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The Dementias: An Overview of Alzheimer Disease and Related Disorders

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Introduction: The Problem with Identification of Cognitive Abnormality

Dementia is a nonspecific term denoting a constellation of impairments in memory, language, visuospatial processing, and behavior that are associated with organic brain disease. The diagnosis of dementia poses a particular challenge due to the difficulty in distinguishing between changes in cognition associated with healthy aging, and those due to various neuropathologies. Although Alzheimer disease is one of the most common causes of dementia, there are many other commonly occurring diseases that can cause dementia. Distinguishing Alzheimer disease (AD) from other neurodegenerative disorders poses a difficult, yet important, clinical problem. The diagnosis of dementia poses a particular challenge due to the difficulty in distinguishing between changes in cognition associated with healthy aging and those due to various neuropathologies. Because patients with dementia present with language and other cognitive impairments, allied health professionals must be knowledgeable of the deficits associated with these disorders. This chapter serves to identify many of the common dementias affecting older adults including AD, Parkinson disease, vascular dementia, frontotemporal dementias, Huntington disease, and progressive supranuclear palsy. Etiologies, incidence, and common clinical presentations are discussed for each disorder. Differences in clinical and neuropathalogic features between related disorders are also identified.

Dementia and Its Significance

Dementia is becoming a clinical problem that is soon projected to reach a critical level in our rapidly aging population. Dementia is an umbrella term that refers to acquired intellectual or cognitive impairments that are caused by brain dysfunction. A number of different neurologic disorders whose cognitive and linguistic profiles are distinctive occur under the umbrella of the term "dementia." Dementia therefore does not constitute a global impairment of intellectual function, but rather a diffuse collection of symptoms that compromise cognition. Dementia is characterized by a loss of mental functions that are acquired, persistent, and not caused by delirium. The term dementia can refer to the loss of intellectual function in one or more cognitive domains including language, memory, visuospatial perception, executive function, social behavior, emotional expression, and semantic knowledge. Although many forms of dementia include memory impairment as a core feature (e.g. Alzheimer disease), this is not true of all dementia subtypes. For example, impairment of episodic memory is not one of the core diagnostic features of frontotemporal dementia (FTD) (Neary et al., 1998).

As the population of the United States and other developed countries continues to age, dementia will become an increased financial, clinical, and psychosocial problem. Dementia diagnosis accounts for a significant illness burden in older adults, affecting 4 to 12% of individuals 65 and older, and almost half of individuals over 85 worldwide (Canadian Study of Health and Aging Working Group, 1994; D. A. Evans, Scherr, Smith, Albert, & Funkenstein, 1990; Henderson, 1990; Katzman, 1993). The incidence of dementia is higher in developed countries such as the United States, the United Kingdom, and Canada, although this partially may be attributed to a lengthier lifespan (Breteler, Claus, van Duijn, Launer, & Hofman, 1992; General Accounting Office Report, 1998). The costs of caring for patients with dementia are enormous. For example, it is estimated that the cost of caring for just one Alzheimer patient in the U.S. is between $20,000 and $30,000 a year (Ernst & Hay, 1994). In the United States alone, it is estimated that dementia care costs over $100 billion per year (National Institutes on Aging, 2001).

Normal Aging and Cognition (Table 5–1)

Diagnosis of dementia remains a challenge. Cognitive decline occurs in healthy aging and must be carefully distinguished from deficits due to neurodegenerative disease processes. Normal age-related declines in cognitive performance may be due to impaired attentional control (Balota, Dolan, & Ducheck,

Table 5–1. Typical Cognitive Declines Seen in Healthy Aging

General cognitive slowing
Impaired attentional control
Reduced working memory capacity
Inability to represent task goals
Difficulty recalling specific labels (e.g., names)
Set-shifting impairments (e.g., perseverative behavior)
Disinhibition

2000), reduced working memory capacity (Hedden & Park, 2001), the inability to represent task goals (Paxton, Barch, Racine, & Braver, 2008), or a generalized slowing of cognition (Myerson, Hale, Wagstaff, Poon, & Smith, 1990; Salthouse, 1996). One of the most common memory complaints in older adults is increased difficulty in recalling specific labels or names (Cohen & Burke, 1993). Specifically, naming ability for names of persons, places, and objects declines with age (Fleischman & Gabrieli, 1998; D. C. Park et al., 1996; S. M. Park et al., 1998). For example, the older adult may have difficulty recalling the name of a movie or a new restaurant. This information typically is not "lost" from memory, and can be accessed spontaneously or through the use of phonological cues. Finally, neuropsychological performance can be affected by normal declines in hearing and visual acuity, motor deficits, and decreased sleep.

Another challenge in the diagnosis of dementia is the huge cognitive and cultural variability of the older adult population (Birren, Schaie, Abeles, Gatz, & Salthouse, 2006; Craik & Bialystok, 2006). Normal cognition in younger and older adults can be affected by a number of factors including environmental exposure, cultural upbringing, and life experiences. Life experiences can directly impact plasticity in the brain, and may provide additional "cognitive reserve" in the older adult (Stern et al., 1995; Stern, 2006). Cognitive reserve refers to the brains ability to use alternate neural strategies and to recruit additional neural resources to complete a task, even in the face of neuronal degeneration. Both increases in level of education, and specific practice with certain skills appear to result in improved cognitive function (Kahana, Galper, Zilber, & Korczyn, 2003). In addition, changes in brain function and volume can result from specific life experiences. For example, London taxi drivers, who are required to have extensive knowledge of the London street system, have greater hippocampal volumes than control subjects (Maguire et al., 2000). In addition, the taxi drivers with more job experience had larger hippocampi than those with less time on the job. The hippocampus is a medial temporal lobe structure that is involved in a number of memory functions, including spatial memory. It is important to note that these types of plastic brain changes may be domain specific—the London taxi drivers may show greater spatial memory ability as a result of their increased hippocampal volume, but may not show improvements in other cognitive domains. Finally, personality differences or cognitive style may also play a role in the strategies that a person may apply to cognitive processing (Cuttler & Graf, 2007). For example, individuals who use visual imagery may remember names or other words better than individuals with more verbal cognitive styles, (Neils-Strunjas, Krikorian, Shidler, & Likoy, 2001).

Differential Effects of Healthy Aging on the Brain

Age-related cognitive decline is variable across cognitive domains. Several of the cognitive declines associated with healthy aging also occur during the early stages of disease processes that produce dementia. There are numerous factors that may contribute to this

variability in cognitive functions in healthy aging. For instance, age-related cortical atrophy is nonuniform across the brain. In general, older adults show generalized atrophy and enlargement of the ventricular spaces in structural MRIs (Minati, Grisoli, & Bruzzone, 2007). Furthermore, age-related atrophy is more prominent in the prefrontal and parietal cortices (Allen, Bruss, Brown, & Damasio, 2005). In contrast, other regions, such as the primary visual cortex, are relatively spared from age-related atrophy (Raz et al., 2005). Cognitive decline in aging has also been associated with a number of genetic factors (apoE4 genotype) (Packard et al., 2007), the presence of cardiovascular disease (Cherubini et al., 2007), and behavioral factors including lack of exercise and a sedentary lifestyle (Boyle, Buchman, Wilson, Bienias, & Bennett, 2007; Buchman, Boyle, Wilson, Tang, & Bennett, 2007; Hillman, Erickson, & Kramer, 2008). Another factor that may affect cognitive decline is the variable impact of neuropathology on cognition; whereas older adults without cognitive problems may be spared from neurofibrillary plaques and tangles, which are commonly seen in AD patients (DeKosky, Ikonomovic, Hamilton, Bennett, & Mufson, 2006), other individuals with mild pathology may be able to compensate for decline in one area of the brain and appear to be functionally normal. However, many individuals will not be able to compensate for neuropathologies and other insults, and will demonstrate cognitive impairment. Many of these individuals will be diagnosed with dementia or loss of intellectual ability due to a variety of diseases; the most common medical diagnosis is Alzheimer disease (AD) (Drachman, 2006). The risk of AD increases with advancing age, and as the elderly population increases so will the prevalence of AD (Hebert, Beckett, Scherr, & Evans, 2001; Schoenberg, Kokmen, & Okazaki, 1987).

With healthy aging, there may be changes in neural networks that directly impact cognition. There is a general reduction in perfusion (i.e., blood flow) in some older adults that can affect how brain regions are recruited during a task (Beason-Held, Kraut, & Resnick, 2008; Takahashi, Yamaguchi, Kobayashi, & Yamamoto, 2005). In addition to its effects in healthy aging, vascular insufficiencies can cause dementia outright (i.e., vascular dementia), and also can affect the clinical presentation of other forms of dementia such as Alzheimer disease (AD) (Roman & Royall, 2004). Healthy older adults commonly show under-recruitment of specific prefrontal regions, particularly during memory encoding as compared to younger adults (Grady & Craik, 2000). However, other prefrontal brain regions may show increases in activation with age, particularly during tasks that heavily tax attention and executive resources (Cabeza, 2002). These differential patterns of brain activation have been referred to as dedifferentiation or compensation. Differentiation and compensation can affect both basic brain regions such as the visual system (D. C. Park et al., 2004) and regions involved in higher cognitive functions such as memory (Cabeza, 2001).

Dedifferentiation refers to the nonspecific recruitment of brain regions in older adults that are not normally activated by younger adults. The cognitive implication for dedifferentiation has yet to be determined; however, as a general rule, a diffuse pattern of cortical activation coupled with underactivation

of specific task-related regions coupled with generalized activation may account for slower processing time or an increase in errors. For example, Vandenbulke et al. speculated that slow written word identification in persons with mild cognitive impairment may be the result of dedifferentiation of the connection between brain regions supporting the orthographic word forms and their associated meaning (Vandenbulcke, Peeters, Dupont, Van Hecke, & Vandenberghe, 2007). In contrast, compensatory changes in brain activation may serve to maintain or increase cognitive abilities (Cabeza, 2001).

