological tests (Ferman et al., 2006; Guidi et al., 2006; Johnson et al., 2005; Kraybill et al., 2005; Stavitsky et al., 2006) (see Figure 8-7). The robustness of these deficit patterns (particularly of the disproportionate visuospatial deficits in DLB) may have important clinical utility in distinguishing between AD and DLB in mildly demented patients (Tiraboschi et al., 2006).

Alzheimer’s Disease vs. Frontotemporal Dementia

AD and FTD are clinically similar and difficult to distinguish during life (Mendez et al., 1993; Varma et al., 1999). Indeed, Mendez and colleagues (1993) found that 86% of autopsy-confirmed FTD patients had been clinically misdiagnosed with AD during life. Some success has been achieved in differentiating between FTD and AD on the basis of behavioral symptoms (e.g., Barber et al., 1995; Bozeat et al., 2000; Kertesz et al., 2000; Mendez et al., 1998; Miller et al., 1997), but this success has been limited. These findings have led some investigators to
Figure 8–7. The average scores achieved by normal control (NC) subjects (n = 24), patients with Alzheimer’s disease (AD; n = 24), and patients with dementia with Lewy bodies (all with the Lewy body variant (LBV) of AD; n = 24) on several neuropsychological tests. The LBV patients were disproportionately impaired compared to the AD patients on tests of visuospatial ability (Visual Reproduction Copy and Block Design), but less impaired on tests of verbal memory (Logical Memory Savings Score). The patient groups did not differ on a test of confrontation naming (Boston Naming Test) (Adapted from Hamilton et al., 2004).

Propose that FTD and AD might be differentiated on the basis of the nature and severity of their cognitive deficits. Unfortunately, studies that directly compare neuropsychological deficits in FTD and AD have provided inconsistent results. A number of studies showed a greater verbal fluency deficit in FTD than in AD (Frisoni et al., 1995; Lindau et al., 1998; Mathuranath et al., 2000), but others did not replicate this result (Binetti et al., 2000; Pasquier et al., 1995; Thomas-Anterion et al., 2000). Similarly, visuospatial and constructional abilities were found to be less impaired in FTD than in AD in some studies (Elfgren et al., 1994; Mendez et al., 1996), but not others (Frisoni et al., 1995; Lindau et al., 1998; Mathuranath et al., 2000; Pachana et al., 1996). Several studies found better visuospatial memory in FTD than in AD (Frisoni et al., 1995; Pachana et al., 1996), but others failed to replicate this finding (Binetti et al., 2000; Lindau et al., 1998; Thomas-Anterion et al., 2000). Reduced verbal output, stereotyped
language, and echolalia are observed clinically in FTD (Johanson & Hagberg, 1989; Miller et al., 1997; Neary et al., 1988), but these characteristics have not been formally compared in FTD and AD patients. There appears to be little or no difference between FTD and AD patients on measures of confrontation naming (Binetti et al., 2000; Mendez et al., 1996; Pachana et al., 1996; Thomas-Anterion et al., 2000).

Several studies that examined profiles of cognitive deficits associated with FTD and AD demonstrated a subtle difference in the patterns of deficits engendered by the two disorders (Forstl et al., 1996; Starkstein et al., 1994). In these studies, patients with FTD had a more severe deficit in executive functions than in other cognitive abilities, whereas AD patients had executive dysfunction that was proportional to their deficits in language and visuospatial abilities, and less prominent than their episodic memory deficit. These results were confirmed by a more recent study that directly compared neuropsychological deficit profiles in autopsy-confirmed FTD and AD patients who were matched for level of dementia (i.e., MMSE scores) at the time of testing (Rascovsky et al., 2002). Rascovsky and colleagues (2002) found that FTD patients performed significantly worse than AD patients on word generation tasks sensitive to frontal lobe dysfunction (i.e., letter and category fluency tests), but significantly better on tests of memory (i.e., Mattis DRS Memory subscale) and visuospatial abilities (i.e., Block Design and Clock Drawing tests) sensitive to dysfunction of medial temporal and parietal association cortices, respectively (see Figure 8–8). A logistic regression model using letter fluency, Mattis DRS Memory subscale, and the Block Design test provided good discriminability between the groups, correctly classifying approximately 86% of FTD and AD patients (91% of AD patients and 77% of FTD patients).