Finally, factors such as degree of education and occupational attainment may moderate the presentation cognitive declines associated with healthy and pathological aging. There is increasing evidence for the neuroprotective effects of environmental stimulation. Older adults who have higher levels of education are less likely to be diagnosed with Alzheimer disease. For instance, uneducated individuals older than 75 have over double the incidence of dementia as those who have completed the eighth grade (Kahana, Galper, Zilber, & Korczyn, 2003). Different education levels also may partially explain the differences in incidence of dementia between men and women in many countries (Kahana et al., 2003). It also has been found that the stimulation that occurs with continuing education and physical activity in the later years either through self-education or high occupational attainment provides an optimal environment for maintaining cognition (Colcombe et al., 2004; Stern et al., 1994). Nevertheless, these findings should be interpreted with caution as higher education levels are associated with higher socioeconomic status during childhood (which can affect nutrition and environmental exposure), and participation in more professional activities during later adulthood. In addition, fluid intelligence, which is correlated with educational attainment, has been shown to be neuroprotective (Corral, Rodriguez, Amenedo, Sanchez, & Diaz, 2006).

Life experiences may also affect the rate of decline seen in dementing disorders. For example, in AD, higher premorbid intelligence, education, and occupations requiring "people skills" is inversely correlated with cerebral metabolism in cortical association regions, which may serve to delay AD diagnosis (Stern et al., 1995; Stern, 2006). Higher levels of intellectual leisure activity (e.g., crossword puzzles) were also found to be neuroprotective for AD (de Medeiros, Kennedy, Cole, Lindley, & R, 2007; Helzner, Scarmeas, Cosentino, Portet, & Stern, 2007). Grady et al., 2003 suggests that there is a compensatory prefrontal network in Alzheimer disease based on functional neuroimaging (Grady et al., 2003). Most likely, the degree to which this prefrontal network may be called upon results in variation in an individual's functional status; however, this hypothesis re-quires further study.

Mild Cognitive Impairment

Some older adults develop cognitive deficits that are greater than expected for healthy aging, but not extensive enough to qualify as a specific dementia. These adults are characterized as having mild cognitive impairment (MCI). The MCI group may be further divided into cognitive impairment that is domain general (amnestic MCI multidomain), or cognitive impairment that is specific to memory (amnestic MCI).

Amnestic MCI is clinically defined by the presence of a subjective complaint of memory decline corroborated by an informant, objective impairment of episodic memory on routine neuropsychological assessment, and minimal impact on instrumental activities of daily living (IADL) (Petersen, 2004). Those with amnestic MCI multidomain may have additional impairments in cognitive areas other than memory, such as naming (Adlam, Bozeat, Arnold, Watson, & Hodges, 2006).

There is considerable variability in the progression of MCI. About 30 to 80% of patients with MCI, particularly those with more general cognitive impairment, later go on to receive a diagnosis of Alzheimer disease (DeKosky et al., 2006; Manly et al., 2008). Tabert and colleagues found that of 148 individuals with the diagnosis of MCI, 50% of those with memory plus or generalized cognitive impairment and 10% of pure amnestic patients converted to AD (Tabert et al., 2006). Plaque and tangle disease, which is characteristic of AD, may be a critical factor in the conversion of MCI to AD. Morris and Price noted that diffuse beta amyloid plaques throughout the cortex (and not just in memory centers of the medial temporal lobes) are most likely to result in dementia associated with Alzheimer disease (Morris & Price, 2001). However, some individuals maintain the mild cognitive deficit for many years, if not until death. Interestingly, some individuals resist deteriorating into dementia despite a considerable amount of plaque pathology in their medial temporal lobe (DeKosky et al., 2006). Therefore, a diagnosis of MCI does not imply that the individual will certainly convert to AD.

Alzheimer Disease

Alzheimer disease (AD), as defined today, was first described in 1906 in a lecture by Dr. Alois Alzheimer, a prominent German psychiatrist. In his 1907 paper, Dr. Alzheimer described the 5-year course of a 51-year old patient, named August D., who presented with progressive presenile dementia and memory impairment (A. Alzheimer, 1907; A. Alzheimer, Stelzmann, Schnitzlein, & Murtagh, 1995). He additionally described the autopsy findings of this patient to include neuronal loss, amyloid plaques, and neurofibrillary tangles. These neuropathologies remain important markers for autopsy confirmed cases of AD today. The pattern of cognitive decline seen in August D. was somewhat atypical for what we consider the common clinical features of AD today. However, Dr. Alzheimer's initial description allowed clinicians and scientists to begin distinguishing AD from other forms of dementia. The hallmark cognitive decline seen in AD is memory and learning impairments. However, other cognitive deficits including those in attention, visuospatial function, and language are common in the disorder.

Incidence and Age of Onset of Alzheimer Disease

AD is the most common cause of dementia associated with aging, affecting approximately 6 percent of adults over 65 years of age (Canadian Study of Health and Aging Working Group, 1994; General Accounting Office Report, 1998). In the year 2000, it was estimated

that 4.5 million individuals suffered from AD in the United States alone, and this number is estimated to rise to 14 million by the year 2050 (Hebert, Beckett, Scherr, & Evans, 2001). This disorder is a major health care problem; Alzheimer disease was ranked 13th as a leading cause of death in the United States in 1996, and it is estimated that AD may play a role in one-third of all deaths in North America (National Center for Health Statistics, 1997). In addition to the significant mortality associated with AD, there are also enormous costs associated with caring for individuals with the disease. Interestingly, although the prevalence of AD in developed countries such as the United States is relatively high, the prevalence of AD in developing countries is much smaller (Chandra et al., 1998; Hendrie et al., 2001). Although a definitive explanation for this difference is unclear, reduced exposure to environmental and genetic risk factors coupled with lower life spans may partially explain this difference.

Although the exact cause of Alzheimer disease is not known, several risk factors for developing AD have been identified. The primary risk factor for development of AD is advancing age. In addition, AD affects women about 1.5 times more often than men (Fratiglioni et al., 1997; Heyman, Peterson, Fillenbaum, & Pieper, 1996). It is thought that the gender differences in the incidence of AD may be due to lower levels of education, the decline in estrogen after menopause, or different environmental exposures (Katzman et al., 1994). There also is evidence of ethnic differences in the incidence of AD, although this partially may be due to different geographic and environmental influences that affect individuals of different ethnic backgrounds (White et al., 1996). Other major risk factors for AD include: family history of the disorder (Graves et al., 1990), the apolipoprotein E e4 (APOE e4) genotype (Dal Forno et al., 2002; Heyman et al., 1996), Down syndrome (Brugge et al., 1994; Van Duijn et al., 1994), and a history of prior head trauma (Guo et al., 2000; Lye & Shores, 2000). Individuals with low educational levels may also be at higher risk for developing AD (Snowdon et al., 1996). Current research is exploring the role of environmental exposure to substances such as aluminum, zinc, and exposure to electromagnetic fields, although the exact role, if any, of these types of environmental exposures is unclear (Breitner & Welsh, 1995; Cuajungco & Lees, 1997; Graves et al., 1990; Sobel & Davanipour, 1996; Sobel, Dunn, Davanipour, Qian, & Chui, 1996). Finally, medical conditions including high total and HDL cholesterol, and late life clinical depression may also be risk factors for AD (Buntinx, Kester, Bergers, & Knottnerus, 1996; R. M. Evans et al., 2000; Kivipelto et al., 2002; Simons et al., 2002).

Genetics and Neuropathology of Alzheimer Disease

Scientists have been aware of genetic influences on the risk of developing AD since early in the 20th century (Lowenberg & Waggoner, 1934). Generally, having a first-degree relative with AD significantly increases one's risk for developing AD (Breitner, Silverman, Mohs, & Davis, 1988). Genetic contributions to AD may be monogenic (controlled by one gene) or polygenic

(controlled by the interactions of two or more genes). It is estimated that monogenetic familial forms of AD account for less than 1% of total AD diagnoses (Campion et al., 1999). Monogenic forms of AD include mutations in the amyloid precursor protein gene (APP), and presenilin (PS) 1 and PS 2 genes (Goate et al., 1991; Levy-Lahad et al., 1995; Sherrington et al., 1995). These monogenetic mutations generally lead to early onset AD. As many as 40% of later onset familial AD cases are associated with the APOE e4 genotype (Strittmatter et al., 1993). The relationship between APOE e4 genotype and AD severity is modulated by age, sex, and ethnicity (Farrer et al., 1997; Farrer et al., 2003; V. S. Rao et al., 1996). APOE genes are thought to influence the formation of amyloid deposits via direct or indirect mechanisms (Lambert & Amouyel, 2007).

Despite the evidence for genetic inputs in familial cases of AD, a single definitive genotype for AD remains elusive. In fact, to date, almost 200 genes have been linked to the onset of AD (Lambert & Amouyel, 2007). Understanding how mutations in genes such as APP, PS1, PS2, and APOE e4 can lead to the development of AD is paramount for determining the etiology of AD. Genetic studies also will be critical for developing future pharmacologic targets to treat the disorder. Future genome-wide screens and high-throughput genetic analysis will lead to the identification of additional candidate genes involved with AD, but further work must be done to elucidate the biological mechanisms behind the development of AD neuropathology before the impact of these genetic factors can be fully understood.

The pathogenesis of AD remains an area of active investigation. Many researchers today point to the amyloid hypothesis as a proposed mechanism for the development of the characteristic neuropathologic changes seen in AD, and the resultant dementia. Under this hypothesis, the underlying neuropathology of AD can be characterized by overproduction and/or abnormal accumulation of amyloid beta protein (Ab) in the brain (D. J. Selkoe, 2001). The Ab protein is encoded by the b-amyloid protein precursor (bAPP) gene (Robakis, Ramakrishna, Wolfe, & Wisniewski, 1987). Mutations in the bAPP gene, or those genes that regulate it, can cause alterations in how much Ab is produced in the brain. Generally, Ab levels in the brain increase with age, even in cognitively normal individuals (Funato et al., 1998; Morishima-Kawashima et al., 2000). However, as Ab levels rise due to advancing age or genetic predisposition, Ab aggregation and deposition of tangles and plaques occur. Ab aggregations transform into fibrils, and are neurotoxic both in their oligomer and fibril forms (Klein, Stine, & Teplow, 2004). Ab aggregates have a number of neurotoxic effects in the brain. Accumulation of Ab can lead to hyperphosphorylation of tau proteins, cell death, inflammation, and astrocytic glosis (scar formation) (Cummings, 2003).

Diagnosis of definite AD requires histopathologic evidence of neurofibrillary tangles (NFTs) and neuritic plaques at autopsy or biopsy greater than one would expect given the patient's age (Khachaturian, 1985; Mirra et al., 1991). Neurofibrillary tangles (NFTs) typically occur in the pyramidal neurons of the neocortex and medial temporal lobe structures including the

hippocampus and amygdala (D. J. Selkoe, 1997). Formation of NFTs disrupts axonal transport, a process critical for moving proteins, neurotransmitters, and other cellular components throughout the neuron. It is important to note that the presence of NFTs is not limited to patients with AD; individuals with progressive supranuclear palsy, and elderly patients with Down syndrome may also show this pathology. Neuritic plaques are also a prominent feature of AD pathology. Plaque formation disrupts adjacent synapses (junctions that allow nerve cells to communicate with each other), leading to cognitive decline. The number of neuritic plaques in the brain correlates with the extent of dementia disability, and poorer psychological test performance (Sweet et al., 2000) AD patients also demonstrate problems with neurotransmitter systems, particularly the cholinergic system. Abnormalities in the cholinergic system are related to the cognitive and behavioral changes seen in AD (Cummings & Back, 1998). Specifically, AD patients demonstrate diminished levels of acetylcholine, and several current pharmacological treatments (such as Aricept) inhibit the breakdown of acetylcholine in order to increase the levels of this neurotransmitter in the brain.

Progression and Survival in Alzheimer Disease

Alzheimer disease is primarily a disorder of the elderly. The majority of patients with AD are diagnosed when they are 65 years of age are older, although onset can occur as early as 30, especially in familial cases of AD. There appear to be no major pathological differences between patients with young or old onset (M. F. Mendez & Cummings, 2003). The prevalence of AD also increases with increasing age. Generally, the prevalence of AD doubles every 5 years after 60 years of age. More specifically, AD affects approximately 1% of 60-year-olds, 2% of individuals between 65 and 69 years of age, 4% of those between 70 and 74, 8% between 75 and 79, 16% of 80 and 85-year-olds, and 26 to 45% of individuals 85 years or older (Canadian Study of Health and Aging Working Group, 1994; Drachman, 1994; General Accounting Office Report, 1998; Paykel et al., 1994; Wernicke & Reischies, 1994).

The progression of AD can be measured in several clinical stages. The preclinical stage is marked by isolated, often mild impairments in memory function (Morris et al., 2001; Petersen et al., 1999). Patients at this stage are often diagnosed with mild cognitive impairment (MCI). Patients with preclinical AD may also have difficulty with complex visual construction tasks, word-list generation, and mild anomia (word finding difficulties) (Mendez & Cummings, 2003). As the disease progresses, patients with Stage II AD show a much faster decline in cognitive functioning. Memory, language, and visuospatial deficits become severe and impair day-to-day activities including driving, basic housework, and even personal hygiene (Mendez & Cummings, 2003). In Stage III AD, individuals become more severely demented. Basic functions become so impaired that the patient is at increased risk for incontinence recurrent infections, and aspiration pneumonia (Mendez & Cummings, 2003). Patients diagnosed with AD have a mean survival of 10.3 years after

symptom onset (Mann, Mohr, Gearing, & Chase, 1992). Diagnosis of AD shortens the projected total life span for an individual by about 4.5 years (Kokmen, Beard, O'Brien, & Kurland, 1996; Mann et al., 1992; Molsa, Marttila, & Rinne, 1995; Moritz, Fox, Luscombe, & Kraemer, 1997), which generally is due to complications of later stage disease including progressive malnutrition, infections and dehydration.

Diagnostic Criteria for Alzheimer Disease

One major challenge in Alzheimer disease treatment and research is accurate diagnosis. The diagnosis of AD is complicated by the fact that AD can co-occur with other neuropathologies including vascular dementia or Parkinson disease (Azuma, Cruz, Bayles, Tomoeda, & Montgomery, 2003; Cummings, 2004; H. Grossman, Bergmann, & Parker, 2006; Libon, Price, Heilman, & Grossman, 2006).There are two sets of criteria that are commonly used to diagnose AD. The first set of criteria was developed by the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association Work Group (NINCDS-ADRDA) (McKhann et al., 1984). The NINCDS-ADRDA criteria classify AD diagnosis into clinically probable, possible, and definite categories (Table 5–2).

Per the NINCDS-ADRDA criteria, "probable AD" requires evidence of dementia and deficits in two or more areas of cognition, as long as there are no other disorders that could account for the progressive memory impairments and cognitive decline. For example, patients with dementia associated with a variety of other conditions including Parkinson disease or drug intoxication could not be diagnosed with probable AD if the characteristics of the disease are consistent with that diagnosis alone. The diagnosis of probable AD using the NINCDS-ADRDA criteria is supported by age of onset between 40 and 90, progressive worsening of memory and other specific cognitive impairments, family history of AD, and impairments in activities of day to day life. The NINCDS-ADRDA criteria also include a "possible AD" category. Possible AD includes cases with an atypical temporal profile, presence of a co-occurring disorder that is not thought to cause the dementia, or if there is a progressive deficit in only one cognitive domain. Diagnoses of "definite AD" can only be made if the patient meets the clinical criteria for probable AD, and presents adequate histopathologic evidence obtained from a biopsy or autopsy. Specifically, the diagnosis of definite AD requires examination of brain tissue for the presence of more neurofibrillary tangles (NFTs) and neuritic plaques than are expected for the patient's age (Khachaturian, 1985; Mirra et al., 1991; Newell, Hyman, Growdon, & Hedley-Whyte, 1999). The National Institute of Neurological and Communicative Disorder and Stroke and the AD and Related Disorder Association (NINDCS-ADRDA) Work group criteria also describe several criteria that make AD diagnosis unlikely including: sudden onset of dementia and cognitive deficits, focal neurologic signs including sensory loss, visual field deficits or hemiparesis, and the presence of seizures or gait abnormalities early in the course of the illness.

The second most commonly used clinical criteria for AD diagnosis are

Table 5–2. Clinical Criteria for Alzheimer Disease Diagnosis

Probable Alzheimer Disease
Dementia
Cognitive deficits in at least two cognitive domains
Progressive memory and cognitive decline
Absence of delirium
Age of onset between 40 and 90
Absence of other systemic or neurologic disease that could cause dementia
Definite Alzheimer Disease
Meets clinical criteria for probable AD
Histopathologic signs of AD at autopsy or brain biopsy
Possible Alzheimer Disease
Atypical onset, presentation, or progression without known cause
Presence of systemic or neurologic disease that could cause dementia, but is not thought to be the underlying cause of dementia symptoms
Progressive decline of a single cognitive domain with no known cause
Unlikely Alzheimer Disease
Sudden onset of symptoms (rather than progressive decline)
Focal neurologic signs indicative of localized brain damage
Gait disturbance or seizures present early in the illness progression

described in the American Psychiatric Association's *Diagnostic and Statistical Manual-IV* (DSM-IV) (American Psychiatric Association, 1994). DSM-IV criteria for AD include the development of multiple cognitive deficits including progressive memory impairment and one or more specific cognitive deficits such as aphasia (difficulty with language production or comprehension), apraxia (difficulty executing learned, purposeful movements), agnosia (difficulty recognizing objects or people), or disturbances in executive functioning. The DSM-IV criteria further specify that the cognitive deficits must be present for at least 6 months, and cause a significant impairment in social and/or occupational functioning. Additionally, the deficits may not be caused by any other neurologic, psychiatric or systemic disorder.

The establishment of formal clinical criteria has improved the correct identification of patients who demonstrate AD pathology at autopsy. In early studies, only 50 to 60% of patients with a clinical diagnosis of AD showed AD-related neuropathology at autopsy (Mendez, Mastri, Sung, & Frey, 1992).

After the introduction of the NINCDS-ADRDA and DSM-IV diagnostic criteria, 85 to 95% of patients with a lifetime diagnosis of AD had confirmed AD at autopsy (Galasko et al., 1994; Gearing et al., 1995; Rasmusson et al., 1996). However, despite this improvement in autopsy-correct identification of AD, problems still exist in distinguishing AD from other types of dementia and neuropathologic conditions that also lack reliable clinical tests. Patients with AD pathology at autopsy are commonly misdiagnosed with other forms of dementia such as vascular dementia, Parkinson disease, and frontotemporal dementia (Mendez, Mastri, Sung, Zander, & Frey, 1991). Therefore, there is a pressing need for further research to improve the differential diagnosis between AD and other related dementias.

One recent improvement in the diagnosis of AD and other dementias is the use of clinical neuroimaging techniques. Structural neuroimaging techniques such as computerized axial tomography (CT) and magnetic resonance imaging (MRI) can be used to exclude other brain pathologies such as strokes, tumors, hydrocephalus (abnormal accumulation of cerebrospinal fluid in the brain), and subdural hematomas that could cause dementia. Additionally, the presence of hippocampal atrophy or volume loss on an MRI could be indicative of AD pathology (Jack et al., 2000; Jack et al., 2002; Petersen et al., 2000; Wolf et al., 2001).

Cognitive Deficits in Alzheimer Disease

General cognitive ability may be thought of as mental status or intellectual ability including memory and attention. However, it is useful to think about the effects of AD in terms of cognitive deficits or types of thinking ability impairment. If an older adult acquires Alzheimer disease, the disease itself will impair certain aspects of cognition beyond what is expected in healthy aging (Bayles, 2001). The patient themselves, a family member, or clinicians may become aware of significant changes in cognition (Bayles & Tomoeda, 1991).

Memory Deficits in Alzheimer Disease

Memory decline is the hallmark cognitive deficit of Alzheimer disease and often constitutes as one of the first clinical signs. During the preclinical phase of AD, episodic memory deficits may occur without other obvious symptoms of dementia (Backman, Small, & Fratiglioni, 2001). In everyday tasks, a person with episodic memory impairment may forget appointments, have difficulty learning new routes to locations, and forget information told to them in conversation. One sensitive clinical test of memory impairment in AD is delayed recall of a story after 30 minutes (Chen et al., 2000). The person with Alzheimer disease will recall few facts related to the story or perhaps not remember having heard a story at all. In addition, the person with AD will have difficulty with delayed recall on word list learning, and show a decreased primacy effect (Bayley et al., 2000; Chen et al., 2000). The primacy effect is the tendency to recall initial list items better relative to items in the middle or at the end of a list. Many clinicians mistakenly think that the memory impairment of AD is in immediate recall,

although this is generally not the case when working memory is intact. Patients with AD may be able to recall digits, words or even a story when immediately repeated back, but may not be able to recall this information after a delay. However, at some point in the disease progression, working memory may become impaired (Stopford, Snowden, Thompson, & Neary, 2007). This working memory deficit also overlaps greatly with impaired sustained attention, which may also contribute to poor immediate memory performance (Cook, Bookheimer, Mickes, Leuchter, & Kumar, 2007). Finally, it is important to understand that remote memory, such as memories for childhood events, may be fairly well preserved in AD patients, with better recall for the most remote information (Squire & Bayley, 2007). As a result, individuals with AD will usually be able to engage in historical and autobiographical discussions. In addition, there is relative preservation of procedural and implicit memory (or the learning of motor tasks) until the late stages of the illness (van Halteren-van Tilborg, Scherder, & Hulstijn, 2007). In addition, they will maintain overlearned motor tasks such as folding clothes, loading and unloading a dishwasher, riding a stationary bicycle, serving a tennis ball, or swimming.