In a subsequent study, Rascovsky and colleagues (2007) sought to determine whether or not autopsy-confirmed FTD and AD patients who were matched for level of dementia at the time of testing differed in the pattern of deficits they exhibited on letter and semantic category fluency tasks. Although both verbal fluency tasks engage frontal-lobe-mediated executive processes, distinct patterns were hypothesized because semantic category fluency requires a search through semantic memory and is critically dependent upon an adequate knowledge of the physical and/or functional attributes that define a particular semantic category. In contrast, letter fluency requires the use of phonemic cues to guide retrieval and may thus require greater effort and more active strategic search than semantic category fluency. Results showed that FTD patients performed worse than AD patients overall, and showed that FTD patients had similar impairment in letter and semantic category fluency, whereas AD patients had greater impairment in semantic fluency than letter fluency. A measure of the disparity between letter and semantic fluency (the Semantic Index) correctly classified 26 of 32 AD patients (82%) and 12 of 16 FTD patients (75%). Interestingly, the misclassified FTD subjects all had clinical presentations of progressive nonfluent aphasia (Mesulam, 1982) or Semantic Dementia (i.e., severe naming and word comprehension impairments in the context of fluent speech; Hodges et al., 1992; Snowden et al., 1989). When these cases were excluded and the analyses repeated, dissociations were apparent in letter worse than semantic fluency for the FTD patients and semantic worse than letter fluency for the AD patients. In addition, the Semantic Index now correctly classified 90% of FTD and AD patients. These unique patterns of fluency deficits may be indicative of differences in the relative contribution of frontal lobe-mediated retrieval deficits and temporal-lobe-mediated semantic deficits in FTD and AD.

Similar levels of discriminability were observed in a number of additional studies that attempted to differentiate between FTD and AD on the basis of tests of executive functions, visuospatial abilities, and memory (Elfgren et al., 1994; Gregory et al., 1997; Libon et al., 2007; Lipton et al., 2005). For example, Grossman et al. (2007) achieved 88% diagnostic accuracy in differentiating between autopsy-confirmed FTD and AD patients on the basis of clinical and neuropsychological features. These results indicate that distinct cognitive profiles are associated with FTD and AD, and suggest that cognitive assessment may provide useful information when making the differential diagnosis of FTD.
Figure 8–8. Age- and education-adjusted means (and SEM) for the number of words produced in the letter and category fluency tasks and a scores achieved on the WISC-R Block Design test, command condition of the Clock Drawing Test and Mattis Dementia Rating Scale (MDRS) memory subscale by patients with Frontotemporal dementia (FTD) (black bars) or Alzheimer’s Disease (AD) (clear bars). Patients with FTD performed significantly worse than those with AD on verbal fluency tasks, but significantly better on tests of memory and visuospatial abilities. All group differences are significant at $p < .05$. (Adapted from Rascovsky et al., 2002).

Alzheimer’s Disease vs. Vascular Dementia

Studies of the neuropsychological deficits associated with VaD have primarily focused on differentiating between subcortical VaD and AD (see also chapter by Brown in this volume). For the most part, these studies show that patients with subcortical VaD are more impaired than those with AD on tests of executive functions, whereas patients with AD are more impaired than those with subcortical VaD on tests of episodic memory (particularly delayed recall) (Desmond, 2004; Graham et al., 2004; Kertesz & Clydesdale, 1994; Lalosse et al., 1997; Lamar et al., 1997). These studies also suggest that executive dysfunction is usually the most prominent deficit in subcortical VaD, presumably because subcortical pathology interrupts frontosubcortical circuits that mediate this aspect of cognition. Consistent with this possibility, Price and colleagues (2005) found that VaD patients with a significant volume of white matter abnormality on imaging exhibited a profile of greater
executive and visuoconstructional deficits than impairment of memory and language abilities.

Most of the studies that have shown distinct cognitive profiles in subcortical VaD and AD employed clinically diagnosed patients without autopsy confirmation of diagnosis. The lack of autopsy confirmation may have allowed some degree of diagnostic misclassification since AD and VaD often overlap in their clinical presentations. In a study that avoided this potential confound, Reed and colleagues (2007) found that patients with autopsy-confirmed AD had a deficit in episodic memory (both verbal and nonverbal memory) that was significantly greater than their executive function deficit. In contrast, patients with autopsy-confirmed subcortical VaD had a deficit in executive functions that was greater than their deficit in verbal (but not nonverbal) episodic memory. An analysis of individual patient profiles showed that 71% of AD patients exhibited a profile with memory impairment more prominent than executive dysfunction, whereas only 45% of patients with subcortical VaD exhibited a profile with more prominent executive dysfunction than memory impairment. Interestingly, relatively severe cerebrovascular disease at autopsy was often not associated with clinically significant cognitive decline. When the profile analysis was restricted to those patients who exhibited significant cognitive impairment at their clinical assessment, the distinction between subcortical VaD and AD patients was more pronounced. A low memory profile was exhibited by 79% of AD patients (5% with a low executive profile) and a low executive profile by 67% of subcortical VaD patients (0% with a low memory profile). The results suggest that relatively distinct cognitive deficit profiles might be clinically useful in differentiating between subcortical VaD and AD, but additional research with autopsied patients is needed to further define the deficit profile that will be most useful in this regard.