Language Impairments in Alzheimer Disease

Language may be an early presenting symptom in the progression of AD (Galton, Patterson, Xuereb, & Hodges, 2000) and may be exhibited in listening, speaking, reading or writing. Rapidly worsening word finding difficulty is often the first language-related sign of AD, but this must be distinguished from word-finding deficits (anomia) common in healthy aging. A highly sensitive test for anomia is a word fluency test (Groves-Wright, Neils-Strunjas, Burnett, & O'Neill, 2004). In this test, a patient must name as many items in a category, such as animals, or provide as many words as possible that start with a certain letter, such as the letter "F." Some mildly affected persons with Alzheimer disease may have memory impairment and other cognitive deficits while maintaining language functions within the normal range. However, there is considerable evidence that the lexical semantic decline seen in AD begins with lexical retrieval impairment in the prodromal (Vandenbulcke et al., 2007) or early stage of AD (Bayles & Tomoeda, 1983; Hodges, Patterson, Graham, & Dawson, 1996; Hodges, Salmon, & Butters, 1992). Lexical retrieval impairment may be evident in naming, spelling and reading, where the individual cannot retrieve the oral or written word label (S. L. Rogers & Friedman, 2008). This lexical retrieval impairment eventually results in impairment of semantic memory (Grossman et al., 2003; Rogers, Lambon Ralph, Hodges, & Patterson, 2004). Persons with Alzheimer disease with semantic memory impairment are not able to recall or demonstrate details of concepts, persons, events, and objects. Abstract and concrete items that are distinguishable by a few features or attributes are difficult to discriminate by the person with moderate AD. For example, a person with Alzheimer disease may have difficulty identifying how objects are the same or different or in listing characteristics (Bayles, Tomoeda, Cruz, & Mahendra, 2000).

Despite this language decline, persons with Alzheimer disease may continue to have good social skills including eye contact, nonverbal communication, and turn-taking (Bayles & Kim, 2003). In addition, there is a relative sparing of phonology and syntax, giving the impression of good form without much density of content information. On certain tests of reading and writing that include common, frequently occurring words, persons with AD may continue to be able to read aloud and to write familiar words to dictation. Repetition also may be relatively intact at least to the extent that immediate and working memory is functional. This relative sparing of automatic aspects of reading, writing, and speech produces a profile analogous to transcortical sensory aphasia (Gates, Beiser, Rees, D'Agostino, & Wolf, 2002; Noble, Glosser, & Grossman, 2000). Patients with transcortical sensory aphasia have poor language comprehension, with fluent grammatical speech and relatively intact repetition skills. Care must be taken to ensure that language deficits are not due to other neuropathological insults. For example, the presence of dysarthria (poor articulation) may indicate that the patient has AD with concomitant vascular AD, Parkinson disease, or another cause of dementia altogether.

Executive Function in Alzheimer Disease

Several researchers have suggested that AD patients experience an overall decline in executive function that affects many other cognitive abilities and has a strong impact on everyday functioning. Executive functions are those that allow a person to function as an executive and to gain control at a micro and macro level. Executive function deficits in AD are strongly related to decision-making and everyday problem solving skills (Willis et al., 1998). Persons with AD may have difficulty inhibiting certain actions or alternatively may perseverate on one response or one mode of response. Perseverative behavior, or "the inability to shift gears," may be measured with the Behavioral Dyscontrol Scale or the Wisconsin Card Sort Test (Nagahama et al., 2003). Patterns of executive function deficits may vary in AD patients; not all individuals with AD have equivalent involvement of the frontal lobe, and frontal lobe pathology is strongly associated with cognitive impairment related to executive control (Royall, 2006).

Visuospatial Function in Individuals with Alzheimer Disease

Visuospatial impairments may be evident in AD patients early in the course of the disease. Although basic visual functions are relatively spared in AD, patients may experience decreases in visual attention, visual search, and pattern recognition. (Rizzo, Anderson, Dawson, & Nawrot, 2000; Rizzo, Anderson, Dawson, Myers, & Ball, 2000; Rosler et al., 2000) This visuospatial impairment can lead to difficulty perceiving objects, recognizing people, drawing familiar shapes such as a daisy or clock from memory, copying elementary and three-dimensional representations, and finding familiar driving destinations (Mendez, Mendez, Martin, Smyth, & Whitehouse, 1990; Smith, Esiri, Barnetson, King, & Nagy, 2001). In addition, AD patients

commonly show disruptions in spatial orientation, which may cause significant impairment in driving, and even navigating around their own homes (Cherrier, Mendez, & Perryman, 2001).

Behavior, Personality, and Psychiatric Changes in Alzheimer Disease

In early stages of AD, personality and social behavior remains relatively normal, which allows patients to continue their normal social functioning. However, as the disease progresses, several behavioral and personality changes often develop. One of the most common behavioral changes is the development of indifference and apathy (Mega, Cummings, Fiorello, & Gornbein, 1996). AD patients may also become anxious, irritable, aggressive, and disinhibited (Mendez & Cummings, 2003). Aimless wandering and pacing become more frequent. About 25% of AD patients become verbally and/or physically aggressive as their disease progresses (Mendez, Martin, Smyth, & Whitehouse, 1990). AD patients commonly suffer depression, although this is inconsistently recognized by clinicians (Wragg & Jeste, 1989). Paranoia may develop as a function of the misinterpretation of events due to memory, perceptual, and executive deficits (Fukuhara et al., 2001; Geroldi et al., 2000; Paulsen et al., 2000). Cognitive and psychiatric symptoms may be exacerbated by changes in sleep. AD patients suffer from abnormal circadian rhythms (Volicer, Harper, Manning, Goldstein, & Satlin, 2001), which can lead to a sundowning effect. Sundowning refers to a period of agitation and other negative behaviors that typically occur later in the day.

Frontotemporal Dementia

Frontotemporal dementia (FTD) is a neurodegenerative disease associated with progressive atrophy that compromises circumscribed regions of frontal and temporal cortex (Cairns et al., 2007; Johnson et al., 2005; Neary, Snowden, & Mann, 2005). The particular anatomic distribution of frontal and temporal lobe loss dictates the phenotype, that is, the cognitive and behavioral symptoms manifested by the patient. For example, when FTD affects regions of inferior frontal cortex patients experience difficulties in word retrieval and speech production, a condition termed progressive nonfluent aphasia (Gorno-Tempini et al., 2006; Hillis, Tuffiash, & Caramazza, 2002; Nestor et al., 2003). In contrast, the temporal lobe variant of FTD, semantic dementia, is associated with fluent speech production in the context of a profound loss of conceptual knowledge (Hodges, Graham, & Patterson, 1995; Hodges, 2003; Snowden, Goulding, & Neary, 1989). Finally, frontal variant FTD is characterized by impairments in social and executive functioning (Liu et al., 2004; Neary et al., 1998; Rascovsky et al., 2007). Thus, FTD subsumes a number of distinctive behavioral variants under the umbrella of a single descriptive moniker.

Prevalence, Incidence, and Age of Onset of Frontotemporal Dementia

The onset of FTD typically is earlier than that of other forms of dementia (Forman et al., 2006; Johnson et al., 2005; Neary et al., 2005; Westbury & Bub,

1997). FTD is considered the second most common form of dementia in the population of adults under the age of 65 (M. Grossman, 2002; Papageorgiou, Kontaxis, & Bonakis A, 2007). Furthermore, unlike other forms of dementia that pose an increasing risk of onset with advanced age, the onset of FTD follows a roughly normal (bell-shaped) distribution. Within this distribution, the most common age of onset of FTD is early within the sixth decade of life, with tapering prevalence during earlier and later years (Johnson et al., 2005; Papageorgiou et al., 2007). Cases of FTD have been reported among adults as young as 21 and as old as 85 (Neary et al., 2005).

Diagnostic specificity of FTD remains a challenge. Relative to better characterized dementias (e.g., Alzheimer disease), large-scale incidence and prevalence data for FTD are lacking. It has been estimated, however, that FTD comprises between 3 to 10% of all of the dementia subtypes (Heutink, 2000; Neary et al., 2005). Once described as a rare form of dementia, the differential diagnosis of FTD is becoming increasingly more common. Accurate discrimination of FTD is of critical importance as this population has unique medical management needs (Goldman et al., 2004).

Genetics and Neuropathology of Frontotemporal Dementia

FTD is broadly classified under the umbrella of a *tauopathy* (i.e., a neurodegenerative diseases characterized by pathogenic levels of the protein tau). Functions of tau include stabilization of microtubules that maintain the skeleton of neuronal axons, facilitation of axonal transport, and maintenance of the electrical potential of neurons (Heutink, 2000). Abnormal levels of tau degrade the integrity of neurons through a cascade process that also involves several related proteins, including ubiquitin and TDP-43 (Johnson et al., 2005; Neumann et al., 2006; Van Deerlin et al., 2007). FTD falls under two broad classes with respect to tau protein. One subset of FTD patients has tau-positive pathology, whereas the other is free of tau-pathology (Forman et al., 2006). About 40% of FTD patients have been identified as having tau-positive aggregations associated with a mutation of the microtubule-associated binding protein tau (MAPT) gene on chromosome 17 (Bian & Grossman, 2007; Goldman et al., 2004). A moderate-to-high proportion of these tau-positive patients have a family history of dementia, thus, indicating a genetic basis for transmission of the disease (Goldman et al., 2004). The genetic basis for FTD among the broader population of patients who are free of tau pathology remains unknown.

Progression and Survival in Frontotemporal Dementia

The progression of FTD appears to show some degree of variability depending on the underlying neuropathology and cortical distribution (Bian & Grossman, 2007). Survival has been estimated at between 2 and 8 years postsymptom onset, although there is considerable variability beyond this range (Hodges, Davies, Xuereb, Kril, & Halliday, 2003; Neary et al., 2005; Rascovsky et al., 2005). FTD, on average, produces a significantly more rapid decline than Alzheimer disease (Rascovsky et al., 2005).

Diagnostic Criteria for Frontotemporal Dementia (Table 5–3)

The phenotypes of FTD differ substantially as a function of the cortical regions impacted during the course of the disease. Such variability presents an inherent challenge in terms of diagnostic specificity. Therefore, the most sensitive clinical diagnostic assessments of FTD take into account a combination of factors, including protein biomarkers, family history, neuroimaging, neuropsychology, speech, and language (Bian & Grossman, 2007; Libon et al., 2007; Libon, Xie, et al., 2007). A consensus meeting was recently held among FTD researchers with the purpose of establishing a core set of diagnostic criteria for the disease (Neary et al., 1998). Common among the FTD variants is an insidious onset in the absence of a focal neurologic event (e.g., stroke). We describe the unique characteristics of language and cognition among three behavioral variants of FTD that follow.

Table 5–3. Prominent Features of Frontotemporal Dementia

Progressive Nonfluent Aphasia
Atrophy in left inferior frontal and anterior perisylvian cortex
Effortful, slow speech
Phonemic paraphasias
Agrammatism
Dysprodia
Progressive mutism
Semantic Dementia
Atrophy confined to anterior, lateral, and ventral temporal cortex
Fluent speech without meaningful content
Loss of word meaning
Semantic paraphasias
Surface dyslexia and dysgraphia
Frontal Variant FTD
Atrophy in the anterior frontal cortex
Gradual decline in appropriate social conduct
Emotional blunting
Impaired inhibitory control
Reduced working memory

Progressive Nonfluent Aphasia

Progressive nonfluent aphasia (PNFA) is a variant of FTD characterized by cortical atrophy that affects left inferior frontal and anterior perisylvian regions (Croot, Patterson, & Hodges, 1998; Gorno-Tempini et al., 2004; Hodges & Patterson, 1996). Figure 5–1 represents a voxel-based morphometric image of gray matter atrophy among a cohort of patients with PNFA. Peak gray matter atrophy, shown by voxels of hot white/yellow intensity, is evident regions of the left frontal cortex.

As regions of left inferior frontal and premotor cortex degrade, patients with PNFA have increasing difficulty producing fluent speech. The hallmark of PNFA is speech that is effortful and slow with the presence of frequent phonemic paraphasias (e.g., "grebe" for glee) (Ash et al., 2004; Ash et al., 2006). Speech in PNFA has also been described as lacking normal variability in pitch and amplitude contours (i.e., dysprosodia) in addition to diminished intensity (Croot et al., 1998; Kertesz, Hudson,

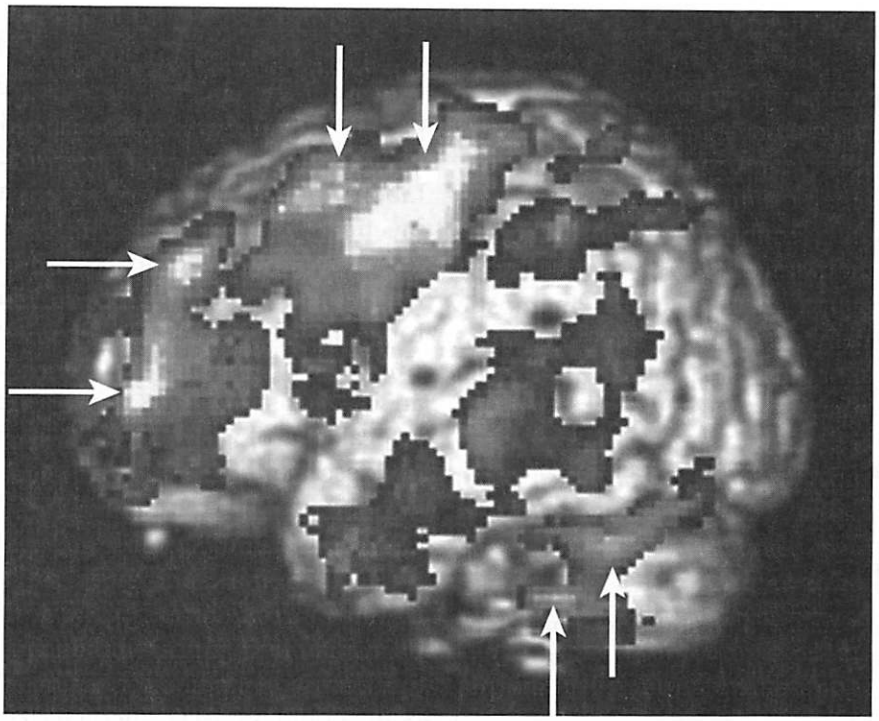

Figure 5–1. Gray matter atrophy in progressive nonfluent aphasia. *Note:* Voxel-based morphometric image of a cohort of patients with PNFA (n = 3) relative to healthy age-matched controls (n = 11). Peak atrophy is shown by arrows; areas of black indicate statistically significant atrophy (p <.05 uncorrected).

Mackenzie, & Munoz, 1994). PNFA may present with comorbid apraxia of speech (Nestor et al., 2003) and may also evolve to complete mutism when the disease compromises subcortical structures (e.g., basal ganglia) that are critical for motor programming (Gorno-Tempini et al., 2006).

Specific diagnostic criteria for PNFA adapted from Neary et al., (1998) include an insidious onset and gradual progression with the presence of nonfluent speech and one or more of the following characteristics: agrammatism, phonemic paraphasias, and anomia (deficits in recalling words or names) (Neary et al., 1998). Supportive features for PNFA diagnosis include stuttering, oral apraxia (difficulty with speech due to motor planning and coordination deficits), impaired repetition, alexia (loss of the ability to read), agraphia (deficits in writing ability), early preservation of word meaning, and late mutism. PNFA is also characterized by early preservation of social skills with late emerging behavioral and motor symptoms such as rigidity and dyskinesia (uncontrollable, involuntary movements).

One might speculate that PNFA produces a profile of language impairment similar to classical Broca aphasia as these conditions share a substantial degree of anatomical overlap. That is, PNFA patients should show agrammatism and/or selective deficits in verb comprehension similar to those sometimes manifested in Broca aphasia.

Studies of PNFA have yielded mixed results with respect to this prediction. For example, Graham and colleagues recently demonstrated that PNFA patients showed similar ratios of verbs to nouns elicited in spoken and written narrative performance with relative preservation of syntactic complexity in the context of a dramatic reduction in phrase length (Graham, Patterson, & Hodges, 2004; Patterson, Graham, Lambon Ralph, & Hodges, 2006). Other researchers, however, have reported selective deficits for verbs in PNFA relative to nouns as well as reduced syntactic complexity consistent with agrammatism (Hillis et al., 2002; Hillis, Sangjin, & Ken, 2004; Thompson, Ballard, Tait, Weintraub, & Mesulam, 1997). The nature of both phonological and grammatical impairment associated with PNFA remains debated.

Semantic Dementia

Semantic dementia (SD) is a form of FTD that is characterized by cortical atrophy that remains relatively confined to anterior, lateral, and ventral portions of the temporal lobe early during the course of the disease (Mummery et al., 2000; J. S. Snowden et al., 1989). SD often compromises the left cerebral hemisphere first, later spreading to homologous regions of the right hemisphere (Lambon Ralph, McClelland, Patterson, Galton, & Hodges, 2001). Figure 5–2 represents characteristic temporal lobe atrophy among a cohort of patients with SD.

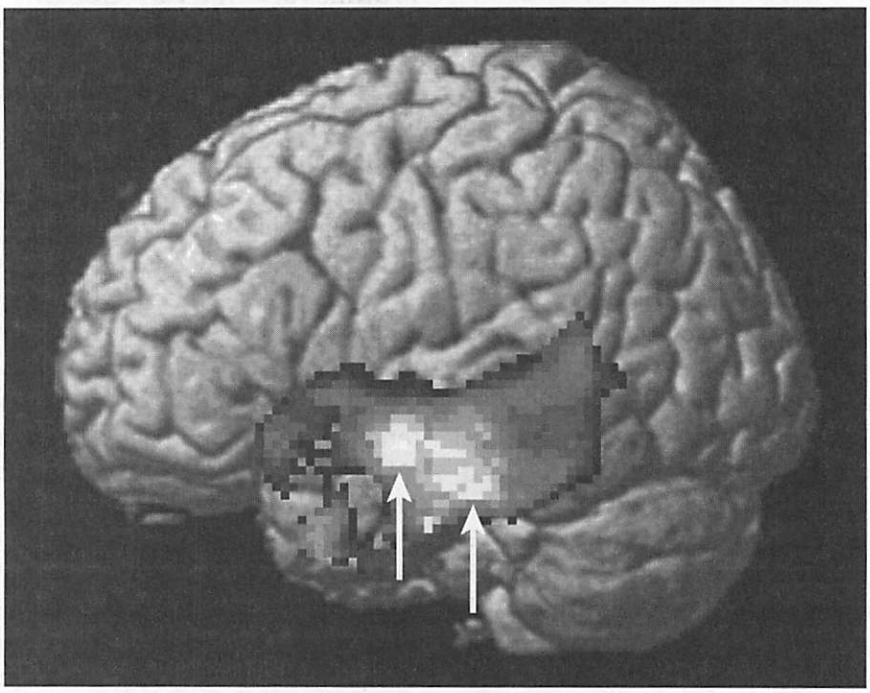

Figure 5–2. Gray matter atrophy in semantic dementia. *Note:* Voxel-based morphometric image of a patient with semantic dementia relative to healthy age-matched controls (n = 11). Peak atrophy is shown by arrows; areas of black indicate statistically significant atrophy (p <.05 uncorrected).