Chapter Summary

A wealth of neuropsychological research has shown that the cognitive deficits associated with AD are distinct from age-associated cognitive decline. Quantitative and qualitative differences between early AD and normal aging effects are especially apparent in episodic memory (particularly delayed recall), semantic knowledge, and some aspects of executive functions. There is also emerging evidence that the cortical neuropathology of AD causes a loss of functional connectivity that adversely affects interaction between distinct and relatively intact cortical information-processing systems. This loss may cause, for example, an impaired ability to "bind" distinct visual stimulus features that are effectively processed in different cortical streams (i.e., motion and color). The qualitatively distinct pattern of cognitive impairment associated with early AD appears to be less salient in very old patients than in younger patients when they are compared to their age-appropriate cohort. This finding may be driven in large part by the age-associated decline in certain cognitive abilities (e.g., speed of information-processing, retrieval processes) that occurs with normal healthy aging. Progress has been made in identifying cognitive markers of "prodromal" AD that are apparent before the development of the dementia syndrome. Decline in episodic memory is usually the earliest cognitive change that occurs during the prodromal stage of AD, but decline in other cognitive domains, and asymmetry in cognitive abilities (e.g., high verbal vs. low visuospatial performance), may also predict the imminent onset of dementia. Neuropsychological research has also identified patterns of cognitive impairment that might help distinguish AD from other neuropathologically distinct neurodegenerative disorders such as HD, DBL, FTD, and VaD. Knowledge of these differences is clinically important for distinguishing among various causes of dementia, and provides useful information about the brain–behavior relationships that mediate cognitive abilities affected by various neurodegenerative diseases.

Conclusions and Future Directions

Clinical and experimental neuropsychological research has made great strides in differentiating between the cognitive changes that signal the onset of a dementia syndrome and those that occur as a normal consequence of aging. Many of the basic cognitive processes that are adversely affected by AD have been identified,
and the prodromal cognitive changes that predict the subsequent development of dementia are being uncovered. Considerable progress has also been made in delineating different patterns of relatively preserved and impaired cognitive abilities that distinguish between AD and other age-associated neurodegenerative disorders. Understanding the cognitive distinctions between these disorders can aid in the development of better differential diagnosis and reveal the nature of brain–behavior relationships underlying memory, language, executive functions, and other cognitive abilities that are affected.

The search for antecedent markers of dementia is predicated on the notion that significant neural dysfunction and cell death occurs well in advance of the clinical diagnosis. It is imperative to reliably identify individuals prior to the development of significant clinical symptoms in order to begin treatments that might halt or slow disease progression. Therefore, the identification and validation of subtle cognitive abnormalities (e.g., poor delayed recall performance, cognitive asymmetry) for prodromal diagnosis of AD remains an extremely important goal. The role of cortical disconnectivity in producing the specific pattern of cognitive deficits that occurs in early AD has only begun to be assessed, but the identification of cognitive processes that are particularly vulnerable to the effects of cortical disconnectivity might provide a useful cognitive marker for the disease and a means by which to assess the effects of interventions that specifically target cortical function (e.g., the NMDA receptor antagonist memantine). Clearly, additional research is needed in this area.

Despite intense research focus, it remains difficult to estimate rate of cognitive decline in AD and other age-related neurodegenerative diseases, although there is promising evidence that certain aspects of current cognitive performance can predict subsequent rate of global cognitive decline in patients with AD (e.g., Chan et al., 1995). Further research is needed to confirm this possibility and to generalize it to other neurodegenerative disorders such as DLB and FTD (e.g., see Wicklund et al., 2007). In addition, there is a continuing need to identify differences in the profiles of cognitive deficits associated with AD and other age-related neurodegenerative diseases (e.g., DLB, FTD), and to determine how these profiles can be incorporated with other clinical features to improve the accuracy of differential diagnosis in very mildly demented individuals. Accurate early diagnosis is a particularly important goal since the various neurodegenerative disorders are likely to respond differently to potential treatments for dementia that are in development. Finally, the strides made in understanding the neuropsychology of dementia need to be linked to those made in neuroimaging research with consonant goals of early detection and maximization of intervention efforts. This approach will lead to better understanding of the brain–behavior relationships underlying dementia.

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