In contrast to PNFA, patients with SD tend to produce speech that is fluent, but generally empty in terms of meaningful content. Diagnostic criteria for SD adapted from Neary et al. (1998) include an insidious onset and gradual progression with worsening impairment in the representation of object identity and word meaning. Autobiographical and episodic day-to-day memory skills appear to remain largely intact until later stages of the disease. Language disorder associated with SD is characterized by fluent but empty speech, loss of word meaning (affecting both naming and comprehension), and the presence of semantic paraphasias (e.g., producing "ball" for "apple"). Patients with SD may also show a perceptual disorder characterized by prosopagnosia (impaired recognition of familiar faces) and or associative agnosia (impaired recognition of object identity). Supportive features of SD include absence of phonemic paraphasias, idiosyncratic word usage, preserved calculation (i.e., mental arithmetic), and the presence of surface dyslexia and dysgraphia (Halpern et al., 2004; Neary et al., 1998). The latter disorders of reading and writing are characterized by deficits in writing and reading aloud orthographically irregular words (e.g., yacht). One logical hypothesis regarding the prevalence of surface dyslexia in SD is that patients show an "overreliance" on reading via a direct grapheme-to-phoneme conversion process (Coltheart, 2006; Woollams, Ralph, Plaut, & Patterson, 2007). That is, patients with relatively focal semantic impairment compensate for their degraded semantic knowledge by reverting to preserved phonological and orthographic abilities. Surface dyslexia accordingly has been described as "reading without semantics" (Shallice, Warrington, & McCarthy, 1983).

There has been an explosion of interest in SD during the last two decades within the cognitive neuroscience community. This interest is largely due to the fact that SD presents an in vivo model for evaluating the effects of a selective impairment of semantic memory on language processing (Warrington, 1975). Just as there is controversy surrounding the nature of phonological impairment in PNFA, so too is there debate regarding the nature of the impairment underlying SD. Moreover, at the present time very little remains known about the potential for language rehabilitation in this population (Jokel, Rochon, & Leonard, 2006; Reilly, Martin, & Grossman, 2005; Snowdon et al., 1996).

Frontal Variant FTD—Social Dysexecutive Disorder

When primary cortical atrophy affects anterior regions of the frontal lobe such as the orbitofrontal cortex, patients may experience progressive impairment of social and executive functioning (Liu et al., 2004; Neary et al., 1998; Rascovsky et al., 2007). This FTD syndrome is distinctive from the aphasic variants of the disease (i.e., PNFA and SD) where personality, organization, and attention tend to show relative preservation (Neary et al., 1998; Neary et al., 2005). This disease variant accordingly has been referred to as FvFTD (frontal variant, frontotemporal dementia), and social-dysexecutive disorder (Ash et al., 2004; M. Grossman et al., 2007; Liu et al., 2004; Rascovsky et al., 2007). Diagnostic criteria identified by Neary et al. (1998) for FvFTD include an insidious onset and gradual decline in social conduct

(e.g., inappropriate sexual jokes, risk taking, and hypersexuality), loss of insight, and early emotional blunting. Supportive diagnostic features include a decline in personal hygiene, increased rigidity, hyperorality and diet changes, and the emergence of utilization behavior (e.g., compulsive use of implements such as pens and combs that are present in view of the patient).

Although aphasia is not an explicit symptom of FvFTD, a number of researchers have recently demonstrated the impact of FvFTD on cognitive-linguistic ability. Patients with FvFTD often present with severe executive functioning difficulties that manifests as impaired inhibitory control (i.e., attending to salient stimuli while ignoring nonsalient distracters), poor sequencing ability, limited working memory, and reduced thematic cohesion within narrative production (Ash et al., 2006; Cooke et al., 2003; M. Grossman, 2002).

Vascular or Multi-Infarct Dementia

Vascular dementia (VaD) describes a heterogeneous group of dementias that are caused by cerebrovascular insults. VaD can result from a wide variety of insults including small single strokes, multiple subcortical strokes, thromboembolism, cerebral hypoxemia, mixed vascular-Alzheimer pathology and many other cerebrovascular diseases with genetic and environmental components. As the brain requires diffuse perfusion (i.e. blood flow), vascular compromise can occur at many locations. As such, there is great heterogeneity in the pattern of cognitive deficits associated with VaD.

Prevalence, Incidence, and Age of Onset of Vascular Dementia

In part because of the wide variety of cerebrovascular events that can lead to VaD, vascular dementia is one of the most common dementing diseases, accounting for 10 to 30% of all dementias (Canadian Study of Health and Aging Working Group, 1994; Fratiglioni et al., 2000; Lobo et al., 2000; Traykov et al., 1999). It is thought that the incidence of VaD is underestimated, especially as less severe forms of vascular cognitive impairment are often not explicitly identified, and also because VaD may be concomitant with other dementia diseases (Rocca & Kokmen, 1999; Rockwood, Howard, MacKnight, & Darvesh, 1999; Traykov et al., 1999; van Gijn, 1998). One complicating issue in the diagnosis of VaD is that as many as one-half of all VaD patients demonstrate mixed vascular-Alzheimer pathologies (Lin et al., 1998; Rocca et al., 1990; Rockwood, 1997; Rockwood, Bowler, Erkinjuntti, Hachinski, & Wallin, 1999; Shiba et al., 1999; Traykov et al., 1999). The incidence of VaD increases with advancing age, the male gender, and presence of known strokes (Gorelick, 1997; Hebert & Brayne, 1995; Kokmen, Whisnant, O'Fallon, Chu, & Beard, 1996; Moroney et al., 1996; Nyenhuis & Gorelick, 1998; Skoog, 1998; Yoshitake et al., 1995).

Progression and Survival in Vascular Dementia

Survival duration in VaD is estimated at approximately eight years (median = 3.9), although this figure reflects considerable variability due to the heterogeneous nature of cerebrovascular insults

(Fitzpatrick, Kuller, Lopez, Kawas, & Jagust, 2005). Mortality in VaD is strongly correlated with vascular risk factors, diabetes mellitus, pulmonary status and nutrition. Failure to thrive is a common cause of death in individuals with VaD and concurrent Alzheimer pathology (Fitzpatrick et al., 2005).

VaD has a number of known risk factors that affect presentation, course of illness, and mortality. Age and hypertension are the strongest risk factors for developing VaD (Hebert et al., 2000; Meyer, Rauch, Rauch, Haque, & Crawford, 2000; Posner et al., 2002; Shiba et al., 1999; Skoog, 1998). 80% or more of all VaD patients have a prior history of hypertension (Forette et al., 1998; Hebert et al., 2000; Kohara et al., 1999; Launer, White, Petrovitch, Ross, & Curb, 2001; Meyer et al., 2000). Hypertension has been shown to be deleterious to cognition in general; even without the presence of strokes or Alzheimer pathology, middle-age hypertension has been associated with poor cognitive function in later life (Knopman et al., 2001; Petrovitch et al., 2001). Diabetes mellitus affects 20% of VaD patients and constitutes another major risk factor (Boston, Dennis, & Jagger, 1999; Bots et al., 1993; Hebert & Brayne, 1995; Hebert et al., 2000). Even in the absence of VaD, repeated hypoglycemic episodes are known to contribute to cortical atrophy in diabetics (Perros & Frier, 1997). Other major risk factors include cardiac disease and cardiac surgery, and atherosclerosis (Alafuzoff, Helisalmi, Manermaa, & Soininen, 2000; Bonarek et al., 2000; Bots et al., 1993; Hebert & Brayne, 1995; Kohara et al., 1999). Several risk factors for cerebrovascular disease are also associated with increased incidence of VaD including: smoking, high alcohol consumption, cocaine use, and other environmental exposures such as pesticides and fertilizers (Boston et al., 1999; Bots et al., 1993; Forette et al., 1998; Hebert & Brayne, 1995; Hebert et al., 2000; Klonoff, Andrews, & Obana, 1989; Meyer et al., 2000; Pohjasvaara et al., 1998).

Management of VaD risk factors can aid in prevention of cerebrovascular insults and development of VaD. It is known that treatment of hypertension is neuroprotective against the development of cognitive deficits, even in the absence of stroke (Clarke, 1999; Forette et al., 1998). The risk of stroke can be decreased by controlling diabetes, reducing low-density lipoprotein cholesterols, and smoking cessation (Skoog, Marcusson, & Blennow, 1998). Early treatment of stroke with tissue thromboplastin activator (rt-PA) may ameliorate the neurological damage leading to VaD and improve outcome. Once cerebrovascular insults have occurred, rehabilitation may improve the cognitive and motor functions of patients with VaD. Speech and language therapy can be used to aid patients with aphasia or dysarthria. Management of poststroke depression and psychosis may also improve patient outcomes.

Diagnostic Criteria for Vascular Dementia

One particular difficulty in the diagnosis of VaD is the heterogeneity of affected brain regions due to the variable location and extent of cerebrovascular insults. This heterogeneity leads to a wide range of affected cognitive functions, depending on which brain regions were damaged. In addition, there are five formally proposed sets of clinical criteria for VaD diagnosis that are not interchangeable, and lack the

sensitivity necessary to make a correct diagnosis of VaD. These clinical criteria include the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) (American Psychiatric Association, 1994), the Alzheimer Disease Diagnostic and Treatment Centers (ADDTC) (Chui et al., 1992), the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) (Roman et al., 1993), the Hachinski Ischemic Score (HIS) (Hachinski et al., 1975), and the 10th revision of the International Classification of Diseases (ICD-10) (World Health Organization, 1992). The current criteria for VaD are dependent on recognizing dementia, evidence of cerebrovascular disease, and a probable association between the cerebrovascular disease and dementia. Cerebrovascular disease can be diagnosed based on vascular risk factors, evidence of vascular changes on CT scans and MRI scans, and the presence of focal neurologic signs and symptoms. When a temporal relationship between the onset of cognitive decline and cerebrovascular insult exists, VaD should be suspected. The cognitive decline may have an abrupt onset, or, in the case of multiple smaller insults (such as a series of mini strokes), show a stepwise decline. However, although a temporal correlation between cognitive and suspected cerebrovascular insult may be noted, a causal relationship between the two may not easily be determined (Chui et al., 2000). Determining causal relationships between vascular events and cognitive decline is especially difficult when the dementia onset is gradual, evidence of co-morbid Alzheimer pathology exists, or when the exact timing of a stroke is unknown (Ransmayr, 1998).

Although the cognitive decline seen in VaD is highly variable, cognitive evaluation remains the most effective screening tool for VaD (Chaves et al., 1999). Commonly used cognitive tests for VaD differential diagnosis include the Modified Mini-Mental State evaluation (Teng & Chui, 1987), letter fluency and reaction time tests, and the Executive Interview Test (Roman et al., 1993; D. R. Royall, Cordes, & Polk, 1998). VaD patients demonstrate a variable cognitive decline which is associated with psychomotor slowing, attentional deficits and frontal-executive dysfunction such as decreased self-regulation (Almkvist, Fratiglioni, Aguero-Torres, Viitanen, & Backman, 1999; Bennett, Gilley, Lee, & Cochran, 1994; Matsuda, Saito, & Sugishita, 1998; Villardita, 1993). VaD patients may have deficits in working memory, procedural memory, and retrieval of stored knowledge (Bennett et al., 1994; Bowler et al., 1997; Looi & Sachdev, 1999; Reed, Eberling, Mungas, Weiner, & Jagust, 2000; Villardita, 1993). In the absence of aphasia, VaD patients may show other language deficits including deficits in verbal fluency for letters, sentence complexity, and prosody (Almkvist, 1994; Looi & Sachdev, 1999; Lukatela, Malloy, Jenkins, & Cohen, 1998; Tierney et al., 2001; Villardita, 1993).

Parkinson Disease and Lewy Body Dementia

Parkinson disease (PD) was originally described by the British physician, James Parkinson, two centuries ago in a work entitled, "An Essay on the Shaking Palsy" (1817). Today, the most common impression of PD remains that of a

primary movement disorder characterized by resting tremor, bradykinesia (i.e., slowed movement), rigidity, and postural instability (Jellinger, Wenning, & Seppi, 2007; Khandhar & Marks, 2007; von Campenhausen et al., 2005). Despite classification as a movement disorder, it is clear that PD also results in a constellation of cognitive and linguistic deficits. For example, recent point prevalence studies have reported that as many as 30% of nondemented PD patients show marked impairment in neuropsychological measures of global cognition at a given time (Emre et al., 2007). For purposes of this chapter, we describe these associated cognitive-linguistic deficits as they pertain to both PD and Lewy body disease. Furthermore, we limit our discussion primarily to idiopathic forms, that is, disease variants that arise spontaneously of unknown etiology.

Incidence, Prevalence, and Age of Onset of Parkinson Disease and Lewy Body Disease

PD shows great heterogeneity in symptom course and regional prevalence, thus limiting the availability of population statistics. This variability has been attributed to both genetic and environmental factors. Regarding environment, the prevalence of PD is significantly higher in agricultural regions and in areas with high soil and water concentrations of specific metals such as manganese (Dorsey et al., 2007; Khandhar & Marks, 2007; Nussbaum & Ellis, 2003). Estimates for idiopathic PD in the world's 10 most populated nations range from 4.1 to 6.6 million in 2005, with a projected expansion to 8.7 to 9.3 million by 2030 (Dorsey et al., 2007). The risk of developing PD advances after the age of 50, and men have a greater likelihood of contracting the disease (Khandhar & Marks, 2007; Nussbaum & Ellis, 2003). Early onset PD (ages 21 to 40) is not uncommon, constituting about 8% of new PD cases annually (Khandhar & Marks, 2007).

Lewy body dementia (LBD) is a relatively new dementia classification that has about one-half the prevalence of Alzheimer disease (Rahkonen et al., 2003). Depending on the specific population study, LBD is as common if not more common than vascular dementia, thus, making it the second most frequent form of dementia worldwide behind Alzheimer disease (Geser, Wenning, Poewe, & McKeith, 2005; Heidebrink, 2002; Rahkonen et al., 2003; Weisman & McKeith, 2007; Zaccai, McCracken, & Brayne, 2005). Reports of the prevalence of LBD vary substantially across studies with estimates ranging between 15 and 35% of all dementia cases (Geser et al., 2005; Zaccai et al., 2005). Postmortem studies of LBD have shown co-morbid Alzheimer pathology in a moderate proportion of patients (Geser et al., 2005; Jellinger & Attems, 2008; Weisman & McKeith, 2007). Age of onset of LBD is similar to Alzheimer disease, with a mean age of 68 (range 50 to 85) (Jellinger et al., 2007; Korczyn & Reichmann, 2006; Neef & Walling, 2006).

Genetics and Neuropathology of Parkinson Disease and Lewy Body Disease

The etiology of PD and LBD remains unclear. However, researchers have established a strong causal link between

cognitive deficits in PD and the accumulation of Lewy bodies (i.e., cytoplasmic inclusions of the large protein alpha-synuclein) (Chiba-Falek & Nussbaum, 2003; Emre et al., 2007; Singleton et al., 2003). The abnormal accumulation of Lewy bodies within neurons results in cell death. In PD, Lewy body induced cell death destroys nuclei within the midbrain in a structure known as the substantia nigra (Bear, Connors, & Paradiso, 2007). The substantia nigra, whose Latin translation is *black substance,* produces the neurotransmitter dopamine, which is critical for regulating communication between the basal ganglia and the motor cortex via a motor loop system that also involves the striatum. Dopamine depletion compromises the integrity of this cortical-striatal motor loop, producing impairment in the relative timing and initiation of willful movement (Louis & Frucht, 2007; S. S. Rao, Hofmann, & Shakil, 2006; Spencer & Rogers, 2005). Typically, when greater than 80% of the cells of the substantia nigra are destroyed, patients develop the characteristic motor symptoms of Parkinson disease (Louis & Frucht, 2007).

The accumulation of Lewy bodies in subcortical regions produces PD. In contrast, aggregation of Lewy bodies in cortical regions produces Lewy body dementia. In both conditions, cell death is not restricted to a particular brain region. Thus, PD may evolve into LBD, and LBD often evolves into a parkinsonian movement disorder. This considerable overlap between Parkinson disease dementia (PD-D) and Lewy body dementia (LBD) has led to the claim that PD-D and LBD are both spectrum disorders of Lewy body disease. However, it also has been argued that there are substantive differences in the clinicopathologic and neuropsychological features of these populations (Jellinger et al., 2007).

PD and LBD have been linked to both environmental and genetic factors, and the onset of these diseases may involve an interaction of these components. PD has been linked to environmental factors such as exposure to pesticides, metals (i.e., manganese), toxic drugs (i.e., synthetic heroin), and neuroleptic antipsychotic medications (Ascherio et al., 2006; Gao et al., 2007; Lai, Marion, Teschke, & Tsui, 2002). Idiopathic PD and LBD have also been linked to several gene mutations including SNCA, PRKN, PINK1, DJ-1, and LRRK-2 (Pankratz & Foroud, 2007; Theuns & Van Broeckhoven, 2008). In addition, both PD and LBD are classified under the umbrella of a synucleinopathy (i.e., a disease characterized by abnormal accumulation of the alpha-synuclein protein) (Nussbaum & Ellis, 2003; Singleton et al., 2003; Theuns & Van Broeckhoven, 2008). Despite these genetic links, the large majority of PD and LBD patients have no family history of the disease and in only 5% of cases have specific gene mutations been identified as underlying the disorders (Chiba-Falek & Nussbaum, 2003; Khandhar & Marks, 2007; Pankratz & Foroud, 2007).

Progression and Survival in Parkinson Disease and Lewy Body Disease

PD shows great variability in its progression, and survival duration depends on a number of factors, including motor abilities and conversion to dementia. It has been estimated that within 10 years

of the onset of parkinsonian movement disorder, there is a 70 to 80% conversion rate to parkinsonian dementia (Emre et al., 2007). Once patients convert to PD-D, their survival duration is roughly similar to that of LBD, with a median survival of 5 years (mean 6.7 years) (Emre et al., 2007; Geser et al., 2005). Predictors of decreased survival duration in PD-D and LBD include older age at onset, fluctuating cognition, severity of hallucinations, severity of akinesia, and degree of concurrent Alzheimer disease pathology (Jellinger et al., 2007).

Diagnostic Criteria for Idiopathic Parkinson Disease, Parkinsonian Dementia, and Lewy Body Disease

The four cardinal motor symptoms of idiopathic PD include distal resting tremor (i.e., characteristic "pill rolling" motion of thumb and fingers in 3 to 6 Hz range), rigidity, bradykinesia (slowness in the initiation of movement), and asymmetrical onset (G. Rao et al., 2003; S. S. Rao et al., 2006). Supporting features of idiopathic PD include postural instability, decreased olfaction, micrographia (excessively small writing), and positive response to a dopamine agonist such as levodopa (S. S. Rao et al., 2006).

Conversion to PD-D is difficult to diagnose because patients with idiopathic PD often demonstrate some degree of mild cognitive impairment. Cognitive change in idiopathic PD is insidious rather than an "all or nothing" phenomenon. Core diagnostic criteria for PD-D include an established diagnosis of PD within which the onset of cognitive impairment occurs. Cognitive impairment must be present in at least two of the following four domains: (1) attention; (2) executive functioning; (3) visuospatial processing; and (4) verbal free recall. For the diagnosis of probable PD-D, patients must also show at least one behavioral symptom (e.g., apathy, depression, hallucinations, delusions, or excessive daytime sleepiness) (Emre et al., 2007). A particular challenge regards differentiation of PD-D from LBD as both diseases share very similar histopathologic profiles (i.e., Lewy body pathology in cerebral cortex) (Ballard et al., 2006; McKeith, 2000; Neef & Walling, 2006). Current diagnostic practice indicates the "one-year rule" in terms of discriminating LBD and PD-D. That is, dementia preceding the onset of a movement disorder by one year is classified as LBD, whereas dementia that occurs within the context of an existing movement disorder is classified as PD-D (Emre et al., 2007).

The central feature required for a diagnosis of LBD is progressive cognitive decline that results in functional social and occupational impairment (Geser et al., 2005). Core diagnostic features of LBD include fluctuating cognition, visual hallucinations, and movement impairment (McKeith, 2006). An estimated 70% of patients with LBD develop a symmetric akinetic-rigid syndrome (Geser et al., 2005). Supportive features of LBD include syncope, postural instability with repeated falls, transient loss of consciousness, delusions, and multimodal hallucinations (e.g., auditory and tactile) (McKeith, 2006; Weisman & McKeith, 2007).

Speech and Cognitive Deficits in Parkinson Disease and Lewy Body Disease

Deficits in speech are well characterized in PD. Production deficits include hypokinetic dysarthria, hypophonia (low volume), and dysprosodia (i.e. flattening of pitch and amplitude contours), whereas receptive deficits include insensitivity to emotional and linguistic prosody, lexical stress patterns, and subtle frequency distinctions (Bunton, 2005; Harel, Cannizzaro, Cohen, Reilly, & Snyder, 2004; Pell & Leonard, 2003; Pell, Cheang, & Leonard, 2006; Spencer & Rogers, 2005). Moreover, recent work has demonstrated that even in the absence of a frank dementia, PD is associated with a number of higher level cognitive and linguistic deficits (Caballol, Marti, & Tolosa, 2007; M. Grossman et al., 2000; Henry & Crawford, 2004; Hochstadt, Nakano, Lieberman, & Friedman, 2006; Mahieux et al., 1998; Riedel et al., 2008).

Many researchers have argued that the primary source of language difficulties in PD is a dysexecutive disorder characterized by resource limitations that affect inhibitory control, speed of processing, vigilance, and cognitive flexibility (M. Grossman et al., 2000; M. Grossman, Lee, Morris, Stern, & Hurtig, 2002; Hochstadt et al., 2006). It has been hypothesized that resource-related deficits associated with dysfunction of prefrontal cortex produce "ripple effects" that are evident in tasks such as category fluency naming, sentence comprehension, and narrative production (M. Grossman et al., 2003; Henry & Crawford, 2004; Hochstadt et al., 2006). That is, patients with PD would be expected to show impairment on working memory intensive tasks that require sequencing, attentional vigilance, rapid switching, and topic maintenance. Additional language and communicative deficits in PD include difficulties with inference, metaphor comprehension, and perception of emotional prosody (Monetta & Pell, 2007; Pell & Leonard, 2003; Pell & Leonard, 2005). At the single word level, patients with PD have shown greater anomia for actions relative to objects, although both word classes are impaired relative to controls (Cotelli et al., 2007). As PD evolves into PD-D, cognitive-linguistic difficulties worsen, and there may be greater overlap in the symptoms with LBD. Nonetheless, there have been very few systematic investigations of language in PD-D and LBD.

In addition to speech and language deficits, PD patients show declines in a number of executive functions related to frontal lobe functioning including task planning, cognitive control, and sequencing (Bassett, 2005; Brown & Marsden, 1990; Dubois & Pillon, 1997). Learning and memory impairments in PD also have been noted in cognitive skill acquisition, immediate recall, and word list learning (Daum et al., 1995; Taylor, Saint-Cyr, & Lang, 1986; Taylor, Saint-Cyr, & Lang, 1990). These deficits may result from reduced dopamine neurotransmission and reduced brain activation in striatal and frontal cortical brain regions. For example, PD patients that show executive function impairments underrecruit specific striatal and frontal lobe regions during working memory tasks (Lewis, Dove, Robbins, Barker, & Owen, 2003). In addition, the degree of cognitive impairment in PD correlates with the degree of bradykinsesia

(Levy et al., 2000), perhaps in part because both cognitive slowing and motor slowing correlate in severity in PD (Sawamoto, Honda, Hanakawa, Fukuyama, & Shibasaki, 2002).

Huntington Disease

Huntington disease (HD) is an autosomal dominant genetic disorder that affects 3 to 10 per 100,000 people (Folstein, 1989). Sporadic cases of HD (cases with no known genetic link) account for approximately 3% of new HD diagnoses (Sanchez et al., 1997). Patients with HD exhibit uncontrollable, random, and jerky movements (chorea), dementia, and major psychopathological symptoms including depression, anxiety, and aggressive behaviors. The gene involved in HD is the Huntington (HTT) gene, which is located on the short arm of chromosome 4 (The Huntington Disease Collaborative Research Group, 1993). HD is characterized as a trinucleotide repeat disorder, because the HTT gene includes a cytosine-adenine-guanine (CAG) sequence in the DNA that is repeated multiple times (The Huntington Disease Collaborative Research Group, 1993). This series of CAG repeats causes instability during the DNA replication process and leads to degeneration of neuronal cells. Physical symptoms of HD usually appear between the ages of 40 to 50, although juvenile HD (onset before the age of 20) can also occur, particularly when the faulty gene is inherited from the father (Ridley, Frith, Crow, & Conneally, 1988).

A core feature of HD is chorea (or jerky, repetitive movements) combined with athetosis (slow, writhing movements). Early in the disease course, patients may exhibit facial grimacing and other movements that may be disguised as nervous twitching. As the disease progresses, these movements become almost constant, except during sleep (van Vugt, van Hilten, & Roos, 1996). The cognitive and intellectual decline in HD is progressive. There is a line of evidence that suggests that changes in cognition occur before the onset of chorea (Paulsen et al., 2001). Early cognitive changes include decreased inhibitory control and reduced set-shifting ability (i.e., ability to switch between tasks) (Lawrence et al., 1998), and psychomotor slowing (Brandt et al., 1990). As the disease progresses, HD patients demonstrate significant impairment in attention, delayed recall, verbal fluency, visuospatial functioning, and frontal-executive tasks (J. Snowden, Craufurd, Griffiths, Thompson, & Neary, 2001; Zakzanis, 1998). On neuropsychological testing batteries, HD patients show deficits in digit span (a working memory measure), digit symbols (a measure of mental flexibility and visuomotor coordination), object recall, and Stroop performance (a measure of inhibitory ability) (Bachoud-Levi et al., 2001; Paulsen et al., 2001). HD patients also exhibit a number of memory deficits, specifically in retrieval and procedural learning (Bylsma, Rebok, & Brandt, 1991). Recall in HD patients can be improved by priming, semantic retrieval cues, and encoding enrichment (Maki, Bylsma, & Brandt, 2000). HD patients demonstrate a variety of speech and language impairments including dysarthria, decreased verbal fluency, and decreased speech output (Lawrence et al., 1998; Murray & Lenz, 2001).The dysarthria seen in HD is

largely a result of choreathetic movements that affect the lips and tongue. These movements affect speech timing, pronunciation, and articulation. Choreiform movements can also affect the diaphragm, causing alterations in speech volume, rate, and phrase length. In later stages of HD, patients have minimal spontaneous speech output, and may be functionally mute.

In addition to the cognitive decline, HD patients present with a wide range of personality changes and psychiatric symptoms including depression, anxiety and aggressive behaviors (Folstein, 1989). Psychiatric symptoms often precede motor symptoms (Folstein, 1989). In addition, at least 40% of HD patients exhibit a mood disorder including depression, bipolar disorder, and schizophrenia (Shiwach, 1994). About 6% of HD patients exhibit psychotic symptoms including delusions, and schizophrenia-like illnesses (Dewhurst, Oliver, Trick, & McKnight, 1969). As the disease progresses, HD patients show dramatic personality changes which can include, irritability, disinhibition, antisocial and criminal behavior, violent behaviors, apathy, withdrawal, loss of interest in everyday activities, and addictive behaviors (Cina, Smith, Collins, & Conradi, 1996; De Marchi, Morris, Mennella, La Pia, & Nestadt, 1998).

Progressive Supranuclear Palsy

Progressive supranuclear palsy (PSP), which is also called Steele-Richardson-Olzewki syndrome, is an atypical parkinsonian syndrome that is characterized by neuropil threads and neurofibrillary tangles in basal ganglia and brainstem structures (Hauw et al., 1994; Lantos, 1994; Litvan et al., 1996). Neuropil threads are threadlike structures made up mostly of hyperphosphorylated tau proteins. Both neurofibrillary tangles and neuropil threads are present in other dementing disorders. Further complicating diagnosis, PSP patients may also suffer from other CNS pathologies such as vascular disease and as well as other neurodegenerative disorders (Gearing, Olson, Watts, & Mirra, 1994). PSP affects approximately 1.4 per 100,000 individuals in the United States after age adjustment (Golbe, Davis, Schoenberg, & Duvoisin, 1988). Many cases are undiagnosed until very late in the progression of the disease (Golbe et al., 1988). PSP is characterized by postural instability, visual disturbances, dysarthria, and cognitive/behavioral disturbances (Diroma et al., 2003). Patients with PSP display characteristic visual disturbances early in the disease progression. Initially, patients demonstrate supranuclear gaze deficits that involve either downward or upward gaze. Diplopia (double vision), blurred vision, burning eyes, problems with voluntary saccades, convergence, and sensitivity to light also may occur (Litvan, Mangone et al., 1996). Motor deficits in PSP patients generally present as postural instability and falls, gait abnormalities bilateral bradykinesia, dysarthria, and dysphagia (Litvan, Mangone et al., 1996). In contrast to the "stooped" gait of Parkinson patients, PSP patients have an unsteady, upright but slow gait.

In addition to these motor and visual disturbances, PSP patients demonstrate a number of cognitive and behavioral changes. Forgetfulness, irritability, apathy, and depression are often noted at

clinical presentation (Nath, Ben-Shlomo, Thomson, Lees, & Burn, 2003). Patients with PSP exhibit a "dysexecutive dementia" which is characterized by deficits in motor inhibition, verbal fluency, and planning (Grafman, Litvan, & Stark, 1995). PSP patients show deficits in speech initiation and spontaneous speech production (Magherini & Litvan, 2005). Psychomotor slowing is also evident. Memory deficits in PSP may be due to underlying deficits in memory recall rather than deficits in either short-term or long-term recognition (Litvan, Grafman, Gomez, & Chase, 1989).

Summary

The differential diagnosis between healthy aging, mild cognitive impairment and various forms of dementia remains an important clinical challenge. As the world population ages, dementia will pose an ever increasing psychosocial and economic burden. For example, more than five million American adults currently live with Alzheimer disease or an associated form of dementia, and epidemiologists predict the rapid expansion of this population during the next three decades (Hebert, Beckett, Scherr, & Evans, 2001). Health care providers must be aware of the cognitive deficits associated with both common and less common forms of dementia, and be able to distinguish them from the cognitive decline seen in healthy aging. Further research will help to define the specific deficits associated with the dementias discussed in this review. This research should also investigate the impact of genetic, environmental, and other factors on the development of dementia. Nevertheless, current research points to a number of factors that can help to reduce one's risk of developing dementia. As previously discussed, lowering blood pressure and cholesterol levels is known to reduce dementia risk. Controlling diabetes, managing weight and smoking cessation also lowers risk. Research into rehabilitation may devise new ways to lessen the impact of neuropathologic insult on cognitive decline. Finally, improved diagnosis of various forms of dementia will both aid future research, and allow for more appropriate, early clinical intervention for individual patients.

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